Lewis acid/palladium catalyzed synthetic transformations of pentafulvenes and its derivatives: Facile synthesis of indole appended carbocycles and heterocycles

Thesis Submitted to AcSIR for the Award of the Degree of
DOCTOR OF PHILOSOPHY
in Chemical Sciences

By
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January, 2016

.....To My Parents and Teachers

DECLARATION

I hereby declare that the Ph.D. thesis entitled "**Lewis acid/palladium catalyzed synthetic transformations of pentafulvenes and its derivatives: Facile synthesis of indole appended carbocycles and heterocycles**" is an independent work carried out by me at the Chemical Sciences and Technology division, CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST), Thiruvananthapuram under the supervision of Dr. K. V. Radhakrishnan, Principal Scientist, and it has not been submitted anywhere else for any other degree, diploma or title.

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CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled "**Lewis acid/palladium catalyzed synthetic transformations of pentafulvenes and its derivatives: Facile synthesis of indole appended carbocycles and heterocycles**" *submitted by* ***Mr. Sarath Chand S*** *to Academy of Scientific and Innovative Research (AcSIR), New Delhi, in partial fulfilment of the requirements for the award of the* ***Degree of Doctor of Philosophy in Chemical Sciences****, embodies original research work under my guidance. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma.*

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ACKNOWLEDGEMENTS

It is with great respect and immense pleasure that I express my humble and deep sense of gratitude to my research supervisor ***Dr. K. V. Radhakrishnan*** *for introducing me to the fascinating area of organic synthesis and also for his excellent guidance, constant encouragement, wholehearted help and constructive criticism throughout my research work.*

I am grateful to Dr. A. Ajayaghosh, Director, CSIR-NIIST and former Directors Dr. Suresh Das and Dr. Gangan Prathap for providing the laboratory facilities to carry out the research work.

I would like to acknowledge Dr. Mangalam S. Nair, AcSIR programme coordinator at CSIR-NIIST for her timely help and advice for the academic procedures of AcSIR.

I would like to acknowledge Dr. Gopidas K. R., Head and Dr. D. Ramaiah, Former Head, Chemical Sciences and Technology Division for their support.

I am very thankful to Dr. R. Luxmi Varma, Dr. Ravi Shankar L., Dr. U. S. Hareesh, (DAC members) for their immense support for the completion of my research work.

I thank Dr. G. Vijay Nair, Emeritus Scientist, Organic Chemistry Section for his inspiring presence and fruitful discussions.

I would like to acknowledge Dr. A. Jayalekshmy, Dr. Kaustabh Kumar Maiti and Dr. B. S. Sasidhar, Dr. Ganesh Nandi, Scientists of Organic Chemistry Section, for the encouragement and support.

I would like to thank Mrs. Saumini Mathew, Mr. B. Adarsh, Mr. Arun, Mr. Vipin M. G., Mr. Saran P.Raveendran, Mr. Syam and Mr. Rakesh Gokul for recording NMR spectra. Thanks are also due to Mrs. S. Viji and Ms. Aathira for mass spectral analysis.

I also wish to thank Dr. Sunil Varughese, CSIR-NIIST, Dr. E. Suresh, CSIR-CSMCRI, Bhavnagar, and Dr. Alex Andrews, IISER, Trivandrum for Single Crystal X-ray analysis.

I would also like to acknowledge Prof. Jan Szymoniak, Dr. Florian Jaroschik, Dr. Dominique Harakat and Dr. Jean-Luc Vasse, Universite de Reims, France for sharing their knowledge.

I am grateful to Dr. Praveen Prakash, Dr. Nayana Joseph and Ms. Dhanya S. R. for their immense support during all stages of my doctoral studies.

I express my sincere thanks to Dr. Ajish K. R., Mr. Sajin Francis and Mr. Ajesh Vijayan for their great companionship during my stay in Trivandrum.

I would like to extend special thanks to Dr. Jijy. E., Mr. Preethanuj P., Ms. Dhanya. B. P., Mrs. Saranya S., Ms. Santhini P. V., Ms. Tanwistha Ghosh., Ms. Gouri Chandran, Mr. Sasikumar P. and Ms. Greeshma Gopalan for their assistance in conducting some of the experiments reported in this thesis.

I would like to extend my thanks to Mr. Baiju T.V., Ms. Shimi M., Ms. Aparna P. S., Ms. Prabha B., Ms. Santhi, Mr. Rajeev K. K., and Mrs. Remya Raj for their companionship and great support.

I also wish to thank Dr. Jisha Babu, Ms. Anupriya S., Mr. Mineesh E. G., Ms. Athira Krishna, Ms. Maya R. J., Ms. Sreedevi P., Dr. Sinu C. R., Dr. Anu Jose, Dr. Rony Rajan Paul, Mrs. Seetha Lakshmi, Ms. Padmaja D. V. M., Mrs. Parvathy R., Mr. Maniganda S., Ms. Nisha N., Ms. Jyothi B. Nair, Mrs. Ramya A. N., Ms. Varsha K., Mr. Sujai P. T., Mr. Jayakrishnan A., and Mr. Jagadeesh K. for their friendship and help.

I express my sincere thanks to former colleagues: Dr. Jubi John, Dr. Sholly Clair George, Dr. Rani Rajan, Dr. Sreeja T., Dr. Suchitra M. V., Dr. Smitha Mohanlal, Dr. Selvakumar K. and Dr. Praveen L. for their valuable suggestions and support during different stages of my research career.

I express my sincere gratitude to Dr. Anil Kumar, Director, M. S. Swaminathan Research Foundation - Community Agro biodiversity Centre (MSSRF-CAbC), Kalpetta, Wayanad, Kerala for providing the facilities to carry out my CSIR-800 project.

I would like to acknowledge the scientists and staff, especially to Mr. V. V. Sivan, Mr. Jithin, and Mr. P. Jayesh of MSSRF- CAbC, Wayanad for the successful completion of the ethnobotanical survey in the remote tribal areas of Wayanad as part of my CSIR-800 project work.

I am indebted to Dr. S. Nesamani, Retired Research Officer, Central Council for Research in Ayurvedic Sciences (CCRAS, New Delhi), for inspiring me with his boundless knowledge on Ayurvedic plants, to carry out my CSIR-800 project.

I am grateful to UGC, CSIR and DST New Delhi, for the financial assistance.

I would like to extend my sincere thanks to all my friends at CSIR-NIIST.

The successful completion of dissertation would have been practically impossible without the support, encouragement and unconditional love and support from my family.

Above all, I thank Almighty for giving me all these people to help and encourage me, and for the skills and opportunity for the successful completion of the research work.

Sarath Chand S

CONTENTS

ABBREVIATIONS

Ac	: acetyl	DMF	: dimethyl formamide
AcOH	: acetic acid	DIOP	: 2,2-Dimethyl-4,5- ((diphenyl
Ar	: argon		phosphino)dimethyl)dioxolane
aq	: aqueous	dppb	: bis(diphenylphosphino)butane
acac	: acetylacetonate	dppe	: bis(diphenylphosphino)ethane
BINAP	: 2,2'-bis(diphenylphosphino)-1,1'	dppf	: bis(diphenylphosphino)ferrocene
	binaphthyl	dppm	: bis(diphenylphosphino)methane
Bn	: benzyl	dppp	: bis(diphenylphosphino)propane
Boc	: tertiary butyloxycarbonyl	EI	: electron impact
^{t}Bu	: tertiary butyl	Et	: ethyl
bpy	: bipyridine	FAB	: fast atom bombardment
BDPP	: diphenylphosphinopentane	Ga	: gallium
calcd	: calculated	h	: hour
cod	: 1,5-cyclooctadiene	HRMS	: high resolution mass spectra
Cpd	: cyclopentadiene	Hz	: hertz
d	: doublet	In	: indium
dba	: dibenzylidene acetone	IR	: infrared
dd	: doublet of a doublet	*J*	: coupling constant
DME	: dimethoxyethane	LA	: Lewis acid
DMAP	: dimethyl aminopyridine	LDA	: lithium diisopropylamine
DCC	: dicyclohexylcarbodiimide	m	: multiplet
DDQ	: dichlorodicyanobenzoquinone	Me	: methyl
DBU	: 1,8-diazabicyclo[5.4.0]undec-7-ene	mg	: milligram

DCM : dichloromethane

Mp : melting point

MS : mass spectroscopy

NBD : norbornadiene

NMR : nuclear magnetic resonance

Nu : nucleophile

o : ortho

p : para

Ph : phenyl

PhH : benzene

Pt : platinum

^{i}Pr : isopropyl

PTAD : 4-phenyl-1,2,4-triazoline-3,5-dione

q : quartet

R_f : retention factor

RT : room temperature

s : singlet

t : triplet

mL :millilitre

Tf : triflyl(trifluoromethane sulfonyl)

TFA : trifluoroacetic acid

THF : tetrahydrofuran

TLC : thin layer chromatography

TMS : Trimethyl silyl

Tol : tolyl

TsOH : toluene sulphonic acid

tert : tertiary

UV : ultra violet

PREFACE

One of the most challenging goals in synthetic organic chemistry is to develop mild and efficient conditions for the synthesis and functionalization of biologically important molecules using simple precursors. The pentafulvene system is a very attractive structural unit, not only as a model for theoretical studies but also as a valuable building block to access polycyclic cyclopentanoids through a diverse array of cyclization. A wide range of molecular skeletons have been synthesized through short and easy chemical manipulations of pentafulvenes and its derivatives. The investigations along this line forms the focal theme of this thesis entitled **"Lewis acid/palladium catalyzed synthetic transformations of pentafulvenes and its derivatives: Facile synthesis of indole appended carbocycles and heterocycles."**

The thesis is divided into four chapters. Relevant references are given at the end of each chapter. The first chapter of the thesis gives a brief introductory discussion on the synthetic aspects of pentafulvenes. The definition of the present research problem is also incorporated in this chapter.

Pentafulvene, the first coloured hydrocarbon synthesized in the turn of the last century, is known to be the better-known isomer of benzene. In contrast to the diverse cycloaddition reactions of pentafulvene, less attention has been paid to the addition of nucleophiles or electrophiles to these molecules. The second chapter of the thesis outlines our efforts towards the regioselective nucleophilic addition of indole to the endocyclic ring of pentafulvene by trapping the *in situ* formed fulvenium ion by the catalytic application of a Lewis acid. The developed protocol introduces pentafulvenes as alkene moieties for the regioselective hydroheteroarylation reaction.

The third chapter of the thesis frameworks the Lewis acid catalyzed ring-opening of pentafulvene derived bicyclic olefins with *N*-alkyl as well as free (NH) indoles toward the efficient synthesis of mono and bis-indolyl functionalized

alkylidenecyclopentenes. The developed method leads to the C-3 functionalization of indoles with alkylidenecyclopentenes, along with the formation of bis-indole derivatives. Furthermore, catalytic conditions were tuned for the synthesis of bis-indolyl analogues of alkylidenecyclopentenes.

Catalytic domino transformations allow a rapid increase in molecular complexity from readily available starting materials. The advantage of these transformations is the formation of several bonds and the creation of two or more contiguous stereogenic centers in one pot, without the need for isolation of the intermediate. The fourth chapter of the thesis describes the Pd/Lewis acid catalyzed stepwise and domino synthetic transformation of pentafulvene derived diazabicyclic olefins towards novel spiropentacyclic motifs with indoline and pyrazolidine fused to the cyclopentene core. The strategy was achieved by a Lewis acid catalyzed ring opening of fulvene derived azabicyclic olefin using *o*-iodoaniline followed by the Pd catalysed intramolecular Heck cyclization. The efficiency of this domino reaction was proved by performing the reaction in the presence of a Lewis acid and Pd catalyst using a solvent mixture of acetonitrile and toluene. It may be mentioned that each chapter of the thesis is presented as an independent unit and therefore the structural formulae, schemes and figures are numbered chapter wise.

A summary of the work is given towards the end of the thesis.

CHAPTER 1

Synthetic Aspects of Pentafulvenes

1.1. Introduction

The concept of conjugation, which describes delocalization of electrons across a molecule, has been well established and intriguing as a fundamental aspect of organic chemistry. After the isolation of benzene[1] in 1825, the term 'aromaticity' has come out as a manifestation of cyclic delocalization of π-electrons and resonance.[2] The concept of resonance energy and of aromaticity has proven invaluable in explaining and predicting the structure, stability, and reactivity for the ground states of conjugated molecules. The conjugation between π-bonded molecular fragments is, without doubt, the most thoroughly explored and well understood conjugation type. In addition to the regular linear (or through) conjugation, cross-conjugated molecules are well known in literature along with some rare cases of omniconjugated molecules (Figure 1.1).[3–5]

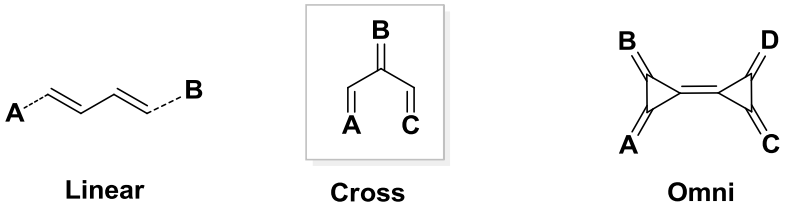


Figure 1.1 Conjugation in organic molecules

Among these conjugated molecules, cross conjugated systems have received considerable attention because of its inherent aromatic behaviour, moreover the non-functionalized carbon-carbon multiple bond systems are recognized as latent

functional groups. Fulvenes, cyclic cross-conjugated molecules with odd number of carbon atoms in the ring belong to the category of non-functionalized carbon-carbon double bonds. At the turn of the last century, in connection with the question regarding the 'nature and origin of aromatic character of non-benzenoid systems', fulvenes were emphasized for its aromatic behaviour. Depending on their dipole moments and reactivity patterns, fulvenes would occupy an intermediate position between the open chain olefinic and aromatic compounds.

Based on their ring skeleton, fulvenes are classified as triafulvene, pentafulvene and heptafulvene (Figure 1.2). Among various fulvenes, pentafulvenes enjoy a coveted status owing to its unique reactivity pattern and the versatility of the reaction products.

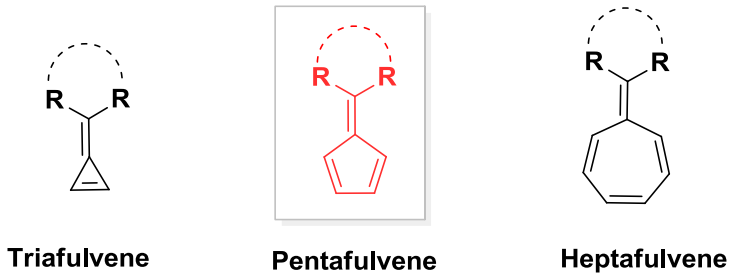


Figure 1.2 Types of fulvenes

1.2. Structural features of pentafulvene

Pentafulvene, the first synthetic cross conjugated hydrocarbon isolated, has been considered as the better known isomer of benzene.[6] Unlike benzene, pentafulvene is not a thermodynamically and kinetically stable system. As per the theoretical evaluation, pentafulvenes are dipolar hydrocarbons since they involve zwitterionic resonance structures with a positively charged exocyclic carbon atom and a negatively charged aromatic cyclopentadienyl ring.[7] The nature of bonding in pentafulvenes has

been described qualitatively as a mesomeric superposition of the covalent structure **A** and the polar structure **B** as depicted in Figure 1.3.

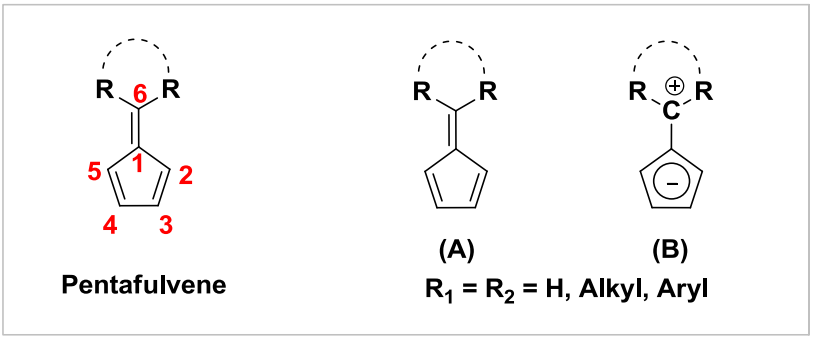


Figure 1.3 The covalent structure and the polar structure of fulvene

1.3. Aromaticity of pentafulvenes

Due to chemical instability of pentafulvenes, they have been considered for a long time as non-aromatic. Later on, it was established that the electronic nature of substituents at the exocyclic position markedly influences the aromatic character of pentafulvenes.[8] Generally electron donating substituents at exocyclic carbon atom shift the electron density towards the ring thereby increasing the aromaticity of pentafulvene (Figure 1.4). For example, the *N*,*N*-dimethyl aminofulvene is more aromatic than 6,6-dialkyl or diarylfulvenes and shows remarkable differences in their reactivity.

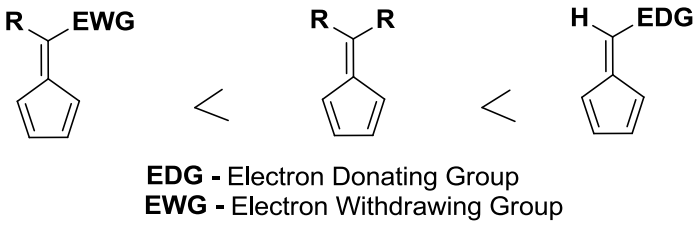
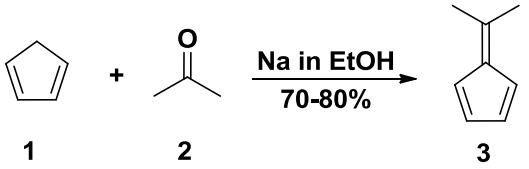


Figure 1.4 Order of aromaticity of pentafulvenes

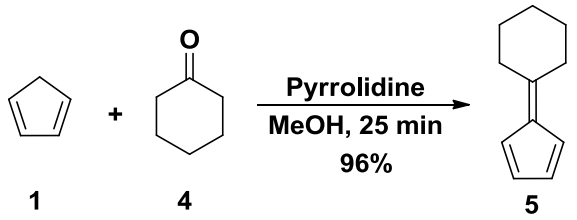
1.4. Synthesis of fulvene

The synthesis of fulvene was first reported by Thiele in 1900, based on the condensation of aldehydes and ketones with cyclopentadiene in presence of metal alkoxides (Scheme 1.1).[9]



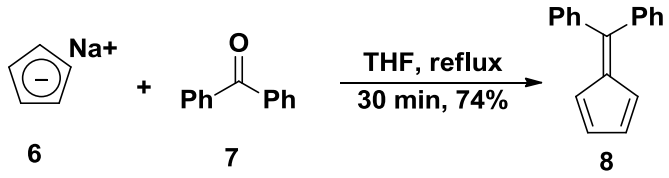
Scheme 1.1

In 1983, Stone and Little introduced a more versatile method for the synthesis of pentafulvenes using pyrrolidine as base (Scheme 1.2).[10]



Scheme 1.2

The pyrrolidine mediated pentafulvene synthesis was unsuccessful with bulky ketones such as diaryl ketones. In order to address this problem, Oda and co-workers developed a typical procedure towards 6,6-disubstituted pentafulvenes using *N*,*N*-dialkylamides, instead of ketones, with organolithium compounds and cyclopentadiene.[11] In 2004, Ottoson reported an improved route to fulvenes in which a ketone is reacted with crystalline sodium or potassium cyclopentadienide in refluxing THF (Scheme 1.3).[12]



Scheme 1.3

In 2011, Erden and co-workers established an efficient procedure for the preparation of a broad range of fulvenes using catalytic pyrrolidine in MeOH/H_2O, which not only give high yields but also minimize product loss during extractive work-up and avoid the use of excess cyclopentadiene whose dimer presents challenging separation problems from the desired fulvenes.[13] This condition is very promising in the synthesis of even low molecular-weight fulvenes such as 6-methyl and 6-ethylfulvene in high yields.

1.5. Fulvenes as the precursor of cyclopentanoids

The chemistry of cyclopentenes, cyclopentanones and cyclopentenones has developed rapidly in the last fifty years. One of the major reasons for this has been the search for synthetic routes to the prostaglandins,[14] prostacyclins,[15] and thromboxanes,[16,17] macrolide antibiotic brefeldin-A[18] and its derivatives (fig. 1.5). To date, several methods are available for 5-membered carbocycle synthesis, including the Pauson–Khand raction[19,20] [2+2+1] annulation, metal-catalyzed [3+2] annulation[21,22] [4+1] annulation strategy involving the reaction of (trialkylsilyl) vinylketenes with carbenoid reagents,[23] the Nazarov cyclization,[24,25] Ring Closing Metathesis (RCM),[26] free radical cyclization,[27] etc.

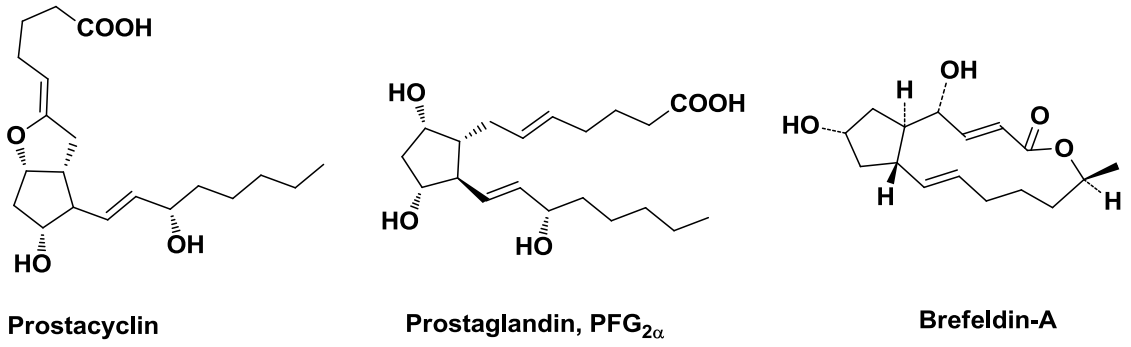


Figure 1.5 Biologically important molecules with cyclopentane core

Cyclopentadiene is an economical and readily available cyclopentane unit; however, the use of substituted cyclopentadienes in natural product synthesis has frequently been complicated by the facile 1,5-sigmatropic rearrangements of these species. A solution to this problem is to block the rearrangement with suitable chemical entities, which may serve as a source of latent functionality.[28] Cyclopentadiene with an exocyclic double bond, generally known as fulvene, plays a great role in this scenario. The pentafulvene system represents a very attractive structural unit, not only as a model for theoretical studies but also as a valuable building block to access polycyclic cyclopentanoids through a diverse array of cyclizations.[29] In 1981, Sakai and Kobori effectively utilized this fascinating system as starting material for the total synthesis of prostaglandin.[30] Fulvenes were also used as key components in the total synthesis of many natural products including (+) and (-)-nigellamines,[31] guanacastepenes,[32] β-vetinones,[33] streptazones,[34] capnellene,[35] abacavir, hinesol, hirsutine, etc. (Figure1.6).[36]

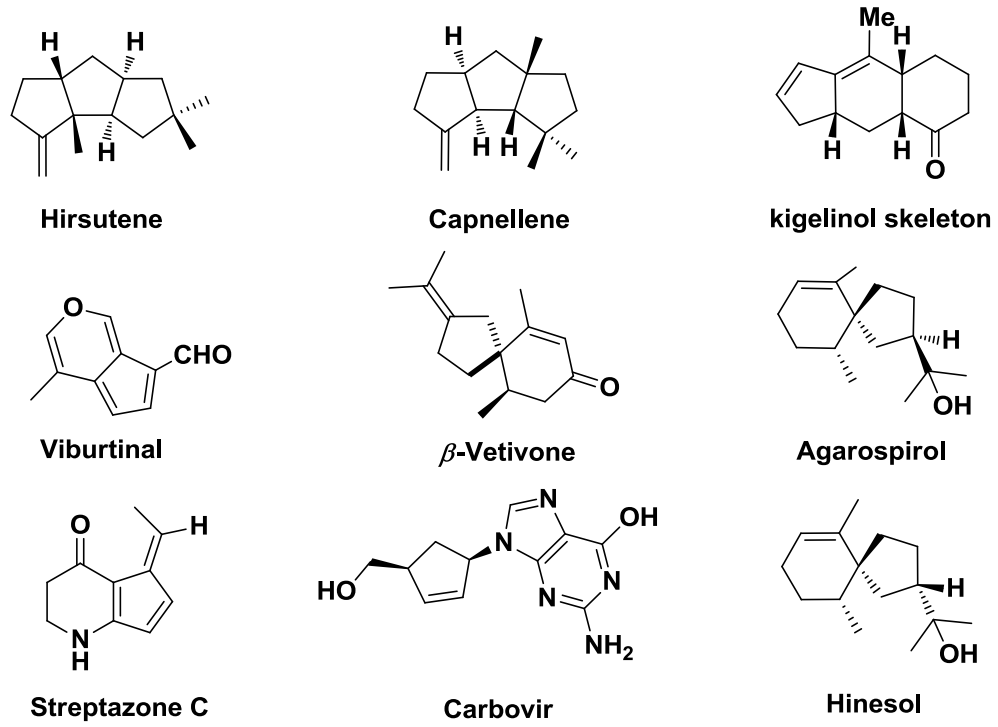


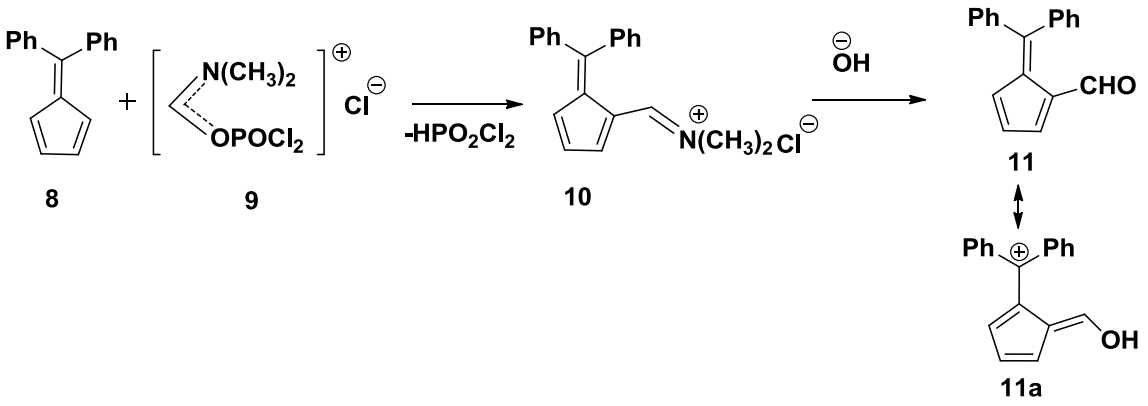
Figure 1.6 Polycyclic compounds with cyclopentanoid core

1.6. Reactivity of pentafulvenes

Pentafulvenes display a wide range of reactivity with nucleophiles, electrophiles and various cycloaddition partners.[7,37] Some of the fulvene derivatives thus obtained strongly resemble the isomeric benzene derivatives and proved to be valuable starting material for the synthesis of both known and novel non-benzenoid compounds.

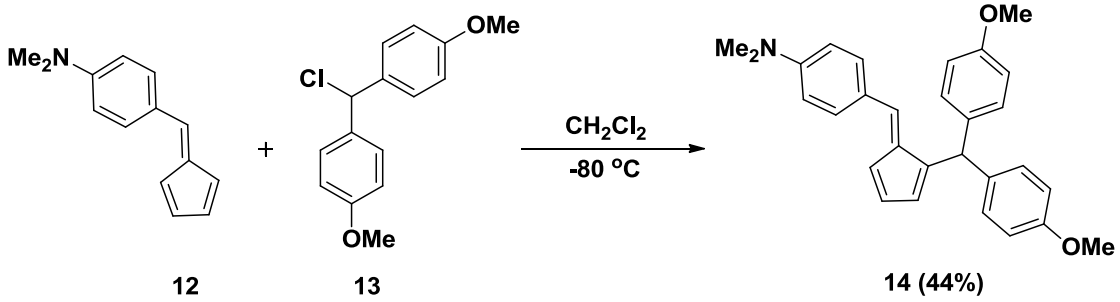
1.6.1. Reactions of pentafulvene with electrophiles

Fulvenes are susceptible to electrophilic substitution reactions as in other non-benzenoid molecule such as azulenes. 6,6- Diphenylfulvene can be formylated with ease and in high yield on treatment with Vilsmeier's complex **10**. The stable red fulvenaldehyde **11** formed undergo protonation at carbonyl oxygen to give the conjugated acid **11a** (Scheme 1.4).[7]



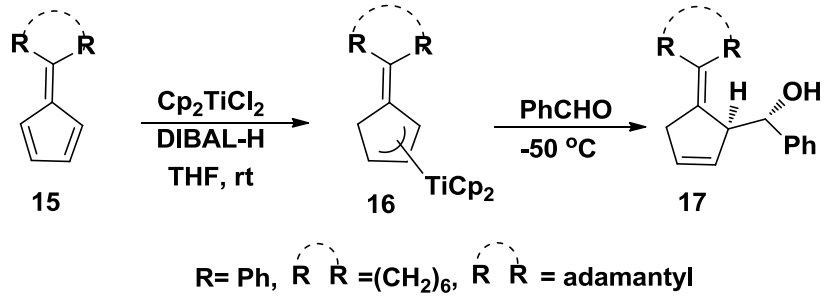
Scheme 1.4

Herbert Mayr found that benzhydryl chloride underwent electrophilic substitution reactions with fulvene while they were studying the nucleophilicity of some selected fulvenes and azulenes.[38] The reaction of fulvene **12** and benzhydryl chloride **13** in CH_2Cl_2 at –80 °C afforded the monosubstitution product **14** in 44% yields (Scheme 1.5).



Scheme 1.5

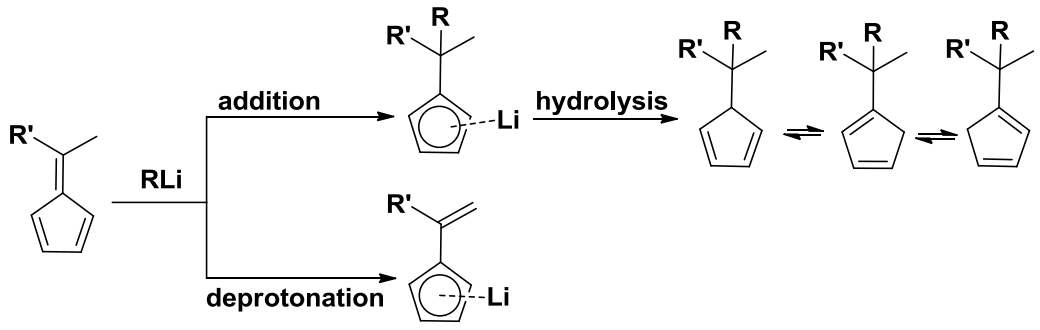
In 2013, a new reactivity pattern of pentafulvenes was disclosed by Szymoniak's research group. They found that allyltitanocene complexes can be generated by reacting pentafulvenes with DIBAL-H and Cp_2TiCl_2. The coupling of η^3 -allyltitanocenes **16** with aldehydes affords homoallylic alcohols **17** in a highly regio- and stereoselective manner (Scheme 1.6).[39,40]



Scheme 1.6

1.6.2. Reaction of pentafulvene with nucleophiles

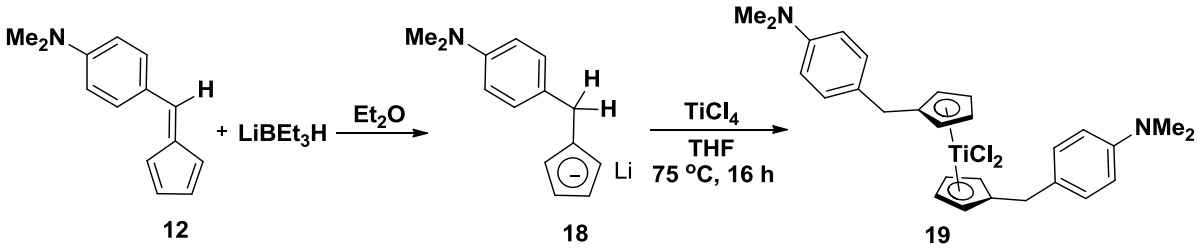
The terminal exocyclic carbon of pentafulvene is electrophilic and can be attacked directly by a suitable nucleophile.[41, 42] In addition, the C-H bonds in the α-position to C-6 carbon of fulvene feature an enhanced C-H acidity and can be removed by a suitable base (Scheme 1.7).



Scheme 1.7

1.6.2.1. Hydridolithiation of pentafulvene

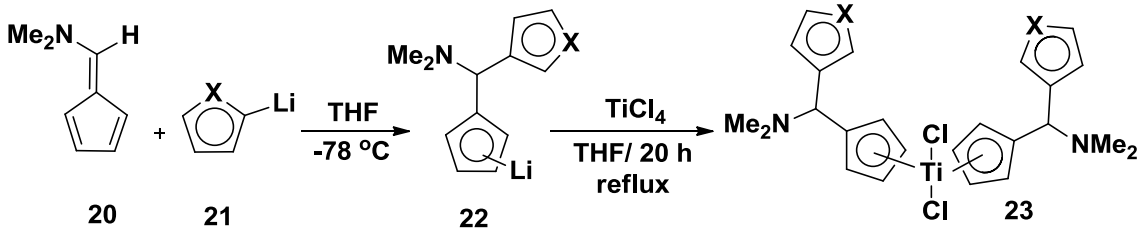
The nucleophilic addition of a hydride to the exocyclic double bond of fulvene **12**, using super hydride ($LiBEt_3H$) as the hydride transfer reagent,[43] resulted in substituted lithium cyclopentadienide intermediate **18** through hydrolithiation. The intermediate on transmetallation with $TiCl_4$ in THF under reflux condition furnished non-bridged substituted titanocene dichloride **19** in good yields (Scheme 1.8).[44]



Scheme 1.8

1.6.2.2. Carbolithiation of pentafulvene

The reaction of aryl or heteroaryl lithium species **21** with 6-(*N*,*N*-dimethylamino) pentafulvene **20** led to carbolithiation of pentafulvene. The reaction is versatile towards the synthesis of a wide variety of highly cytotoxic titanocenedichlorides **23** (Scheme 1.9).[45]

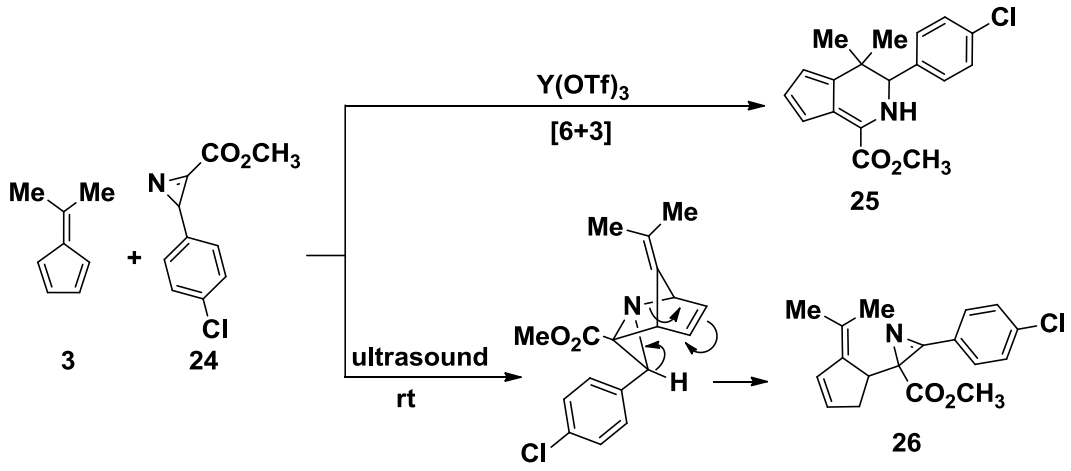


Scheme 1.9

1.6.3. Miscellaneous reactions of pentafulvene

1.6.3.1. Reaction with azirine

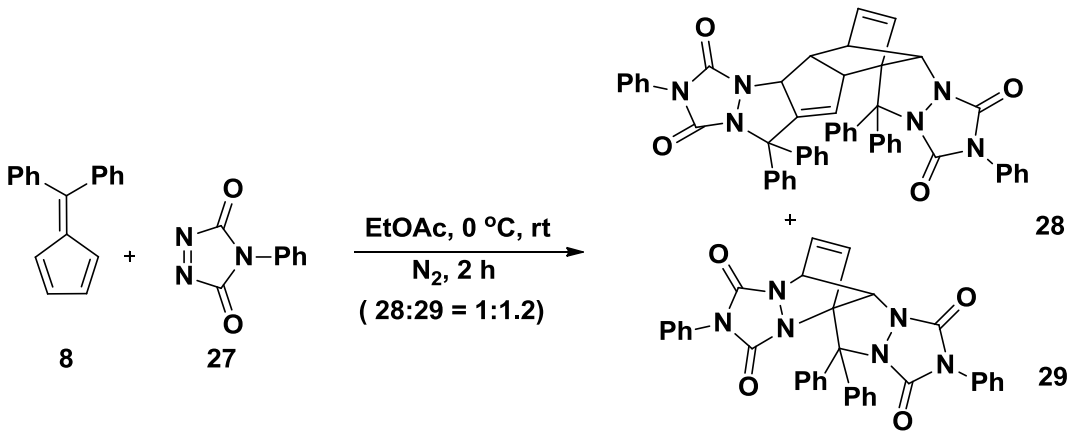
In presence of a Lewis acid, 2H-azirine **24** react with fulvenes through a formal regioselective [6+3] cycloaddition providing an alternative synthesis of [2]pyrindine derivatives **25**. However, under ultrasound conditions the reaction afforded alkylated fulvene azirines **26** through an unexpected rearrangement of the initial Diels-Alder cycloadduct as shown in Scheme 1.10.[46]



Scheme 1.10

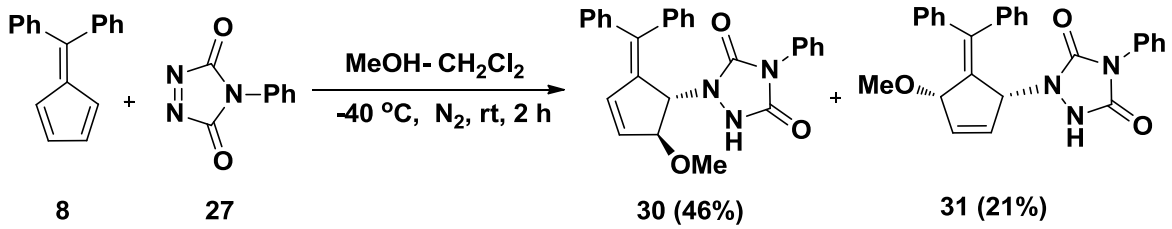
1.6.3.2. Reaction with triazolinediones

Research from our laboratory have revealed that the reaction of pentafulvenes with *N*-substituted-1,2,4-triazoline-3,5-diones **27** leading to the formation of five- and seven-membered azapolycycles.[47] The electronic and frontier molecular orbital features of pentafulvene and triazolinedione suggests that the latter molecule can add to the former one *via* a [4 + 2] cycloaddition at electron rich 3,4 positions of the pentafulvene or by a nucleophilic reaction at the electron deficient exocyclic carbon atom (Scheme 1.11).



Scheme 1.11

The proposed zwitterionic mechanism of the reaction (Scheme 1.11) was explained by trapping of the reactive intermediates with methanol. The cycloaddition between fulvene and **27** in a dichloromethane–methanol mixture (1:5) at -40 ^{o}C afforded a separable mixture of methanol trapped products **30** (46%) and **31** (21%) respectively (Scheme 1.12).

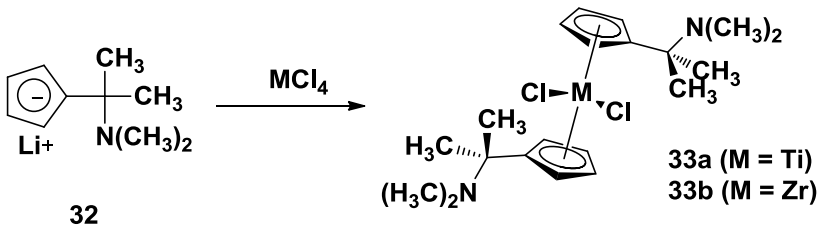


Scheme 1.12

1.6.4. Metallation reactions of pentafulvene

1.6.4.1. Formation of metallocenes

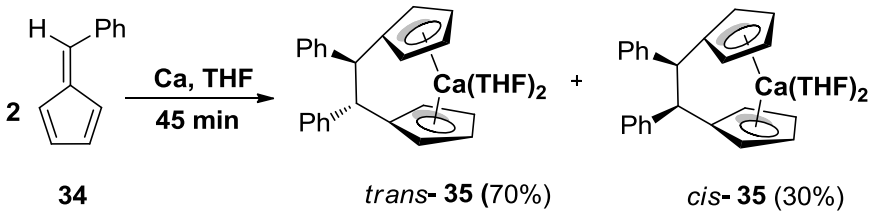
Erker and co-workers found that 6-*N*,*N*-dialkylaminofulvenes undergo lithiation with alkyllithium reagents. Transmetallation of such species with Group 4 metal halides yields the corresponding substituted metallocene complexes **33** (Scheme 1.13).[42] Thus, the reaction of **32** with $TiCl_4$ or $ZrCl_4$ led to the formation of the metallocene dichloride complexes **33a** and **33b** respectively.



Scheme 1.13

1.6.4.2. Reductive coupling of fulvenes with calcium

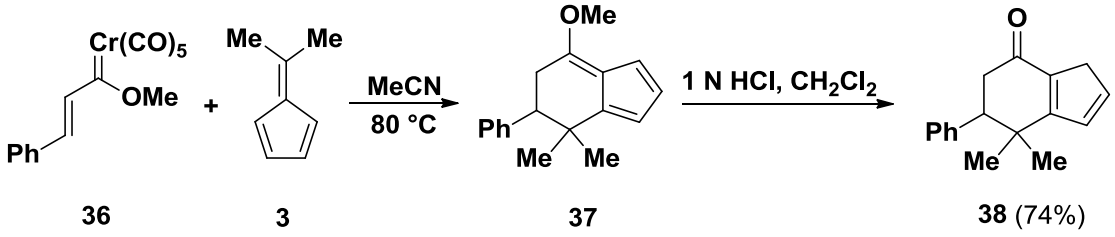
The reductive coupling of phenylfulvene **34** with activated calcium in THF gives nearly quantitative yield of a mixture of *cis*- and *trans*-diphenylethanediyl-bridged ansa-calcocenes.[48] The more soluble cis-isomer **35** can be removed by recrystallization, yielding the C2-symmetric *trans*-isomer **35** (Scheme 1.14).



Scheme 1.14

1.6.4.3. Pentafulvenes with Fischer-carbene complexes

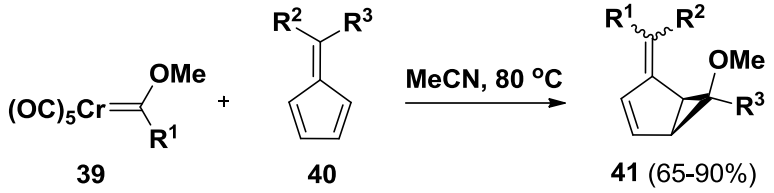
In 2001, Barluenga and co-workers introduced carbene complexes in the metallation chemistry of pentafulvenes.[49] They have showed the [6+3] cycloaddition reaction of alkenylalkoxycarbene complex **36** with dimethylfulvene affording indane and its derivatives in a regioselective manner. (Scheme 1.15).[50]



Scheme 1.15

Later, the same research group extended the carbene-chemistry to the endo-selective cyclopropanation of pentafulvene. The [2+1] cycloaddition of the Fischer

carbene **39** and penafulvene **40** afforded the cyclopropanated product **41** in good to excellent yields (Scheme 1.16).[29]



R' = Ph, 4MeO-C_6C_4, nBu, R^2 = ^{t}Bu, ^{i}Pr, Ph, OAc, R^3 = H, Me

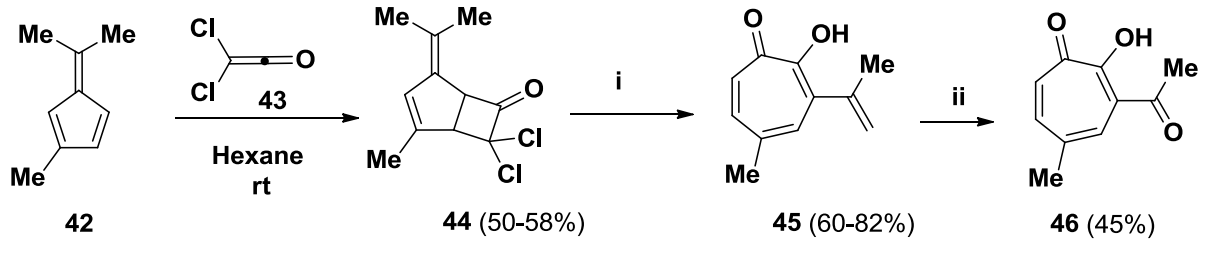
Scheme 1.16

1.6.5. Cycloaddition reactions of pentafulvenes

Cycloaddition reactions have emerged as the most powerful carbon-carbon and carbon-heteroatom bond forming processes in organic synthesis. The cycloaddition chemistry of pentafulvenes has invoked considerable interest in organic synthesis and this was credited to the diverse cycloaddition profiles involved in them and the versatility of the reaction products. Fulvene works flexibly as a 2π, 4π or 6π candidate and have been identified as the well-known construction unit of many fused ring systems through intra- and inter-molecular cycloaddition reactions. The periselectivity of these reactions can be controlled by the substituents on the fulvene and other substrate.

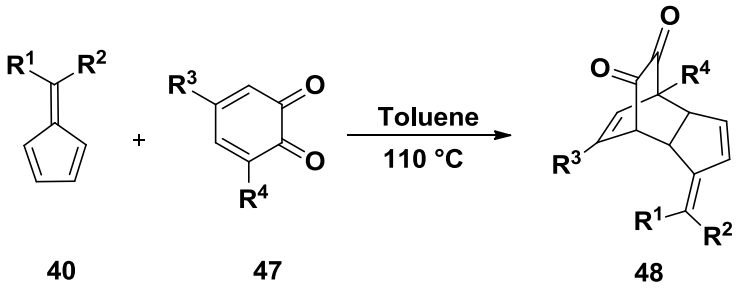
1.6.5.1. Pentafulvene as 2π components

Pentafulvenes behave as 2π components with electron-deficient dienes. Imafuku and co-workers reported the synthesis of substituted tropolone derivatives through a [2+2] cycloaddition between 2-alkyl-6,6-dimethyl fulvene **42** and dichloroketene **43**.[51] The hydrolysis of the cycloadduct **44** followed by the treatment with hydrazoic acid afforded 5-alkyl-3-acetyl tropolone **46** (Scheme 1.17).



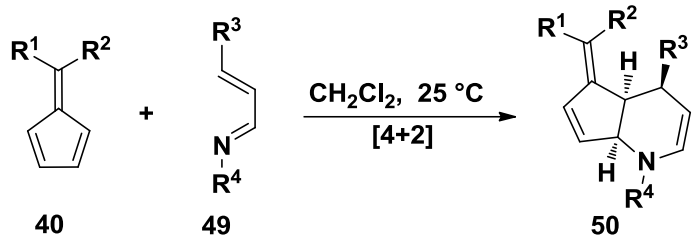
Scheme 1.17

The investigations from our laboratory have revealed that pentafulvene acts as an efficient 2π component in the [4+2] addition with 1,2-benzoquinones. The reaction of 6,6-diphenyl fulvene **40** with the substituted *o*-quinone **47** afforded bicyclo[2.2.2]octen-7,8-dione adduct **48** in excellent yields (Scheme 1.18).[52]



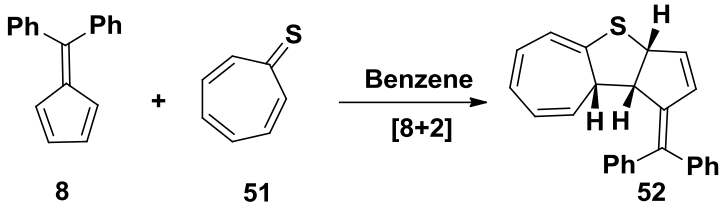
Scheme 1.18

In contrast to this, Hong and co-workers demonstrated a highly regio- and stereoselective inverse electron demand Diels-Alder cycloaddition of pentafulvenes with azadienes as an example for the [4+2] cycloaddition. The methodology provides an efficient route to the synthesis of tetrahydro[1]-pyrindine system **50** (Scheme 1.19).[53]



Scheme 1.19

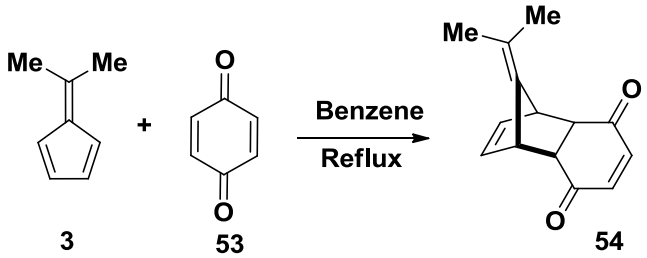
Moreover, the highly conjugated tropothione **51**, which is valence isoelectronic with tropone, reacts with fulvenes in a concerted fashion to afforded [8 + 2] cycloadducts **52** with endo selectivity (Scheme 1.20).[54]



Scheme 1.20

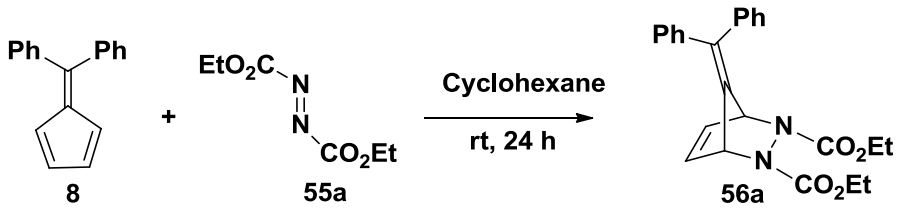
1.6.5.2. Pentafulvene as 4*π* components

As an exceptional behaviour of a cross conjugated triene, pentafulvenes undergo smooth Diels-Alder reaction with dienophiles such as maleimide,[55] *p*-quinone and dialkylazodicarboxylates affording the corresponding bicyclic adducts in good yields.[56] A typical Diels-Alder cycloaddition of pentafulvene **3** with quinone **53** is presented in Scheme 1.21.



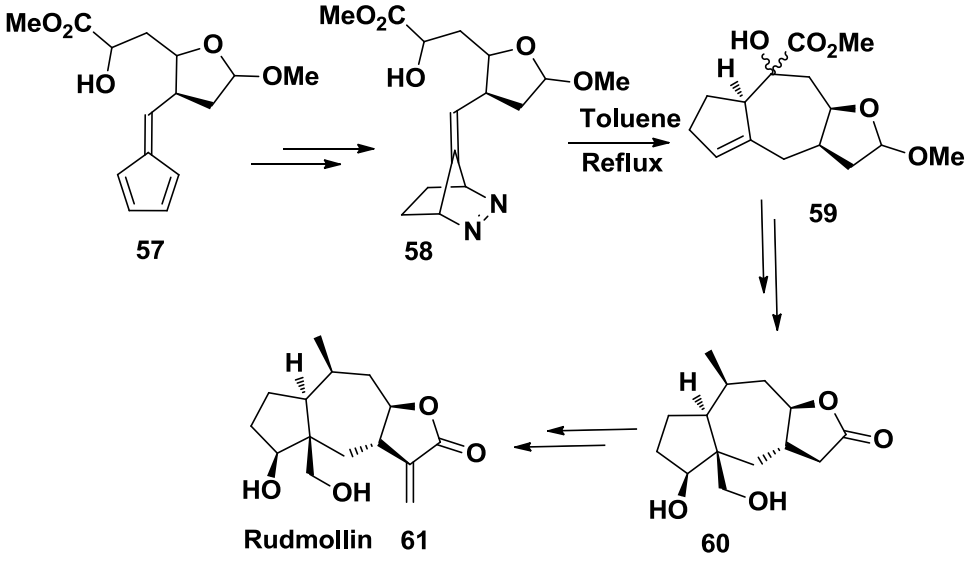
Scheme 1.21

In 1968, Alford *et al.* synthesized 2,3-diazabicyclo[2.2.1]hept-5-ene **56a** by the Diels-Alder cycloaddition of pentafulvene **8** with diethyl azodicarboxylate **55a** (Scheme 1.22).[57]



Scheme 1.22

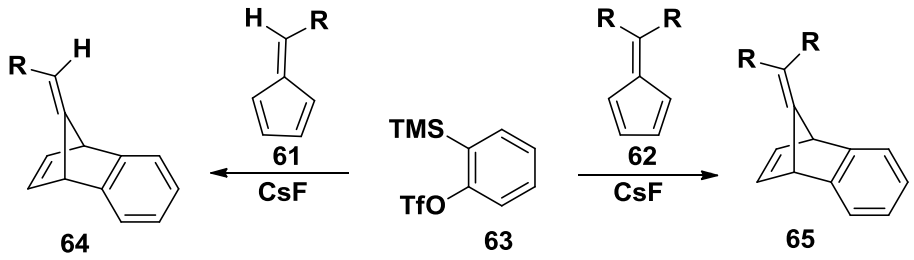
Little and co-workers utilized the azabicyclic adduct derived from pentafulvene **57,** towards the total synthesis of *rudmollin* **61** analogues, which displays *in vivo* activity against P-388 lymphoid leukemia. The key step in the synthesis involves the conversion of the modified cycloadduct **58** in to the tricycle **59**, through an atom transfer cyclization (Scheme 1.23).[58]



Scheme 1.23

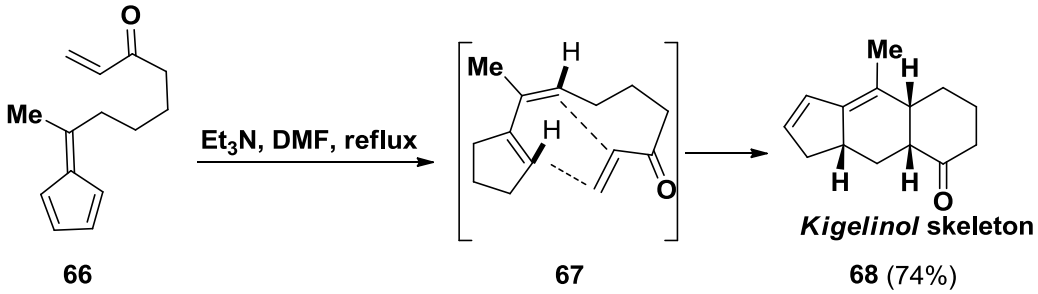
In 2012, Biju *et al.* reported a high-yielding, versatile and practical Diels-Alder reaction of pentafulvenes with arynes under mild reaction conditions. The arynes,

generated by the fluoride induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates **63**, underwent cycloaddition with 6-substituted and 6,6-disubstituted pentafulvenes resulting in the formation of benzonorbornadienes **64** and **65** respectively (Scheme 1.24).[59]



Scheme 1.24

Recently, Hong and co-workers described an elegant intramolecular Diels-Alder (IMDA) cycloaddition of simple acyclic fulvenes towards a variety of polycyclic ring skeletons such as kigelinol, neoamphilactane and kempane.[60] The synthesis of kigelinol skeleton **68** is depicted in Scheme 1.25 as an example of IMDA.

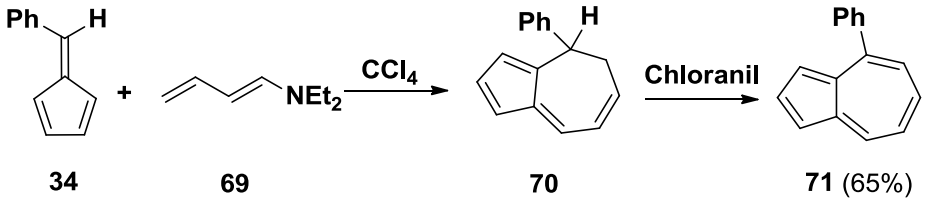


Scheme 1.25

1.6.5.3. Pentafulvene as 6*π* components

Pentafulvenes can provide all the three π bonded electrons to a concerted reaction and can act as a 6*π* component with electron-rich dienes. Pioneering work in this area was revealed by Houk and co-workers with the report of an efficient procedure for

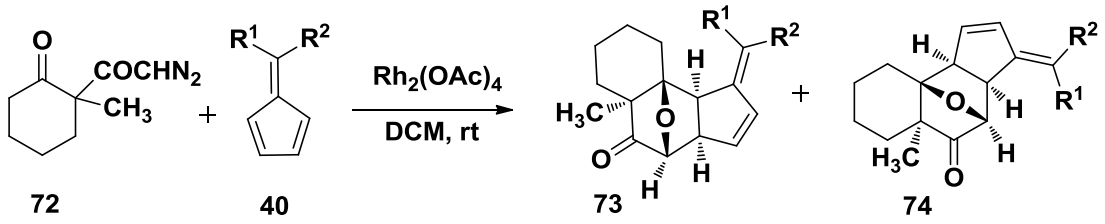
azulene synthesis *via* the [6+4] cycloaddition of pentafulvenes and electron rich amino butadienes.[61] The cycloaddition reaction of 6-phenyl fulvene **34** with 1-diethylamino butadiene **69**, followed by the loss of diethylamine afforded the hydrazulene derivative **70**, which on treatment with chloranil produced the phenyl substituted azulene **71** (Scheme 1.26).



Scheme 1.26

1.6.6. Pentafulvenes in dipolar cycloaddition reactions

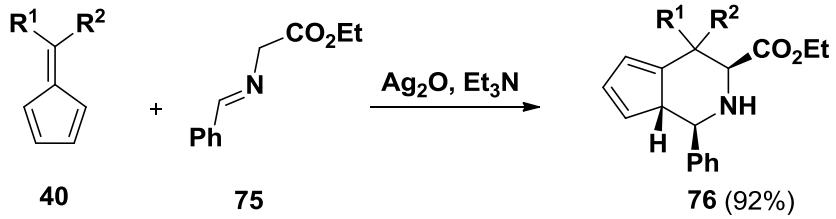
In contrast to the plethora of methods available for the syntheses of carbocycles and heterocycles, the 1,3-dipolar addition offers a remarkably wide range of utility in the synthesis of five-membered heterocycles.[51,62] Muthuswami and co-workers demonstrated that five-membered cyclic carbonyl ylides, generated from rhodium(II) catalyzed reaction of diazo carbonyl compounds, undergo 1,3 dipolar cycloadditions across fulvene bonds in a chemo specific manner to afforded novel polycyclic ring systems **73** and **74** (Scheme 1.27).[63]



Scheme 1.27

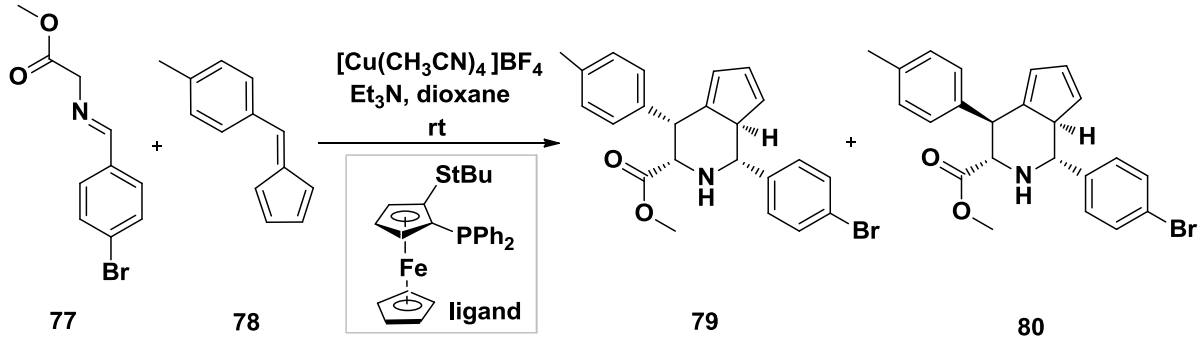
Hong and co-workers disclosed a noteworthy example of the 1,3-dipolar addition to fulvene. In 2003, they reported the [6+3] cycloaddition reaction of azomethine

ylides generated from glycine-N-benzylidene ethyl ester **75** with a series of pentafulvenes leading to biologically relevant [2]-pyrindine systems **76** (Scheme 1.28).[64]



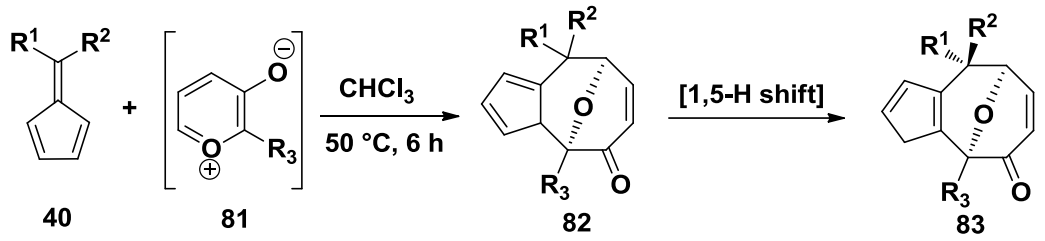
Scheme 1.28

The first catalytic enantioselective [6+3] cycloaddition of azomethine ylides with fulvenes was reported in 2012.[65] The reaction provided piperidine derivatives in 80% yield with ee of 92% for the major compound **79** and diastereomeric ratio 87:13 (Scheme 1.29).



Scheme 1.29

Intrigued by the advances in the pericyclic reactions of pentafulvenes, our research group have unravelled a simple and efficient [6+3] cycloaddition reaction of pentafulvenes with 3-oxidopyrylium betaines **81** and the approach offered a useful methodology for the construction of 5-8 fused cyclooctanoids **83** (Scheme 1.30).[66] The similar chemistry was productively extended to a number of pentafulvenes with various alkyl, aryl and cycloalkyl substituents.



Scheme 1.30

1.7. Synthetic utility of fulvene derived bicyclic olefins: Advances from our laboratory

As mentioned earlier in Scheme 1.23, like in the total synthesis of *rudmollin* **48** from the Diels –Alder cycloadducts derived from fulvenes and corresponding dienophile,[58] the synthetic potential of diazabicyclic olefins derived from pentafulvenes can also be utilized for the diverse synthesis of cyclopentanoids. The reaction protocols developed by our research group for the desymmetrization of the pentafulvene derived azabicyclic olefins (Figure 1.7) are discussed in the following section.

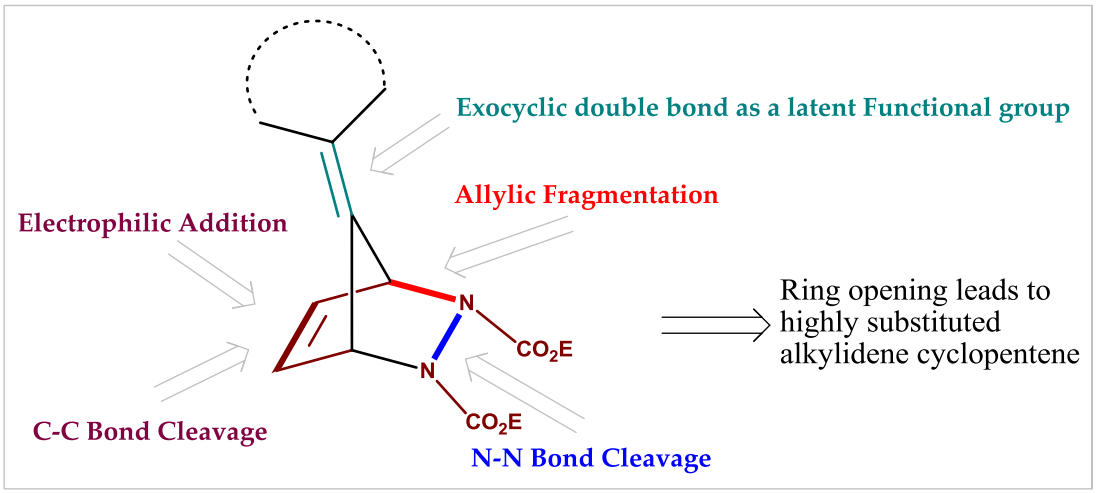


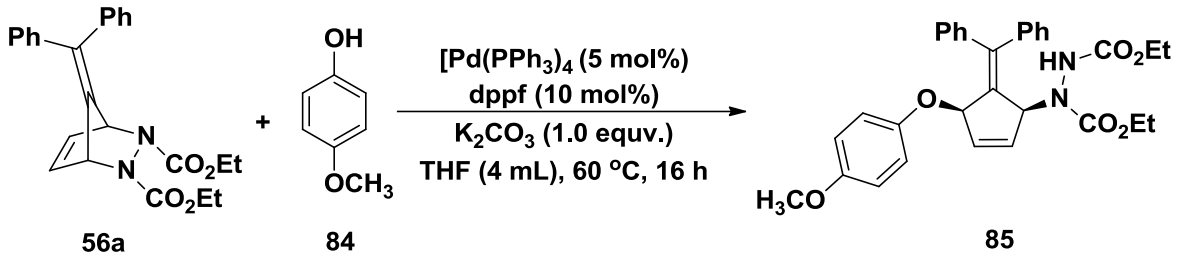
Figure 1.7 The reactivity and reaction protocols for the desymmetrization of pentafulvene derived azabicyclic olefins

The unique bicyclic olefinic structure of the Diels-Alder cycloadduct, derived from fulvenes and dialkylazodicarboxylates, exhibits versatile reactivity than other alkenes due to the ring strain in the molecule. The extra strain energy present in norbornene derivatives may be attributed to increased angle strain in the σ-framework. Recent developments with strained alkenes showcase their unique ability to control chemoselectivity, regioselectivity, and asymmetry, while also promoting otherwise difficult complexity-building transformations.[67] The synthetic potential of bicyclic adducts are also due to (1) the ring fragmentations of adduct *via* nitrogen–nitrogen bond reduction, carbon–carbon oxidative cleavage or ring-opening metathesis or allylic carbon–nitrogen cleavage; and (2) skeletal rearrangements involving carbocationic intermediates.[68,69] We have effectively utilized the intrinsic strain of the bicyclic adduct for its synthetic transformation which is briefly discussed in the following section.

1.7.1. Ring opening reactions of fulvene derived diazabicycic olefins

1.7.1.1. Reaction with soft nucleophiles

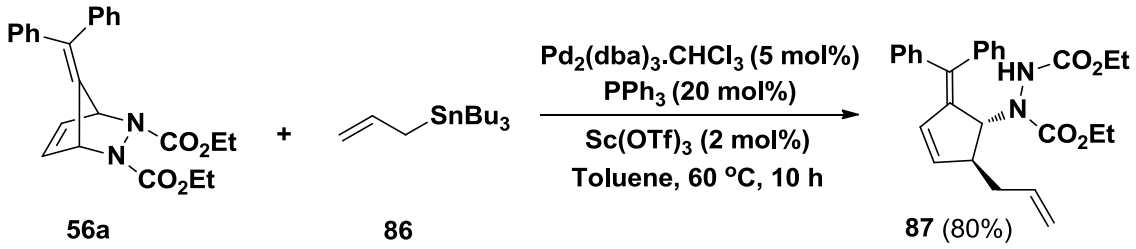
The ring opening of azabicyclic olefins by trapping the allylic reactive species generated from diazabicyclic olefins using soft nucleophiles in the presence of a palladium catalyst was first reported by Micouin and co-workers in 2003.[70] After a while, we extended the protocol towards the ring opening of pentafulvene derived bicyclic hydrazines to access alkylidenecyclopentenes.[71] The desymmetrization of fulvene derived azabicyclic olefin **56a** with 4-methoxyphenol **84** towards the synthesis of *cis*-3,5-disubstituted alkylidenecyclopentene **85** is outlined in the Scheme 1.31.



Scheme 1.31

1.7.1.2. Reactions with organometallic reagents

The desymmetrization of azabicyclic olefins toward 3,4-disubstituted alkylidenecyclopentenes can also be achieved by the use of organometallic reagents. The first report on the ring opening of bicyclic olefins towards 3,4-disubstituted cyclopentene by the application of organostannanes as nucleophiles came from our group in 2005.[72] A similar protocol was used for the synthesis of allyl substituted alkylidenecyclopentene from fulvene derived azabicyclic olefins (Scheme 1.32).[73]

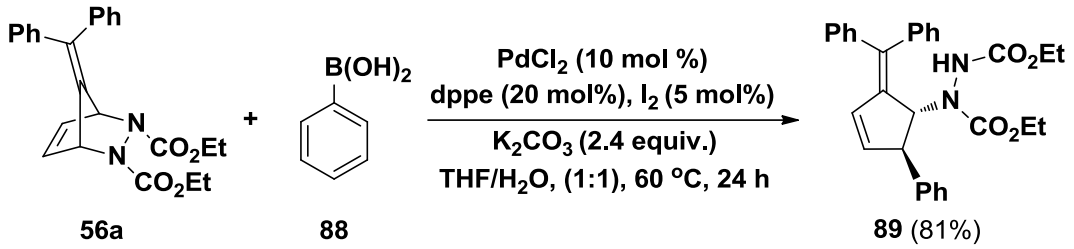


Scheme 1.32

1.7.1.3. Reaction with organoboronic acid

In 2006, we unravelled a novel reactivity of organoboronic acids with bi- and tricyclic hydrazines by utilizing modified Suzuki reaction condition.[74,75] The reaction of fulvene derived azabicyclic alkenes with organoboronic acids afforded the *trans*-3,4-disubstituted alkylidenecyclopentenes in excellent yields (Scheme 1.33). The

catalytic amount of Lewis acid such as scandium triflate or iodine played an important role in assisting this reaction.

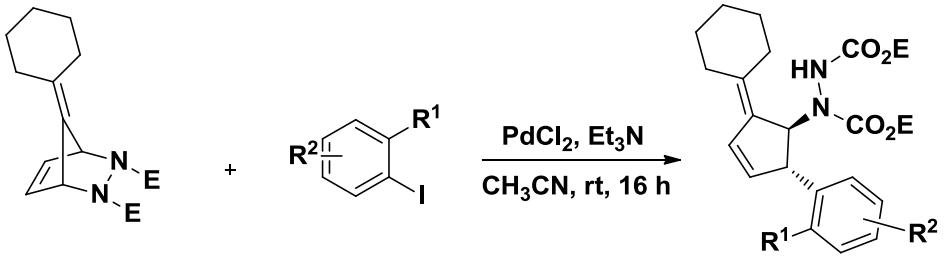


56a **88** **89** (81%)

Scheme 1.33

1.7.1.4. Reaction with aryl iodides

Recently, we have successfully utilized the Heck protocol in ring opening reactions of fulvene derived diazabicyclic olefin. The palladium catalyzed stereoselective ring opening of diazabicyclic olefins **56** with various aryl iodides produced the corresponding disubstituted alkylidenecyclopentenes in good to excellent yields (Scheme 1.34).[76]



56
E = CO_2Et, $CO_2{}^iPr$, $CO_2{}^tBu$, Bn

90
R^1 = OH, NH_2, NO_2
R^2 = H, NO_2

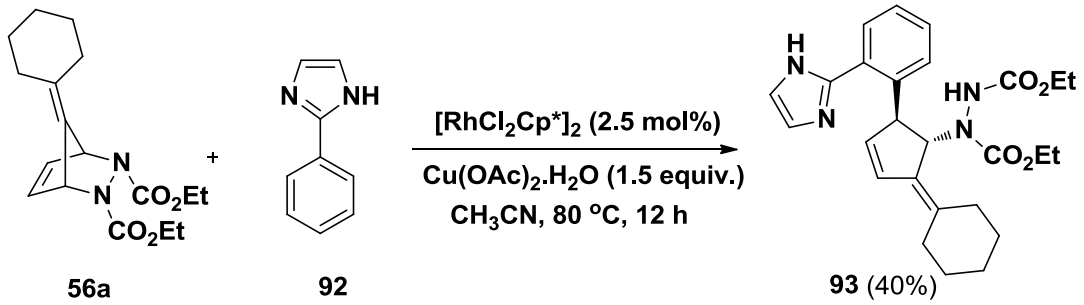
91

Scheme 1.34

1.7.1.5. Ring Opening *via* C-H activation

Very recently, we have developed a Rh catalysed stereoselective C-N bond cleavage of pentafulvene derived diazabicyclic olefins *via* C-H bond activation of

phenylazoles.[77] The Rh catalysed coupling of fulvene derived azabicycic olefin **56a** and phenylazole **92** afforded the corresponding alkylidene cyclopentenyl derivative **93** in 40% yield (Scheme 1.35).



56a **92** **93** (40%)

Scheme 1.35

1.8. Conclusion and present work

The non-functionalized carbon-carbon multiple bond systems are recognized as latent functional groups; however they are generally unreactive towards carbon nucleophiles due to their electron rich π-orbitals. Fulvenes and its derivatives come under this category and its intrinsic reaction profile intrigued chemists for more than a century. From the above discussions, it is clear that a wide range of molecular skeletons have been synthesized through short and easy chemical manipulations of pentafulvenes and its bicyclic adducts. In line with this, the thesis is mainly focused on the methodology development towards the synthetic transformations of pentafulvenes and its derivatives to highly substituted alkylidenecyclopentenes and complex azapolyheterocycles.

Though the cycloaddition and the metallocene chemistry of pentafulvenes are well established, the cyclopentenyl ring functionalization of this fascinating molecule was ambiguous till the report came from Jan Szymoniak's research group, describing the titanium mediated electrophilic addition of an aldehyde to the endocyclic double bond of fulvene leading to alkylidenecyclopentene appended allylic alcohol.[40] In light

of these results and our continuing interest in fulvene chemistry we were prompted to develop a methodology towards the endo-selective nucleophilic addition of pentafulvene. As a diverse approach we have developed a Lewis acid catalyzed regioselective nucleophilic addition of indole to the C-3 carbon of the endocyclic ring of pentafulvene and the details are presented in the second chapter of the thesis.

The addition of heterodienophiles to fulvenes was reported as early in 1968.[57] But the literature reports are scanty for the synthetic transformation of the heterobicyclic adduct so formed. Efforts from our laboratory have partially filled this gap by developing transition metal catalyzed ring opening of fulvene derived azabicyclic olefins to highly substituted alkylidenecyclopentenes. As part of our research interest in developing methodology towards biologically important cyclopentanoids from easily available starting materials, we decided to explore the application of Lewis acids in the ring opening strategy of fulvene derived diazabicyclic hydrazines towards substituted alkylidenecyclopentenes. The details of these investigations describing the Lewis acid catalyzed C-3 alkylidenecyclopentenylation of indoles to access the functionalized indoles and bisindoles are discussed in the third chapter.

The thesis is concluded with our efforts towards the one-pot synthesis of novel spiropentacyclic motifs with indoline and pyrazolidine fused to the cyclopentene core from fulvene derived azabicyclic olefins by the combined application of transition metal and Lewis acid catalysis. The advantage of these transformations is the formation of several bonds and the creation of two or more contiguous stereogenic centers in one pot, without the need for isolation of the intermediates. The stepwise synthesis of this complex heterocycle is also described in the final chapter of the thesis.

1.9. References

1 M. Faraday, *Philos. Trans.*, 1825, **115**, 440–466.

2 P. R. von Schleyer and H. Jiao, *Pure Appl. Chem.*, 1996, **68**, 209–218.

3 M. H. van der Veen, M. T. Rispens, H. T. Jonkman and J. C. Hummelen, *Adv. Funct. Mater.*, 2004, **14**, 215–223.

4 N. F. Phelan and M. Orchin, *J. Chem. Educ.*, 1968, **45**, 633–637.

5 R. Emanuelsson, A. V. Denisova, J. Baumgartner and H. Ottosson, *Organometallics*, 2014, **33**, 2997–3004.

6 A. D. Finke, S. Haberland, W. B. Schweizer, P. Chen and F. Diederich, *Angew. Chem. Int. Ed.*, 2013, **52**, 9827–9830.

7 K. Hafner, K. H. Hafner, C. Konig, M. Kreuder, G. Ploss, G. Schulz, E. Sturm and K. H. Vopel, *Angew. Chem. Int. Ed.*, 1963, **2**, 123–134.

8 T. M. Krygowski, W. P. Oziminski, M. Palusiak, P. W. Fowler and A. D. McKenzie, *Phys. Chem. Chem. Phys.*, 2010, **12**, 10740–10745.

9 Johannes Thiele, *J. Chem. Ber.*, 1900, **36**, 666–673.

10 K. J. Stone and R. D. Little, *J. Org. Chem.*, 1984, **49**, 2–6.

11 H. Kurata, T. Bkinaka, T. Kawase and M. Oda, *Tetrahedron Lett.*, 1993, **34**, 3445–3448.

12 K. Chajara and H. Ottosson, *Tetrahedron Lett.*, 2004, **45**, 6741–6744.

13 N. Coşkun and I. Erden, *Tetrahedron*, 2011, **67**, 8607–8614.

14 W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike and J. L. Thompson, *J. Am.*

Chem. Soc., 1964, **1**, 5895–5896.

15 K. C. Nicolaou, W. J. Sipio, R. L. Magolda, S. Seitz and W. E. Barnett, *J. Chem. Soc. Chem. Commun.*, 1978, 1067–1068.

16 R. C. Kelly, I. Schletter and S. J. Stein, *Tetrahedron Lett.*, 1976, 3279–3282.

17 E. J. Corey, M. Shibasaki, J. Enolle and T. Sugahara, *Tetrahedron Lett.*, 1977, 785–788.

18 T. Kitahara, K. Mori and M. Matsui, *Tetrahedron Lett.*, 1979, 3021–3024.

19 O. Geis and H.-G. Schmalz, *Angew. Chem. Int. Ed.*, 1998, **37**, 911–914.

20 S. E. Gibson and N. Mainolfi, *Angew. Chem. Int. Ed.*, 2005, **44**, 3022–37.

21 T. Akiyama, M. Yamanaka and A. Si, *Tetrahedron Lett.*, 1998, **39**, 7885–7888.

22 M. Meguro and Y. Yamamoto, *J. Org. Chem.*, 1999, **6**, 694–695.

23 J. L. Loebach, D. M. Bennett and R. L. Danheiser, *J. Am. Chem. Soc.*, 1998, **120**, 9690–9691.

24 Z. Wang, in *Comprehensive Organic Name Reactions and Reagents*, 2011, pp. 2011–2016.

25 K. L. Habermas, S. E. Denmark and T. K. Jones, in *Organic Reactions*, 1994, pp. 1–158.

26 R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413–4450.

27 B. Giese, B. Kopping, T. Gröbel, J. Dickhaut, G. Thoma, K. J. Kulicke and F. Trach, in *Organic Reactions*, 1996, pp. 300–370.

28 K. Antczak, J. F. Kingston and A. G. Fallis, *Can. J. Chem.*, 1984, **62**, 2451–

2455.

29 J. Barluenga, S. Martinez, A. L. Suarez-Sobrino and M. Tomas, *J. Am. Chem. Soc.*, 2002, **124**, 5948–5949.

30 K. Sakai and T. Kobori, *Tetrahedron Lett.*, 1981, **22**, 115–118.

31 J. Bian, M. V. Wingerden and J. M. Ready, *J. Am. Chem. Soc.*, 2006, **128**, 7428–7429.

32 M. Mandal, H. Yun, G. B. Dudley, S. Lin, D. S. Tan and S. J. Danishefsky, *J. Org. Chem.*, 2005, **70**, 10619–10637.

33 A. Marshall and C. Johnson, *J. Org. Chem.*, 1970, **35**, 192–196.

34 U. Groenhagen, M. Maczka, J. S. Dickschat and S. Schulz, *Beilstein J. Org. Chem.*, 2014, **10**, 1421–1432.

35 Y. Wang, D. Mukharjee, D. Birney and K. N. Houk, *J. Org. Chem.*, 1990, **55**, 4504–4506.

36 P. Radnia and J. S. McKennis, *J. Am. Chem. Soc.*, 1980, **102**, 6351–6353.

37 G. A. Olah, G. K. S. Prakash and G. Liang, *J. Org. Chem.*, 1977, **42**, 661–666.

38 M. Kędziorek, P. Mayer and H. Mayr, *Eur. J. Org. Chem.*, 2009, **5**, 1202–1206.

39 J. Joseph, F. Jaroschik, D. Harakat, K. V. Radhakrishnan, J.-L. Vasse and J. Szymoniak, *Chem. - Eur. J.*, 2014, **20**, 5433–5438.

40 J. Joseph, F. Jaroschik, K. V Radhakrishnan, J.-L. Vasse and J. Szymoniak, *Chem. Commun.*, 2013, **49**, 4549–51.

41 D. W. Macomber, P. W. Hart and M. D. Rausch, *J. Am. Chem. Soc.*, 1982, **104**,

884–886.

42 G. Erker, *Coord. Chem. Rev.*, 2006, **250**, 1056–1070.

43 K. Strohfeldt and M. Tacke, *Chem. Soc. Rev.*, 2008, **37**, 1174–1187.

44 K. Strohfeldt, H. Müller-Bunz, C. Pampillón, N. J. Sweeney and M. Tacke, *Eur. J. Inorg. Chem.*, 2006, 4621–4628.

45 C. Pampillón, J. Claffey, K. Strohfeldt and M. Tacke, *Eur. J. Med. Chem.*, 2008, **43**, 122–128.

46 B. C. Hong, A. K. Gupta, M. F. Wu and J. H. Liao, *Tetrahedron Lett.*, 2004, **45**, 1663–1666.

47 S. Anas, K. S. Krishnan, V. S. Sajisha, K. S. Anju, K. V. Radhakrishnan, E. Suresh and C. H. Suresh, *New J. Chem.*, 2007, **31**, 237–246.

48 K. M. Kane, P. J. Shapiro, A. Vij and R. Cubbon, *Org. React.*, 1997, **16**, 4567–4571.

49 J. Barluenga, S. Martiínez, A. L. Suárez-Sobrino and M. Tomás, *J. Organomet. Chem.*, 2005, **690**, 5696–5700.

50 J. Barluenga, S. Martínez, A. L. Suárez-Sobrino and M. Tomás, *J. Am. Chem. Soc.*, 2001, **123**, 11113–11114.

51 K. Imafuku and K. Arai, *Synthesis*, 1989, **7**, 501–505.

52 V. Nair, S. Kumar and P. G. Williard, *Tetrahedron Lett.*, 1995, **36**, 1605–1608.

53 B.-C. Hong, J.-L. Wu, A. K. Gupta, M. S. Hallur and J.-H. Liao, *Org. Lett.*, 2004, **6**, 3453–3456.

54 T. Machiguchi, T. Hasegava, Y. Ishii, S. Yamabe and T. Minato, *J. Am. Chem. Soc.*, 1993, **115**, 11536–11541.

55 G. Nzabamwita, B. Kalani and B. Jousseaume, *Tetrahedron Lett.*, 1989, **30**, 2207–2208.

56 B. Hong, Y. Shr and J. Liao, *Org. Lett.*, 2002, **4**, 663–666.

57 N. P. Marullo and J. A. Alford, *J. Org. Chem.*, 1968, **33**, 2368–2370.

58 G. L. Carroll, A. K. Allan, M. K. Schwaebe and R. D. Little, *Org. Lett.*, 2000, **2**, 2531–2534.

59 S. S. Bhojgude, T. Kaicharla, A. Bhunia and A. T. Biju, *Org. Lett.*, 2012, **14**, 4098–4101.

60 B.-C. Hong, F.-L. Chen, S.-H. Chen, J.-H. Liao and G.-H. Lee, *Org. Lett.*, 2005, **7**, 557–560.

61 L. C. Dunn, Y.-M. Chang and K. N. Houk, *J. Am. Chem. Soc.*, 1976, **98**, 7095–7096.

62 R. Huisgen, *Angew. Chem. Int. Ed.*, 1963, **2**, 565–598.

63 S. Muthusamy, S. A. Babu, C. Gunanathan, E. Suresh and P. Dastidar, *Synlett*, 2001, 1407–1410.

64 B.-C. Hong, A. K. Gupta, M.-F. Wu, J.-H. Liao and G.-H. Lee, *Org. Lett.*, 2003, **5**, 1689–1692.

65 M. Potowski, J. O. Bauer, C. Strohmann, A. P. Antonchick and H. Waldmann, *Angew. Chem. Int. Ed.*, 2012, **51**, 9512–9516.

66 K. V. Radhakrishnan, K. S. Krishnan, M. M. Bhadbhade and G. V. Bhosekar,

Tetrahedron Lett., 2005, **46**, 4785–4788.

67 D. K. Rayabarapu and C.-H. Cheng, *Acc. Chem. Res.*, 2007, **40**, 971–983.

68 C. Bournaud, F. Chung, A. Luna, M. Pasco, G. Errasti, T. Lecourt and L. Micouin, *Synthesis*, 2009, **6**, 869–887.

69 V. S. Sajisha, S. Anas, J. John and K. V. Radhakrishnan, *Synlett*, 2009, 2885–2895.

70 A. P. Luna, M. Cesario, M. Bonin and L. Micouin, *Org. Lett.*, 2003, **5**, 4771–4774.

71 R. Rajan, J. John, S. Thulasi, N. Joseph, K. V. Radhakrishnan and R. C. Sawant, *Synthesis*, 2010, **21**, 3649–3656.

72 V. S. Sajisha and K. V. Radhakrishnan, *Adv. Synth. Catal.*, 2006, **348**, 924–930.

73 S. Anas, V. S. Sajisha, J. John, N. Joseph, S. C. George and K. V. Radhakrishnan, *Tetrahedron*, 2008, **64**, 9689–9697.

74 J. John, V. S. Sajisha, S. Mohanlal and K. V. Radhakrishnan, *Chem. Commun.*, 2006, **2**, 3510–3512.

75 S. Anas, J. John, V. S. Sajisha, J. John, R. Rajan, E. Suresh and K. V. Radhakrishnan, *Org. Biomol. Chem.*, 2007, **5**, 4010–4019.

76 N. Joseph, R. Rajan, J. John, N. V. Devika, S. S. Chand, E. Suresh, P. M. Pihko and K. V. Radhakrishnan, *RSC Adv.*, 2013, **3**, 7751.

77 P. Prakash, P. S. Aparna, E. Jijy, P. Santhini, S. Varughese and K. V. Radhakrishnan, *Synlett*, 2013, **25**, 275–279.

CHAPTER 2

Lewis Acid Catalysed Regioselective Hydroheteroarylation of Pentafulvenes

2.1. Introduction

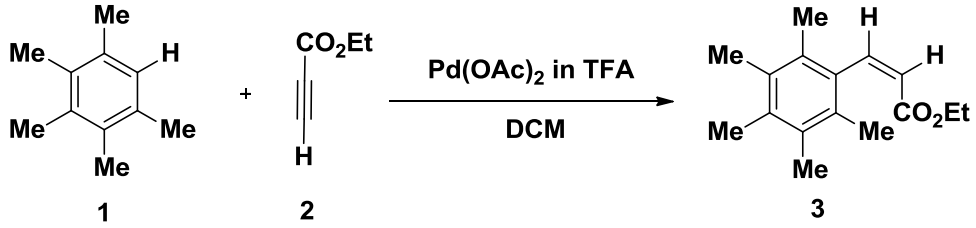
An organic molecule consists of a carbon skeleton and some functional groups. The rest of the molecular framework is covered with hydrogen atoms which are usually inert and are generally regarded as unreactive parts of the molecule. Normally, synthetic transformations are carried out with the aid of functional groups. If a synthetic method that allows the direct use of normally "unreactive" C-H bonds were to become available, an entirely new area of research would be opened.[1] Hydroarylation, the addition of aryl C-H bonds to alkenes has been a rapidly developing field of such necessities.[2] Two major approaches have been developed to accomplish hydroarylations; nondirected C-H activation and directed C-H activation by a pendant functional group or embedded heteroatom. Non-directed C-H activation processes have the benefit of not requiring a functional handle on the starting material; however, the regioselectivity of the functionalization is a major challenge in this area.[3] A vast array of transition metal complexes, including Au,[4,5] Pd,[6,7] Rh,[8] Pt,[9] Ru,[10,] Ir,[11] Ni[12] etc. have been effectively utilized in the hydro(hetero)arylation of unactivated olefins. But the recent advances have shown that even Lewis acidic condition [$Bi(OTf)_3$, $AlCl_3$ or $FeCl_3$][13–15] can lead to hydroheteroarylation of unactivated as well as activated olefins. The hydroarylation or hydroindolization of unsaturated species such as allenes,[16] vinyl ethers,[17] alkynes,[18] alkynoles,[19] styrenes,[15] internal alkenes,[9] etc. have been well documented in the literature. In this context, we introduce pentafulvenes, an interesting class of cross

conjugated trienes, as alkene moities for the regioselective Lewis acid catalyzed hydroheteroarylation reaction. Before going into the details, a brief introduction about the hydroarylation reactions is presented in the following section.

2.2. Hydroarylation reactions

2.2.1. Hydroarylation of activated alkynes

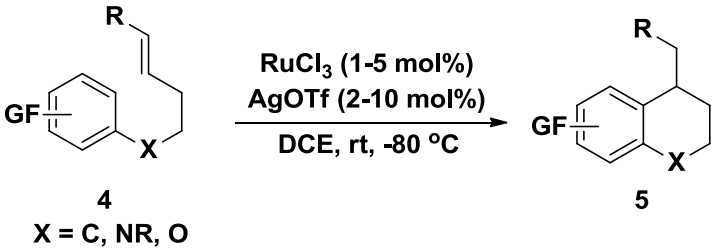
In the year 2000, Fujiwara and co-workers reported an efficient metalation of aromatic C-H bonds at room temperature by the aid of an *in situ* generated highly electrophilic Pd(II) cationic species in trifluoroacetic acid (TFA). Subsequent addition of the cationic species, $[Pd(CO_2CF_3)]^+$ to C-C multiple bonds afforded the hydroarylated product in regio- and stereoselective manner (Scheme 2.1).[6]



Scheme 2.1

2.2.2. Intramolecular hydroarylation of internal alkenes

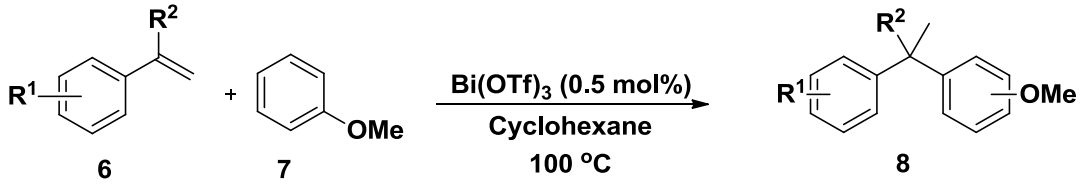
In 2004, Sames identified $RuCl_3$/AgOTf as an intramolecular hydroarylation catalyst for arene-ene substrates.[10] A variety of annulated arene, heterocycles and carbocycles are accessible using this method including chromane, tetralin, terpenoid, dihydrocoumarin, tetrahydroquinoline, indolocyclohexane and cyclopentane systems (Scheme 2.2).



Scheme 2.2

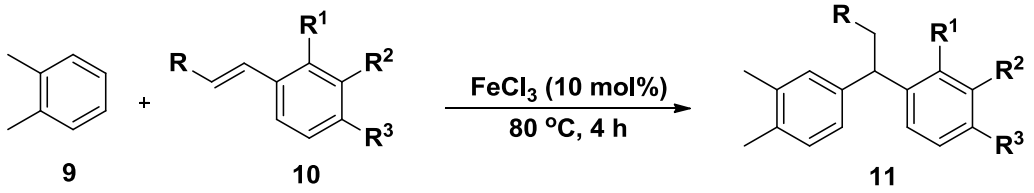
2.2.3. Lewis acid catalyzed hydroarylation of styrenes

After the establishing $Bi(OTf)_3$ catalyzed benzylation[14]of arenes and heteroarenes, Rueping and coworkers employed the same Lewis acid for the hydroarylation of styrenes (Scheme 2.3).[15]



Scheme 2.3

Later on, Matthias Beller introduced $FeCl_3$ as a catalyst for the direct addition of aromatic olefins to arenes towards the synthesis of highly substituted 1,1-diarylalkanes and 1-aryl-1-heteroarylalkanes (Scheme 2.4).[20]



R = H, Me, Ph; R^1 = H, Me, Br; R^2 = H, Me, Br, Cl; R^3 = H, Br, Cl, CF_3, F

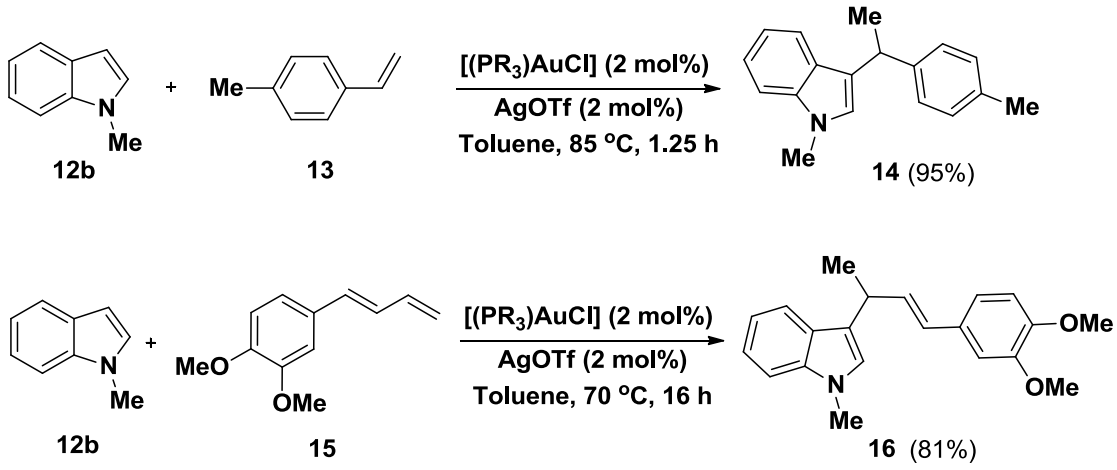
Scheme 2.4

2.3. Hydroindolization for the functionalization of indole

The substituted indole nucleus is a structural component of a vast number of biologically active natural and unnatural compounds. The synthesis and functionalization of indoles has been the object of research for over 100 years. Even though a number of well-established classical methods are available for indole functionalization, the addition of C-C multiple bonds onto indolyl C-H bond stands as an exceptional protocol for the atom economic regio- and stereoselective functionalization of indoles.

2.3.1. Hydroindolization of styrenes

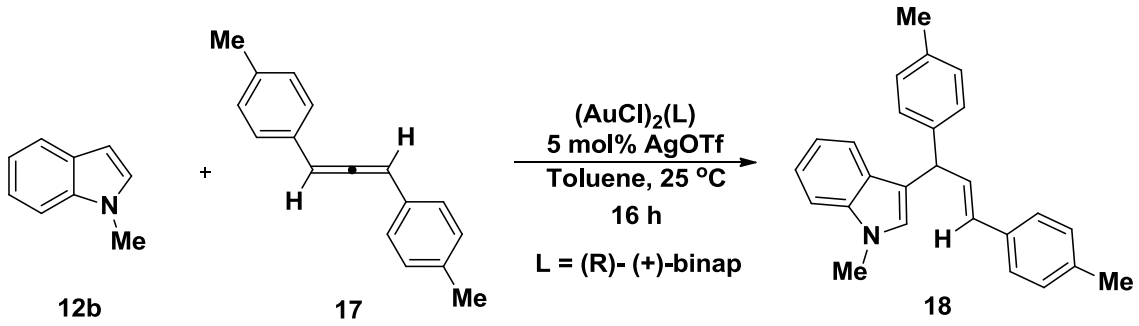
Che *et al.* demonstrated an intermolecular hydroarylation of aryl and aliphatic alkenes with indoles using a combination of [(PR_3)AuCl]/AgOTf as catalyst under thermal and microwave assisted conditions.[4] Under microwave irradiation, coupling of unactivated aliphatic alkenes with indoles gave the corresponding adducts in excellent yield. Selective hydroarylation of terminal C-C double bond of conjugated dienes with indoles also afforded the products in good yields (Scheme 2.5).



Scheme 2.5

2.3.2. Hydroindolization of allene

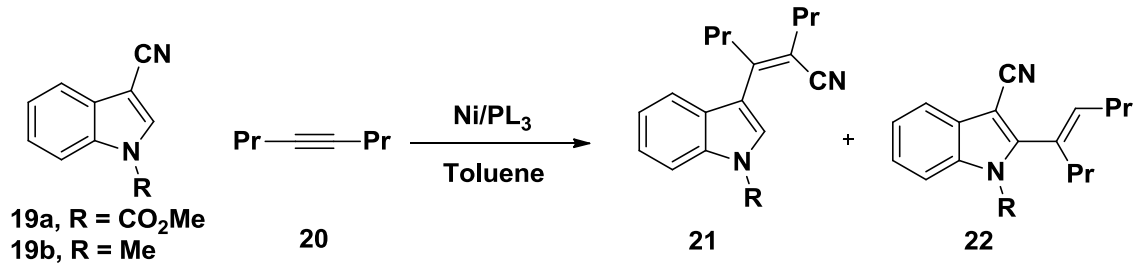
In 2011, the same research group has developed an enantioselective intermolecular hydroarylation of racemic allenes with indole using a 1:2 mixture of a chiral binuclear Au(I) phosphine complex and AgOTf as catalyst (Scheme 2.6).[16]



Scheme 2.6

2.3.3. Hydroindolization of alkynes

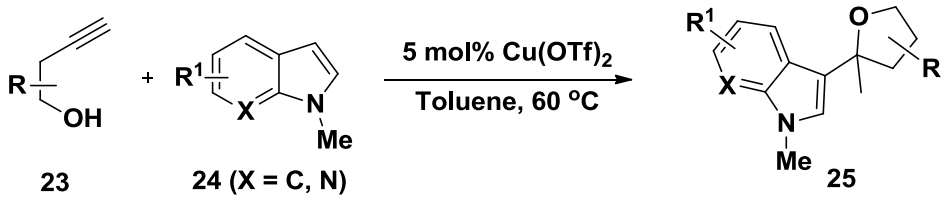
Hiyama demonstrated a divergent nickel catalysis on Ar-H versus Ar-CN activation and extended the catalysis to hydroheteroarylation of alkynes under mild conditions.[12,21] The reaction of 3-cyano-1-methoxycarbonylindole **19a** with 4-octyne **20** in the presence of Ni/PMe_3 catalyst in toluene at 100 °C gave the arylcyanation product **21** in 68% yield after 18 hours along with a minor amount (6%) of **22**. With 3-cyano-1-methylindole **19b**, the corresponding hydroarylation product **21** became dominant even under the same condition and the catalysis was found to be effective even at 35 °C by using $PCyp_3$ as a ligand to afford **22** in 95% yield (Scheme 2.7).



Scheme 2.7

2.3.4. Hydroindolization of alkynols

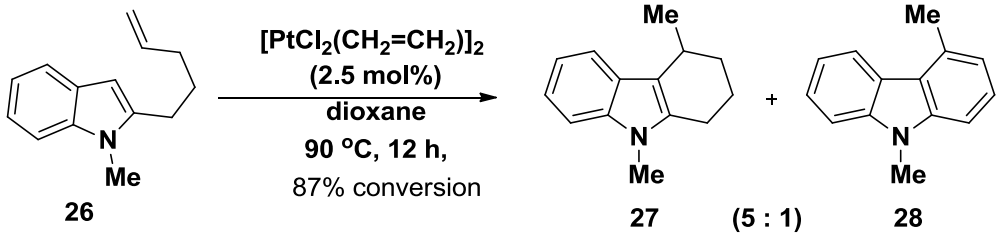
Patel and co-workers used $Cu(OTf)_2$ as catalyst for the tandem hydroalkoxylation-hydroarylation reaction of alkynes tethered with hydroxyl group.[19] The method was shown to be applicable to a broad range of indoles, containing electron-withdrawing and electron-donating substituents, and alkynol substrates bearing sterically demanding substituents in the tether (Scheme 2.8).



Scheme 2.8

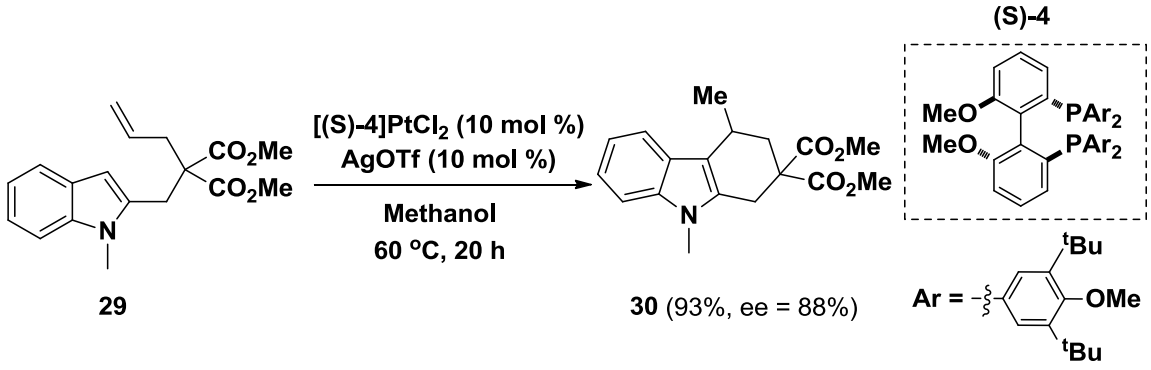
2.3.5. Intramolecular hydroindolyzation

Widenhoefer adopted a platinum-catalyzed intramolecular alkylation of indoles with unactivated olefins for the synthesis of fused polycyclic indole scaffolds including the carbazoles, carbolines and heterocyclic compounds with potent biological activity (Scheme 2.9).[9]



Scheme 2.9

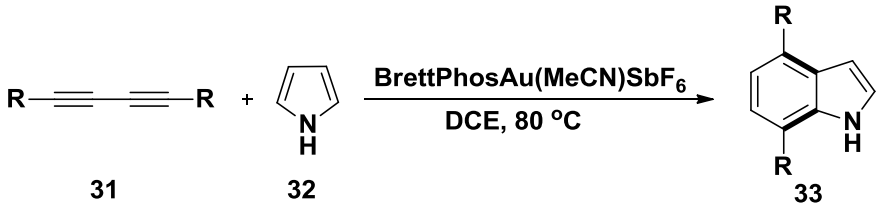
Later, the same group has reported a chiral version of platinum catalysed intramolecular hydroheteroarylation reaction for the ring annulation of 1-methyl-2-(4-pentenyl)indoles by applying chiral phosphine ligand (Scheme 2.10).[22]



Scheme 2.10

2.3.6. Gold(I)- catalyzed indole synthesis by double hydroarylation

Fujii and Onho described an interesting indole synthesis by a gold(I)-catalyzed intermolecular formal [4+2] reaction between 1,3-diynes and pyrroles.[5] This reaction involves the hydroarylation of 1,3-diynes with pyrroles followed by an intramolecular hydroarylation to give the 4,7-disubstituted indoles (Scheme 2.11).



Scheme 2.11

2.4. Statement of problem

Pentafulvenes give rise to a vast array of reaction pathways depending on the substitution patterns and reaction conditions.[16] The cycloaddition profile of fulvenes[23–26] is now well established and new, especially transition-metal mediated transformations are emerging.[27–30] Nucleophilic reactions of these non-benzenoid dipolar hydrocarbons have been mainly exploited in metallocene chemistry, i.e. the exocyclic carbon of fulvenes is partially positively charged and readily reacts with

numerous nucleophiles leading to a cyclopentadienyl precursor for metal complexation. However, nucleophilic attack on the endocyclic ring system of fulvenes is rare. The homopolymerisation of fulvenes under acid catalysis reported by Neuenschwander could be considered as such an example.[31] Low-temperature NMR studies by Olah showed that reaction of super acids with fulvenes lead to fulvenium ions, which should make the endocyclic ring a good target for nucleophilic addition (Fig. 2.1).[32]

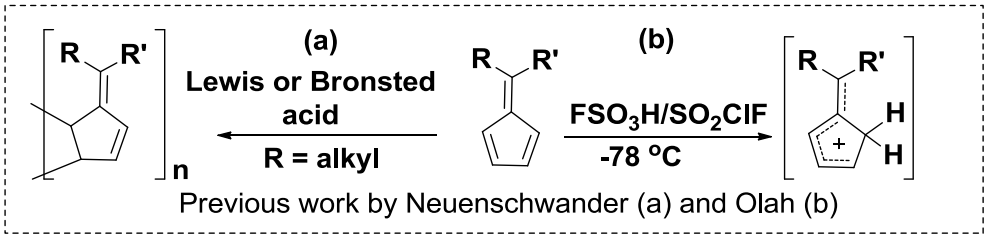


Figure 2.1 Reactivity of fulvene under acidic conditions

In this chapter we disclose our preliminary results on the Lewis acid catalyzed regioselective nucleophilic addition of indoles and pyrrole to the endocyclic ring of pentafulvenes.

2.5. Results and discussion

As an initial attempt, we carried out the reaction between diphenyl fulvene **34a** and indole **12b** by employing 2 mol% $Sc(OTf)_3$ as Lewis acid in acetonitrile at room temperature for 2 hours. To our delight, the indole substitution occurs exclusively at the C-3 carbon of cyclopentadienyl ring system of fulvene instead of the conventional exocyclic C-6 nucleophilic attack and the reaction furnished the product **35ab** in 91% yield (Scheme 2.12).

Scheme 2.12

The structure of the compound **35ab** was established by various spectroscopic analyses. In the ^{1}H NMR spectrum (Figure 2.2), the two olefinic protons were observed individually as doublet of doublets in the region of δ 6.51 ppm (dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz) and δ 6.29 ppm (dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz) respectively. A multiplet at δ 4.37-4.35 ppm represents the proton attached to the carbon (C-3) which is bonded to indole. The two diastereotopic protons in the cyclopentenyl ring (C-4) resonated individually as doublet of doublets at δ 3.24 ppm (dd, J_1 = 17 Hz, J_2 = 7.5 Hz) and δ 3.07 ppm (dd, J_1 = 16.5 Hz, J_2 = 3.5 Hz) respectively. ^{13}C NMR spectrum of **35ab** (Figure 2.3) positioned the two olefinic carbon signals at δ 142.9 and 141.7 ppm respectively. The C-3 and C-4 carbons resonated at δ 42.0 and 40.1 ppm respectively. The characteristic N-CH_3 carbon (C-5) was discernible at δ 32.6 ppm. All other signals were in good agreement with the proposed structure.

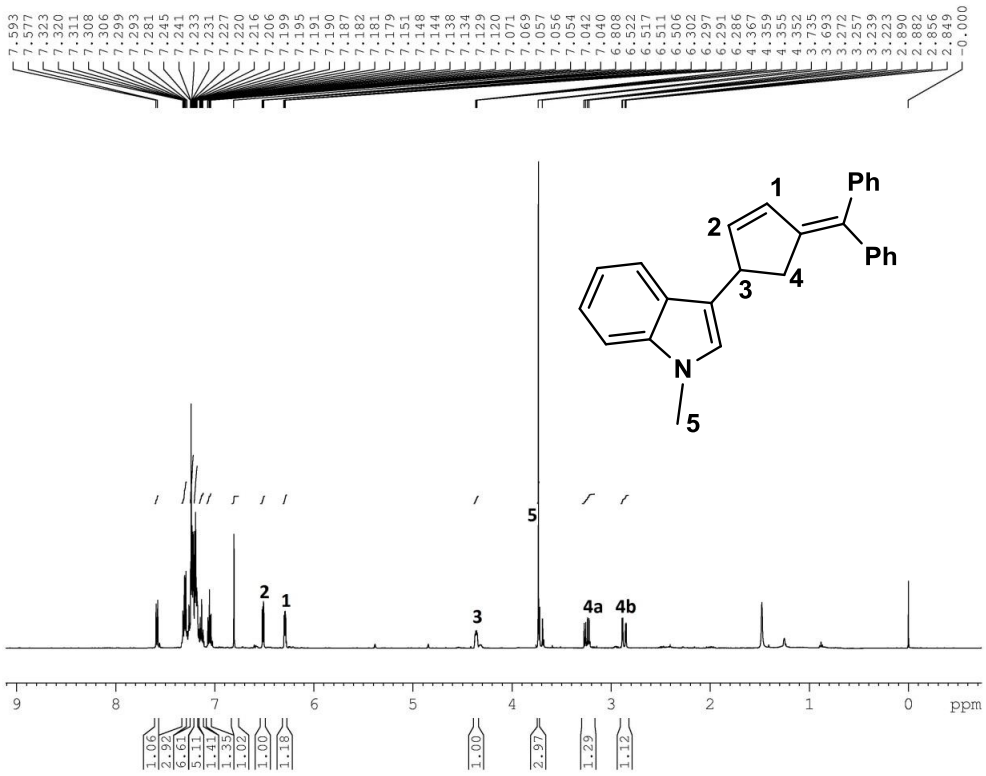


Figure 2.2. ^{1}H NMR spectrum of **35ab**

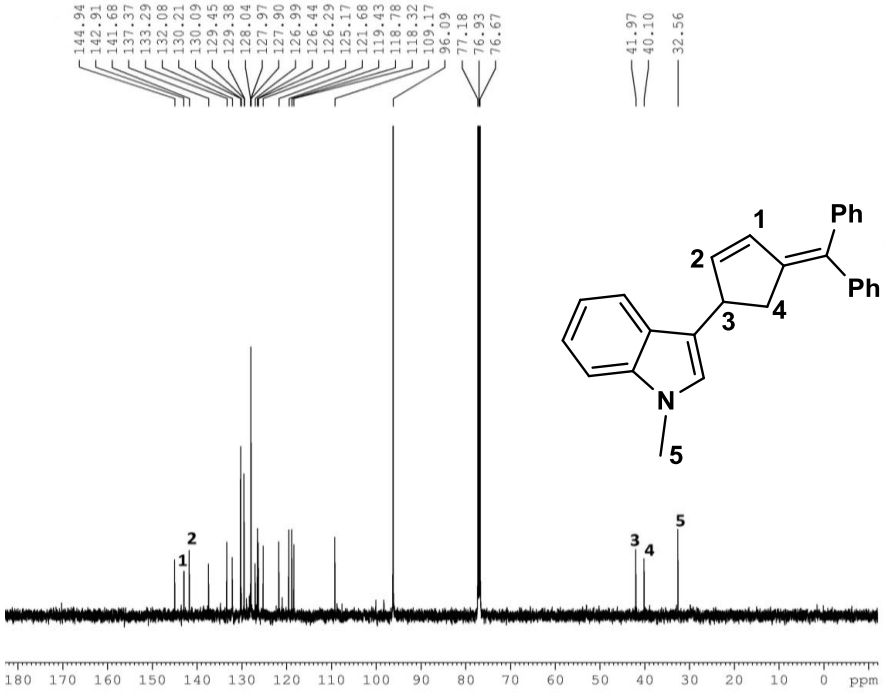


Figure 2.3. ^{13}C NMR spectrum **of 35ab**

The high resolution mass spectral analysis of **35ab** showed the molecular ion peak at *m/z* = 370.15695 (M+Na). The structure and stereochemistry of the product was unambiguously established by single crystal X-ray analysis of the compound **35ac** (Figure 2.4).

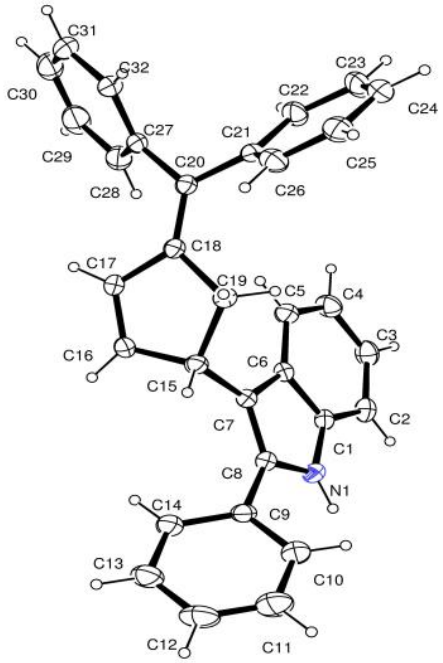
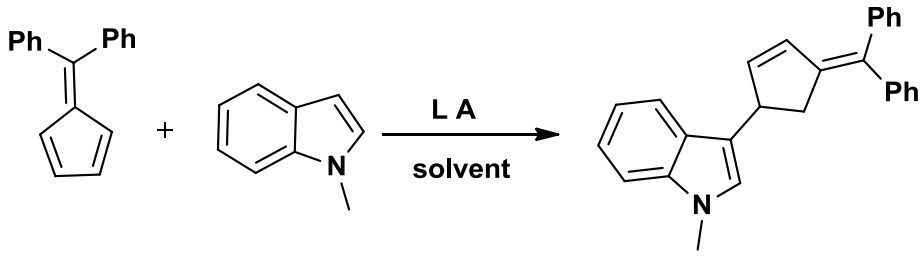


Figure 2.4. ORTEP plot of compound of **35ac**

Encouraged by this unusual regioselective 1,2 addition of indole to fulvene, we screened various reaction parameters to find out the best condition for hydroheteroarylation. From the detailed optimization study (Table 2.1), 2 mol% of $Cu(OTf)_2$ in 2 mL acetonitrile at room temperature for 2 hours was found to be the best catalytic condition for the reaction, affording 99% yield for the product **35ab**. It was found that in the absence of Lewis acid, the starting materials **34a** and **12b** were fully recovered (Table 2.1, Entry 14).

Table 2.1. Optimization for a suitable catalyst system



Entry	Lewis acid	Solvent	Yield %
1	$Sc(OTf)_3$	CH_3CN	91
2	$Cu(OTf)_2$	CH_3CN	99
3	$Yb(OTf)_3$	CH_3CN	-
4	$Zn(OTf)_2$	CH_3CN	22
5	$Sn(OTf)_2$	CH_3CN	93
6	$Fe(OTf)_3$	CH_3CN	-
7	AgOTf	CH_3CN	-
8	BF_3-OEt_2	CH_3CN	28
9	$AlCl_3$	CH_3CN	18
10	$Cu(OTf)_2$	Toluene	45
11	$Cu(OTf)_2$	DCE	25
12	$Cu(OTf)_2$	THF	-
13	$Cu(OTf)_2$	DMF	-
14	-	CH_3CN	-

Reaction Conditions: fulvene (1.0 equiv.), indole (1.0 equiv.), Lewis acid (2 mol%), solvent (2 mL), rt, 2 h.

With the optimized reaction conditions in hand, we investigated the viability of the reaction with substituted indoles (Table 2.2). Indole and N-methyl indole showed remarkable reactivity towards fulvene affording products in excellent yields. The hydroxyl group at the C-5 position of indole **12g** decreased the efficiency of the reaction (Table 2.2, Entry 7), whereas 5- amino indole **12h** (Table 2.2, Entry 8) did not furnish the desired product.

Table 2.2. Exploration of the scope of hydrarylation reaction using differently substituted indoles

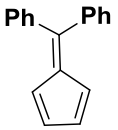
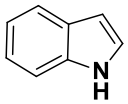
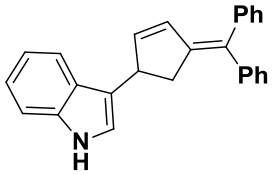
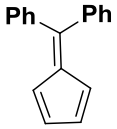
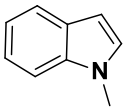
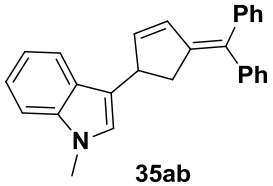
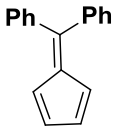
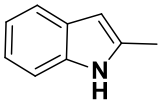
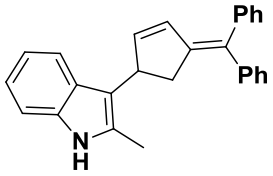
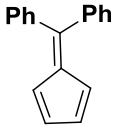
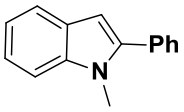
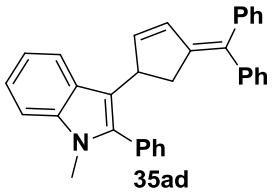
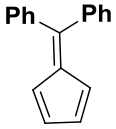
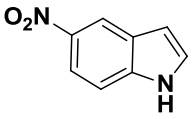
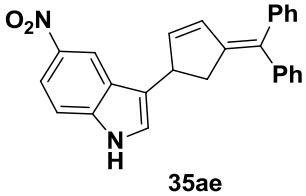
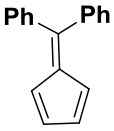
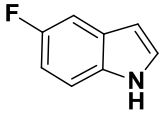
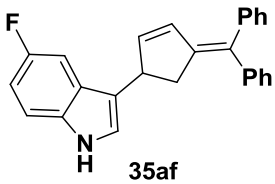
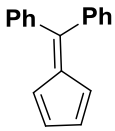
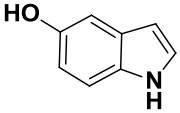
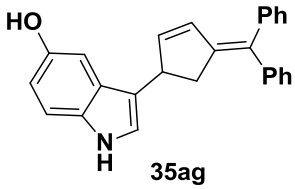
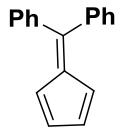
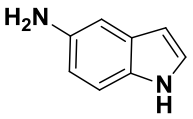
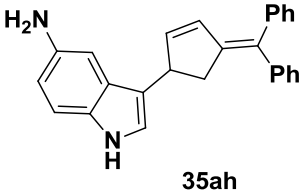
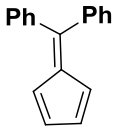
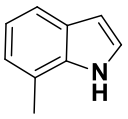
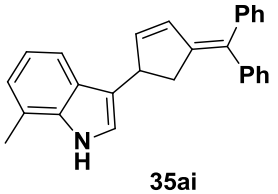
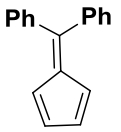
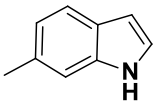
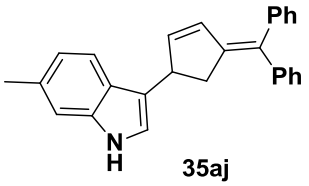
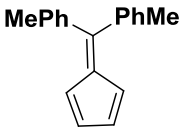
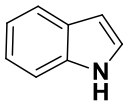
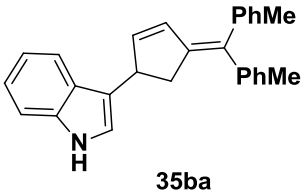
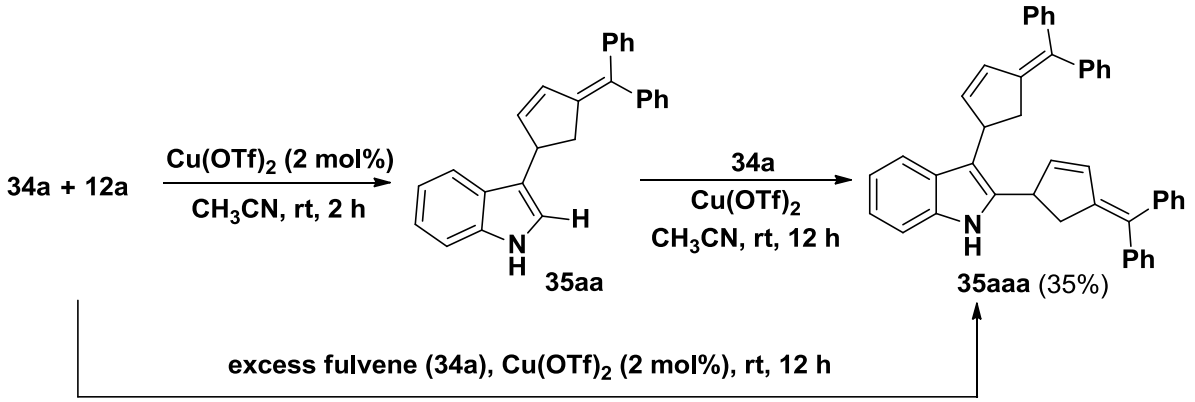
Entry	Fulvene	Indole	Product	Yield (%)
1	 34a	 12a	 35aa	98
2	 34a	 12b	 35ab	99
3	 34a	 12c	 35ac	99
4	 34a	 12d	 35ad	99
5	 34a	 12e	 35ae	75
6	 34a	 12f	 35af	100
7	 34a	 12g	 35ag	42

Table 2.2 continues…

Entry	Fulvene	Indole	Product	Yield (%)
8	 **34a**	 **12h**	 **35ah**	0
9	 **34a**	 **12i**	 **35ai**	98
10	 **34a**	 **12j**	 **35aj**	98
11	 **34b**	 **12a**	 **35ba**	78

Reaction conditions: fulvene (1.0 equiv.), indole (1.0 equiv.), catalyst (2 mol%), solvent (2 mL), at rt for 2 h.

We were pleased to observe the formation of a new product **35aaa** along with **35aa** by doubling the equivalents of fulvene **34a**. The compound **35aaa** was isolated in 35% and was identified as a product of double alkylidenecyclopentenylation of indole at its C-2 and C-3 position. The formation of **35aaa** was further checked by conducting a reaction between 3- alkylidenecyclopentenylated indole **35aa** and 1.0 equivalent of fulvene **34a** (Scheme 2.13), which revealed the nucleophilicity of the C-2 position of indole for hydroarylation reactions in succession.



Scheme 2.13

The spectral analysis IR, NMR and HRMS were employed to establish the structures of the product **35aaa**. In the ^{1}H NMR spectrum (Figure 2.5) of the product **35aaa**, the two olefinic protons attached to the carbon atoms C-2 and C-2' were discernable as multiplets at chemical shift range of δ 6.62-6.61 and 6.55-6.54 ppm respectively. The olefinic protons at C-1 and C-1' observed as distinct multiplets in the region δ 6.25-6.21 ppm and 6.17-6.13 ppm. Two muliplets in the range of δ 4.48-4.47 and δ 4.41-4.40 ppm denote the protons which are attached to C-3 and C-3' carbon atoms. The diastereotopic methylene protons in the cyclopentenyl rings (C-4 and C-4') resonated as multiplets in the range of δ 3.13-3.08 and δ 2.96-2.77 ppm respectively.

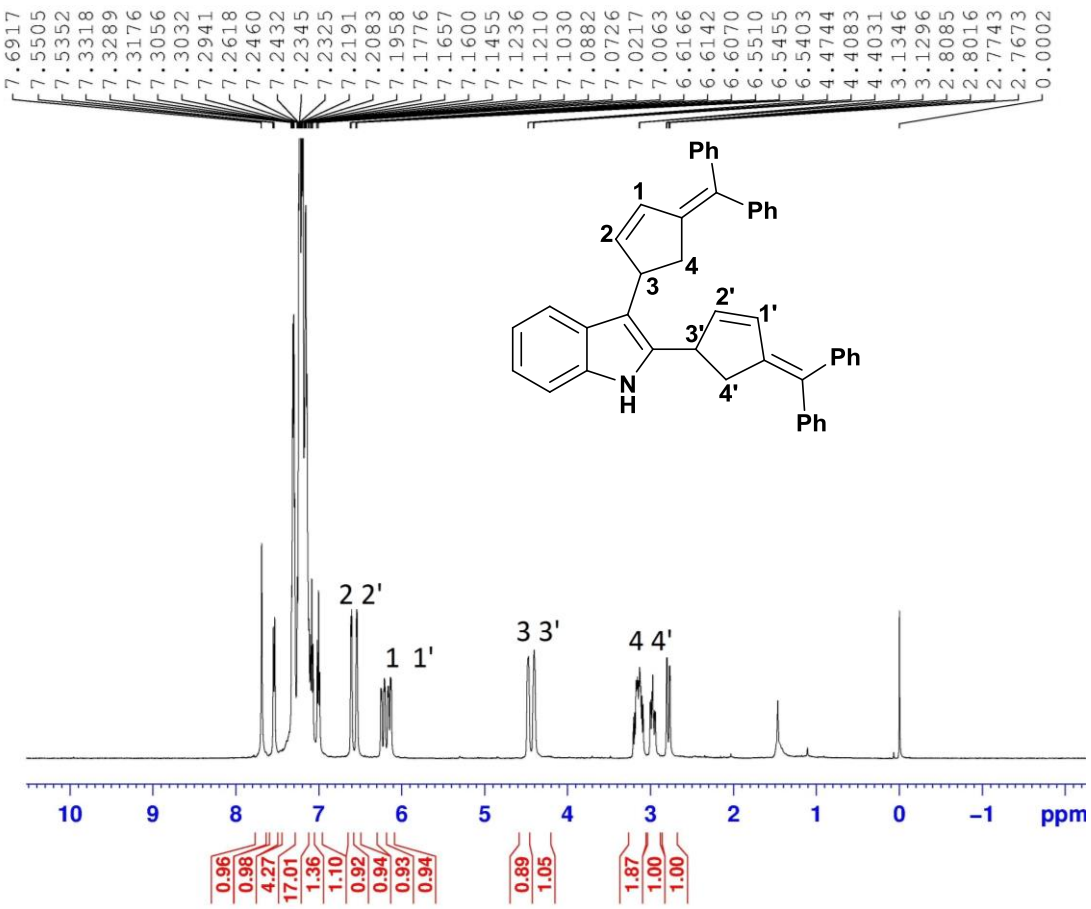


Figure 2.5. ^{1}H NMR spectrum of compound 35aaa

In the ^{13}C NMR spectrum (Figure 2.6), the carbons C-3, C-3' were visible at δ 41.9 and 41.5 ppm. The two methylene carbons C-4 and C-4' were observed at δ 40.1 and 39.6 ppm. All other signals in NMR spectra agreed with the proposed structure. Further evidence for the structure was obtained from HRMS analysis which showed the molecular ion peak at *m/z* 600.26609.

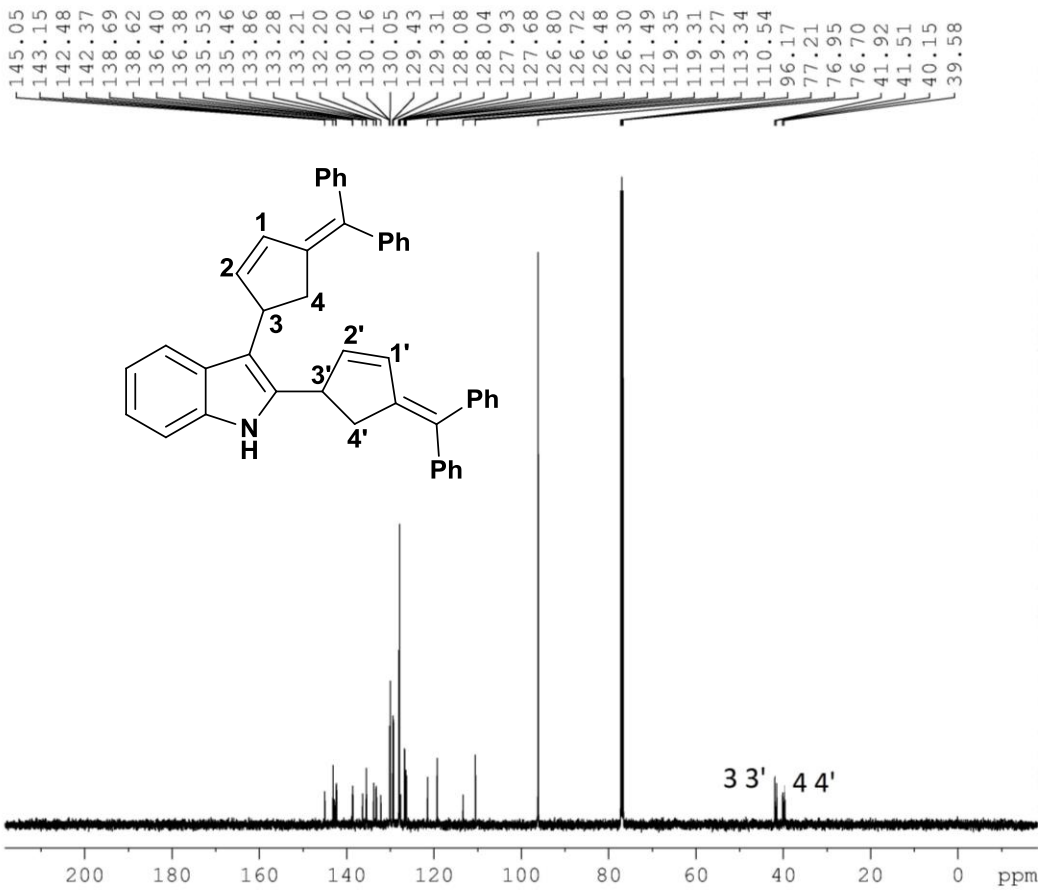
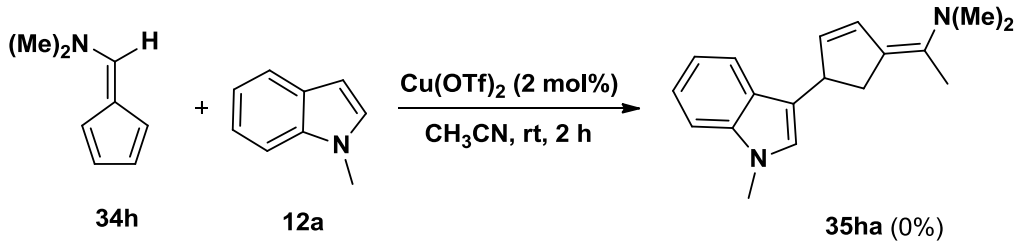


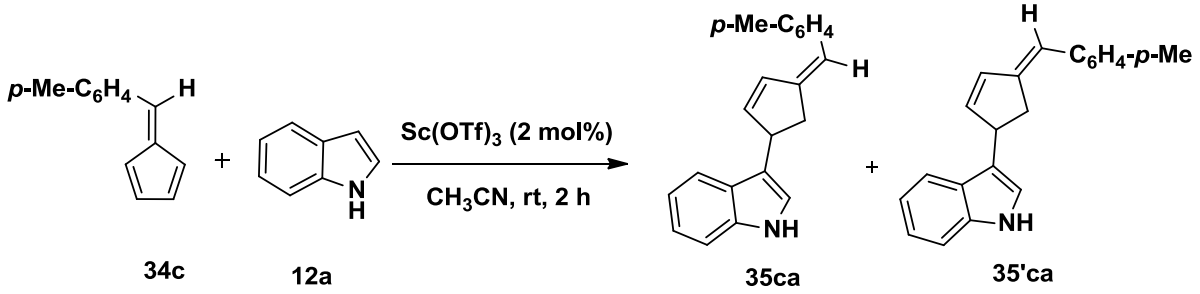
Figure 2.6. ^{13}C NMR spectrum of compound 35aaa

It is worthy to note that the reaction of fulvene with electron donating group at the exocyclic position, for example, *N*,*N*-dimethyl amino fulvene **34h** did not afford the product (Scheme 2.14).



Scheme 2.14

To check the further scope and uniqueness of the reaction we extended the developed strategy to unsymmetrical fulvenes. With a mono-substitution at the exocyclic double bond, unsymmetrical fulvenes are expected to be facile towards nucleophilic addition at the more exposed C-6 position. But the reaction is selective toward endo-selective addition affording the C-3 hydroarylated product **35ca** with a minor amount of the other regioisomer **35'ca** (with indole substituted on the same side as the 6-aryl substitutent) in minor amount (Scheme 2.15).



Scheme 2.15

In the ^{1}H NMR spectrum of the product **35ca** (Figure 2.7), the olefinic protons at C-2 and C-1 were observed as doublet of doublets at nearby values δ 6.44 ppm (dd, J_1 = 5 Hz, J_2 = 2 Hz) and δ 6.25 ppm (dd, J_1 = 5 Hz, J_2 = 2.5 Hz) respectively. The proton attached to the exocyclic carbon atom (C-5) resonated as a singlet at δ 6.41 ppm. The multiplet at δ 4.46-4.45 ppm corresponds to the proton attached to the carbon (C-3), which is bonded to indole. The two diastereotopic protons at C-4 were found to resonate individually as a multiplet in the range of δ 3.44-3.40 ppm and a doublet at δ 2.93 ppm (d, J = 17 Hz).

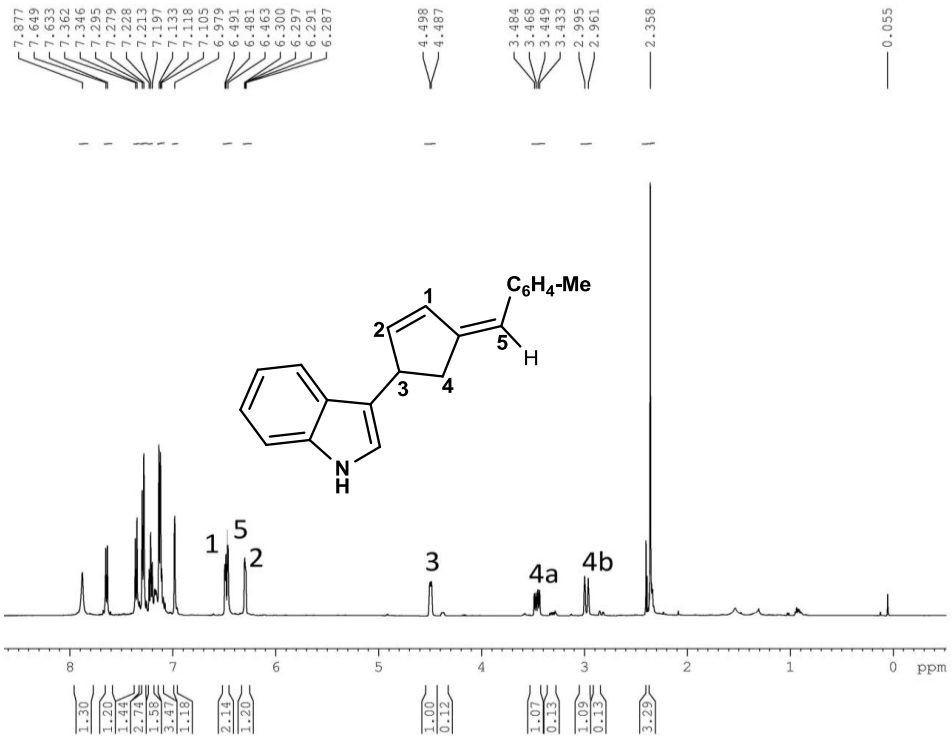


Figure 2.7. ^{1}H NMR spectrum of compound 35ca

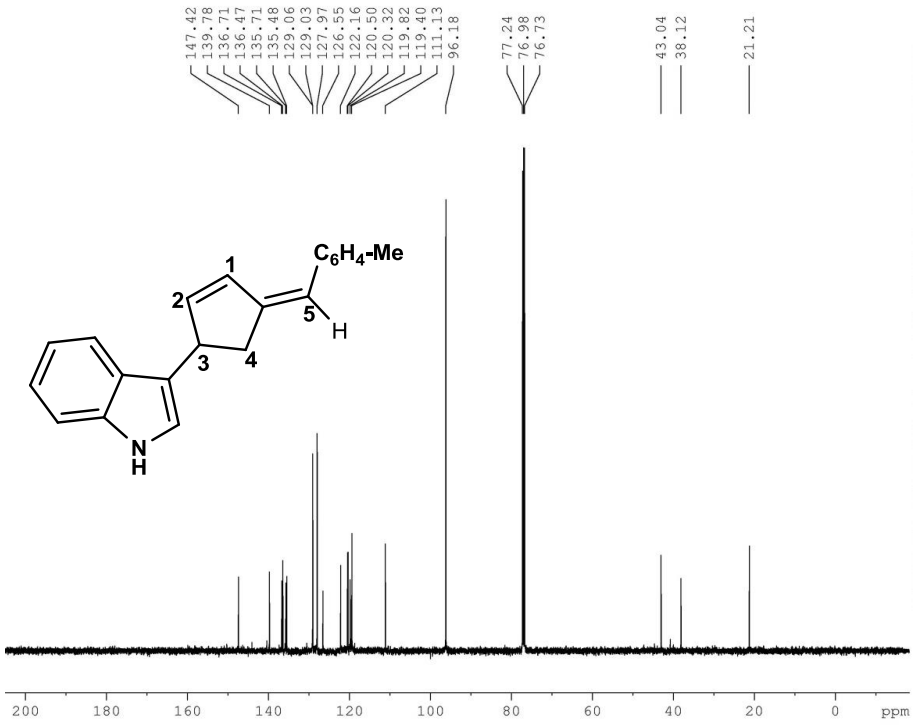
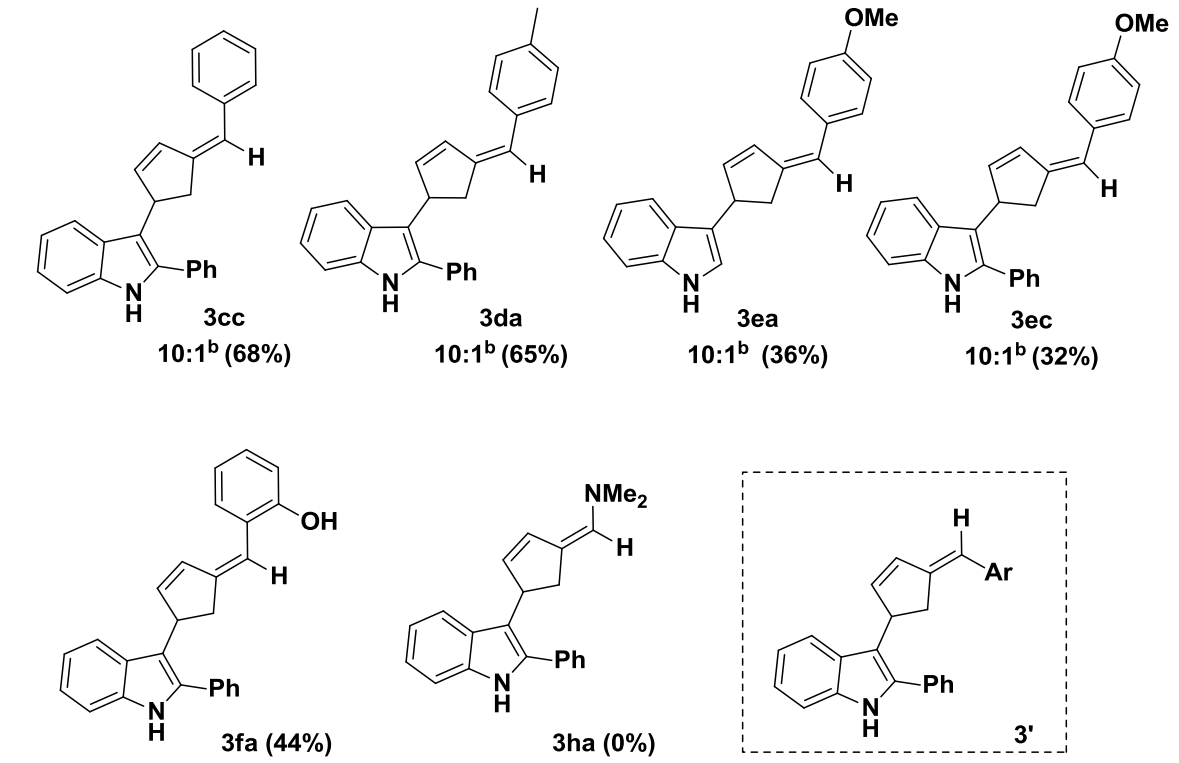


Figure 2.8. ^{13}C NMR spectrum of 35ca

To explore the scope and generality of the above reaction, different varieties of fulvenes were used and the products were obtained in good yields. The results obtained with different fulvenes derived from various aldehydes and substituted indoles are summarized in table 2.3.

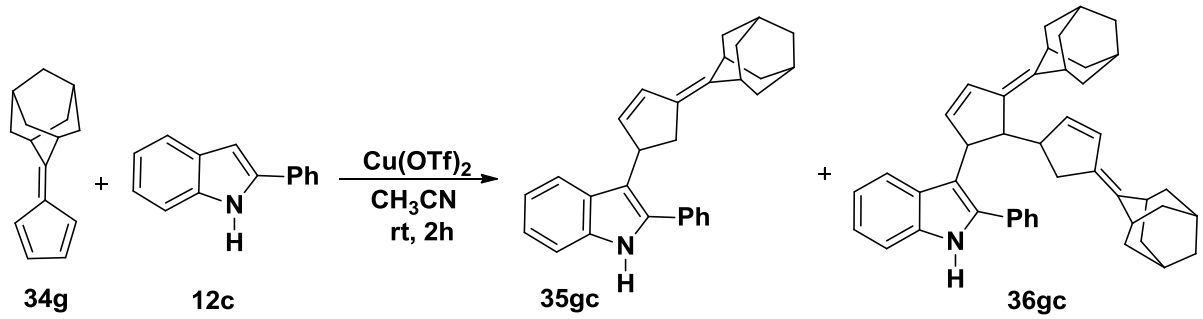
Table 2.3. Scope of hydrarylation reaction using aldehyde derived fulvenes and substituted indoles.



[a] Reaction Conditions: fulvene (1.0 equiv.), indole (1.0 equiv.), $Cu(OTf)_2$ (2 mol%), CH_3CN (2 mL), rt, 2h.
[b]Isomeric ratio represents the ratio of the two isomers 3 (major) and 3' (minor) formed during the reaction and was determined from ^1H NMR.

Subsequently we sought to extend the developed protocol to fulvenes with alkyl substituents at its exocyclic (C-6) position. Interestingly the reaction between adamantanone derived fulvene **34g** and 2-phenyl indole **12c** afforded two products, the expected product **35gc** and product **36gc**, containing two fulvene fragments

(Scheme 2.16). The generality of the reaction was checked with substituted indoles as shown in Table 4.



Scheme 2.16

Spectral data provided sufficient information for the structural characterization of product **35gc**. In the IR spectrum, the signal at 3369 cm^{-1} was diagnostic of the NH absorption. In the ^{1}H NMR spectrum (Figure 2.8), the two olefinic protons were observed as doublet of doublet at 6.56 ppm (dd, J_1 = 5.5 Hz, J_2 = 2 Hz, 1H) and 6.00 ppm (dd, J_1 = 5 Hz, J_2 = 2 Hz, 1H) respectively. A multiplet observed at δ 4.45-4.43 ppm represents the proton attached to the carbon, which is bonded with the C-3 carbon of indole. The two CH_2 protons present in the cyclopentenyl ring resonated individually as a multiplet at 2.97-2.94 and as a doublet of doublet at 2.77 (dd, J_1 = 16.5 Hz, J_2 = 4 Hz, 1H). ^{13}C NMR spectrum of **35gc** (Figure 2.9) positioned the two olefinic peaks at δ 138.2 ppm and δ 128.7 ppm, while the signal due to carbon, which is bonded with the C-3 carbon of indole resonated at δ 41.0 ppm. All other signals were in good agreement with the proposed structure. A well-defined molecular ion peak at *m/z* 414.21928 (M+Na) provided another convincing evidence for the structure.

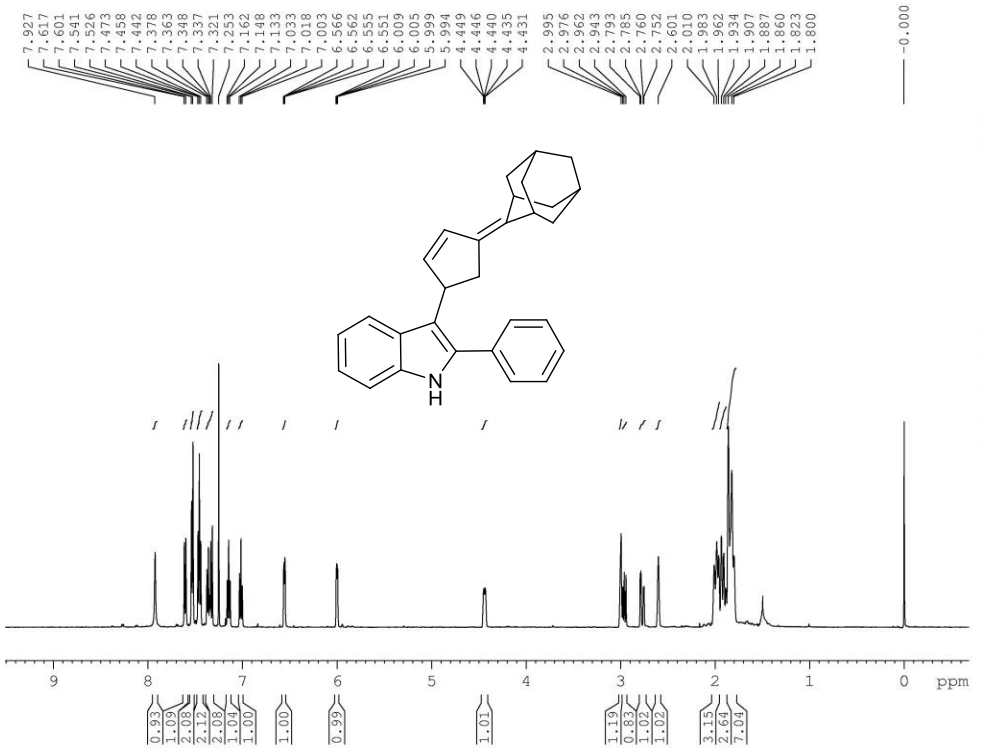


Figure 2.9. ^{1}H NMR spectrum of compound **35gc**

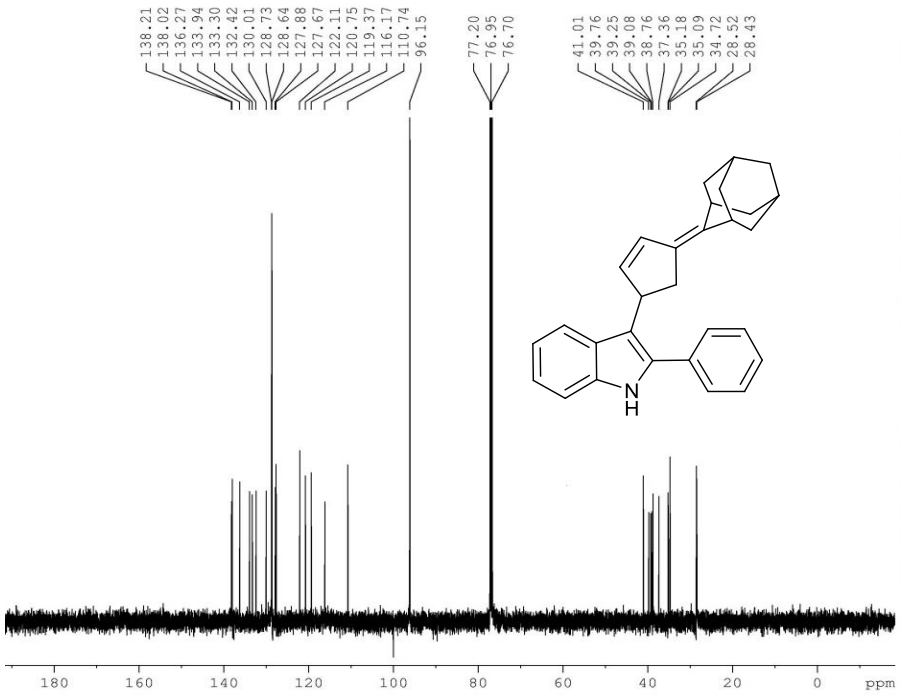


Figure 2.10. ^{13}C NMR spectrum of compound **35gc**

The characterization of the product **36gc** was accomplished by usual spectroscopic analysis. The IR spectrum displayed absorption at 3356 cm^{-1} corresponding to the NH functionality. In the ^{1}H NMR spectrum (Figure 2.10), the signal due to the NH proton was discernible as a broad singlet at δ 7.90 ppm. The four olefinic protons attached to the carbons C-1, C-7, C-2 and C-6 resonated at δ 6.52 (dd, J_1 = 5 Hz, J_2 = 1.5 Hz) ppm, δ 6.35 (d, J= 4.5 Hz, 1H) ppm, δ 5.86 (dd, J_1 = 5.5 Hz, J_2 = 2.5Hz, 1H) ppm and δ 5.73 (dd, J_1 = 5.5 Hz, J_2 = 2 Hz, 1H) ppm respectively. A broad singlet at δ 4.03 was attributed to the C-3 carbon atom which is bonded with indole moiety. ^{13}C NMR spectrum (Figure 2.11) displayed signals at δ 140.5, 138.1, 137.2 and 136.9 ppm for C-2, C-6, C-7 and C-1 carbons respectively. The C-4 carbon resonated at chemical shift values of δ 50.6 while the C-5 and C-3 carbons were visible at δ 49.8 and 43.5ppm. The molecular ion peak at *m/z* 626.37584, observed in the mass spectrum provided backing information for the proposed structure.

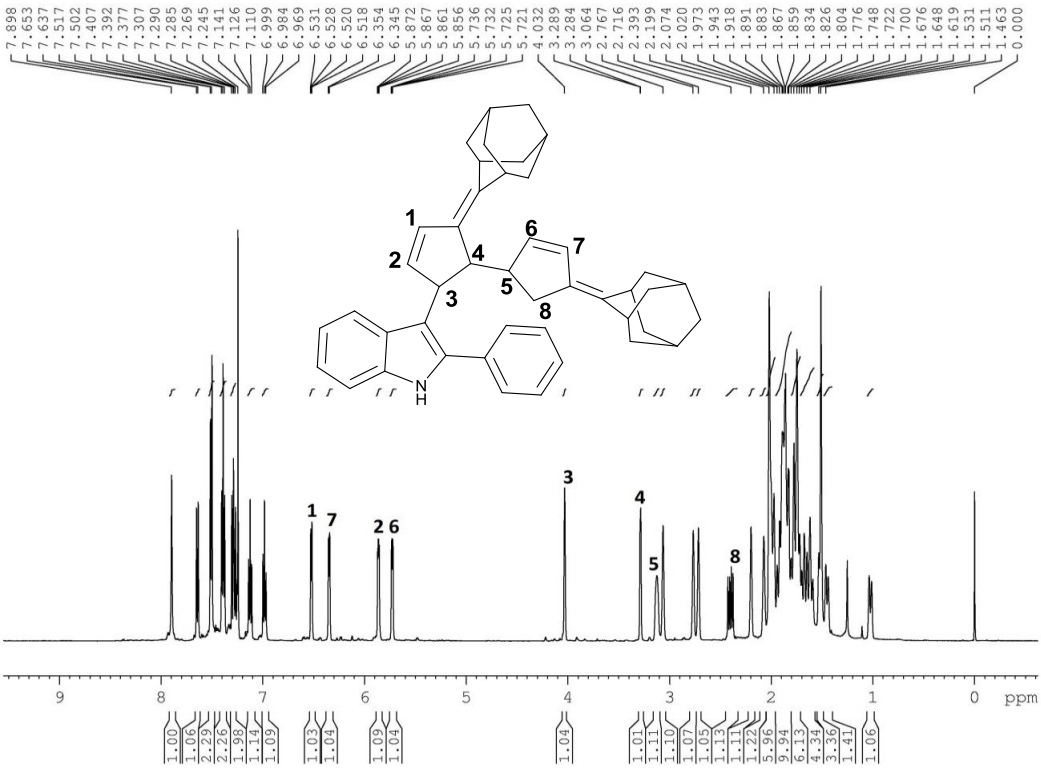


Figure 2.11. ^{1}H NMR spectrum of compound **36gc**

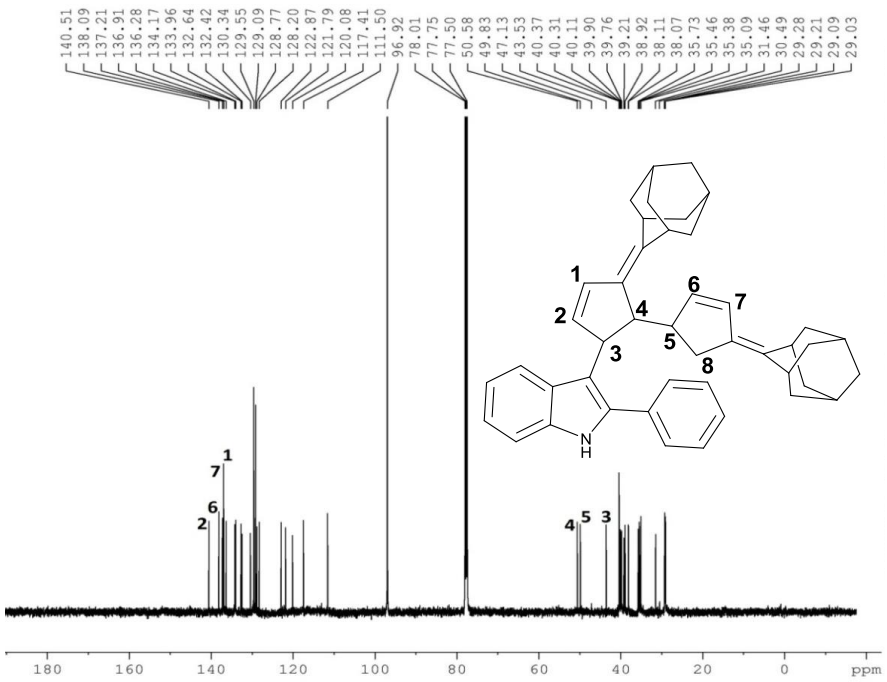


Figure 2.12. ^{13}C NMR spectrum of compound **36gc**

The 2D NMR spectra, ^{1}H-^{1}H COSY of the compound **36gc** shown below was found to be in well agreement with the assigned structure (figure 2.12).

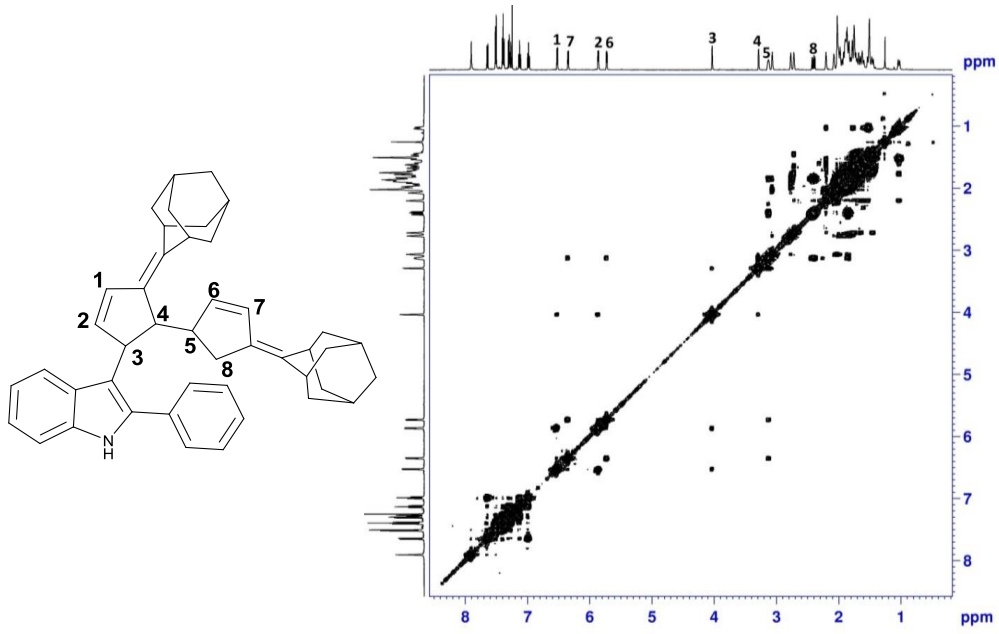
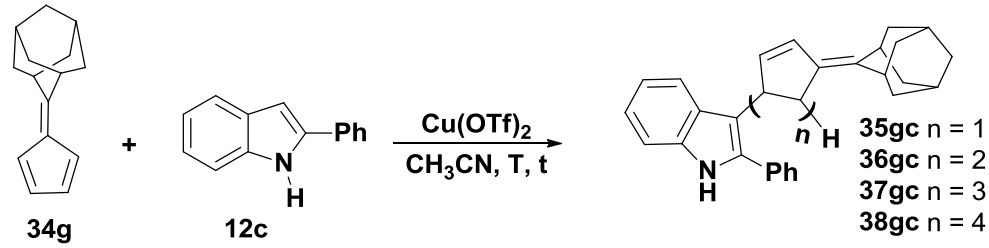


Figure 2.13. ^{1}H-^{1}H COSY spectrum of compound **36gc**

The unprecedented formation of product **36gc** prompted us to optimise the selectivity of the reaction by varying the fulvene/indole ratio and the reaction temperature (Table 2.4). It was found that the best yield of **35gc** was obtained with a small excess of indole at 0°C and a shorter reaction time (entry 9). On the other hand, the optimum yield of **36gc** was isolated with a two-fold excess of fulvene at 0°C (entry 6). Furthermore, increase of fulvene/indole ratio at room temperature allowed the isolation of higher analogues of **35gc** containing three or four fulvene moieties, **37gc** and **38gc,** respectively (entry 3).

Table 2.4. Termination of Lewis acid catalysed polymerization of fulvene with indole



34g **12c**

Entry	**34g** (equiv.)	**12c** (equiv.)	T (°C)	t (h)	Isolated yield (%) **35gc**	**36gc**	**37gc**	**38gc**
1	1.0	1.0	25	2	(20%)	(32%)	-	-
2	1.5	1.0	25	2	(24%)	(37%)	(12%)	(trace)
3	2.0	1.0	25	2	(28%)	(36%)	(14%)	(8%)
4	1.0	1.0	0	0.75	(39%)	(17%)	(trace)	-
5	1.5	1.0	0	0.75	(22%)	(46%)	(trace)	-
6	2.0	1.0	0	0.75	(20%)	(58%)	(trace)	-
7[b]	1.0	1.3	0	0.75	(54%)	(15%)	-	-
8[b]	1.0	2.0	0	0.75	(50%)	(20%)	-	-
9[b]	1.0	1.3	0	0.25	(62%)	(12%)	-	-

[a]Reaction conditions: $Cu(OTf)_2$ (2 mol%), CH_3CN (2 mL).
[b]Reaction is assisted with amount minor of impurites

The previously reported self-polymerisation of fulvene in acidic condition endorses the polymerisation of the dipolar structures of alkyl substituted fulvenes and

its competence with substitution reactions.[32–36] In our case, the self-polymerisation is stopped by indole at different stages depending on the amount of fulvene. This is in contrast to the results obtained in Scheme 2 with diarylfulvene, where two fulvenes were introduced consecutively. This was further shown by the attempted reaction of isolated product **35gc** with fulvene **12g** in the presence of Lewis acid, from which only polymerised fulvene and intact **35gc** was recovered.

The comparison of ^{1}H NMR spectra of all the four products is represented in the Figure 2.13.

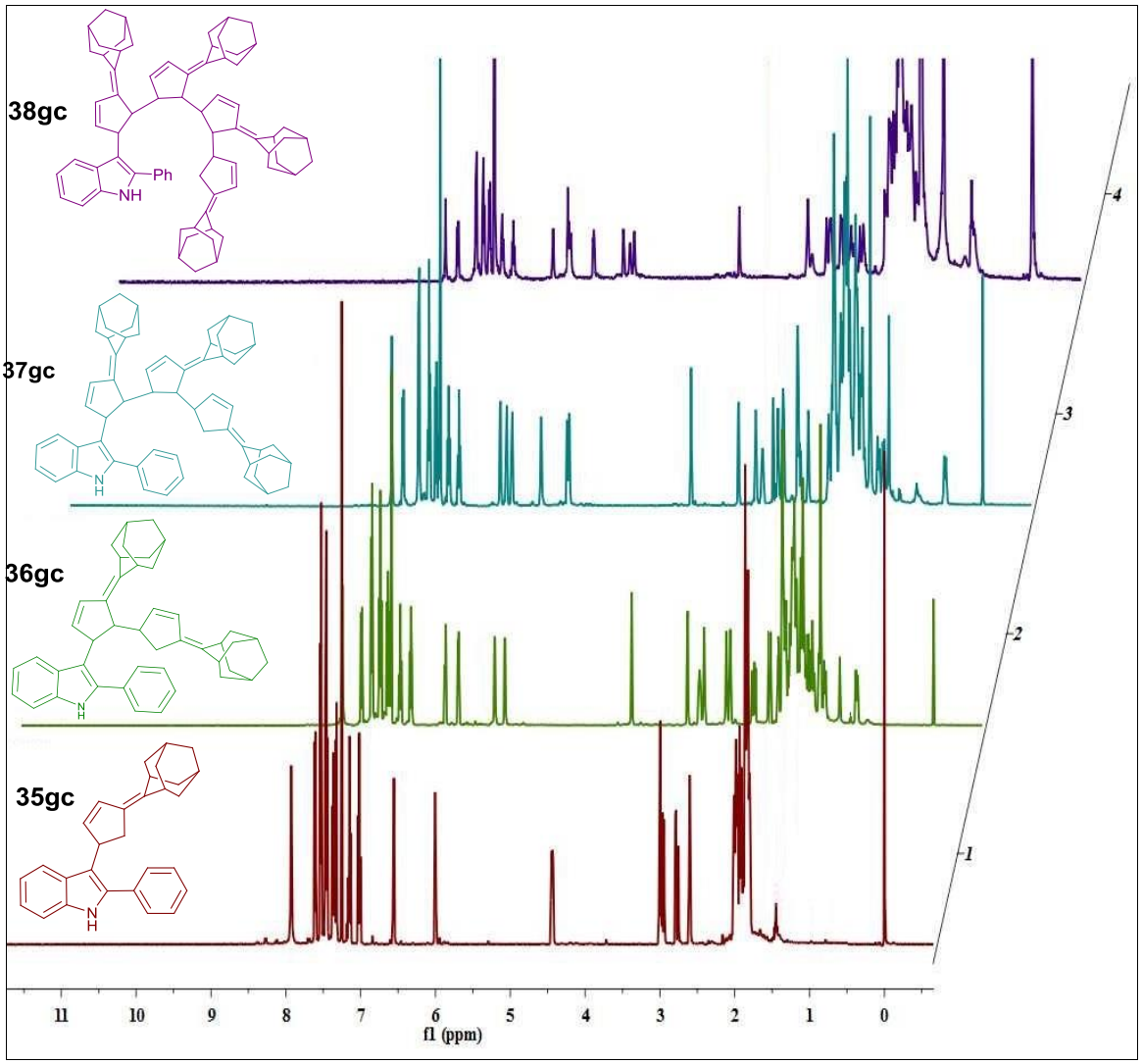
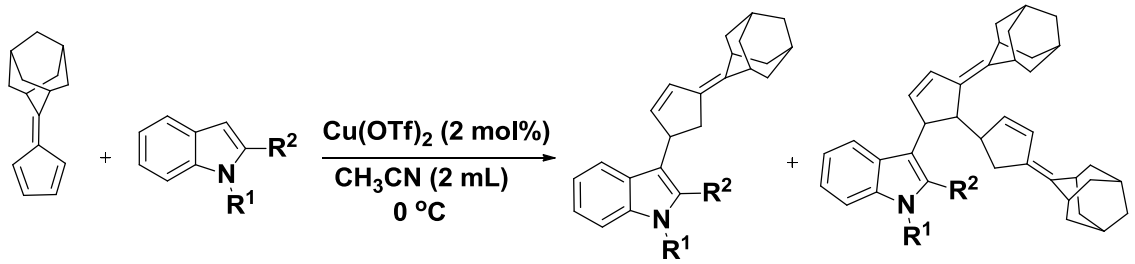


Figure 2.14. Comparison of the ^{1}H NMR of the compounds **35-38 gc**

With the optimised conditions in hand, we have checked the generality of the reaction with differently substituted indoles (Table 2.5).

Table 2.5. Lewis acid catalysed 1,2-addition of indole to 6-adamantyl substituted fulvene

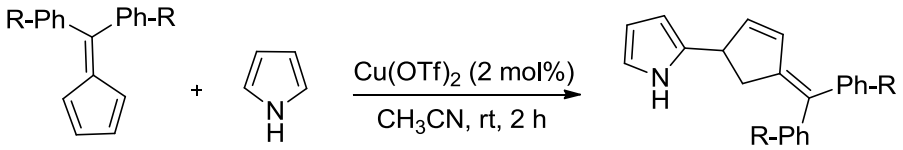


34g **12** **35** **36**

Entry	Indole	Yield (%)	
		Product **3**	Product **4**
1	**2a** (R^1 = H, R^2 = H)	**35ga** (59%)[a] **35ga** (17%)[b]	**36ga** (15%)[a] **36ga** (57%)[b]
2	**2d** (R^1 = Me, R^2 = Ph)	**35gd** (57%)[a] **35gd** (23%)[b]	**36gd** (14%)[a] **36gd** (50%)[b]

[a] Reaction conditions: fulvene (1.0 equiv.), indole (1.3 equiv.), $Cu(OTf)_2$ (2 mol%), 15 min.
[b] Reaction conditions: fulvene (2.0 equiv.), indole (1.0 equiv.), 45 min.

The scope of the reaction was also extended to pyrrole for the synthesis of alkylidene-cyclopentenyl-2,3-dihydro-1H-pyrroles **35ak** and **35bk** (Scheme 2.17).



34a; R = 4-H
34b; R = 4-Me

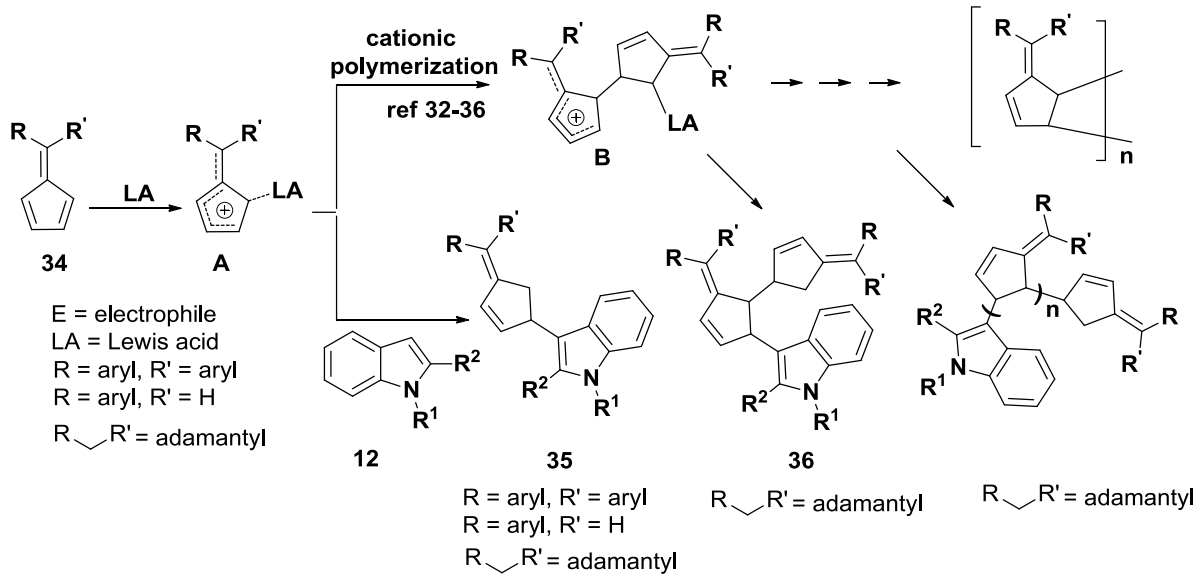
12k

35ak; R = 4-H (40%)
35bk; R = 4-Me(36%)

Scheme 2.17

2.6. Mechanistic pathway

A plausible mechanism for the trapping of Lewis acid generated intermediate **A** by indole leading to the hydroheteroarylation of pentafulvene is illustrated in Scheme 2.18. Electron deficient fulvenes (aromatic substituents at the exocyclic double bond) selectively underwent 1,2-hydroheteroarylation with indole and pyrrole under Lewis acidic condition. Whereas, electron rich fulvene get sufficient time to furnish its cationic dimeric species **B** (and higher oligomeric species) which leads to **36** along with minor amount of higher oligomers, in addition to the expected 1,2-hydroheteroarylation product **35**.



Scheme 2.18 Proposed mechanistic pathway for trapping fulvenium ion by indole.

2.7. Conclusion

In conclusion, we have developed an operationally simple and new strategy towards the regioselective endocyclic ring functionalization of pentafulvene with indoles. The method has provided the C-3 alkylidenecyclopentenylated indole and is the first example for the Lewis acid catalysed endo-selective 1, 2-addition of a

nucleophile to fulvenes. Moreover, we were able to terminate the acid catalysed cationic polymerization of fulvene by trapping the fulvenium ion using indole. This operationally simple reaction protocol does not require dry solvents and easily occur at ambient temperature without inert atmosphere.

2.8. Experimental Section

General methods: All reactions were conducted in oven-dried glasswares. All chemicals were of the best grade commercially available and are used without further purification. All the solvents were purified according to standard procedure; dry solvents were obtained according to the literature methods and stored over molecular sieves. All reactions were monitored by TLC (Silica gel 60 F254, 0.25 mm, Merck), visualization was effected with UV and/or by staining with Enholm yellow solution. Gravity column chromatography was performed using 100-200 mesh silica gel or neutral aluminium oxide and mixtures of hexane-ethyl acetate were used for elution.

Melting point was determined on a Buchi Melting Point apparatus and is uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker Avance DPX 300 and Bruker AMX 500 Spectrophotometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.25 ppm, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (double doublet); ddd (doublet of double doublet); m (multiplet). Coupling constants are reported as *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). Mass spectra were recorded under ESI/HRMS at 60000 resolution using Thermoscientific Exactive Mass Spectrometer. IR spectra were recorded on Bruker Alpha-T FTIR Spectrometer.

General Procedure for the Lewis acid-catalysed hydroarylation of pentafulvenes

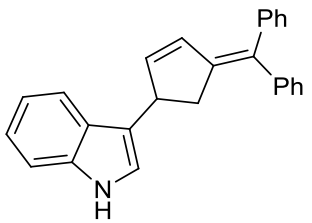
A mixture of pentafulvene (1.0 equiv.), indole (1.0 equiv.) and $Cu(OTf)_2$ (2 mol %) were weighed in a reaction tube, CH_3CN (2 mL) was added and allowed to stir at room temperature for 2 hours. The solvent was evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of hexane-ethyl acetate yielded the products.

Procedure for the Lewis acid-catalysed hydroarylation of alkyl substituted pentafulvenes

A mixture of pentafulvene and indole were weighed in a reaction tube, CH_3CN (2 mL) was added and cooled to 0 ^oC. To the stirred solution 2 mol% of $Cu(OTf)_2$ was added and left at 0 ^oC until the completion of the reaction. The solvent was evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography with mixtures of hexane-ethyl acetate yielded the products. The products obtained were further purified by HPLC technique.

3-(4-(diphenylmethylene)cyclopent-2-enyl)-1H-indole (35aa)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34a** (30 mg, 0.13 mmol), indole **12a** (15 mg, 0.13 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the product **35aa** (44 mg, 98%) as colourless foam.



R_f = 0.45 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3369, 3053, 2918, 1703, 1595, 1489, 1452, 1339, 1223, 742, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.91 (brs, 1H), 7.68 (d, *J* = 8 Hz, 1H), 7.39-7.36 (m, 4H), 7.31-7.20 (m, 7H), 7.16-7.13(m, 2H), 6.98 (s, 1H),

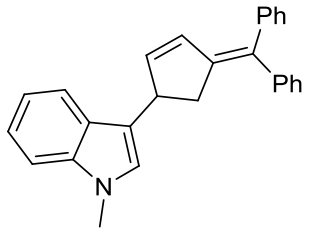
6.60-6.58 (m, 1H), 6.38-6.37 (m, 1H), 4.43 (brs, 1H), 3.31 (dd, J_1 = 16.5 Hz, J_2 = 7.5 Hz, 1H), 2.95 (dd, J_1 = 17 Hz, J_2 = 4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): 145.0, 142.9, 141.7, 136.7, 133.4, 132.1, 130.2, 129.5, 128.0, 126.6, 126.5, 126.4 122.1, 120.5, 119.8, 119.4, 119.3, 111.2, 111.1, 42.1, 39.8.

HRMS (ESI): Calcd for $C_{26}H_{21}NNa$: 370.15717; Found: 370.15695.

3-(4-(diphenylmethylene)cyclopent-2-enyl)-1-methyl-1H-indole (35ab)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34a** (30 mg, 0.13 mmol), indole **12b** (17 mg, 0.13 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the product **35ab** (46 mg, 99%) as colourless foam.



R_f : 0.50 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3064, 2902, 2848, 1959, 1878, 1583, 1477, 1361, 1336, 1250, 758, 711 cm^{-1}.

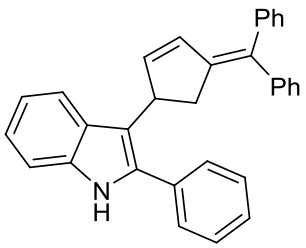
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.58 (d, J = 7.5 Hz, 1H), 7.32-7.28 (m, 3H), 7.25-7.22 (m, 3H), 7.20-7.18 (m, 5H), 7.15-7.12 (m, 1H), 7.07-7.04 (m, 1H), 6.81 (s, 1H), 6.51 (dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 1H), 6.29 (dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 1H), 4.37-4.35 (m, 1H), 3.73 (s, 3H), 3.24 (dd, J_1 = 17.5 Hz, J_2 = 7.5 Hz, 1H), 2.87 (dd, J_1 = 17 Hz, J_2 = 4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 144.9, 142.9, 141.7, 137.4, 133.3, 132.1, 130.2, 130.1, 129.5, 128.0, 127.9, 127.0, 126.4, 126.3, 125.2, 121.7,119.4, 118.8, 118.3, 109.2, 42.0, 40.1, 32.6.

HRMS (ESI): Calcd for $C_{27}H_{23}NNa$: 384.17282; Found: 384.17228.

3-(4-(diphenylmethylene)cyclopent-2-enyl)-2-phenyl-1H-indole (35ac)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34a** (30 mg, 0.13 mmol), indole **12c** (25 mg, 0.13 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the product **35ac** (54 mg, 99%) as white solid.



R_f : 0.53 (hexane/ethyl acetate = 4:1).

Mp : 152-154 ^{o}C,

IR (Neat) ν_{max}: 3864, 3053, 2919, 1599, 1489, 1449, 1308, 742, 699 cm^{-1}.

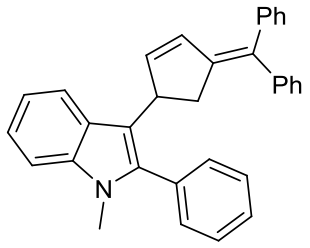
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.72 (d, J = 8 Hz, 1H), 7.50-7.47 (m, 2H), 7.43-7.42 (m, 2H), 7.37-7.31 (m, 4H), 7.24-7.22 (m, 8H), 7.19-7.13 (m, 2H), 7.08-7.06 (m, 1H), 6.57 (t, J = 2.5 Hz, 1H), 6.27 (d, J = 5 Hz, 1H), 4.53 (brs, 1H), 3.22 (dd, J_1 = 17 Hz, J_2 = 4.5 Hz, 1H), 3.14 (dd, J_1 = 17 Hz, J_2 = 7.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 145.1, 143.0, 142.9, 142.8, 136.3, 134.5, 133.2, 133.0, 132.2, 130.2, 129.5, 128.8, 128.6, 127.9, 127.8, 126.3, 120.5, 119.6, 114.8, 110.9, 42.2, 39.8.

HRMS (ESI): Calcd for $C_{32}H_{25}NNa$: 446.18847; Found: 446.11809.

3-(4-(diphenylmethylene)cyclopent-2-enyl)-1-methyl-2-phenyl-1H-indole (35ad)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34a** (30 mg, 0.13 mmol), indole **12d** (27 mg, 0.13 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the product **35ad** (56 mg, 99%) as colourless foam.



R_f : 0.63 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3053, 2919, 1599, 1489, 1449, 1308, 1264, 742, 701 cm^{-1}.

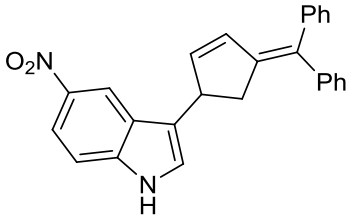
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.72 (d, J = 8 Hz, 1H), 7.50-7.47 (m, 2H), 7.44-7.42 (m, 3H), 7.39-7.32 (m, 3H), 7.27-7.23 (m, 8H), 7.18-7.16 (m, 1H), 7.15-7.12 (m, 1H), 6.54 (dd, J_1 = 7.5 Hz, J_2 = 2 Hz, 1H), 6.25 (dd, J_1 = 7.5 Hz, J_2 = 2 Hz, 1H), 4.26 (brs, 1H), 3.61 (s, 3H), 3.20 (dd, J_1 = 17 Hz, J_2 = 4.5 Hz, 1H), 3.07 (dd, J_1 = 17 Hz, J_2 = 7.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 145.3, 143.1, 143.0, 142.9, 137.6, 137.5, 133.0, 131.9, 131.8, 130.9, 130.2, 129.5, 128.4, 128.1, 127.9, 126.5, 126.4, 126.3, 121.8, 120.1, 119.3, 114.9, 109.4, 42.5, 40.1, 30.8.

HRMS (ESI): Calcd for $C_{33}H_{27}NNa$: 460.20412; Found: 460.20388.

3-(4-(diphenylmethylene)cyclopent-2-enyl)-5-nitro-1H-indole (35ae)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34a** (30 mg, 0.13 mmol), indole **12e** (21 mg, 0.13 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the product **35ae** (38 mg, 75%) as pale yellow coloured foam.



R_f : 0.23 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3367, 3053, 2922, 1621, 1596, 1516, 1468, 1365, 1330, 1094, 897, 741, 701 cm^{-1}.

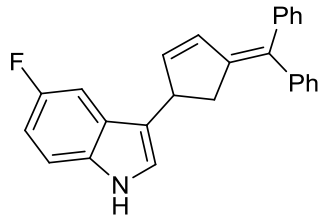
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 8.63 (brs, 1H), 8.62-8.13 (m, 1H), 8.12-8.11 (m, 1H), 7.34-7.31 (m, 2H), 7.29-7.19 (m, 6H), 7.14-7.11 (m, 2H), 7.10-7.08 (m, 2H), 6.61-6.59 (m, 1H), 6.30-6.28 (m, 1H), 4.42-4.40 (m, 1H), 3.38 (dd, J_1 = 17 Hz, J_2 = 8.5 Hz, 1H), 2.80 (dd, J_1 = 16.5 Hz, J_2 = 3 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 144.1, 142.7, 141.6, 140.2, 139.7, 134.2, 133.2, 130.2, 129.4, 128.1, 126.7, 126.6, 126.0, 123.5, 122.6, 117.9, 116.9, 111.2, 41.7, 39.6.

HRMS (ESI): Calcd for $C_{26}H_{20}N_2O_2Na$: 415.14225; Found: 415.14170.

3-(4-(diphenylmethylene)cyclopent-2-enyl)-5-fluoro-1H-indole (35af)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34a** (30 mg, 0.13 mmol), indole **12f** (18 mg, 0.13 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the product **35af** (48 mg, 100%) as colourless foam.



R_f : 0.38 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3661, 3054, 2923, 1705, 1587, 1484, 1453, 1170, 1107, 798, 758, 702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.92 (brs, 1H), 7.37-7.34 (m, 2H), 7.30-7.24 (m, 9H), 7.20-7.18 (m, 1H), 7.03 (s, 1H), 6.97-6.94 (m, 1H), 6.57-6.56 (m,1H), 6.31-6.30 (m, 1H), 4.35-4.34

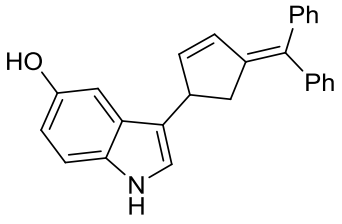
(m, 1H), 3.28 (dd, J_1 = 17 Hz, J_2 = 8 Hz, 1H), 2.86 (dd, J_1 = 17 Hz, J_2 = 4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 158.5, 144.7, 142.8, 141.1, 133.6,133.2, 133.0, 132.4, 130.2, 129.4, 129.1, 128.3, 128.0, 126.8, 126.5, 126.4, 122.3, 119.9, 111.8, 111.7, 110.6, 110.4, 104.4, 104.2, 42.0, 39.6.

HRMS (ESI): Calcd for $C_{26}H_{20}FNNa$: 388.14775; Found: 388.14736.

3-(4-(diphenylmethylene)cyclopent-2-enyl)-1H-indol-5-ol (35ag)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34a** (30 mg, 0.13 mmol), indole **12g** (18 mg, 0.13 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the product **35ag** (20 mg, 42%) as pale yellow viscous liquid.



R_f : 0.13 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3509, 3333, 3051, 2902, 2767, 2351, 1591, 1491, 1443, 1348, 793, 706,631 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.76(brs, 1H), 7.33-7.24 (m, 2H), 7.23-7.18 (m, 7H), 7.16-7.13 (m, 2H), 6.98 (d, J = 7 Hz, 1H), 6.93 (d, J = 2.5 Hz, 1H), 6.73 (dd, J_1 = 8.5 Hz, J_2 = 2.5Hz, 1H), 6.52 (dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 1H), 6.29 (dd, J_1 = 5.5Hz, J_2 = 2.5Hz, 1H) 4.48 (brs, 1H), 4.31-4.28 (m, 1H), 3.21 (dd, J_1 = 17 Hz, J_2 = 7.5 Hz, 1H), 2.86 (dd, J_1 = 16.5 Hz, J_2 = 4 Hz, 1H).

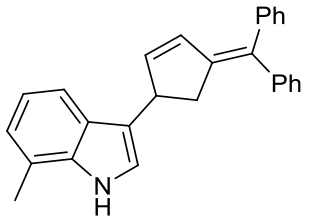
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 149.2, 144.8, 142.8, 141.4, 133.5, 132.1, 132.0, 130.2,

129.4, 129.0, 128.2, 127.9, 126.3, 126.5, 127.3, 121.5, 119.2, 111.9, 111.7, 103.9, 42.1, 39.7.

HRMS (ESI): Calcd for $C_{26}H_{21}NONa$: 386.15208; Found: 386.15179.

3-(4-(diphenylmethylene)cyclopent-2-enyl)-7-methyl-1H-indole (35ai)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34a** (30 mg, 0.13 mmol), indole **12i** (17 mg, 0.13 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the product **35ai** (32 mg, 67%) as pale yellow coloured foam.



R_f : 0.35 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3420, 3052, 2921, 2851, 2683, 1590, 1491, 1436, 1339, 1109, 746, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.83 (brs, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.36-7.35 (m, 2H), 7.33-7.19 (m, 7H), 7.17-7.16 (m, 1H), 7.06-6.99 (m, 3H), 6.57-6.56 (m, 1H), 6.35(dd, J_1 = 5.5 Hz, J_2 = 2 Hz, 1H), 4.41-4.40 (m, 1H), 3.28 (dd, J_1 = 17 Hz, J_2 = 8 Hz, 1H), 2.92 (dd, J_1 = 17 Hz, J_2 = 4 Hz, 1H), 2.50 (s, 3H).

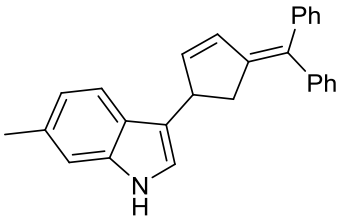
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 144.9, 142.9, 141.6, 136.2, 133.4, 132.1, 130.2, 129.5, 128.2, 127.9, 126.5, 126.3, 126.1, 122.7, 120.4, 120.2, 120.0, 119.6, 117.2, 42.2, 39.9, 16.6.

HRMS (ESI): Calcd for $C_{27}H_{23}NNa$: 384.17282; Found: 384.17251.

3-(4-(diphenylmethylene)cyclopent-2-enyl)-6-methyl-1H-indole (35aj)

Following general procedure for the Lewis acid catalyzed hydroarylation of

pentafulvene. The pentafulvene **34a** (30 mg, 0.13 mmol), indole **12j** (17 mg, 0.13 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the product **35aj** (29 mg, 62%) as pale yellow coloured foam.



R_f : 0.35 (hexane/ethyl acetate = 4:1)

IR (Neat) ν_{max}: 3410, 3048, 2918, 1703, 1684, 1590, 1489, 1446, 1341, 758, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.79 (brs, 1H), 7.51 (d, J = 8 Hz, 1H), 7.36-7.33 (m, 3H), 7.28-7.22 (m, 6H), 7.18-7.14 (m, 3H), 6.95-6.90 (m, 2H), 6.56-6.55 (m, 1H), 4.38-4.37 (m, 1H), 3.27 (dd, J_1 = 16.5 Hz, J_2 = 7.5 Hz, 1H), 2.91 (dd, J_1 = 17 Hz, J_2 = 4 Hz, 1H), 2.48 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 150.0, 142.9, 141.7, 137.2, 133.4, 132.0, 131.8, 130.2, 129.5, 128.2, 127.9, 126.4, 126.3, 124.5, 121.1, 119.6, 119.1, 111.1, 42.2, 39.8, 21.7.

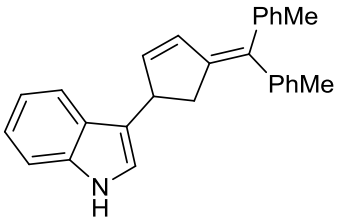
HRMS (ESI): Calcd for $C_{27}H_{23}NNa$: 384.17282; Found: 384.17248.

3-(4-(di-p-tolylmethylene)cyclopent-2-en-1-yl)-1H-indole (35ba)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34b** (30 mg, 0.12 mmol), indole **12a** (14 mg, 0.12 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the product **35ba** (36 mg, 78%) as pale yellow coloured foam.

R_f : 0.53 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3390, 3048, 2920, 1704, 1684, 1590, 1489, 1329, 752, 699 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.73 (brs, 1H), 7.59 (d, *J* = 8 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.16-7.00 (m, 9H), 6.87 (d, *J* = 2.5 Hz, 1H), 6.52(dd, J_1 = 5.5 Hz, J_2 = 2 Hz, 1H), 6.26-6.25 (m, 1H), 4.36-4.33 (m, 1H), 3.23 (dd, J_1 = 17 Hz, J_2 = 8 Hz, 1H), 2.86 (dd, J_1 = 17 Hz, J_2 = 4 Hz, 1H), 2.35 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 144.2, 140.9, 140.3, 140.2, 136.7, 136.0, 135.8, 133.7, 132.0, 130.2, 129.4, 129.0, 128.7, 126.7, 122.1, 120.3, 120.0, 119.5, 119.4, 111.2, 42.1, 40.0, 21.3, 21.2.

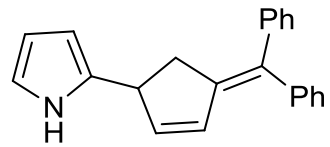
HRMS (ESI): Calcd for $C_{28}H_{235}NNa$: 398.18847; Found: 398.18796.

2-(4-(diphenylmethylene)cyclopent-2-enyl)-1H-pyrrole (35ak)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34a** (30 mg, 0.13 mmol), pyrrole **12k** (8 mg, 0.13 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the product **35ak** (16 mg, 40%) as colourless viscous liquid.

R_f : 0.13 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3388, 3054, 2922, 1683, 1596, 1490, 1441, 761, 701 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.94 (brs,1H), 7.33-7.26 (m, 2H), 7.25-7.20 (m, 3H), 7.18-7.17 (m, 5H), 6.68 (d, *J* = 1.5 Hz, 1H), 6.51-6.50 (m, 1H), 6.19-6.18 (m, 2H), 6.14-6.12 (m, 1H), 5.95 (brs, 1H), 4.18-4.17 (m, 1H), 3.15 (dd, J_1 = 17 Hz, J_2 = 8 Hz, 1H), 2.75 (dd, J_1 = 16.5 Hz, J_2

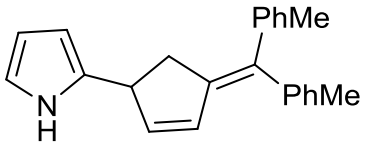
= 3.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 143.8, 142.6, 139.5, 134.8, 134.2, 132.8, 130.1, 129.4, 128.0, 126.6, 126.5, 116.8, 108.4, 104.6, 43.6, 39.8.

HRMS (ESI): Calcd for $C_{22}H_{19}NNa$: 320.14152; Found: 320.14111.

2-(4-(di-p-tolylmethylene)cyclopent-2-en-1-yl)-1H-pyrrole (35bk)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34b** (30 mg, 0.09 mmol), pyrrole **12k** (8 mg, 0.09 mmol) and $Cu(OTf)_2$ (1 mg, 0.002 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the product **35ak** (13 mg, 36%) as colourless viscous liquid.



R_f : 0.13 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3369, 3046, 2922, 1680, 1587, 1490, 1440, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.60 (brs,1H), 7.09-7.04 (m, 10H), 6.47-6.46 (m, 1H), 6.11 (d, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 1H), 5.78-5.77 (m, 1H), 4.10-4.07 (m, 1H), 3.11 (dd, J_1 = 17 Hz, J_2 = 8 Hz, 1H), 2.74-2.69 (m, 1H), 2.35 (s, 3H), 2.31 (s, 3H).

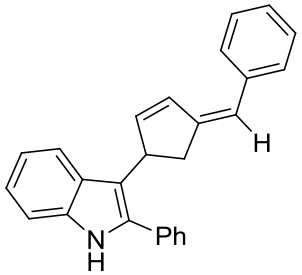
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 143.0, 139.9, 139.0, 138.9, 138.0, 136.7, 136.1, 135.9, 135.8, 135.6, 133.7, 132.0, 130.2, 129.9, 129.4, 129.1, 129.104.6, 43.8, 40.0, 21.2.

HRMS (ESI): Calcd for $C_{24}H_{23}NNa$: 348.17282;

Found: 348.17249.

3-(4-benzylidenecyclopent-2-enyl)-2-phenyl-1H-indole (35cc)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34c** (30 mg, 0.19 mmol), indole **12c** (38 mg, 0.19 mmol) and $Cu(OTf)_2$ (2 mg, 0.004 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the products **35cc** and **35'cc** as colourless viscous foam (46 mg, 68%) with an isomeric ratio of 10:1.



R_f : 0.58 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3379, 3054, 3025, 2931, 1705, 1602, 1488, 1451, 1308, 1157, 1025, 743, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 8.02 (brs, 1H), 7.66-7.60 (m, 3H), 7.56-7.53 (m, 2H), 7.48-7.44 (m, 3H), 7.42-7.40 (m, 1H), 7.38-7.35 (m, 2H), 7.28-7.20 (m, 1H), 7.11-7.08 (m, 1H), 6.60 (s, 1H), 6.57-6.56 (m, 2H), 6.31-6.30 (m, 1H), 4.69-4.68 (m, 1H), 3.45 (dd, J_1 = 17 Hz, J_2 = 7 Hz, 1H), 3.32-3.28 (d, J = 15 Hz, 1H).

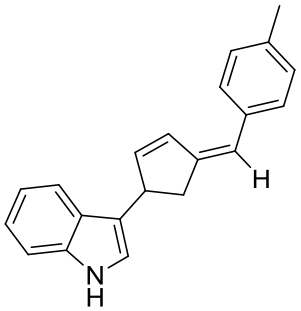
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 148.8, 141.5, 138.6, 136.3, 134.6, 133.0, 128.9, 128.6, 128.4, 128.1, 128.0, 127.7, 126.0, 122.3, 120.6, 120.4, 119.7, 114.6, 111.0, 43.2, 38.0.

HRMS (ESI): Calcd for $C_{26}H_{21}N$: 347.16740; Found: 347.16724.

3-(4-(4-methylbenzylidene)cyclopent-2-enyl)-1H-indole (35da)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34d** (30 mg, 0.18 mmol), indole **12a** (38 mg, 0.18

mmol) and $Cu(OTf)_2$ (2 mg, 0.004 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the products **35da** and **35'da** as colourless viscous foam (33 mg, 65%) with an isomeric ratio of 10:1.



R_f : 0.43 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3381, 3047, 2930, 1670, 1600, 1568, 1451, 1300, 1100, 870, 742, 690 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.88 (brs, 1H), 7.64 (d, *J* = 8 Hz, 1H), 7.35 (d, *J* = 8 Hz, 1H), 7.30-7.28 (m, 2H), 7.23-7.20 (m, 1H), 7.13-7.11 (m, 3H), 6.98 (s, 1H), 6.49-6.46 (m, 2H), 6.30-6.29 (m, 1H), 4.50-4.49 (m, 1H), 3.45 (dd, J_1 = 17.5 Hz, J_2 = 3 Hz, 1H), 3.00-2.96 (m,1H), 2.36 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 147.4, 139.8, 136.7, 136.5, 135.7, 135.5, 129.1, 129.0, 128.0, 126.6, 122.2, 120.5, 120.3, 119.8, 119.4, 111.1, 43.0, 38.1, 21.2.

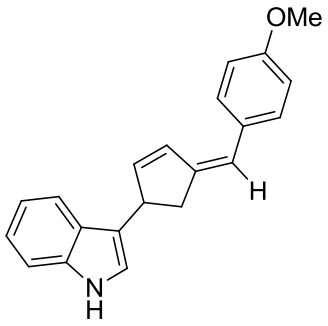
HRMS (ESI): Calcd for $C_{21}H_{19}N$: 285.15175; Found: 285.15137.

3-(4-(4-methoxybenzylidene)cyclopent-2-enyl)-1H-indole (35ea)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34e** (30 mg, 0.16 mmol), indole **12a** (38 mg, 0.16 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the products **35ea** and **35'ea** as colourless viscous foam (18 mg, 36%) with an isomeric ratio of 10:1.

R_f : 0.38 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3379, 3049, 2925, 1704, 1595, 1504, 1459, 1339, 1247, 1223, 1176, 1030, 742, 700 cm^{-1}.



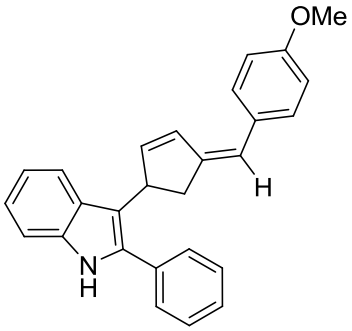
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.93 (brss, 1H), 7.67 (d, *J* = 8 Hz, 1H), 7.39-7.34 (m, 3H), 7.28-7.22 (m, 1H), 7.16-7.13 (m, 1H), 6.99-6.94 (m, 1H), 6.89 (d, *J* = 8.5 Hz, 2 H), 6.50-6.46 (m, 2H), 6.29-6.28 (m, 1H), 4.51-4.50 (m, 1H), 3.83 (s, 3H), 3.46 (dd, J_1 = 17 Hz, J_2 = 7 Hz, 1H), 2.99-2.96 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 157.8, 146.3, 139.3, 136.7, 136.5, 131.5, 129.2, 129.1, 126.5, 122.1, 120.5, 120.0, 119.8, 119.4, 113.9, 111.2, 55.3, 43.0, 38.0.

HRMS (ESI): Calcd for $C_{21}H_{19}NO$: 301.14666; Found: 301.14642.

3-(4-(4-methoxybenzylidene)cyclopent-2-enyl)-2-phenyl-1H-indole (35ec)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34e** (30 mg, 0.16 mmol), indole **12c** (38 mg, 0.16 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the products **35ec** and **35'ec** as colourless viscous foam (20 mg, 32%) with an isomeric ratio of 10:1.



R_f : 0.43 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3385, 3040, 2932, 1673, 1602, 1573, 1452, 1302, 1174, 1104, 870, 742, 688 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 8.03 (s, 1H), 7.61-7.52 (m, 3H), 7.50-7.49 (m, 2H), 7.43-7.41 (m, 1H), 7.40-7.35 (m, 3H), 7.20-7.17 (m, 1H), 7.06-7.03 (m, 1H), 6.93-6.85 (m, 2H), 6.51-6.49 (m, 2H), 6.22- 6.21 (m, 1H), 4.64-4.63 (m, 1H), 3.82 (s, 3H), 3.38 (dd, J_1 = 17.5 Hz, J_2 = 8 Hz, 1H),

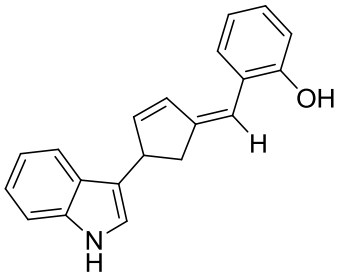
3.24-3.21 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 157.8, 146.5, 140.2, 136.3, 134.4, 133.1, 131.5, 129.3, 128.8, 128.7, 127.9, 127.6, 122.3, 120.5, 120.1, 119.6, 114.8, 113.8, 110.9, 55.1, 43.1, 37.9.

HRMS (ESI): Calcd for $C_{27}H_{23}NO$: 377.17796; Found: 377.17754.

2-((4-(1H-indol-3-yl)cyclopent-2-enylidene)methyl)phenol (35fa)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34f** (30 mg, 0.18 mmol), indole **12a** (38 mg, 0.18 mmol) and $Cu(OTf)_2$ (2 mg, 0.004 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the products **35fa** (22 mg, 44%) as pale yellow viscous liquid.



R_f : 0.15 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3412, 3380, 3053, 2926, 1695, 1600, 1454, 1235, 1096, 1015, 742, 699 cm^{-1}.

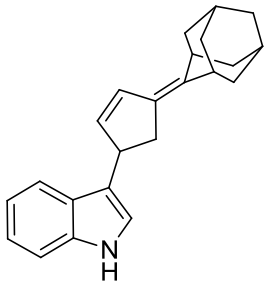
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.96 (brs, 1H), 7.63 (d, J = 8 Hz, 1H), 7.38-7.34 (m, 2H), 7.28-7.20 (m, 1H), 7.14-7.08 (m, 2H), 6.98 (s, 1H), 6.89-6.83 (m, 2H), 6.58 (s, 1H), 6.54-6.53 (m, 1H), 6.39-6.37 (m, 1H), 5.14 (brs, 1H), 4.45-4.43 (m, 1H), 3.35-3.29 (m, 1H), 2.87-2.83 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 152.8, 150.7, 141.4, 136.7, 135.6, 128.5, 127.7, 126.5, 125.3, 122.2, 120.5, 119.5, 119.4, 119.3, 115.3, 112.9, 111.2, 42.5, 37.5.

HRMS (ESI): Calcd for $C_{27}H_{17}NONa$: 310.12078; Found: 310.12039.

Compound 35ga

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34g** (30 mg, 0.15 mmol), indole **12a** (18 mg, 0.15 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the mixture of products **35ga** and **36ga**. The product **35ga** (colourless viscous liquid, 10 mg, 21%) was separated from **36ga** and purified by HPLC.



R_f : 0.48 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3389, 3066, 2931, 2857, 1668, 1620, 1582, 1520, 1455, 1304, 933, 744 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.87 (brs, 1H), 7.60 (d, J = 8 Hz, 1H), 7.32 (d, J = 8 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.94 (s, 1H), 6.54-6.53 (m, 1H), 6.08-6.06 (m, 1H), 4.30-4.28 (m, 1H), 3.06 (dd, J_1 = 16 Hz, J_2 = 9 Hz, 1H), 2.94 (brs, 1H), 2.58 (brs, 1H), 2.53 (dd, J_1 = 16 Hz, J_2 = 4 Hz, 1H), 1.96-1.95 (m, 2H), 1.91-1.89 (m, 2H), 1.86-1.82 (m, 6H), 1.74-1.72 (m, 2H).

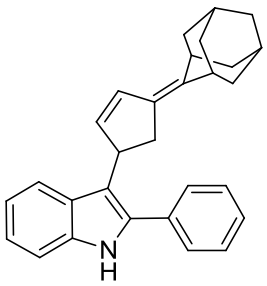
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 138.0, 137.1, 136.7, 131.9, 130.1, 126.6, 121.9, 121.0, 120.0, 119.5, 119.1, 111.0, 41.0, 39.4, 39.2, 38.8, 38.7, 37.3, 35.3, 35.0, 34.6, 28.4, 28.3.

HRMS (ESI): Calcd for $C_{23}H_{25}NNa$: 338.18847; Found: 338.18795.

Compound 35gc

Following general procedure for the Lewis acid catalyzed hydroarylation of

pentafulvene. The pentafulvene **34g** (30 mg, 0.15 mmol), indole **12c** (29 mg, 0.15 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the mixture of products **35gc** and **36gc**. The product **35gc** (colourless viscous liquid, 10 mg, 21%) was separated from **36ga** and purified by HPLC.



R_f : 0.54 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3369, 3060, 2940, 2855, 1670, 1620, 1581, 1520, 1458, 1301, 1291, 1238, 941, 741 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.93 (brs, 1H), 7.61 (d, J = 8 Hz, 1H), 7.54-7.52 (m, 2H), 7.47-7.44 (m, 2H), 7.38-7.32 (m, 2H), 7.16-7.13 (m, 1H), 7.02(t, J = 7.5 Hz, 1H), 6.56 (dd, J_1 = 5.5 Hz, J_2 = 2 Hz, 1H), 6.00 (dd, J_1 = 5 Hz, J_2 = 2 Hz, 1H), 4.45-4.43 (m, 1H), 3.00-2.94 (m, 2H), 2.77 (dd, J_1 = 16.5 Hz, J_2 = 4 Hz, 1H), 2.60 (brs, 1H), 2.01-1.96 (m, 3H),1.93-1.89 (m, 2H), 1.86-1.80 (m, 7H).

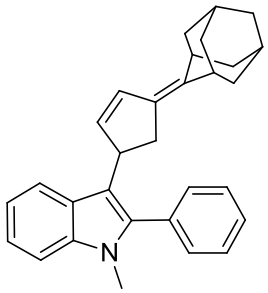
^{13}C NMR(125MHz,$CDCl_3$, TMS): **δ** 138.2, 138.0, 136.3, 133.9, 133.3, 132.4, 130.0, 128.7, 128.6, 127.9, 127.7, 122.1, 120.8, 119.4, 116.2, 110.7, 41.0, 39.8, 39.3, 39.1, 38.8, 37.4, 35.2, 35.1, 34.7, 28.5, 28.4.

HRMS (ESI): Calcd for $C_{29}H_{29}NNa$: 414.21977; Found: 414.21928.

Compound 35gd

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34g** (30 mg, 0.15 mmol), indole **12d** (31 mg, 0.15 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature

for 2 hours gave the mixture of products **35gd** and **36gd**. The product **35gd** (colourless viscous liquid, 13 mg, 22%) was separated from **36gd** and purified by HPLC.



R_f : 00.54 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 2981, 2915, 2833, 1671, 1621, 1586, 1542, 1380, 1042, 957, 931, 743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.62 (d, *J* = 7.5 Hz, 1H), 7.51-7.47 (m, 2H), 7.45-7.40 (m, 3H), 7.33-7.31 (m, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.07-7.04 (m, 1H), 6.51 (dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 1H), 5.95 (dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 1H), 4.15-4.13 (m, 1H), 3.60 (s, 3H), 2.99 (brs, 1H), 2.89 (dd, J_1 = 16.5 Hz, J_2 = 9 Hz, 1H), 2.72 (dd, J_1 = 16.5 Hz, J_2 = 4.5 Hz, 1H), 2.59 (brs, 1H), 2.02-1.81 (m, 12H).

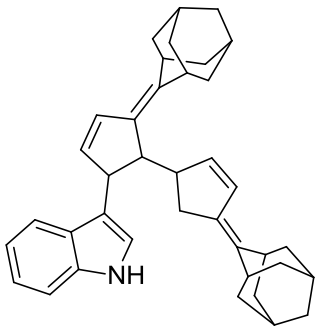
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 138.4, 137.8, 137.5, 137.0, 132.5, 132.1, 130.9, 129.6, 128.3, 127.9, 121.6, 120.4, 119.0, 116.3, 109.2, 41.3, 39.7, 39.0, 38.8, 37.4, 35.3, 35.1, 34.7, 30.8, 30.7, 28.5 ppm.

HRMS (ESI): Calcd for $C_{30}H_{31}N$: 405.24565; Found: 405.24513.

Compound 36ga

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34g** (30 mg, 0.15 mmol), indole **12a** (18 mg, 0.15 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the mixture of products **35ga** and **36ga**. The product **36ga** (colourless

viscous liquid, 23 mg, 29%) was separated from **35ga** and purified by HPLC.



R_f : 00.48 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3356, 3069, 2933, 2857, 1671, 1619, 1582, 1455, 933, 742, 688 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.84 (brs, 1H), 7.57(d, *J* = 8 Hz, 1H), 7.30 (d, *J* = 8 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.03-6.99 (m, 1H), 6.87 (d, *J* = 2 Hz,1H), 6.48 (t, *J* = 4 Hz, 2H), 5.80 (dd, J_1 = 9.5 Hz, J_2 = 4.5 Hz, 1H), 3.73 (brs, 1H), 3.15-3.14 (m, 1H), 3.07-3.01 (m, 2H), 2.92 (brs, 1H), 2.73 (brs, 1H), 2.58-2.53 (m, 2H), 2.37-2.33 (m, 1H), 2.00-1.77 (m, 24H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 139.6, 136.7, 136.5, 136.0, 135.9, 132.3, 131.5, 129.3, 126.4, 121.8, 120.9, 120.3, 119.8, 119.0, 110.9, 51.5, 48.6, 42.6, 39.6, 39.5, 39.4, 39.3, 39.1, 38.7, 37.3, 37.2, 35.0, 34.9, 34.6, 34.5, 31.1, 28.5, 28.4.

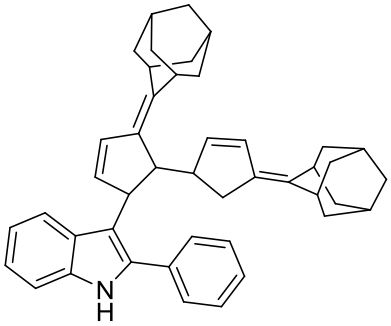
HRMS (ESI): Calcd for $C_{38}H_{43}N$: 513.33955; Found: 513.33916.

Compound 36gc

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34g** (30 mg, 0.15 mmol), indole **12c** (29 mg, 0.15 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the mixture of products **35gc** and **36gc**. The product **36gc** (colourless viscous liquid, 29 mg, 32%) was separated from **35gc** and purified by HPLC.

R_f : 0. 0.54 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3048, 2909, 2852, 1589, 1472, 1379, 744, 690 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.90 (brs, 1H), 7.64 (d, *J* = 8 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.41-7.38 (m, 2H), 7.31-7.25 (m, 2H), 7.14-7.11 (m, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.52 (dd, J_1 = 5 Hz, J_2 = 1.5 Hz, 1H), 6.35 (d, *J*= 4.5 Hz, 1H), 5.86 (dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 1H), 5.73 (dd, J_1 = 5.5 Hz, J_2 = 2 Hz, 1H), 4.03 (brs, 1H), 3.29 (brs, 1H), 3.10 (brs, 1H), 3.06 (brs, 1H), 2.77 (brs, 1H), 2.72 (brs, 1H), 2.47-2.36 (m, 1H), 2.20 (brs, 1H), 2.07 (brs, 1H), 2.02-1.92 (m, 5H), 1.89-1.83 (m, 10H), 1.86-1.80 (m, 4H),1.77-1.67 (m, 2H), 1.65-1.62 (m, 1H), 1.53-1.51 (m, 1H), 1.50-1.46 (m, 1H), 0.96-1.13 (m, 1H).

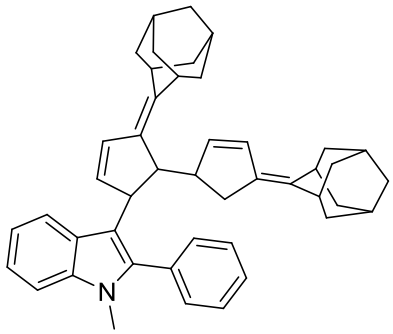
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 140.5, 138.1, 137.2, 136.9, 136.3, 134.2, 34.0, 132.6, 132.4, 130.3, 129.6, 129.1, 128.8, 128.2, 122.9, 121.8, 120.1, 117.4, 111.5, 50.6, 49.8, 47.1, 43.5, 40.4, 40.3, 40.1, 39.9, 39.8, 39.2, 38.9, 38.1, 35.7, 35.5, 35.4, 35.1, 31.5, 30.5, 29.3, 29.2, 29.1, 29.0.

HRMS (ESI): Calcd for $C_{44}H_{47}N$: 589.37085; Found: 589.37055.

Compound 36gd

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34g** (30 mg, 0.15 mmol), indole **12d** (31 mg, 0.15 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the mixture of products **35gd** and **36gd**. The product **36gd**

(colourless viscous liquid, 24 mg, 30%) was separated from **35gd** and purified by HPLC.



R_f : 0.62 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3058, 2978, 2908, 1580, 1467, 1445, 1249, 1022, 745 cm^{-1}.

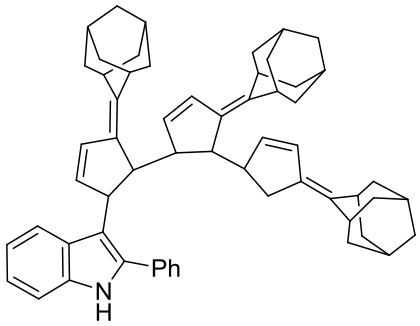
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.67-7.65 (m, 1H), 7.45-7.42 (m, 2H), 7.38-7.31 (m, 4H), 7.26-7.19 (m, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.44 (d, *J* = 5.5 Hz, 1H), 6.30 (d, *J* = 5 Hz, 1H), 5.77 (dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 1H), 5.68 (d, *J* = 2.5 Hz, 1H),3.78 (brs, 1H), 3.60-3.56 (m, 3H), 3.23 (brs, 1H), 3.10-3.03 (m, 2H), 2.76 (brs, 2H), 2.48-2.42 (m, 1H), 2.37 (m, 1H), 2.19(m, 1H), 2.08-1.52 (m, 24H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 139.3, 137.4, 136.7, 136.1, 135.7, 132.1, 131.5, 129.1, 128.3, 127.5, 127.3, 126.6, 121.6, 120.6, 118.9, 116.5, 115.6, 109.2, 49.7, 49.4, 43.2, 39.5, 39.2, 38.7, 38.5, 37.4, 34.9, 34.3, 30.9, 30.8, 28.4.

HRMS (ESI): Calcd for $C_{45}H_{49}N$: 603.38650; Found: 603.38596.

Compound 37gc

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34g** (30 mg, 0.15 mmol), indole **12c** (31 mg, 0.10 mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the mixture of products **35gc**, **36gc** and **37gc**. The product **37gc** (colourless viscous liquid, 10 mg, 12%) was separated and purified by HPLC.



R_f : 0.62 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3378, 3058, 2978, 2908, 1580, 1467, 1445, 1022, 745 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.89 (brs, 1H), 7.74 (d, *J* = 8 Hz, 1H), 7.54-7.53 (m, 2H), 7.41-7.38 (m, 2H), 7.32-7.25 (m, 2H), 7.14-7.13 (m, 1H), 7.01-7.00 (m, 1H), 6.45-6.44 (m, 1H), 6.37-6.36 (m, 1H), 6.29-6.28 (m, 1H), 5.91-5.89 (m, 1H), 5.56-5.52 (m, 2H), 3.90 (brs, 1H), 3.27-3.26 (m,1H), 3.03 (brs, 1H) 2.79 (brs, 1H), 2.74 (brs, 1H), 2.67 (brs, 2H), 2.48-2.45 (m, 3H), 2.33 (brs, 1H), 2.06 (brs, 1H), 2.01-1.95 (m, 8H), 1.90-1.77 (m, 18H), 1.75-1.69 (m, 5H), 1.68-1.63 (m, 2H), 1.61 (brs, 1H), 1.40-1.25 (m, 2H), 0.52-0.46 (m, 1H).

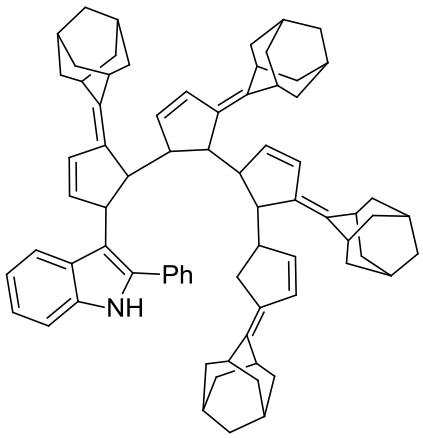
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 139.4, 137.9, 137.8, 136.5, 136.2, 136.1, 136.0, 135.9, 134.2, 133.5, 133.4, 132.4, 131.3, 131.2, 128.9, 128.1, 127.3, 122.0, 121.4, 119.2, 116.5, 110.7, 51.3, 50.7, 48.8, 45.4, 42.9, 39.8, 39.7, 39.6, 39.5, 39.4, 39.2, 39.1, 39.0, 38.7, 38.6, 38.5, 38.0, 37.4, 37.2, 35.1, 35.0, 34.9, 34.6, 34.4, 34.1.

HRMS (ESI): Calcd for $C_{59}H_{65}N$: 787.51170; Found: 787.51126.

Compound 38gc

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34g** (30 mg, 0.15 mmol), indole **12c** (31 mg, 0.10

mmol) and $Cu(OTf)_2$ (1 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature for 2 hours gave the mixture of products **35gc**, **36gc**, **37gc** and **38gc**. The product **38gc** (colourless viscous liquid, 6 mg, 8%) was separated and purified by HPLC.



R_f : 0.48 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3212, 3028, 1673, 1584, 1452, 1300, 1248, 1181, 1104, 874, 742, 691 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.89 (brs, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.43-7.42 (m, 2H), 7.34-7.23 (m, 4H), 7.08-7.07 (m, 1H), 6.93-6.92 (m, 1H), 6.40 (brs, 1H), 6.21-6.16 (m, 3H), 5.85 (t, *J* = 2.5 Hz, 1H), 5.46-5.31 (m, 3H), 3.91 (brs, 1H), 2.99-2.41 (m,15H), 1.84-1.18 (m, 46H), 0.81-0.88 (m, 3H).

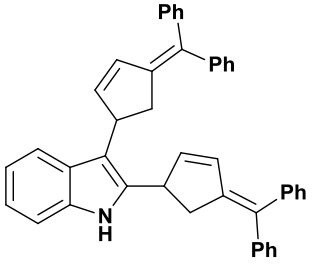
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 136.1, 136.0, 132.4, 130.9, 128.8, 128.7, 127.6, 122.0, 121.4, 119.0, 110.5, 48.6, 46.7, 45.5, 39.9, 39.6, 39.5, 39.2, 39.1, 38.9, 38.8, 38.7, 38.5, 37.5, 37.4, 35.1, 35.0, 34.8, 34.6, 34.4, 34.3, 31.9, 31.1, 29.7, 28.6, 28.5, 28.2, 28.1.

HRMS (ESI): Calcd for $C_{74}H_{83}NNa$: 1008.64232; Found: 1008.64163.

2,3-bis(4-(diphenylmethylene)cyclopent-2-enyl)-1H-indole (35aaa)

Following general procedure for the Lewis acid catalyzed hydroarylation of pentafulvene. The pentafulvene **34a** (30 mg, 0.13 mmol), indole **12a** (30 mg, 0.26 mmol) and $Cu(OTf)_2$ (2 mg, 0.006 mmol), in 2 mL acetonitrile at room temperature for 12 hours gave the product **35aaa** (34 mg, 45%) as pale yellow coloured foam. (or) A mixture of compound **35aa** (1.0 eqiuv.), fulvene **34a** (1.0 equiv.) and $Cu(OTf)_2$ (2

mol %) were weighed in a reaction tube, CH_3CN (2 mL) was added and allowed to stir at room temperature for 12 hours. The solvent was evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography yielded the product **35aaa** (26 mg, 35%) as pale yellow coloured foam.



R_f : 0.58 (hexane/ethyl acetate = 4:1).

IR (Neat) ν_{max}: 3294, 2857, 2366, 2335, 1647, 1590, 1369, 942, 887, 702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.69 (brs, 1H), 7.54 (d, *J* = 7.5 Hz 1H), 7.33-7.29 (m, 4H), 7.26-7.15 (m, 17H), 7.12-7.00 (m, 2H), 6.62-6.61 (m, 1H), 6.55-6.54 (m, 1H), 6.25-6.21 (m, 1H), 6.17-6.13 (m, 1H), 4.48-4.47 (m, 1H), 4.41-4.40 (m, 1H), 3.13-3.08 (m, 2H), 2.96-2.92 (m, 1H), 2.81-2.77 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 145.1, 143.2, 142.5, 142.4, 138.7, 138.6, 136.4, 135.5, 135.4, 133.9, 133.3, 133.2, 132.2, 130.2, 130.1, 129.4, 129.3, 128.1, 128.0, 127.9, 127.7, 126.8, 126.7, 126.5, 126.3, 121.5, 119.4, 119.3, 119.2, 113.3, 110.5, 41.9, 41.5, 40.2, 39.6.

HRMS (ESI): Calcd for $C_{44}H_{35}Na$: 600.26672; Found: 600.26609.

2.9. Reference

1 F. Kakiuchi and S. Murai, *Acc. Chem. Res.*, 2002, **35**, 826–834.

2 K. L. Tan, S. Park, J. A. Ellman and R. G. Bergman, *J. Org. Chem.*, 2004, **69**, 7329–7335.

3 R. K. Thalji, K. A. Ahrendt, R. G. Bergman and J. A. Ellman, *J. Org. Chem.*, 2005, **70**, 6775–6781.

4 M.-Z. Wang, M.-K. Wong and C.-M. Che, *Chem. - Eur. J.*, 2008, **14**, 8353–8364.

5 Y. Matsuda, S. Naoe, S. Oishi, N. Fujii and H. Ohno, *Chem. - Eur. J.*, 2015, **21**, 1463–1467.

6 C. Jia, D. Piao, J. Oyadama, W. Lu, K. Tsugio and Y. Fujiwara, *Science*, 2000, **287**, 1992–1995.

7 S. Liu and J. S. Zhou, *Chem. Commun.*, 2013, **49**, 11758–60.

8 T. A. Davis, T. K. Hyster and T. Rovis, *Angew. Chem. Int. Ed.*, 2013, **52**, 14181–14185.

9 C. Liu, X. Han, X. Wang and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2004, **126**, 3700–3701.

10 S. W. Youn, S. J. Pastine and D. Sames, *Org. Lett.*, 2004, **6**, 581–584.

11 G. Bhalla, J. Oxgaard, W. A. Goddard and R. A. Periana, *Organometallics*, 2005, **24**, 3229–3232.

12 Y. Nakao, K. S. Kanyiva, S. Oda and T. Hiyama, *J. Am. Chem. Soc.*, 2006, **128**, 8146–8147.

13 R. Beaud, R. Guillot, C. Kouklovsky and G. Vincent, *Chem. - Eur. J.*, 2014, **20**, 7492–7500.

14 M. Rueping, B. J. Nachtsheim and W. Ieawsuwan, *Adv. Synth. Catal.*, 2006, **348**, 1033–1037.

15 M. Rueping, B. J. Nachtsheim and T. Scheidt, *Org. Lett.*, 2006, **8**, 3717–3719.

16 M.-Z. Wang, C.-Y. Zhou, Z. Guo, E. L.-M. Wong, M.-K. Wong and C.-M. Che, *Chem. Asian J.*, 2011, **6**, 812–824.

17 Y. Ebe and T. Nishimura, *J. Am. Chem. Soc.*, 2015, **137**, 5899–5902.

18 J. Park, S.-Y. Kim, J.-E. Kim and C.-G. Cho, *Org. Lett.*, 2014, **16**, 178–181.

19 N. T. Patil, V. S. Raut, R. D. Kavthe, V. V. N. Reddy and P. V. K. Raju, *Tetrahedron Lett.*, 2009, **50**, 6576–6579.

20 J. Kischel, I. Jovel, K. Mertins, A. Zapf and M. Beller, *Org. Lett.*, 2006, **8**, 19–22.

21 Y. Nakao, S. Oda and T. Hiyama, *J. Am. Chem. Soc.*, 2004, **126**, 13904–13905.

22 X. Han and R. A. Widenhoefer, *Org. Lett.*, 2006, **8**, 3801–3804.

23 K. Imafuku and K. Arai, *Synthesi.*, 1989, **7**, 501–505.

24 N. Vijay, S. Kumar, G. Anilkumar and J. Somarajan Nair, *Tetrahedron*, 1995, **51**, 9155–9166.

25 N. Vijay, C. N. Jayan, K. V. Radhakrishnan, G. Anilkumar and N. P. Rath, *Tetrahedron*, 2001, **57**, 5807–5813.

26 Z.-L. He and C.-J. Wang, *Chem. Commun.*, 2015, **51**, 534–536.

27 G. Erker, *Coord. Chem. Rev.*, 2006, **250**, 1056–1070.

28 J. Barluenga, S. Martiínez, A. L. Suárez-Sobrino and M. Tomás, *J. Organomet. Chem.*, 2005, **690**, 5696–5700.

29 J. Joseph, F. Jaroschik, D. Harakat, K. V. Radhakrishnan, J.-L. Vasse and J. Szymoniak, *Chem. - Eur. J.*, 2014, **20**, 5433–5438.

30 J. Joseph, F. Jaroschik, K. V Radhakrishnan, J.-L. Vasse and J. Szymoniak, *Chem. Commun.*, 2013, **49**, 4549–51.

31 G. Zbang and M. Neuenschwander, *Helv. Chem. Acta*, 1995, **78**, 1091–1105.

32 G. A. Olah, G. K. S. Prakash and G. Liang, *J. Org. Chem.*, 1977, **42**, 661–666.

33 C. Rentsch, M. Slongo, S. Schönholzer and M. Neuenschwander, *Makromol. Chem*, 1980, **181**, 19–29.

34 M. Slongo, S. Schönholzer, C. Rentsch and M. Neuenschwander, *Makromol. Chem*, 1980, **181**, 31–36.

35 S. Schönholzer, M. Slongo, C. Rentsch and M. Neuenschwander, *Makromol. Chem*, 1980, **181**, 37–45.

36 M. Neuenschwander, M. Doris and H. Schaltegger, *Helv. Chem. Acta*, 1963, **6**, 1760–1765.

CHAPTER 3

Lewis acid catalyzed C-3 alkylidenecyclopentenylation of indoles by using fulvene derived azabicyclic olefins: An easy access to functionalized indoles and bis-indoles

3.1. Introduction

The substituted indole nucleus is a structural component of a vast number of biologically active natural and unnatural compounds.[1] A careful inspection of a notable array of indole containing compounds evidences the tryptamine backbone as a common recognizable motif in the whole molecular structure.[2] Tryptamine derivatives such as Serotonin, Melatonin etc. are used as drugs for treating 5HT receptor related disorders.[3,4] Similar to triptamine derivatives, bis-indole analogues such as Violacein,[5] Staurosporine[6] and Rebeccamycin[7] have also received much attention due to its diverse biological activities (Figure 1).[8] In line with the search for such novel indole scaffolds, we have developed a Lewis acid catalyzed synthetic strategy towards alkylidenecyclopentene functionalized indoles and bis-indoles using fulvene derived azabicyclic olefins and is described in the present chapter. Before going into the details, a brief introduction of indole functionalization is presented in the following section.

3.2. Functionalization of indoles

Owing to the great prevalence of indole nucleus, enormous research efforts have been devoted towards the synthesis and functionalization of this privileged heterocycle. Indole serves as an ambient nucleophile; the selective targeting of C-H

bonds in the presence of a reactive N-H functionality represents a challenging goal in indole functionalization. The selective alkylation at C-2 or C-3 position will be complementary to the known N-alkylation methodology and holds significant synthetic potential. The derivatization of indoles are most efficiently achieved by Friedel-Crafts reaction or by using 2- or 3-haloindoles to couple with alkenes, alkynes, organostannanes, organozincs and aryl boronic acids etc.[9] Various synthetic methodologies involving Lewis acids, Brønsted acids, organocatalysts or transition metal catalysts have been developed for the selective C-3 functionalization of indoles.

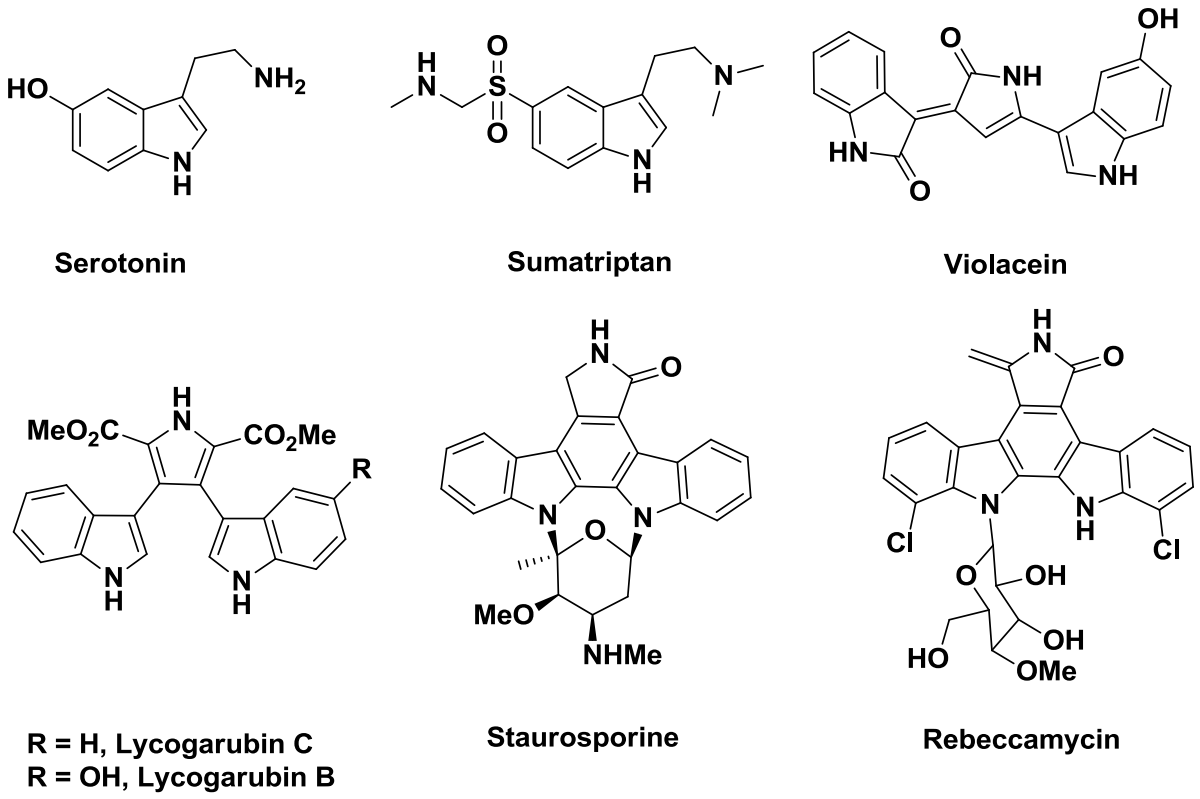


Figure 3.1 Bioactive compounds with indole or bisindole scaffolds

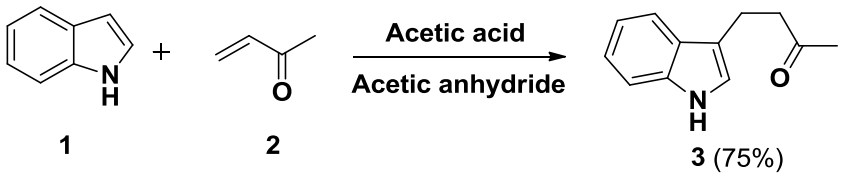
3.2.1. Alkylation of indoles

The addition of aromatic C-H bonds to alkenes leading to the formation of a new C-C bond is of considerable interest and remains as a long-term challenge for

chemists. Such a reaction would provide a simple and attractive method for the formation of aryl substituted compounds from easily available starting materials. The acid promoted addition of indoles to electron deficient alkenes comes under this category. The following section describes the alkylation of indoles with various alkylating agents.

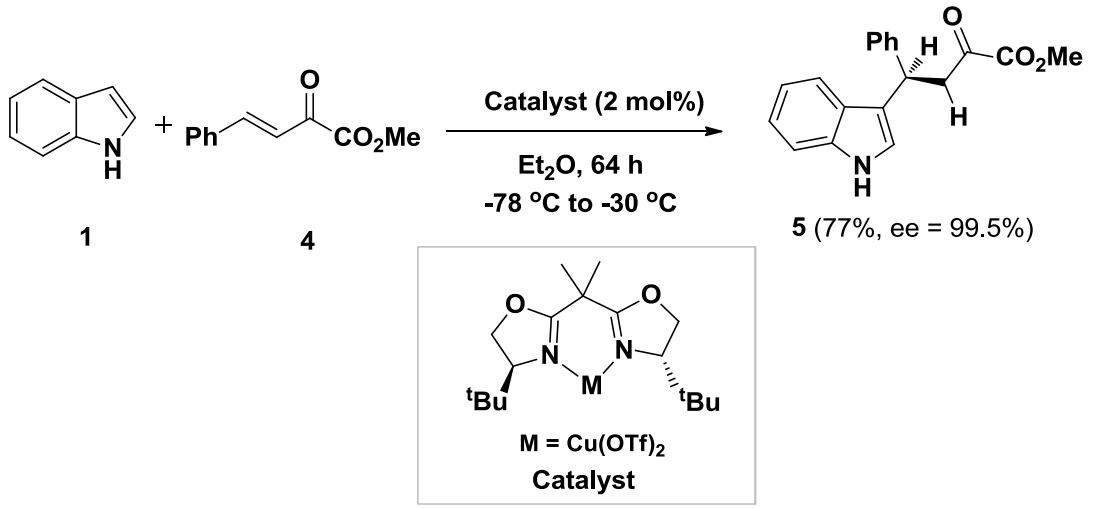
3.2.2. Conjugate addition of indoles

The acid catalysed addition of indole to α,β–unsaturated ketones,[10] β,γ-unsaturated-α-ketoesters,[11] acyl phosphonates,[12] alkylidene malonates,[13] α-hydroxyenones,[14] 2-acyl imidazoles,[15] nitroalkenes[16] and other acyl heterocycle compounds are also well known in literature. In 1957, Szmuszkovicz described the conjugate addition of indole to methyl vinyl ketone (MVK). The reaction afforded 75% of the addition product **3** (Scheme 3.1).[17]



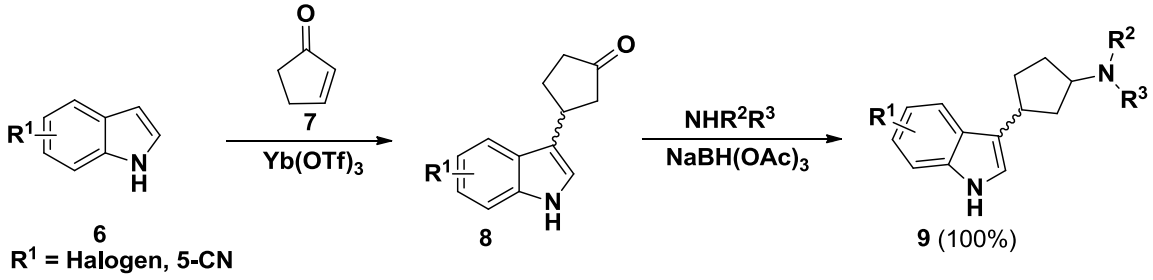
Scheme 3.1

Jørgenson *et al.* reported the first catalytic highly enantioselective Friedel-Crafts alkylation reaction of indoles with β,γ-unsaturated-α-ketoesters using chiral bisoxazoline copper (II) complexes (Scheme 3.2).[11]



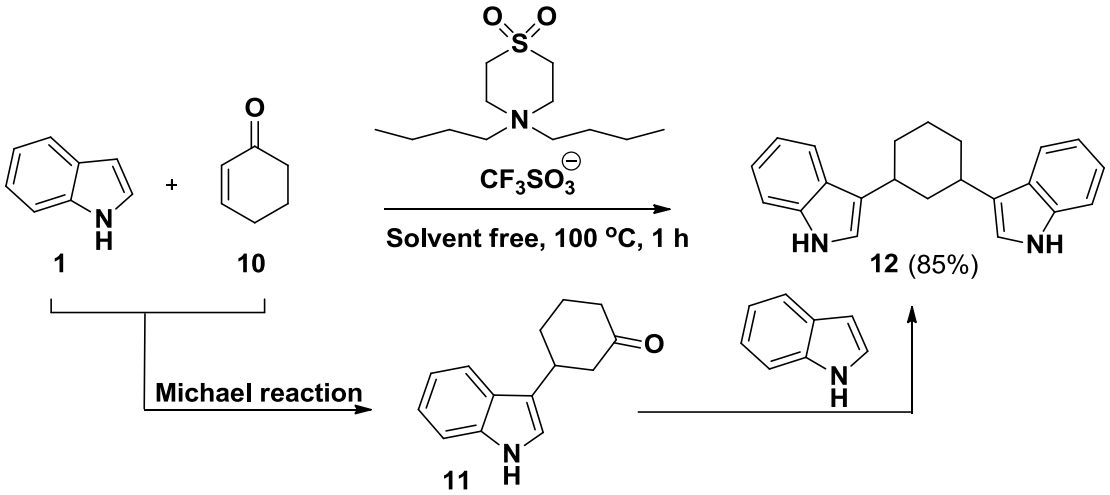
Scheme 3.2

In 2010, King and co-workers explored the Lewis acid catalyzed Michael addition of indole to cyclopent-2-enone for the preparation of 3-*cis*-(3-aminocyclopentenyl) indoles, which serve as potent inhibitors of hSERT (Scheme 3.3).[4]



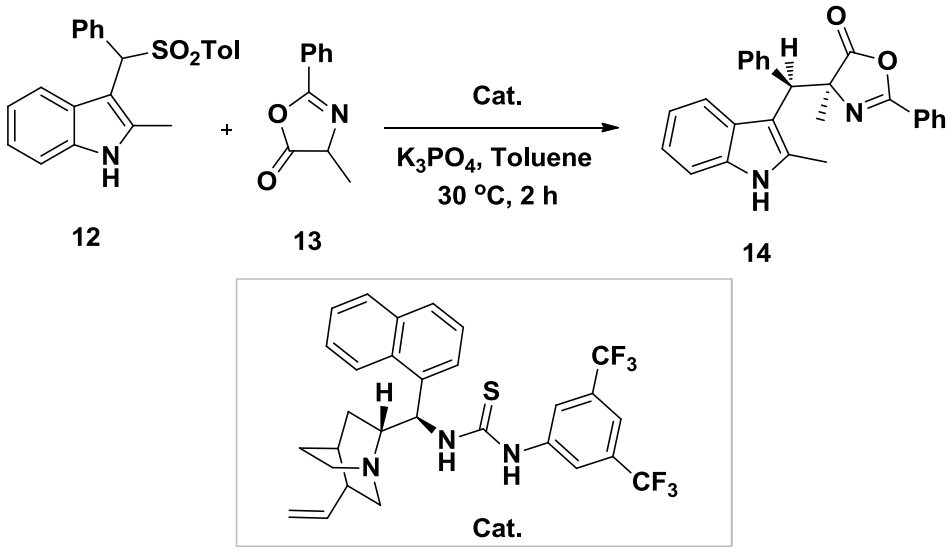
Scheme 3.3

Very recently, Yanlong Gu and co-workers synthesized C-3 cycloalkylated indoles through its reductive alkylation with cyclic ketone using a sulfonyl-functionalized Brønsted acid ionic liquid as a catalyst (Scheme 3.4).[18]



Scheme 3.4

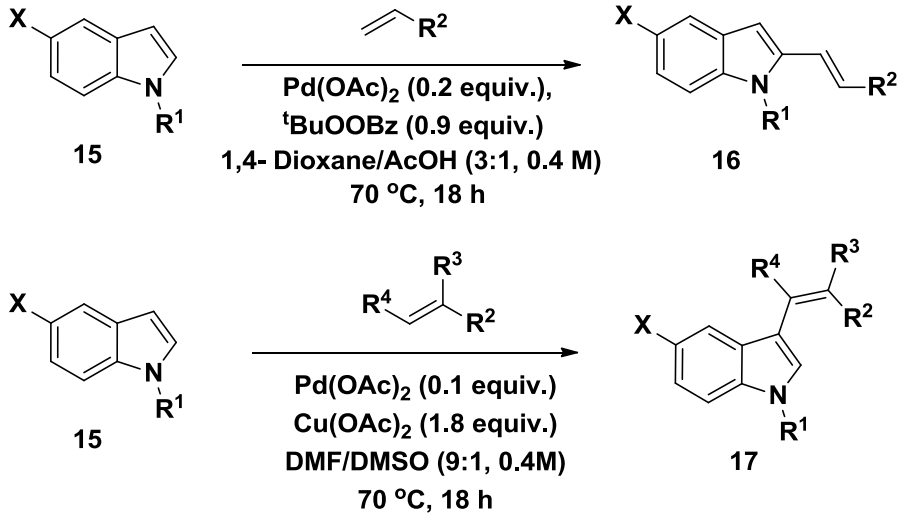
Jing and co-workers developed a thiourea based organocatalyst for the stereoselective Michael addition reaction of oxazolones to vinylogous imine intermediates generated *in situ* from arylsulfonyl indoles.[19] The reaction of arylsulfonyl indole **12** and oxazolone **13** in presence of cinchona alkaloid derived thiourea catalysts afforded the corresponding product **14** with 63% yield and 97% ee (Scheme 3.5).



Scheme 3.5

3.2.3. Alkenylation of indoles by palladium catalysis

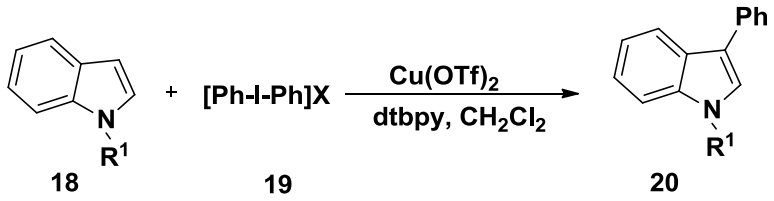
The natural reactivity of indole suggested that palladation and Heck coupling would take place preferentially at the C-3 position of indole. But in 2005, Gaunt *et al.* have unraveled a new switchable solvent-controlled regioselective palladium catalyzed indole alkenylation on both C-2 and C-3 position of indole by C-H functionalization (Scheme 3.6).[20]



Scheme 3.6

3.2.4. Arylation of indoles with diaryl-iodine (III) reagents

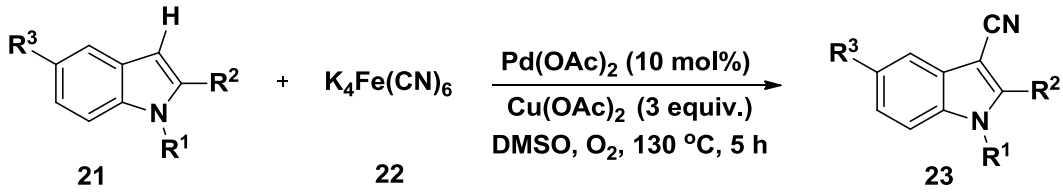
In 2008, the same group developed a Cu(II)-catalyzed C-H bond arylation strategy that enables direct and site-selective indole functionalization with phenyl group.[21] They proposed that Cu(I) catalyst undergo oxidation with diaryl-iodine(III) reagents to form a highly electrophilic aryl-Cu(III) intermediate which would enable the mild arylation process (Scheme 3.7).



Scheme 3.7

3.2.5. Cyanation of indoles with $K_4[Fe(CN)_6]$

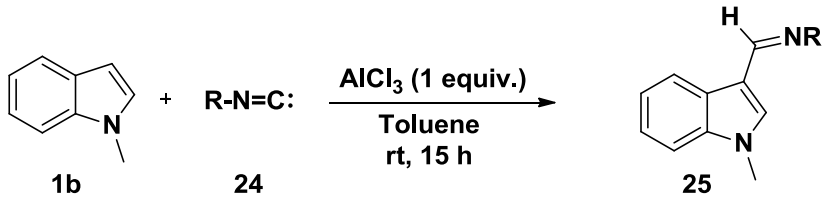
The first regio-selective cyanation of indoles through a Pd-catalyzed direct C-H bond functionalization was reported in 2010.[22] The reaction uses safe and nontoxic $K_4[Fe(CN)_6]$ as cyanating agent and selectively introduces a cyano group into the 3-position of indoles with high efficiency (Scheme 3.8).



Scheme 3.8

3.2.6. Reductive imination of indoles with isocyanides

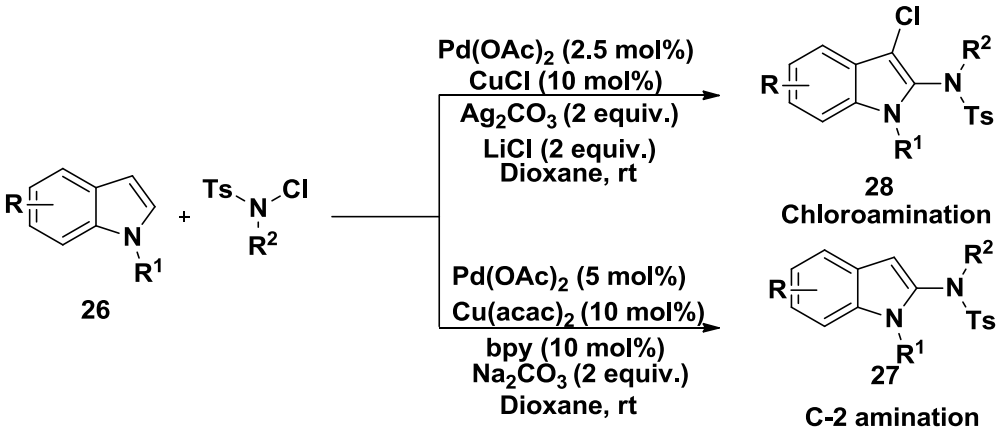
In 2007, Chatani developed an imine synthesis by a Lewis acid promoted insertion of isocyanides into C-H bonds of electron-rich aromatic compounds (Scheme 3.9).[23]



Scheme 3.9

3.2.7. Chloroamination of indoles with chlorosulfonamides

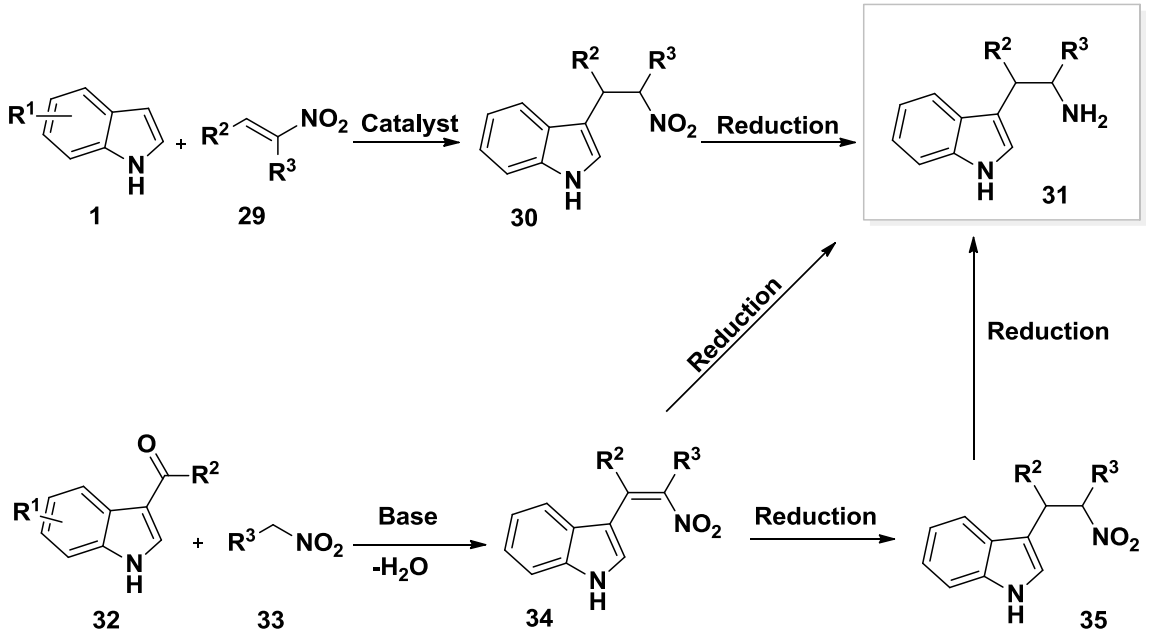
As a complementary methodology of Buchwald- Hartwig coupling, Yuan Liu reported a palladium/copper catalyzed intermolecular direct C-H amination and chloroamination of indoles using chlorosulfonamides as the nitrogen source (Scheme 3.9).[24]



Scheme 3.10

3.2.8. Towards triptans: Reaction of indole with nitroalkenes

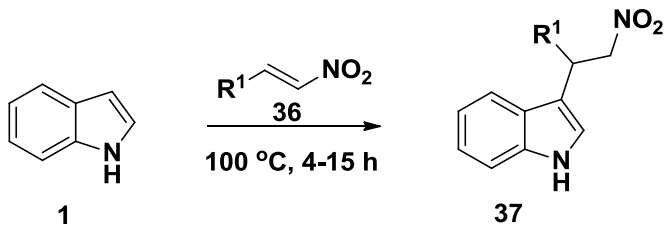
The literature reports are scanty for the direct and selective installation of an aminoalkyl moiety on indole ring, toward the synthesis of triptans (triptamine derivatives). Alternatively, it is possible to use the reactants bearing nitrogen atoms (nitroalkanes or nitroalkenes) for the nitoralkylation of indoles. A subsequent reduction of the nitro group after the addition reaction ensures an efficient entry to tryptans (Scheme 3.11).[2]



Scheme 3.11

3.2.8.1. Uncatalyzed Friedel-Crafts reaction

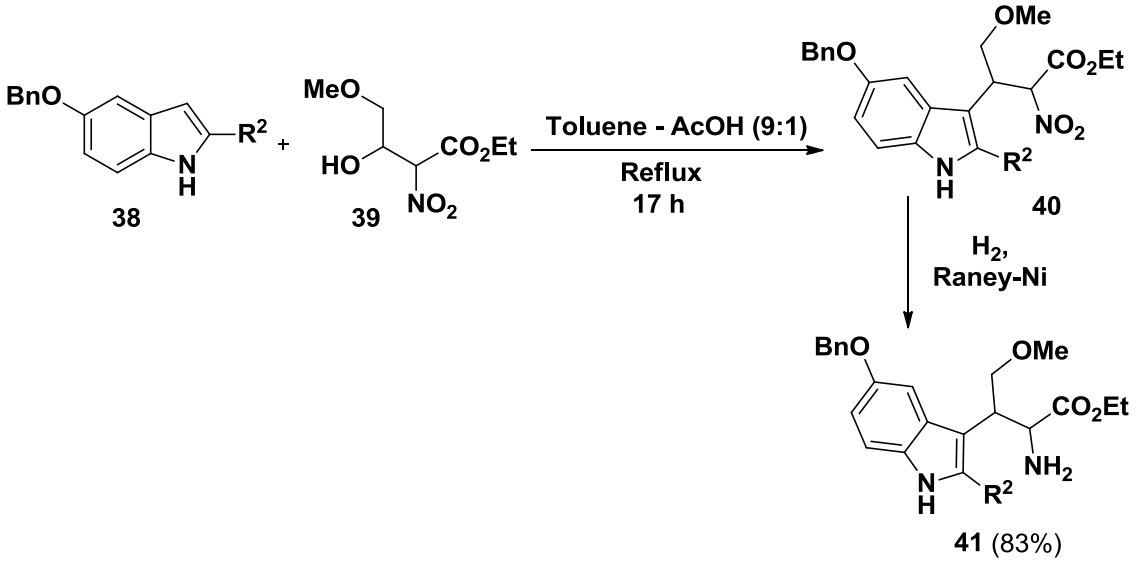
Ching-Fa Yao established a mild, green and easy procedure for conjugative addition of indole to *β*-nitrostyrenes in aqueous medium at elevated temperature without any catalyst. Here, the simple heating of reaction mixture is often enough to provide the successful reaction of indoles with electron-withdrawing nitroalkenes (Scheme 3.12).[25]



Scheme 3.12

3.2.8.2. Brønsted acid catalyzed Friedel-Crafts reaction

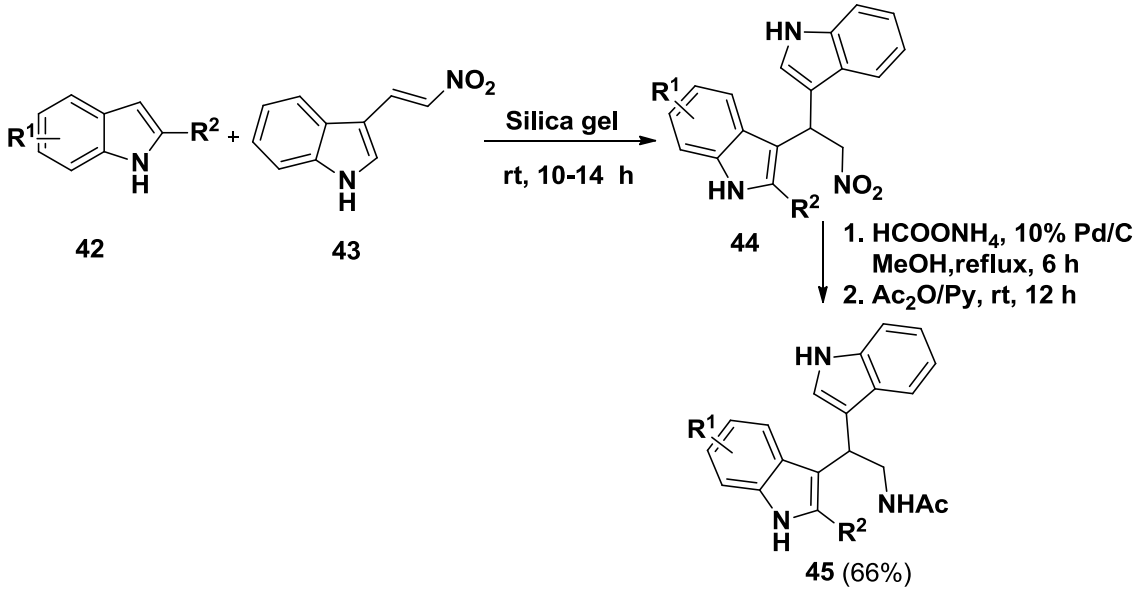
Nitro alcohol **39** reacts with 5-(benzyloxy)-1H-indole **38** in a solvent mixture of toluene-acetic acid (9:1) at reflux condition affording the nitroester **40**, which can be reduced to the tryptophan derivative **41** (Scheme 3.13).[2]



Scheme 3.13

3.2.8.3. Lewis acid catalyzed Friedel-Crafts reactions

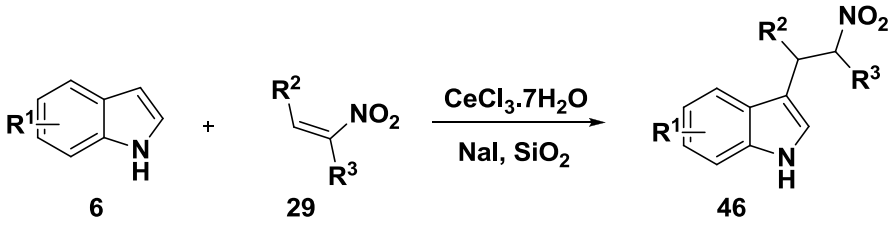
Interaction of nitroalkenes with Lewis acids is the most exploited way of activation in their reaction with indoles. Protonation of the nitro group at oxygen provides a notable enhancement of the electrophilic character of nitroalkenes.[26] This allows an effective Friedel-Craft reaction to occur even using weak acids as proton source. Unsymmetrical bisindolyl derivatives **45** can be readily obtained by reaction of indoles with 3-indolylnitroalkene **43** in the presence of silica gel (Scheme 3.14).[27]



42 43 44

Scheme 3.14

Similarly, the treatment of indole **6** with *trans*-*β*-nitrostyrene **29** in the presence of $CeCl_3.7H_2O$ and NaI supported on SiO_2 gives a heterogeneous mixture that affords the corresponding 2-indolyl-1-nitroalkane **46** in good yield (Scheme 3.15).[28]



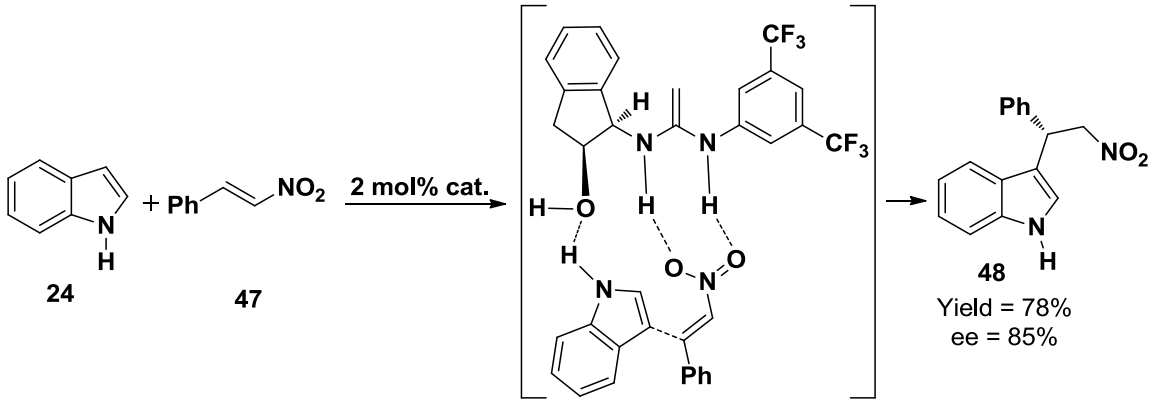
6 29 46

Scheme 3.15

3.2.8.4. Organocatalyzed Friedel-Crafts reactions

Organocatalyzed reactions involving nitro derivatives are mainly based on hydrogen bonding interactions established between the nitro oxygen and acidic hydrogen atoms linked to the catalyst. Thioureas are generally more effective than other organocatalysts in the reaction of indoles with nitroalkenes because of the superior acidity of the N-H bonds in this sulfur containing compounds. In 2005, Ricci

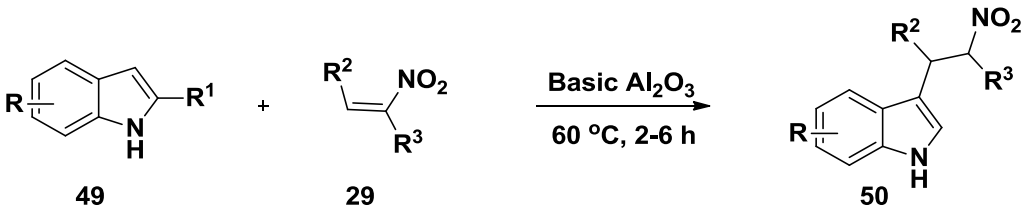
and co-workers have achieved thiourea based organo catalysis for the enantioselective Friedel-Crafts alkylation of indoles with nitroalkenes. The reaction provided optically active 2-indolyl-1-nitro derivatives **48** in fairly good yields and enantioselectivities (Scheme 3.16).[29]



Scheme 3.16

3.2.8.5. Base promoted conjugate addition of indoles to nitroalkenes

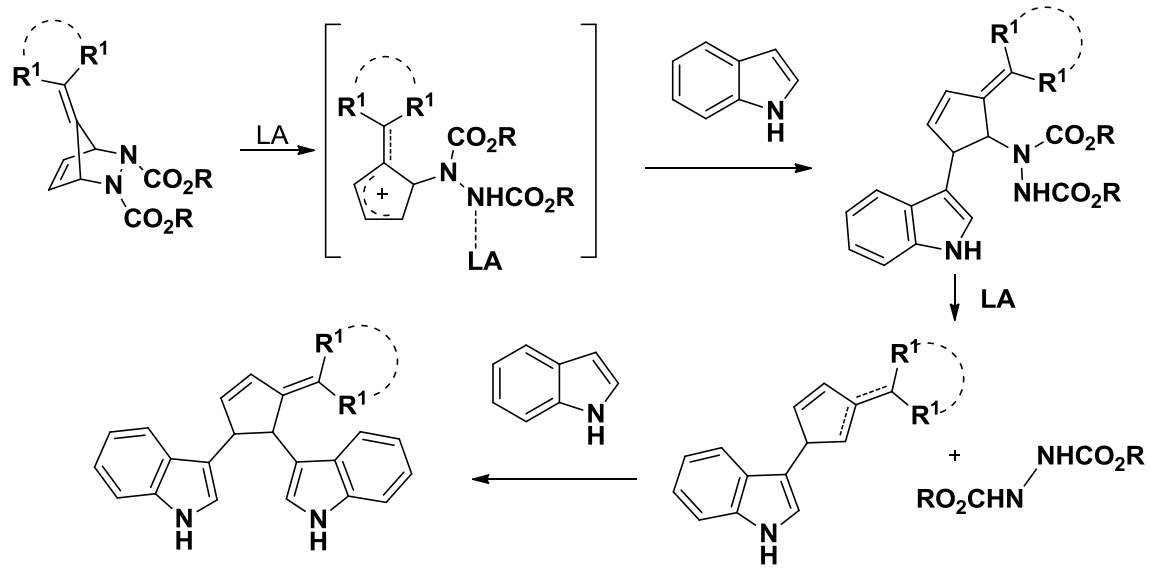
The majority of the processes involving reaction of indoles with nitroalkenes are based on the Friedel-Crafts reaction which is generally carried out under neutral or acidic conditions. However, the enhanced acidity of the indole N-H bond, which closely resembles that of an alcohol, can be suitably exploited in order to generate the corresponding indolyl anion upon reaction with basic reagents. More recently, basic alumina has been used as indole activator and solid support for the conjugate addition to nitroalkenes under solvent free conditions (Scheme 3.17).[30]



Scheme 3.17

3.3. Statement of the problem

One of the ultimate goals and challenges in synthetic organic chemistry is to develop novel and efficient strategies for the creation of suitably functionalized molecules. It is evident from the literature that the Lewis acid catalyzed selective functionalization of indoles has great potential to achieve biologically and pharmaceutically relevant targets. In this context, we wish to demonstrate a Lewis acid catalyzed C-3 alkylidenecyclopentenylation of indoles towards the synthesis of functionalized indoles and bisindoles using pentafulvene derived bicyclic hydrazines. The results of the detailed investigation of trapping the Lewis acid generated allylic carbocation derived from pentafulvene derived azabicyclic olefins and its subsequent transformation to bisindole analogues (Schme 3.18) are presented in the following sections.

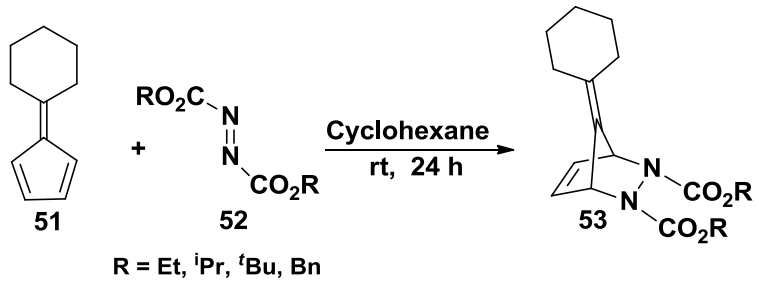


Scheme 3.18

3.4. Results and discussion

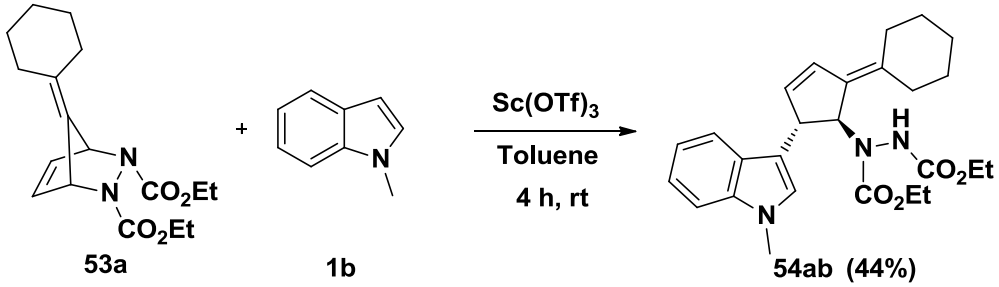
The azabicyclic olefins required for our investigations were prepared following the literature procedures.[31] For example, the 2,3-diazabicyclo[2.2.1]hept-5-ene **53** was

synthesized by the Diels-Alder cycloaddition of pentafulvene **51** with dialkyl azodicarboxylate **52** (Scheme 3.19).



Scheme 3.19

We initiated our investigation by the treatment of pentafulvene derived diazabicyclic olefin **53a** (1.2 equiv.) with *N*-methyl indole **1b** (1 equiv.) in the presence of $Sc(OTf)_3$ (2 mol%) in toluene at room temperature. After 4 hour, the reaction afforded desired *trans*-3,4 disubstituted alkylidenecyclopentene derivative **54ab** in 44% yield (Scheme 3.20).



Scheme 3.20

The structure of **54ab** was established by IR, NMR and Mass Spectrometry. In the IR spectrum, the signal at 1710 cm^{-1} was diagnostic of the carbethoxy group, whereas the NH absorption was discernible at 3323 cm^{-1}.

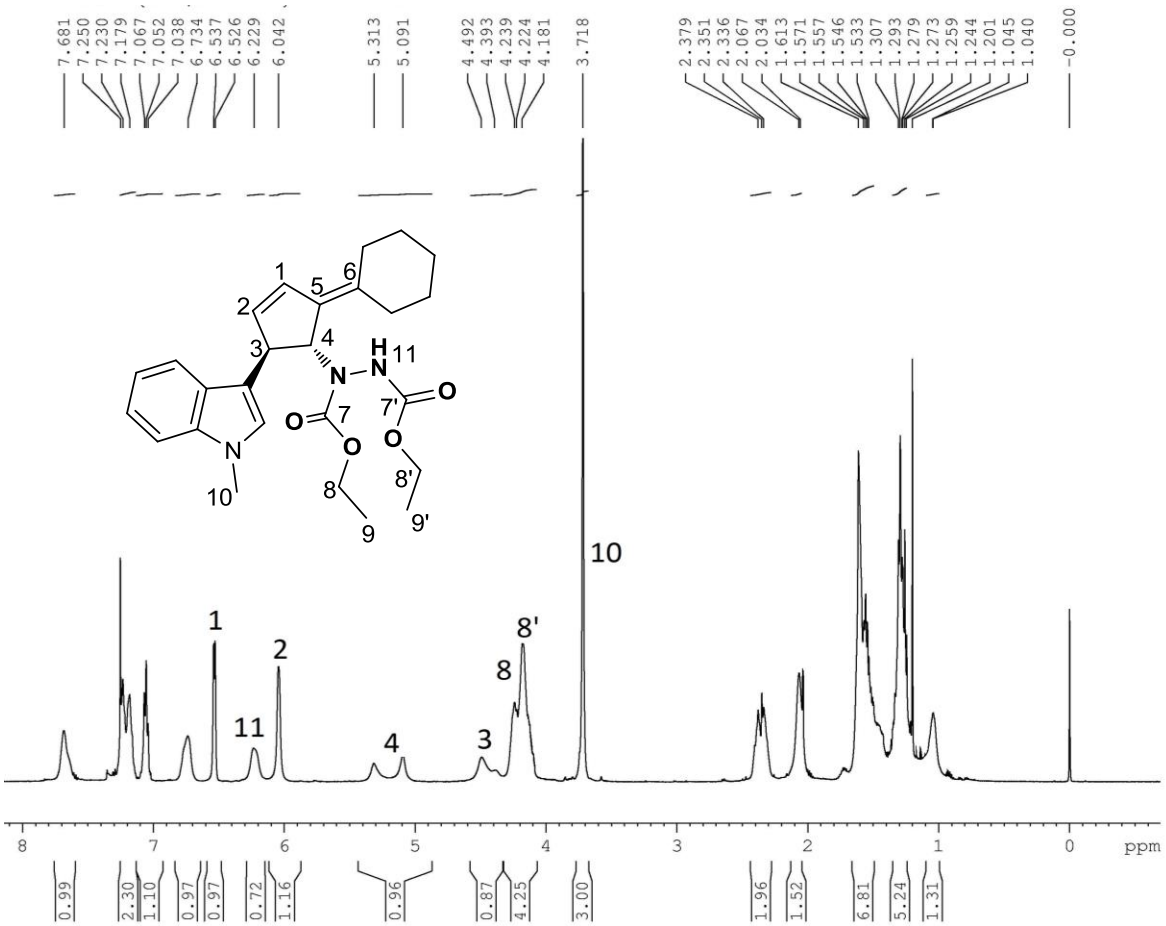


Figure 3.2. ^{1}H NMR spectrum of compound **54ab**

In the ^{1}H NMR spectrum (Figure 3.2), the two ring olefinic protons were observed as a doublet at δ 6.53 ppm and a broad singlet at δ 6.04 ppm respectively. A broad peak at δ 6.23 ppm represents the NH proton presented in the hydrazinyl moiety. The multiplet in the region δ 5.31-5.09 ppm was assigned as the proton on the carbon (C-4) which is attached to the hydrazine moiety. The proton on the carbon (C-3) carrying the indole moiety appeared as a multiplet in the region δ 4.49-4.39 ppm. The methylene protons (C-8 and C-8') of carbethoxy group appeared in the range δ 4.24-4.18 ppm as multiplet. The singlet resonating at δ 3.72 ppm was indicative of protons on N-CH_3.

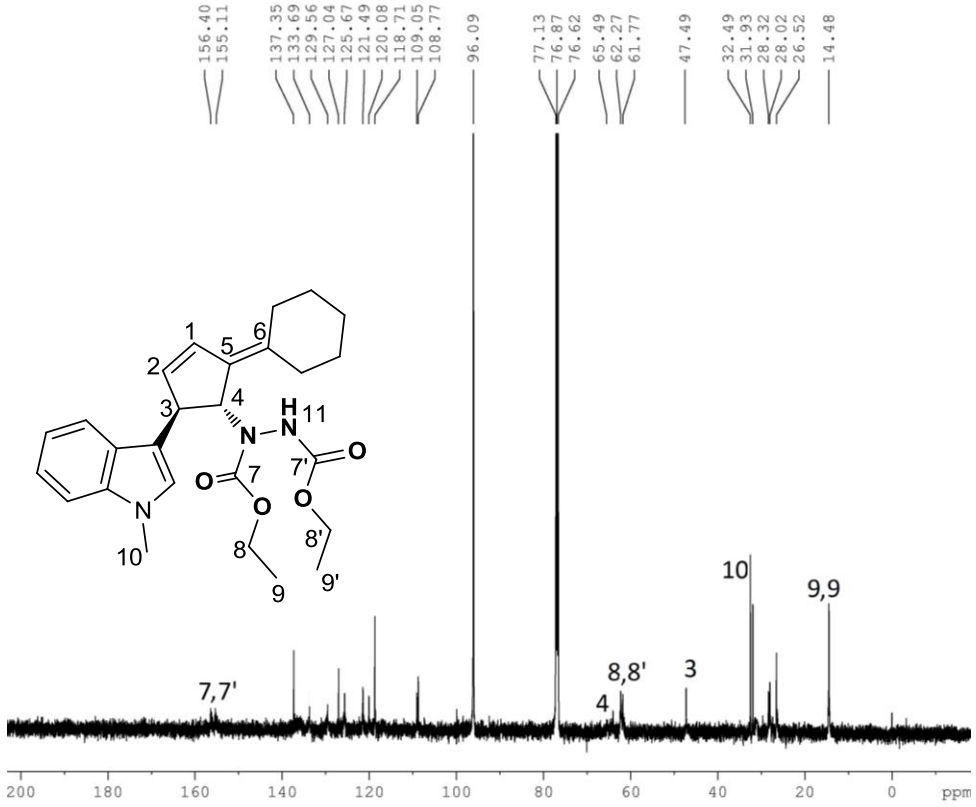


Figure 3.3. ^{13}C NMR spectrum of compound **54ab**

^{13}C NMR spectrum of **54ab** (Figure 3.3) positioned the two carbonyl peaks at δ 156.4 ppm and δ 155.1 ppm, while the signal due to methylene carbons of the carboethoxy groups appeared at δ 62.3 and 61.8 ppm. The C-4 and C-3 carbons were observed at δ 65.5 and 47.5 ppm respectively. The signal at δ 32.5 ppm was characteristic of the N-CH_3 carbon. The signals due to methyl carbons of carbethoxy group appeared at δ 14.5. All other signals were in good agreement with the proposed structure.

The high resolution mass spectral analysis of **54ab** showed the molecular ion peak at *m/z* = 474.23764 (M+ Na). The structure and stereochemistry of the product was unambiguously established by single crystal X-ray analysis of a similar compound **54eb** (Figure 3.4).

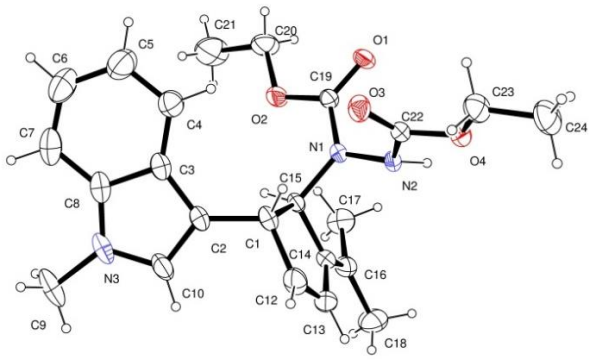
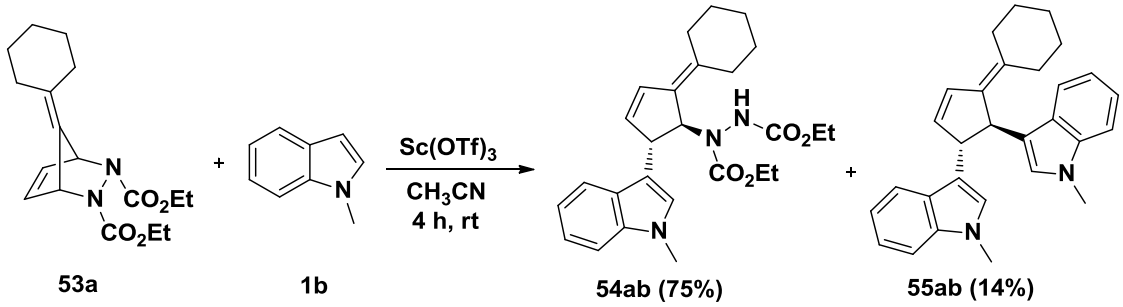


Figure 3.4. ORTEP plot of compound **54eb**

In order to develop a suitable catalytic system for this transformation, we undertook an optimization study using different Lewis acids and solvents, the details are given in Table 2.1. Interestingly, when we carried out the reaction in acetonitrile the reaction afforded a new product **55ab** along with the expected product **54ab (**Scheme 3.21).

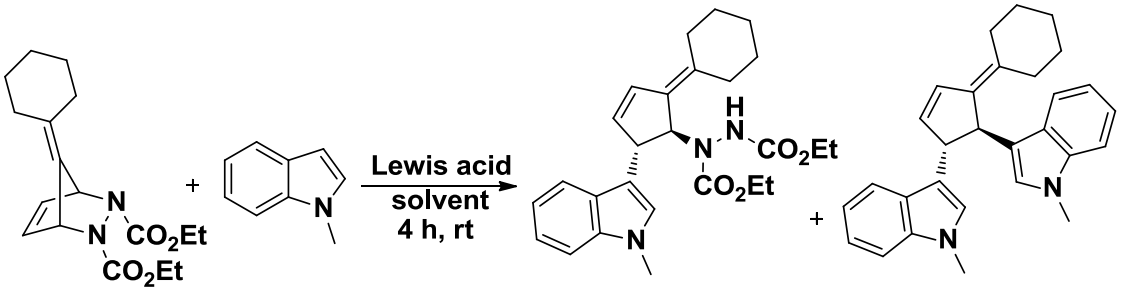


Scheme 3.21

Among the various Lewis acids used, $Sn(OTf)_2$ and $Fe(OTf)_3$ provided the product **54ab** in comparable yields. During optimization studies, we perceived that the change in equivalents of starting materials **53a** or **1b** played a crucial role in outcome of the reaction. Use of 2 equivalents of *N*-methyl indole resulted in the formation of bisindole product **55ab** (58% yield) in excess over **54ab** (31% yield) (Entry 16). Under optimal conditions (2 mol% $Sc(OTf)_3$ in CH_3CN), reaction could be tuned towards the formation of alkylidenecyclopentenyl derivative of indole **54ab** or

bisindole **55ab** by simply altering the equivalents of starting materials **53a** or **1b**.

Table 3.1 Optimization for a suitable catalyst system[a]



Entry	Lewis acid	Solvent	Yield (%)	
			54ab	55ab
1	$Sc(OTf)_3$	toluene	44	–
2	$Sc(OTf)_3$	DMF	38	–
3	$Sc(OTf)_3$	THF	30	–
4	$Sc(OTf)_3$	DCE	65	5
5	$Sc(OTf)_3$	DCM	58	trace
6	$Sc(OTf)_3$	CH_3CN	75	14
7	$Yb(OTf)_3$	CH_3CN	37	–
8	$Zn(OTf)_2$	CH_3CN	trace	–
9	$La(OTf)_3$	CH_3CN	35	–
10	$Cu(OTf)_2$	CH_3CN	46	–
11	$Sn(OTf)_2$	CH_3CN	70	8
12	$Fe(OTf)_3$	CH_3CN	62	6
13	AgOTf	CH_3CN	trace	–
14	$AlCl_3$	CH_3CN	53	trace
15	BF_3OEt_2	CH_3CN	36	–
16[b]	$Sc(OTf)_3$	CH_3CN	31	58

[a] Reaction Conditons: alkene (1.2 equiv.), *N*-Methylindole (1equiv.), catalyst (2 mol%), solvent (2 mL), at rt for 4 h.

[b] Reaction in presence of 1.0 eqiv. of alkene and 2 eqiv. of *N*-methylindole

The structure of **55ab** was assigned based on spectral analysis. In the ^1H NMR spectrum (Figure 3.5), the two ring olefinic protons were observed as doublet of

doublets at δ 6.71 (dd, J_1 = 5.5 Hz, J_2 = 1 Hz, 1H) and 5.97 ppm (dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 1H) respectively. The proton on carbon C-4, near to the exocyclic double bond was observed as a broad singlet at δ 4.26 ppm. The proton on the C-3 carbon appeared as a broad singlet at δ 4.11 ppm. The two sharp singlets at δ 3.77 and 3.74 ppm were indicative of two N-CH_3 protons.

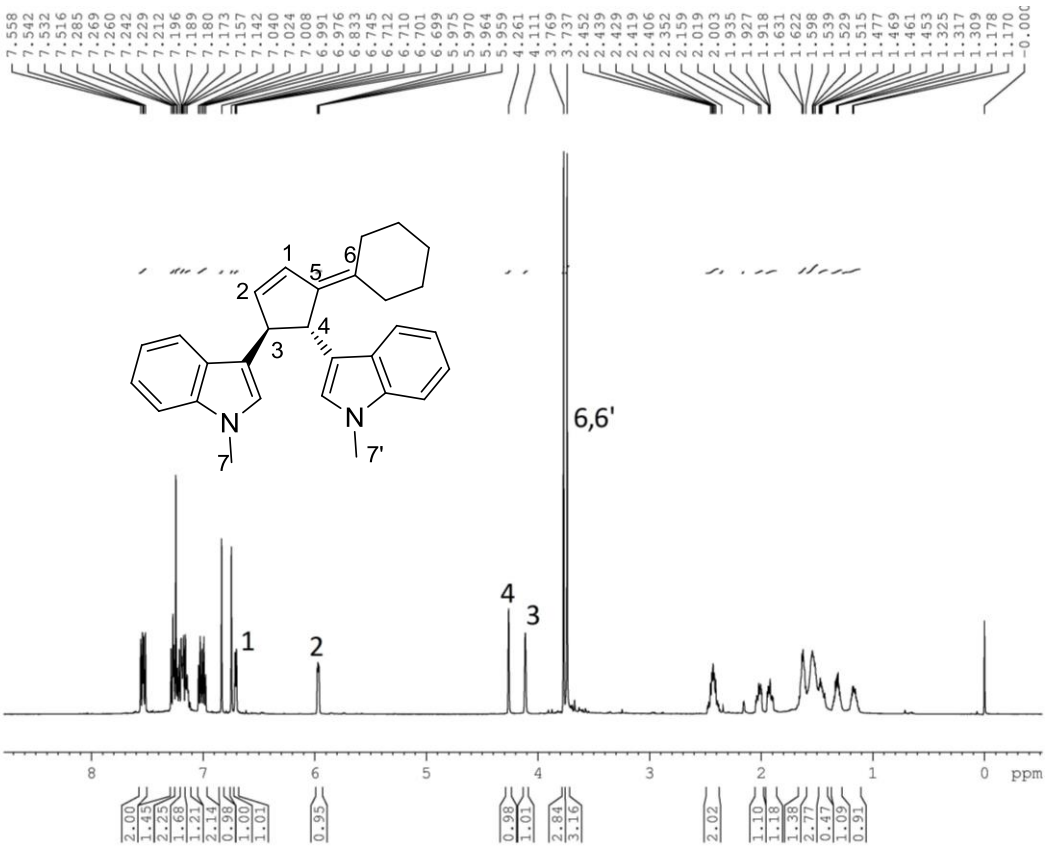


Figure 3.5. ^{1}H NMR spectrum of compound **55ab**

^{13}C NMR spectrum of **55ab** (Figure 3.6) shows two olefinic peaks at δ 136.1 and 129.0 ppm represents the carbons C-1 and C-2. The signal discernible at δ 52.3 characterizes C-4 carbon and the peak at δ 45.8 ppm was responsible for C-3 carbon atom. The signal due to the two N-CH_3 groups appeared at δ 32.6 ppm. All other signals were in good agreement with the proposed structure.

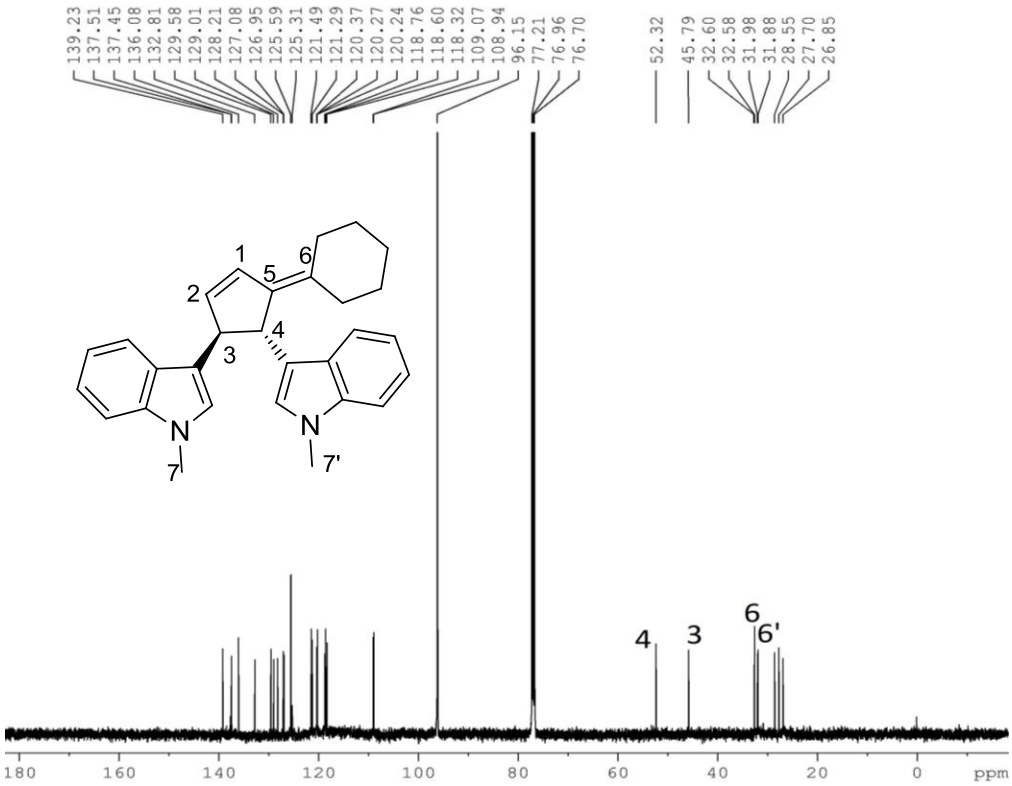


Figure 3.6. ^{1}H NMR spectrum of compound **55ab**

The structure was further supported by the mass spectral analysis which showed a molecular ion peak at *m/z* = 429.23102 (M+Na). The structure and stereochemistry of the product was unambiguously established by single crystal X-ray analysis (Figure 3.7) of the analogues compound **55ha** (Table 2.3, Entry 7).

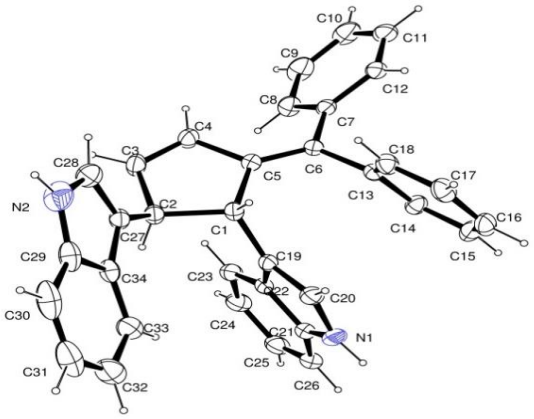


Figure 3.7. ORTEP plot of compound **55ha**

Under the optimized catalytic conditions for the preparation of alkylidenecyclopentenenyl derivative of indole (Table 2.2, Entry 6) and bisindole (Table 2.2, Entry 16), we examined the scope of different olefins and indoles (Table 2.2). Diazabicyclic alkenes **53a-d** easily underwent ring opening with 1*H*-indole **1a** and gave the corresponding indole derivatives **54aa-da** and bisindole **55aa** in good to moderate yields (Entries 1-4). To demonstrate the generality of the reaction, several C-1, C-2 and C-5 substituted indoles **1b-f** was subjected to C-3 alkylidenecyclopentenylation. Reaction was found to be compatible to a variety of indoles having substituents such as -F, -OH, -NO_2 etc. and yielded the C-3 functionalized indoles and bisindoles (Table 2.2, Entries 5-9).

Table 3.2 Substrate scope of indoles with various 6,6-pentamethylene fulvene derived diazabicyclic olefins.

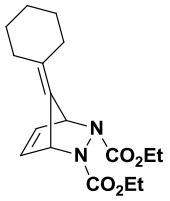
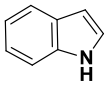
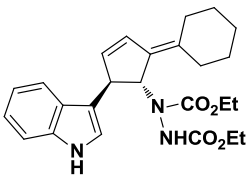
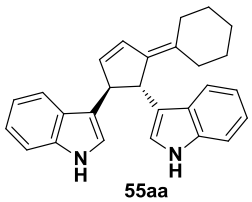
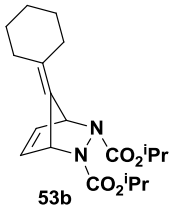
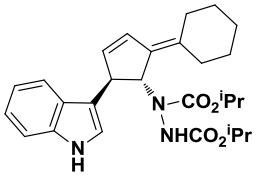
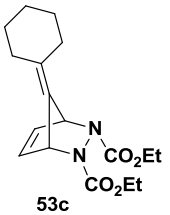
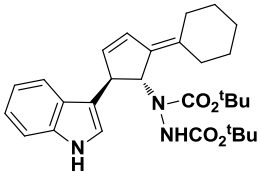
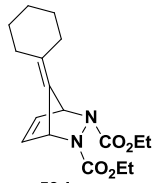
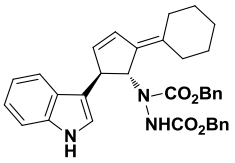
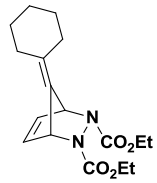
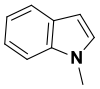
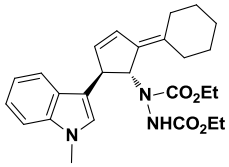
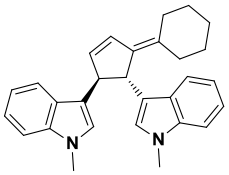
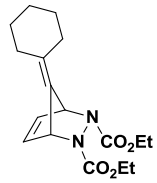
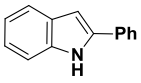
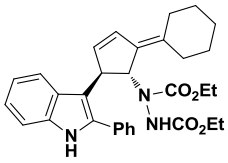
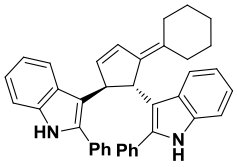
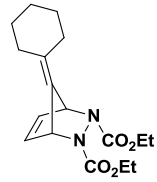
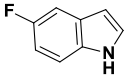
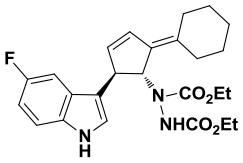
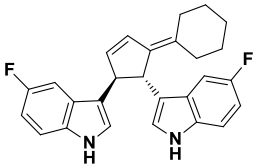
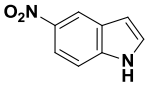
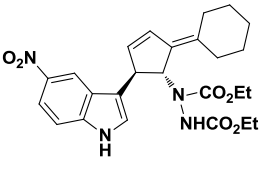
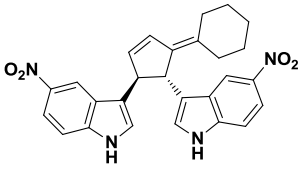
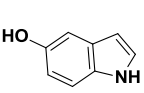
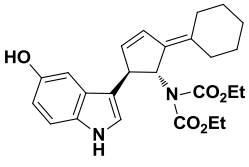
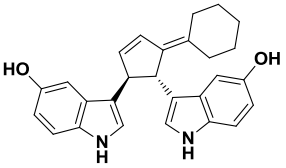
Entry	Bicyclic olefin	Indole	Product 54	Product 55	Yield (%) 54	Yield (%) 55
1	 53a	 1a	 54aa	 55aa	73 27[a]	16 64[a]
2	 53b	1a	 54ba	55aa	72 14[a]	16 72[a]
3	 53c	1a	 54ca	55aa	42 27[a]	14 28[a]

Table 3.2 continues…

Entry	Bicyclic olefin	Indole	Product 54	Product 55	Yield (%) 54	Yield (%) 55
4	 53d	1a	 54da	55aa	39 17[a]	12 33[a]
5	 53a	 1b	 54ab	 55ab	75 31[a]	14 58[a]
6	 53a	 1c	 54ac	 55ac	78 32[a]	11 54[a]
7	 53a	 1d	 54ad	 55ad	61 24[a]	14 52[a]
8	53a	 1e	 54ae	 55ae	59 26[a]	12 48[a]
9	53a	 1f	 54af	 55af	56 28[a]	8 39[a]

Reaction Conditons: alkene (1.2 equiv.), indole (1equiv.), catalyst (2 mol%), solvent (2 mL), at rt. for 4 h

[a] Reaction in presence of 1equiv. of alkene and 2 equiv. of indole

Next, we turned our attention to explore the scope of C-3 functionalization of indoles with diazabicyclic olefins derived from different pentafulvenes (Table 2.3). Alkylidenecyclopetenylation of indoles proceeds efficiently through the ring opening of diazabicyclic alkenes **53e-h** to provide the desired indole and bisindole derivatives. For example, the reaction of diphenylfulvene derived bicyclic olefin **53h** with indole **1a** leads to the formation of alkylidenecyclopetenylated indole and bisindole derivatives in adequate yield and is tunable towards each product.

Table 3.3 Substrate scope of various pentafulvene derived diazabicyclic olefins for the C-3 functionalization of indole

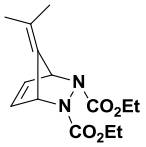
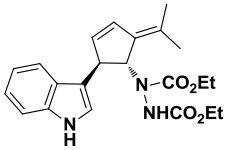
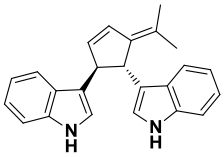
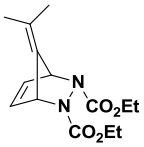
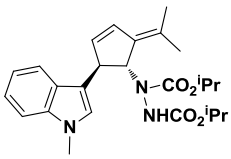
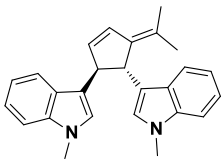
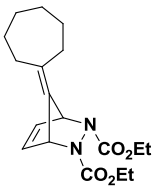
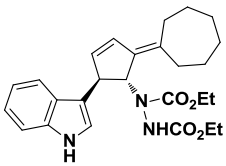
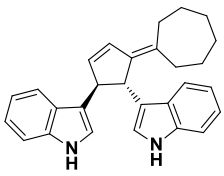
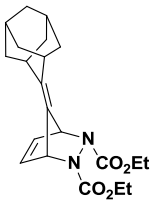
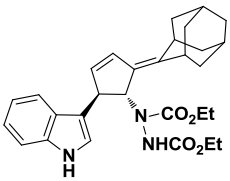
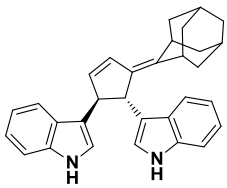
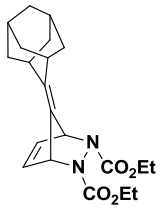
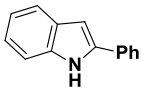
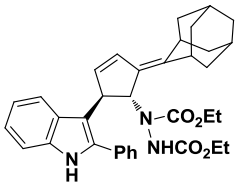
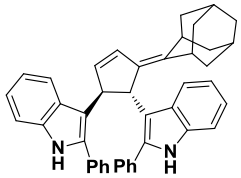
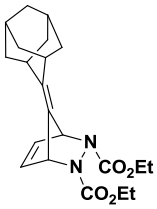
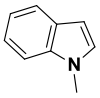
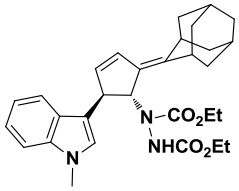
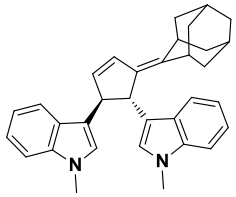
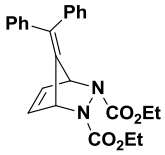
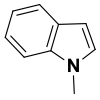
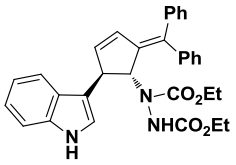
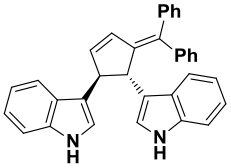
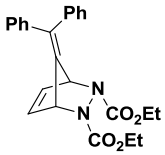
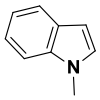
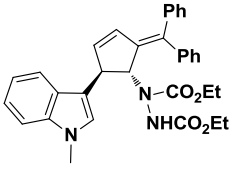
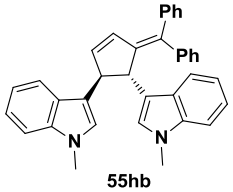
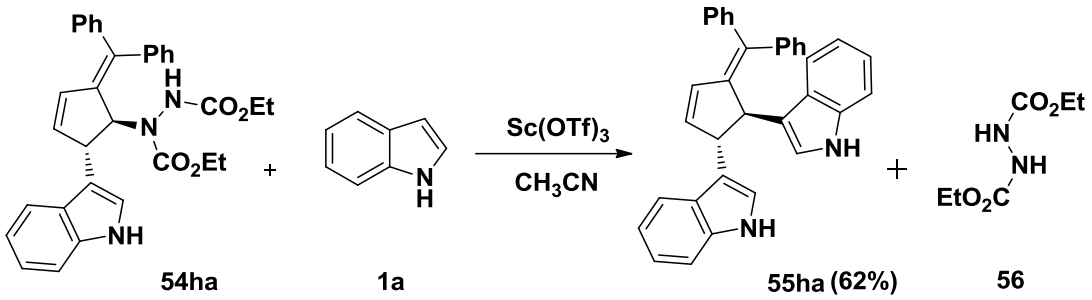
Entry	Bicyclic olefin	Indole	Product 54	Product 55	Yield (%) 54	Yield (%) 55
1	 53e	 1a	 54ea	 55ea	69 24[a]	18 64[a]
2	 53e	 1b	 54eb	 55eb	65 27[a]	15 56[a]
3	 53f	 1a	 54fa	 55fa	70 25[a]	9 53[a]
4	 53g	 1a	 54ga	 55ga	66 30[a]	24 58[a]

Table 3.3 continues…

Entry	Bicyclic olefin	Indole	Product 54	Product 55	Yield (%) 54	Yield (%) 55
6	 53g	 1c	 54gc	 55gc	66 13[a]	14 74[a]
5	 46g	 1b	 54gb	 55gb	70 32[a]	16 55[a]
7	 53h	 1a	 54ha	 55ha	62 8[a]	28 84[a]
8	 53h	 1b	 54hb	 55hb	68 10[a]	24 81[a]

Reaction Conditons: alkene (1.2 equiv.), indole (1equiv.), catalyst (2 mol%), solvent (2 mL), at rt for 4 h
[a] Reaction in presence of 1equiv. of alkene and 2 equiv. of indole

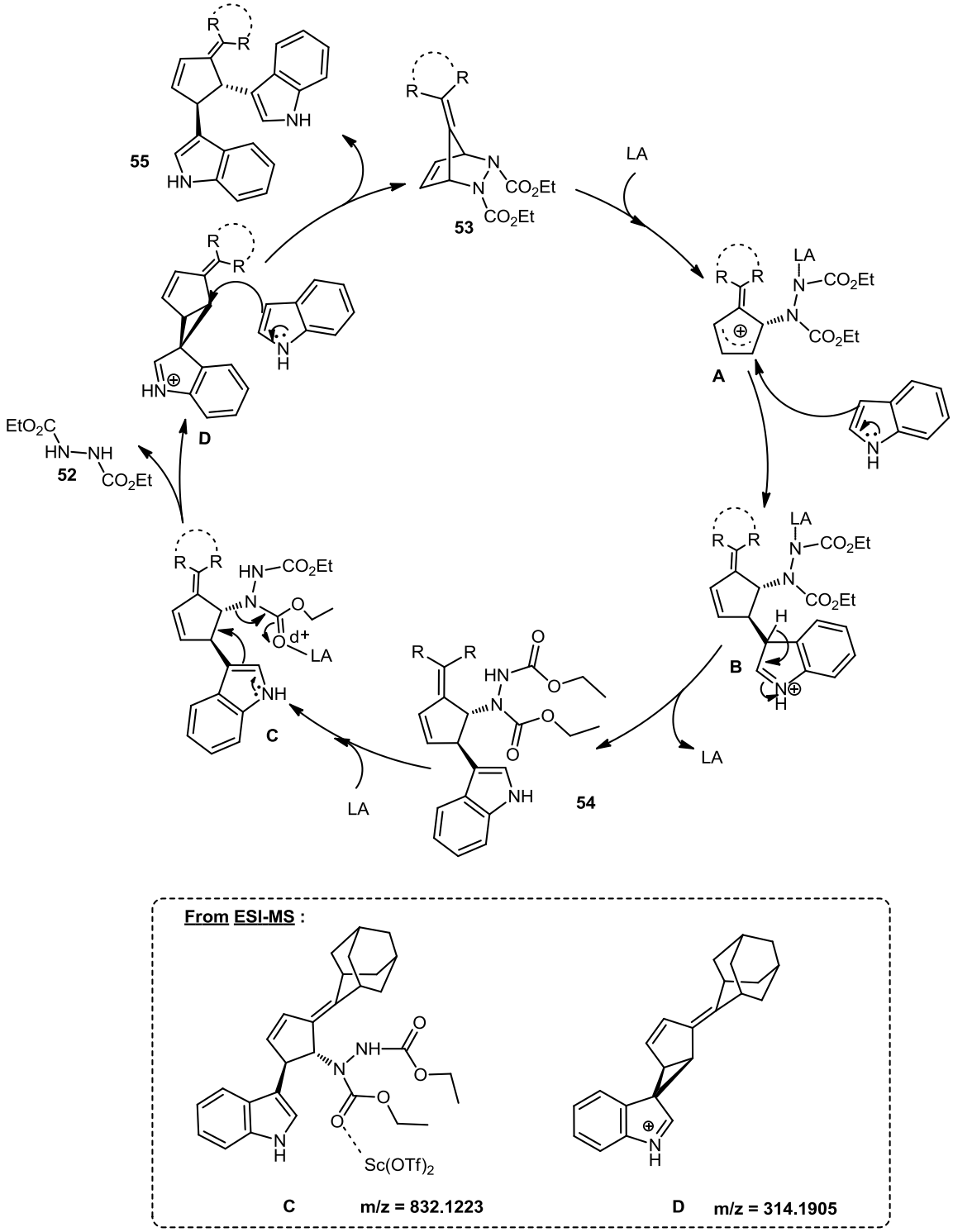
To confirm the Lewis acid catalyzed generation of an intermediate from **54ha** by the elimination of hydrazine moiety **56**, we have carried out a reaction with 1 equiv. of 3,4-disubstituted alkylidenecyclopentene **54ha** and 1.2 equiv. of indole **1a** (Scheme 3.22). As expected, bisindole product **55ha** was obtained in 62% yield, supporting the role of 3,4-disubstituted alkylidenecyclopentene as an intermediate in the course of reaction.



Scheme 3.22

3.5. Mechanistic pathway

Based on these results we propose a plausible mechanism as shown in Scheme 3.23. The catalytic cycle is initiated by coordination of the Lewis acid with the carbonyl oxygen of one of the carbamate groups of diazabicyclic olefin **53a** and subsequent cleavage of C–N bond leads to the generation of a transient allylic cation species **A**. Regioselective nucleophilic attack of indole from the opposite side with respect to hydrazine moiety of intermediate **A** delivers *trans*-3,4-disubstituted alkylidenecyclopentene **54**. In the next step, the Lewis acid coordinates with the carbonyl group of hydrazine moiety, followed by the elimination of hydrazine group through C-N bond cleavage resulting in the formation of intermediate **D**. Attack of the second molecule of indole to intermediate **D** furnishes the bisindole product **55**. Furthermore, ESI-MS studies provided strong supporting evidence for the formation of intermediates **C** and **D** in the proposed mechanism of catalytic cycle.



Scheme 3.23 Proposed mechanism of the reaction

3.6. Conclusion

In summary, we have developed a Lewis acid catalyzed C-3 alkylidene-cyclopentenylation of indoles through the ring opening of pentafulvene derived diazabicyclic olefins. The developed method provides an efficient synthetic route to furnish pharmaceutically valuable indole and bisindole derivatives of alkylidenecyclopentenes from easily accessible starting materials. While multiple steps are involved in conventional synthetic strategies, this protocol offers a one-pot access to cyclopentene-bisindole hybrids. Moreover, the present strategy is compatible with both *N*-alkyl and free (NH) indoles.

3.7. Experimental Section

General methods: All reactions were conducted in oven-dried glasswares. All chemicals were of the best grade commercially available and are used without further purification. All the solvents were purified according to standard procedure; dry solvents were obtained according to the literature methods and stored over molecular sieves. All reactions were monitored by TLC (Silica gel 60 F254, 0.25 mm, Merck), visualization was effected with UV and/or by staining with Enholm yellow solution. Gravity column chromatography was performed using 100-200 mesh silica gel or neutral aluminium oxide and mixtures of hexane-ethyl acetate were used for elution.

Melting point was determined on a Buchi Melting Point apparatus and is uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker Avance DPX 300 and Bruker AMX 500 spectrophotometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.25 ppm, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (double doublet); ddd (doublet of double doublet); m (multiplet). Coupling constants are reported as *J* value in Hz. Carbon nuclear magnetic resonance

spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). Mass spectra were recorded under ESI/HRMS at 60000 resolution using Thermoscientific Exactive Mass Spectrometer. IR spectra were recorded on Bruker Alpha-T FTIR Spectrometer.

General Procedure for the Lewis acid catalyzed reaction of pentafulvene derived bicyclic hydrazines towards the synthesis of 54.

A mixture of pentafulvene derived bicyclic hydrazine (1.2 eqiuv.), indole (1.0 equiv.) and $Sc(OTf)_3$ (2 mol %) were weighed in a Schlenk tube and degassed for 10 minutes. Dry CH_3CN (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at room temperature for 4 hours. The solvent was evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography yielded *trans*-3,4-disubstituted alkylidenecyclopentene (**54**) along with minor amount *trans*-3,4-disubstituted bisindolyl product (**55)**.

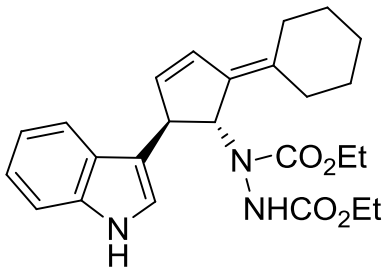
General Procedure for the Lewis acid catalyzed reaction of pentafulvene derived bicyclic hydrazines towards the synthesis of 55.

A mixture of pentafulvene derived bicyclic hydrazine (1.0 eqiuv.), indole (2.0 equiv.) and $Sc(OTf)_3$ (2 mol %) were weighed in a Schlenk tube and degassed for 10 minutes. Dry CH_3CN (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at room temperature for 4 hours. The solvent was evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography yielded *trans*-3,4-disubstituted bisindolyl product (**55)** along with minor amount *trans*-3,4-disubstituted alkylidenecyclopentene (**54**).

Compound 54aa

Following general procedure for the Lewis acid catalyzed reaction of pentafulvene derived bicyclic hydrazines towards the synthesis of compound **54**. The pentafulvene derived bicyclic hydrazine **53a** (110 mg, 0.34 mmol), indole **1a** (34 mg, 0.28 mmol) and $Sc(OTf)_3$ (3 mg, 0.005 mmol), in 2 mL acetonitrile at room

temperature under argon atmosphere for 4 hours gave the product **54aa** (91 mg, 73%) as pale yellow solid along with minor amount *trans*-3,4-disubstituted bisindolyl product **55aa** (17 mg, 16%).



R_f : 0.31 (hexane/ethyl acetate = 3:1).

Mp : 122–124 ^oC

IR (Neat) ν_{max}: 3334, 3054, 2976, 2920, 2853, 1709, 1586, 1458, 1410, 1330, 1220, 1120, 1052, 920, 745 cm^{-1}.

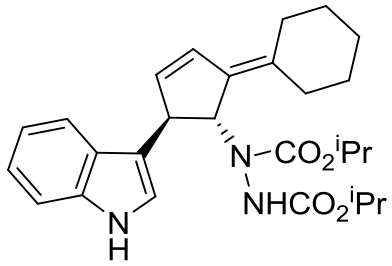
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 8.10 (brs, 1H), 7.68 (brs, 1H), 7.29-7.23 (m, 1H), 7.16- 7.13 (m, 1H), 7.06-7.03 (m, 1H), 6.84 (s, 1H), 6.53(d, *J* = 6 Hz, 1H), 6.26 (brs, 1H), 6.04 (brs, 1H), 5.34-5.12 (m, 1H), 4.50-4.40(m, 1H), 4.24-4.17 (m, 4H), 2.39- 2.33 (m, 2H), 2.08- 2.07 (m, 2H), 1.66-1.53 (m, 6H), 1.30-1.29 (m, 5H), 1.02 (brs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 156.6, 155.1, 136.7, 136.2, 134.0, 129.7, 126.6, 121.9, 120.0, 119.2, 118.1, 110.0, 65.4, 64.1, 62.4, 61.9, 47.4, 32.0, 31.0, 28.4, 28.1, 26.6, 14.5, 14.2.

HRMS (ESI): Calcd for $C_{25}H_{31}N_3O_4Na$: 460.22123; Found: 460.22171.

Compound 54ba

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53b** (80 mg, 0.23 mmol), indole **1a** (22 mg, 0.19 mmol) and $Sc(OTf)_3$ (3 mg, 0.004 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **54ba** (64 mg, 72%) as pale yellow viscous liquid along with minor amount *trans*-3,4-disubstituted bisindolyl product **55ba** (12 mg, 16%).



R_f : 0.33 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3331, 3068, 2981, 2932, 2857, 1688, 1621, 1583, 1514, 1462, 1380, 1304, 1238, 1108, 1042, 957, 931, 743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 8.16 (brs, 1H), 7.75-7.71 (m, 1H), 7.31-7.23 (m, 1H), 7.18-7.05 (m, 2H), 6.88 (brs, 1H), 6.56-6.27 (m, 2H), 6.07 (brs, 1H), 5.34-5.14 (m, 1H), 5.00-4.95 (m, 2H), 4.53-4.43 (m, 1H), 2.36 (brs, 2H), 2.09-1.81 (m, 2H), 1.61-1.51 (m, 6H), 1.44-1.22 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 156.5, 154.7, 136.8, 133.8, 129.8, 129.0, 128.2, 126.7, 125.3, 121.7, 119.1, 110.9, 69.9, 69.5, 63.9, 47.2, 31.6, 30.8, 29.7, 28.3, 26.9, 22.7, 22.4, 22.1.

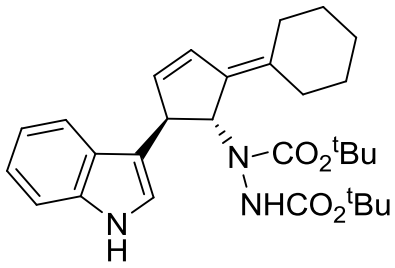
HRMS (ESI): Calcd for $C_{27}H_{35}N_3O_4Na$: 488.25253; Found: 488.25286.

Compound 54ca

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53c** (100 mg, 0.27 mmol), indole **1a** (26 mg, 0.22 mmol) and $Sc(OTf)_3$ (3 mg, 0.01 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **54ca** (46 mg, 42%) as pale yellow viscous liquid along with minor amount *trans*-3,4-disubstituted bisindolyl product **55ca** (12 mg, 14%).

R_f : 0.40 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3375, 3078, 2992, 2943, 2836, 1690, 1610, 1583, 1565, 1468, 1462, 1400, 1316, 1238, 1152, 1123, 969, 938, 746 cm^{-1}.



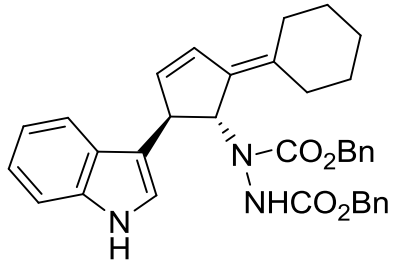
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 8.00 (d, *J* = 11 Hz,1H), 7.99-7.79 (m, 1H), 7.32-7.28 (m, 1H), 7.20-7.06 (m, 2H), 6.87 (s, 1H), 6.55 (d, *J* = 5.5 Hz, 1H), 6.15-6.00 (m, 2H), 5.30-5.08 (m, 1H), 4.54-4.44 (m, 1H), 2.37 (brs, 2H), 2.12 (brs, 2H), 1.63-1.53 (m, 24H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 155.7, 154.0, 136.7, 136.5, 126.7, 122.1, 121.8, 119.2, 118.2, 111.1, 110.9, 110.7, 81.3, 80.7, 65.5, 44.3, 32.0, 31.1, 28.3, 28.2, 28.0, 26.6.

HRMS (ESI): Calcd for $C_{29}H_{39}N_3O_4Na$: 516.28383; Found: 516.28414.

Compound 54da

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53d** (95 mg, 0.21 mmol), indole **1a** (21 mg, 0.18 mmol) and $Sc(OTf)_3$ (3 mg, 0.01 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **54da** (39 mg, 39%) as yellow viscous liquid along with minor amount *trans*-3,4-disubstituted bisindolyl product **55da** (8 mg, 12%).



R_f : 0.31 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3358, 3059, 3027, 2920, 2858, 1702, 1580, 1489, 1449, 1400, 1311, 1281, 1050, 1000, 743 cm^{-1}.

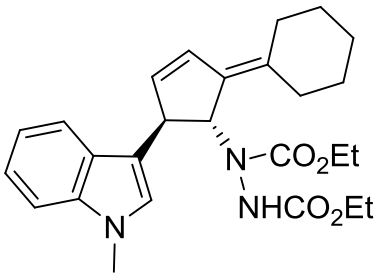
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 8.28 (brs, 1H), 7.66 (brs, 1H), 7.39-6.90 (m, 13H), 6.75 (brs, 2H), 6.46 (s, 1H), 5.98-5.86 (m, 1H), 5.36 -5.05 (m, 5H), 4.52-4.29 (m, 1H), 2.36-2.32 (m, 2H), 2.02-1.94 (m, 2H), 1.56-1.26 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 156.4, 154.8, 136.7, 135.8, 133.4, 128.6, 128.5, 128.3, 128.2, 127.9, 126.6, 122.0, 121.2, 119.9, 119.4, 117.5, 110.9, 68.1, 67.6, 47.5, 32.0, 31.0, 28.3, 28.0, 26.5.

HRMS (ESI): Calcd for $C_{35}H_{35}N_3O_4Na$: 584.25253; Found: 584.25288.

Compound 54ab

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53a** (110 mg, 0.34 mmol), indole **1b** (38 mg, 0.29 mmol) and $Sc(OTf)_3$ (3 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **54ab** (97 mg, 75%) as pale yellow solid along with minor amount *trans*-3,4-disubstituted bisindolyl product **55ab** (16mg, 14%).



R_f : 0.33 (hexane/ethyl acetate = 3:1).

Mp : 120-122 ^oC,

IR (Neat) ν_{max}: 3323, 3055, 2981, 2932, 2855, 1710, 1619, 1583, 1513, 1458, 1415, 1339, 1302, 1227, 1096, 1061, 920, 743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.68 (brs, 1H), 7.25-7.23 (m, 2H), 7.05 (t, J = 7 Hz,1H), 6.73 (s, 1H), 6.53(d, J = 5.5 Hz, 1H), 6.23 (brs, 1H), 6.04 (s, 1H), 5.31-5.09 (m, 1H), 4.49-4.39 (m, 1H), 4.24-4.18 (m, 4H), 3.72 (s, 3H), 2.38-2.34 (m, 2H), 2.07-2.03 (m, 2H), 1.61-1.53 (m, 6H), 1.31-1.26 (m, 5H), 1.05-1.04 (brs, 1H).

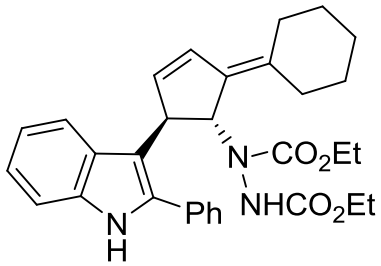
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 156.4, 155.1, 137.4, 133.7, 129.6, 127.0, 125.7, 121.5, 120.1, 118.7, 109.1, 108.8, 65.5, 62.3, 61.8, 47.5,

32.5, 31.9, 28.3, 28.0, 26.5, 14.5.

HRMS (ESI): Calcd for $C_{26}H_{33}N_3O_4Na$: 474.23688; Found: 474.23764.

Compound 54ac

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53a** (110 mg, 0.34 mmol), indole **1c** (55 mg, 0.29 mmol) and $Sc(OTf)_3$ (3mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **54ac** (115 mg, 78%) as yellow viscous liquid along with minor amount *trans*-3,4-disubstituted bisindolyl product **55ac** (17 mg, 11%).



R_f : 0.36 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3324, 2980, 2930, 2854, 1701, 1519, 1472, 1420, 1382, 1332, 1261, 1233, 1097, 1060 cm^{-1}.

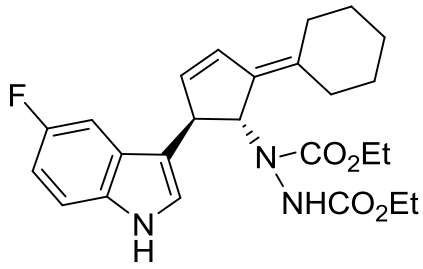
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 8.16 (brs, 1H), 7.60-7.25 (m, 6H), 7.19-7.03 (m, 2H), 7.03 (d, *J* = 7 Hz, 1H), 6.55 (brs, 1H), 6.20-6.03 (m, 1H), 5.91 (brs, 1H), 5.59-5.45 (m, 1H), 4.68-4.53 (m, 1H), 4.16-4.12 (m, 4H), 2.58 (brs, 1H), 2.39-2.12 (m, 3H), 1.75-1.59 (m,6H), 1.29-0.88 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 156.2, 155.4, 137.7, 136.3, 134.7, 132.8, 129.0, 128.6, 128.2, 127.6, 125.3, 121.9, 120.3, 119.4, 110.9, 62.4, 61.7, 60.3, 48.3, 34.6, 32.1, 26.9, 26.7, 21.5, 14.5, 14.2.

HRMS (ESI): Calcd for $C_{31}H_{35}N_3O_4Na$: 536.25253; Found: 536.25289.

Compound 54ad

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53a** (110 mg, 0.34 mmol), indole **1d** (39 mg, 0.29 mmol) and $Sc(OTf)_3$ (3mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **54ad** (80 mg, 61%) as colourless viscous liquid along with minor amount *trans*-3,4-disubstituted bisindolyl product **55ad** (17 mg, 14%).



R_f : 0.26 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3363, 3277, 3054, 2984, 2931, 2854, 1711, 1582, 1500, 1149, 1411, 1330, 1120, 1050, 1010, 919, 744 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 8.26 (s, 1H), 7.34 (brs, 1H), 7.27-7.22 (m, 1H), 6.96-6.92 (brs, 1H), 6.65-6.56 (m, 2H), 6.40-6.31 (m, 1H), 6.02 (d, *J* = 3.5 Hz, 1H), 5.32-5.11 (m, 1H), 4.46-4.18 (m, 5H), 2.41- 2.33 (m, 2H), 2.07-2.05 (m, 2H), 1.62-1.45 (m, 6H), 1.35-1.07 (m, 6H).

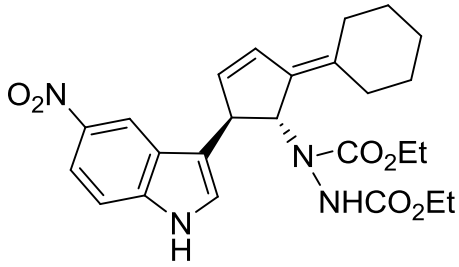
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 158.5, 156.8, 155.3, 136.9, 133.3, 130.0, 126.9, 123.1, 118.1, 111.5, 110.3, 104.9, 65.4, 62.6, 62.3, 47.5, 32.0, 31.1, 28.3, 28.0, 26.5, 14.4.

HRMS (ESI): Calcd for $C_{25}H_{30}FN_3O_4Na$: 478.21180; Found: 478.21223.

Compound 54ae

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53a** (110 mg, 0.34 mmol), indole **1e** (46 mg, 0.29 mmol) and $Sc(OTf)_3$ (3 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere

for 4 hours gave the product **54ae** (81 mg, 59%) as pale yellow solid along with minor amount *trans*-3,4-disubstituted bisindolyl product **55ae** (16 mg, 12%).



R_f : 0.22 (hexane/ethyl acetate = 3:1).

Mp : 132-134 ^oC,

IR (Neat) ν_{max}: 3365, 3071, 2960, 2852, 1712, 1623, 1582, 1469, 1410, 1380, 1318, 1245, 1173, 1115, 1058, 743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 9.22 (brs, 1H), 8.56(s, 1H), 7.92 (brs, 1H), 7.17-7.13 (m, 1H), 6.92-6.82 (m, 1H), 6.61 (d, 1H, *J* = 4.5 Hz), 6.34 (brs, 1H), 5.98 (brs, 1H), 5.39-5.17 (m, 1H), 4.49-4.23 (m, 5H), 2.56-2.06 (m, 4H), 1.76-1.22 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 156.3, 155.6, 141.3, 139.8, 137.7, 130.1, 129.0, 128.2, 125.5, 125.3, 124.2, 117.6, 117.2, 111.0, 64.3, 62.9, 62.2, 47.5, 32.1, 31.3, 28.2, 26.6, 21.5, 14.5, 14.2.

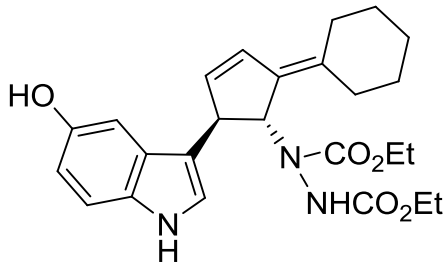
HRMS (ESI): Calcd for $C_{25}H_{30}N_4O_6Na$: 505.20630; Found: 505.20668.

Compound 54af

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53a** (110 mg, 0.34 mmol), indole **1f** (38 mg, 0.29 mmol) and $Sc(OTf)_3$ (3 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **54af** (70 mg, 56%) as pale yellow viscous liquid along with minor amount *trans*-3,4-disubstituted bisindolyl product **55af** (10 mg, 8%).

R_f : 0.17 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3380, 3280, 3054, 2976, 2928,



2853, 1709, 1586, 1499, 1149, 1410, 1330, 1220, 1120, 1052, 1011, 920, 745 cm^{-1}.

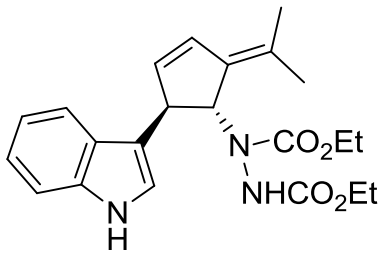
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.89 (brs, 1H), 7.23-7.15 (m, 2H), 6.79-6.77 (m, 1H), 6.56-6.28 (m, 2H), 6.05 (brs, 1H), 5.32-5.09 (m,1H), 4.45-4.11 (m, 5H), 2.37-2.33 (m, 2H), 2.07-2.06 (m, 2H), 1.60-1.38 (m, 6H), 1.29-1.13 (m, 5H), 0.99 (brs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 155.2, 154.5, 147.5, 135.8, 135.0, 134.3, 127.2, 126.8, 125.3, 111.9, 111.8, 108.5, 104.5, 64.9, 62.8, 62.2, 41.9, 32.0, 28.2, 26.5, 19.4, 19.2, 14.5.

HRMS (ESI): Calcd for $C_{25}H_{31}N_3O_5Na$: 476.21614; Found: 476.21658.

Compound 54ea

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53e** (90 mg, 0.32 mmol), indole **1a** (31 mg, 0.27 mmol) and $Sc(OTf)_3$ (3mg, 0.006 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **54ea** (73 mg, 69%) as colourless viscous liquid along with minor amount *trans*-3,4-disubstituted bisindolyl product **55ea** (16 mg, 18%).



R_f : 0.29 (hexane/ethyl acetate = 3:1)

IR (Neat) ν_{max}: 3317, 3056, 2982, 2931, 1719, 1620, 1582, 1512, 1415, 1382, 1229, 1096, 1062, 744 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 8.30 (s, 1H), 7.71 (brs, 1H), 7.34-7.27 (m, 1H), 7.19-7.08 (m, 2H), 6.86-6.78 (m, 2H), 6.52 (d, 1H, J = 5 Hz), 6.05 (s, 1H), 5.35-5.14 (m, 1H), 4.53-4.18 (m, 5H),

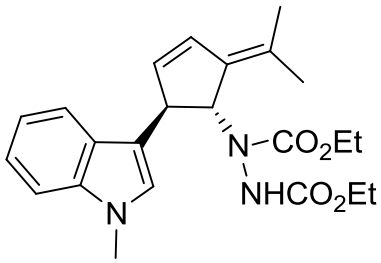
1.89 (s, 3H), 1.67 (brs, 3H), 1.29-1.26 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 156.9, 155.8, 136.8, 136.6, 135.5, 129.0, 126.7, 125.3, 121.7, 119.9, 119.1, 119.0, 117.9, 111.3, 66.0, 62.6, 62.2, 47.6, 21.5, 14.4.

HRMS (ESI): Calcd for $C_{22}H_{27}N_3O_4Na$: 420.18993; Found: 420.18866.

Compound 54eb

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53e** (90 mg, 0.32 mmol), indole **1b** (35 mg, 0.27 mmol) and $Sc(OTf)_3$ (3 mg, 0.005 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **54eb** (72 mg, 65%) as colourless solid along with minor amount *trans*-3,4-disubstituted bisindolyl product **55eb** (15 mg, 15%).



R_f : 0.33 (hexane/ethyl acetate = 3:1).

Mp : 124-126 ^oC

IR (Neat) ν_{max}: 3385, 3055, 2981, 2924, 1707, 1611, 1474, 1413, 1379, 1321, 1265, 1219, 1163, 1122, 1061, 1021, 933, 739 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.73 (s, 1H), 7.29-7.23 (m, 2H), 7.10 (t, *J* = 7 Hz, 1H), 6.77 (brs, 1H), 6.53 (d, *J* = 5 Hz, 1H), 6.39 (brs, 1H), 6.07 (s, 1H), 5.36-5.14 (m, 1H), 4.53-4.20 (m, 5H), 3.73 (s, 3H), 1.90 (s, 3H), 1.69 (s, 3H), 1.31-1.05 (m, 6H).

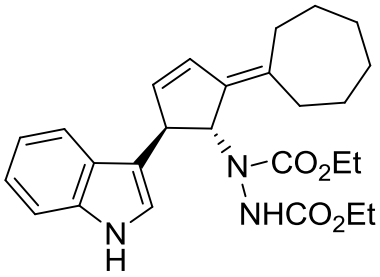
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 156.7, 155.6, 137.5, 136.7, 135.6, 130.5, 128.3, 127.1,

125.9, 121.6, 120.1, 118.8, 116.7, 109.0, 66.2, 62.5, 61.9, 47.5, 32.6, 21.5, 13.8.

HRMS (ESI): Calcd for $C_{23}H_{29}N_3O_4Na$: 434.20588; Found: 434.20615.

Compound 54fa

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53f** (95 mg, 0.28 mmol), indole **1a** (24 mg, 0.28 mmol) and $Sc(OTf)_3$ (3 mg, 0.005 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **54fa** (75 mg, 70%) as colourless viscous liquid along with minor amount *trans*-3,4-disubstituted bisindolyl product **54fa** (8 mg, 9%).



R_f : 0.31 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3348, 3056, 2924, 2853, 1708, 1617, 1458, 1414, 1380, 1226, 1177, 1121, 1061, 741 cm^{-1}.

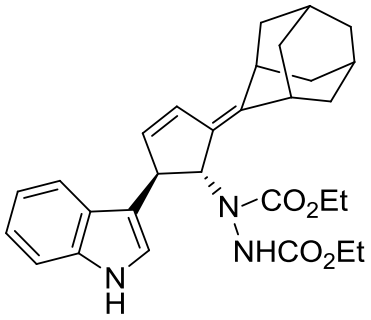
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 8.09 (brs, 1H), 7.66 (brs, 1H), 7.28 (brs, 1H), 7.16-7.04 (m 2H), 6.84 (brs, 1H), 6.51 (d, *J* = 5.5 Hz, 1H), 6.25-6.21 (m, 1H), 6.04 (brs, 1H), 5.33-5.11 (m, 1H), 4.50-4.18 (m, 5H), 2.50-2.41 (m, 2H), 2.20-2.16 (brs, 2H), 1.71-1.03 (m, 14H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 156.3, 155.5, 136.8, 129.0, 128.2, 126.6, 125.3, 121.7, 119.0, 119.0, 111.1, 62.4, 61.9, 47.6, 32.7, 32.3, 29.1, 28.2, 27.6, 14.5, 14.2.

HRMS (ESI): Calcd for $C_{26}H_{33}N_3O_4Na$: 474.23688; Found: 474.23714.

Compound 54ga

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53g** (100 mg, 0.27 mmol), indole **1a** (26 mg, 0.22 mmol) and $Sc(OTf)_3$ (3 mg, 0.005 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **54ga** (72 mg, 66%) as colourless viscous liquid along with minor amount *trans*-3,4-disubstituted bisindolyl product **54ga** (23 mg, 24%).



R_f : 0.33 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3323, 3057, 2920, 2848, 1713, 1620, 1475, 1413, 1381, 1305, 1294, 1216, 1116, 1085, 1065, 1025, 742 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 8.21 (brs, 1H), 7.70 (brs, 1H), 7.32-7.25 (m, 2H), 7.20-7.05 (m, 3H), 6.86 (brs, 1H), 6.56 (d, J = 5.5 Hz, 1H), 6.29 (brs, 1H), 6.05 (brs, 1H), 5.39-5.16 (m, 1H), 4.53-4.41 (m, 1H), 4.30-4.13 (m, 4H), 3.06 (brs,1H), 2.59 (brs,1H), 2.08-1.64 (m, 12H), 1.35-1.08 (m, 6H).

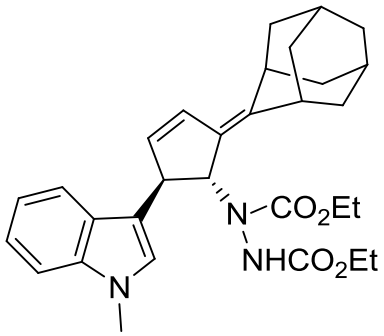
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 156.7, 155.2, 144.4, 136.5, 130.2, 129.0, 128.3, 126.6, 125.3, 121.4, 121.1, 119.9, 119.0, 117.1, 111.1, 63.8, 62.5, 62.0, 47.6, 39.9, 39.5, 39.1, 37.0, 35.1, 34.4, 28.1, 28.0, 21.5, 14.6.

HRMS (ESI): Calcd for $C_{29}H_{35}N_3O_4$: 512.25253; Found: 515.25290.

Compound 54gb

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53g** (100 mg, 0.27 mmol), indole **1b** (29 mg, 0.22 mmol) and $Sc(OTf)_3$ (3 mg, 0.005 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere

for 4 hours gave the product **54gb** (79 mg, 70%) as pale yellow viscous liquid along with minor amount *trans*-3,4-disubstituted bisindolyl product **55gb** (16 mg, 16%).



R_f : 0.36 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3315, 3054, 2910, 2852, 1711, 1612, 1472, 1413, 1379, 1305, 1221, 1124, 1061, 1019, 740 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.71 (brs, 1H), 7.7-7.21 (m, 2H), 7.07 (t, *J* = 7 Hz, 1H), 6.80 (brs, 1H), 6.55 (d, *J* = 5.5 Hz, 1H), 6.25 (brs, 1H), 6.05 (s, 1H), 5.35-5.12 (m, 1H), 4.53-4.28 (m, 1H), 4.23-4.13 (m, 4H), 3.75 (s, 3H), 3.05 (s, 1H), 2.58 (brs, 1H), 2.02-1.63 (m, 12H), 1.37-1.09 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 156.6, 154.9, 137.4, 130.2, 127.1, 125.8, 121.5, 120.2, 118.7, 108.9, 62.3, 61.9, 47.2, 39.6, 37.0, 35.1, 34.7, 32.6, 28.1, 26.9, 25.3, 22.9, 20.8, 14.9.

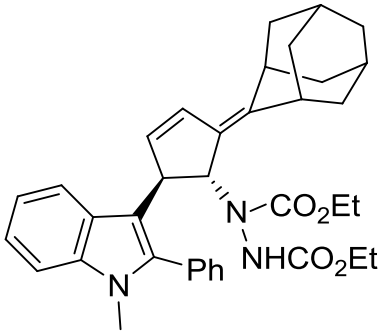
HRMS (ESI): Calcd for $C_{30}H_{37}N_3O_4Na$: 526.26818; Found: 526.26862.

Compound 54gc

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53g** (100 mg, 0.27 mmol), indole **1c** (43 mg, 0.22 mmol) and $Sc(OTf)_3$ (3 mg, 0.005 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **54gc** (83 mg, 66%) as pale yellow viscous liquid along with minor amount *trans*-3,4-disubstituted bisindolyl product **55gc** (18 mg, 44%).

R_f : 0.38 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3378, 3058, 2978, 2908, 2848, 1756, 1704, 1467, 1445, 1409, 1379, 1364, 1338, 1308, 1277, 1248, 1218, 1172, 1157, 1097, 1062,



1022 cm^{-1}.

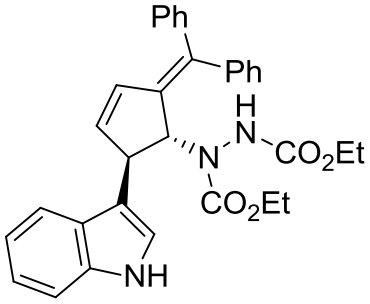
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.58- 7.44 (m, 6H), 7.33-7.19 (m, 3H), 7.04 (brs, 1H), 6.50-6.42 (m, 1H), 6.12-5.81 (m, 2H), 5.45 (brs, 1H), 4.25-4.15 (m, 4H), 3.58 (s, 3H), 3.06 (brs, 1H), 2.65-2.61 (m, 1H), 2.03-1.85 (m, 10H), 1.59-1.25 (m, 2H), 1.01-0.87 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 156.4, 155.3, 137.4, 131.3, 130.6, 128.1, 128.0, 121.5, 120.2, 119.0, 113.5, 109.3, 65.9, 62.3, 61.7, 47.8, 39.5, 39.4 37.0, 35.1, 34.6, 30.8, 28.2, 28.1, 14.7.

HRMS (ESI): Calcd for $C_{36}H_{41}N_3O_4Na$: 602.29948; Found: 602.29977.

Compound 54ha

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53h** (90 mg, 0.22 mmol), indole **1a** (22 mg, 0.19 mmol) and $Sc(OTf)_3$ (2 mg, 0.004 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **54ha** (60 mg, 62%) as pale yellow solid along with minor amount *trans*-3,4-disubstituted bisindolyl product **55ha** (24 mg, 28%).



R_f : 0.24 (hexane/ethyl acetate = 3:1).

Mp : 182-184 ^oC

IR (Neat) ν_{max}: 3362, 3051, 2968, 2911, 2852, 1736, 1710, 1552, 1514, 1467, 1454, 1411, 1384, 1364, 1308, 1287, 1243, 1231, 1168, 1157, 1069, 1063, 1022, 742 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.85-7.79 (m, 1H), 7.42-7.03 (m, 12H), 6.90-6.59 (m, 3H),

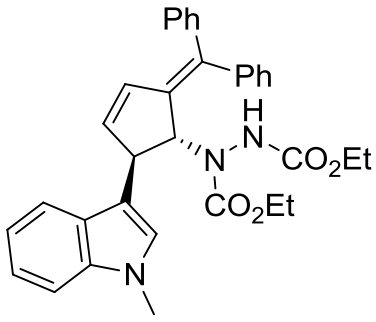
6.32-6.22 (brs, 1H), 6.04-5.91 (m, 2H), 5.08 (brs, 1H), 4.23-4.13 (m, 4H), 3.92-3.73 (m, 1H), 1.35-1.01 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 156.0, 154.7, 142.5, 142.4, 141.3, 140.8, 137.4, 130.0, 129.9, 128.6, 128.2, 127.7, 127.4, 126.8, 121.6, 120.2, 119.1, 116.9, 115.5, 110.2, 65.6, 62.0, 61.8, 47.9, 14.8.

HRMS (ESI): Calcd for $C_{32}H_{31}N_3O_4Na$: 544.22123; Found: 544.22151.

Compound 54hb

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53h** (90 mg, 0.22 mmol), indole **1b** (24 mg, 0.19 mmol) and $Sc(OTf)_3$ (2 mg, 0.004 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **54ha** (68 mg, 68%) as yellow viscous liquid along with minor amount *trans*-3,4-disubstituted bisindolyl product **54hb** (22 mg, 24%).



R_f : 0.29 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3340, 3068, 2981, 2932, 2857, 1688, 1621, 1602, 1583, 1555, 1514, 1462, 1380, 1315, 1238, 1108, 1042, 931, 743 cm^{-1}.

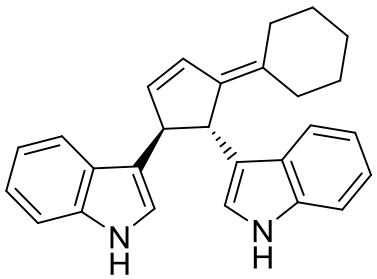
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.79 (brs, 1H), 7.34-7.19 (m, 14H), 7.09-6.97 (m, 2H), 6.61-6.55 (m, 1H), 6.32 (brs, 1H), 5.82-5.56 (m, 2H), 4.70-4.65 (m, 1H), 4.25-4.15 (m, 4H), 3.76 (brs, 3H), 1.32- 1.29 (m, 4H), 1.03 (brs, 1H), 0.69 (brs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 156.9, 154.9, 142.6, 142.3, 141.3, 140.7, 137.4, 130.0, 129.9, 128.5, 128.1, 127.4, 127.3, 127.1, 126.6, 121.4, 120.2, 118.8, 116.0, 115.3, 108.9, 65.5, 62.0, 61.8, 47.6, 32.6, 14.5,13.8.

HRMS (ESI): Calcd for $C_{33}H_{33}N_3O_4Na$: 558.23688; Found: 558.23721.

Compound 55aa

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53a** (55 mg, 0.17 mmol), indole **1a** (40 mg, 0.34 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **55aa** (42 mg, 64%) as pale yellow coloured solid along with minor amount the product **54aa** (20 mg, 27%).



R_f : 0.43 (hexane/ethyl acetate = 3:1).

Mp : 152-154 ^oC

IR (Neat) ν_{max}: 3405, 2922, 2851, 2362, 2349, 1590, 1459, 1421, 1364, 1120, 1033 cm^{-1}.

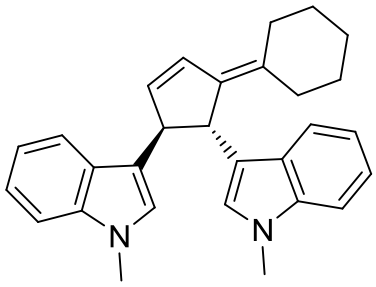
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.93 (s, 1H), 7.85 (s, 1H), 7.61-7.57 (m, 2H), 7.38-7.34 (m, 2H), 7.22-7.17 (m, 2H), 7.09-6.94 (m, 4H), 6.78 (d, J = 5.5 Hz, 1H), 6.04 (dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 1H), 4.32 (brs, 1H), 4.19 (brs, 1H), 2.46 (t, J = 6 Hz, 2H), 2.04-1.97 (m, 2H), 1.67-1.29 (m, 6H).

^{13}C NMR(125 MHz,$CDCl_3$, TMS): δ139.1, 136.9, 135.9, 133.0, 129.9, 129.1, 128.3, 126.7, 126.6 , 125.4, 121.9, 121.8, 121.0, 120.9, 120.2, 120.1, 119.6, 118.9, 111.2, 111.0, 52.3, 45.8, 32.1, 31.8, 28.6, 27.7, 26.9.

HRMS (ESI): Calcd for $C_{27}H_{26}N_2Na$: 401.19937; Found: 401.19968.

Compound 55ab

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53a** (55 mg, 0.17 mmol), indole **1b** (45 mg, 0.34 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **55ab** (41 mg, 58%) as pale yellow viscous liquid along with minor amount the product **54ab** (24 mg, 31%).



R_f : 0.48 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 2935, 2855, 2358, 2353, 1680, 1595, 1449, 1431, 1358, 1156, 1120, 1033 cm^{-1}.

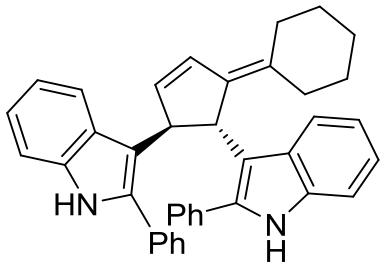
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.56-7.52 (m, 2H), 7.28-7.16 (m, 4H), 7.14-6.99 (m, 2H), 6.83 (s, 1H), 6.75 (s, 1H), 6.71 (dd, J_1 = 5.5 Hz, J_2 = 1 Hz, 1H), 5.97 (dd, J_1 = 5.5 Hz, J_2 = 2.5Hz, 1H), 4.26 (s, 1H), 4.11 (s, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2.45-2.41 (m, 2H), 2.02-2.00 (m, 1H), 1.94-1.92 (m, 1H), 1.63-1.45 (m, 4H), 1.34-1.31 (m, 1H), 1.18-1.17 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 139.2, 137.5, 137.4, 136.1, 132.8, 129.6, 129.0, 128.2, 127.1, 126.9, 125.6, 125.3, 121.5, 121.3, 120.4, 120.3, 120.2, 118.8, 118.6, 118.3, 109.1, 108.9, 52.3, 45.7, 32.6, 32.5, 32.0, 31.9, 28.6, 27.7, 26.9.

HRMS (ESI): Calcd for $C_{29}H_{30}N_2Na$: 429.23067; Found: 429.23102.

Compound 55ac

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53a** (55 mg, 0.17 mmol), indole **1c** (66 mg, 0.34 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **55aa** (49 mg, 54%) as pale yellow solid along with minor amount the product **54aa** (28 mg, 32%).



R_f : 0.52 (hexane/ethyl acetate = 3:1).

Mp : 160–164^oC

IR (Neat) ν_{max}: 3342, 3075, 2953, 2912, 2857, 1695, 1611, 1514, 1462, 1380, 1238, 1100, 1030, 931, 740 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.98 (s, 1H), 7.88 (s, 1H), 7.68 (d, *J* = 8Hz, 1H), 7.59 (d, *J* = 8 Hz, 1H), 7.42-7.37 (m, 4H), 7.28-6.80 (m, 13H), 6.14 (m, 1H), 4.76 (brs, 1H), 4.71 (brs, 1H), 2.51-2.49 (m, 1H), 2.38-2.18(m, 1H), 1.83-1.07 (m, 8H).

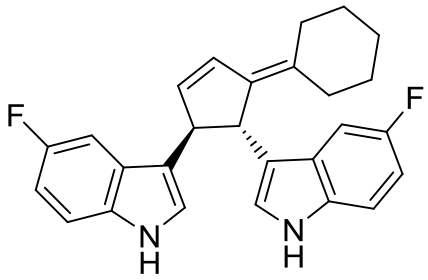
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 138.4, 136.5, 136.4, 136.3, 135.1, 134.5, 133.4, 132.6, 132.5, 130.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.4, 127.3, 122.3, 122.2, 121.3, 120.9, 119.6, 119.2, 117.3, 114.7, 110.5, 110.3, 50.6, 44.8, 32.5, 30.8, 28.6, 27.1, 26.8.

HRMS (ESI): Calcd for $C_{39}H_{34}N_2Na$: 553.26197; Found: 553.26233.

Compound 55ad

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53a** (55 mg, 0.17 mmol), indole **1d** (46 mg, 0.34 mmol) and $Sc(OTf)_3$ (2

mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **55ad** (37 mg, 52%) as pale yellow viscous liquid along with minor amount the product **54ad** (19 mg, 24%).



R_f : 0.40 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3356, 3052, 2978, 2939, 2849, 1689, 1619, 1583, 1514, 1462, 1415, 1402, 1380, 1304, 1238, 1111, 1047, 942, 740 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 8.03 (s, 1H), 7.94 (s, 1H), 7.31-7.20 (m, 4H), 7.07 (s, 1H), 7.00-6.77 (m, 4H), 6.00 (t, 1H, *J* = 3 Hz), 4.22 (s, 1H), 4.09 (s, 1H), 2.46- 2.42 (m, 2H), 2.06-2.04 (m, 1H), 1.96- 1.94 (m, 1H), 1.67- 1.44 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 158.5, 156.7, 138.5, 135.3, 133.8, 133.5, 130.3, 126.9, 122.9, 122.7, 121.9, 120.3, 111.7, 111.6, 110.5, 110.3, 110.2, 105.2, 105.0, 45.6, 32.0, 31.8, 28.5, 27.6, 26.8.

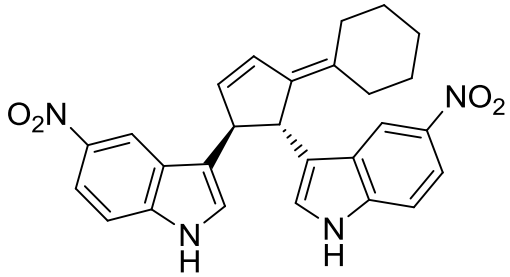
HRMS (ESI): Calcd for $C_{27}H_{24}F_2N_2Na$: 437.18052; Found: 437.18088.

Compound 55ae

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53a** (55 mg, 0.17 mmol), indole **1e** (56 mg, 0.34 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **55ae** (39 mg, 48%) as orange red viscous liquid along with minor amount the product **54ae** (22 mg, 26%).

R_f : 0.40 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3326, 3056, 2955, 2932, 2850,



1675, 1629, 1583, 1457, 1385, 1300, 1238, 1100, 1040, 931, 7445 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 8.91 (s, 1H), 8.74 (s, 1H), 8.53-8.52 (m, 2H), 8.12-8.09 (m, 2H), 7.45-7.41 (m, 2H), 7.26 (d, *J* = 10.5Hz, 1H), 7.14 (s, 1H), 6.86 (d, *J* = 5.5Hz, 1H), 5.99 (d, *J* = 4.5Hz, 1H), 4.33 (s, 1H), 4.22 (brs, 1H), 2.61-2.58 (m, 1H), 2.44-2.42 (m, 1H), 2.07-2.04 (m, 1H), 1.93-1.90 (m, 1H), 1.89-1.37 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 141.4, 141.2, 140.1, 140.0, 137.6, 135.1, 134.6, 130.9, 125.9, 125.7, 124.1, 124.0, 123.8, 122.2, 117.7, 117.6, 117.5, 112.9, 111.3, 52.3, 45.7, 32.1, 32.0, 28.2, 27.7, 26.7.

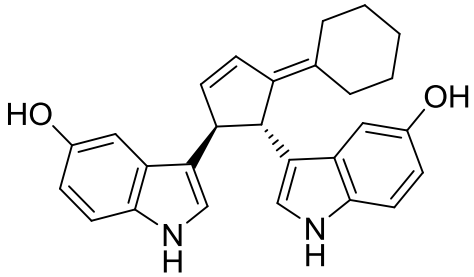
HRMS (ESI): Calcd for $C_{27}H_{24}N_2O_4Na$: 491.16952; Found: 491.16993.

Compound 55af

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53a** (55 mg, 0.17 mmol), indole **1f** (40 mg, 0.34 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **55af** (28 mg, 39%) as pale yellow viscous liquid along with minor amount the product **54af** (21 mg, 28%).

R_f : 0.19 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3339, 3061, 2990, 2940, 2842, 1680, 1623, 1580, 1514, 1380, 1302, 1240, 1110, 1042, 931, 740 cm^{-1}.



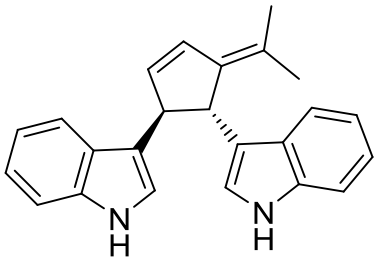
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.87 (brs, 1H), 7.78 (brs, 1H), 7.27-7.22 (m, 2H), 7.03-6.98 (m, 3H), 6.92 (d *J* = 2Hz, 1H), 6.81-6.74 (m 3H) ,6.01-6.00 (dd, J_1 = 6 Hz, J_2 = 3 Hz, 1H), 4.82 (d, *J* = 6.5Hz, 2H), 4.16 (s, 1H), 4.07(s, 1H), 2.45-2.39 (m, 2H), 1.99-1.94 (m, 2H),1.50-1.44 (m 3H), 1.33-0.87 (m 5H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 149.1, 148.9, 138.8, 135.6, 133.1, 132.1, 130.0, 127.3, 122.2, 121.3, 119.8, 111.8, 111.7, 111.6, 111.6, 104.8, 104.7, 51.7, 45.8, 32.0, 31.8, 28.6, 27.6, 26.8.

HRMS (ESI): Calcd for $C_{27}H_{26}N_2O_2Na$: 433.18920; Found: 433.18954.

Compound 55ea

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53e** (45 mg, 0.16 mmol), indole **1a** (38 mg, 0.32 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **55ea** (35 mg, 64%) as colourless viscous liquid along with minor amount the product **54ea** (15 mg, 24%).



R_f : 0.45 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3315, 2920, 2857, 2377, 1648, 1590, 1520, 1468, 1367, 1160, 1119, 1037 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.99 (s, 1H), 7.92 (s, 1H), 7.60-7.56 (m, 2H), 7.40- 7.37 (m, 2H), 7.23-7.18 (m, 3H), 7.09-7.05 (m, 3H), 7.00 (s, 1H), 6.94 (s, 1H), 6.74 (dd, 1H, J_1 = 5.5 Hz, J_2 = 2 Hz), 6.05 (dd, 1H, J_1 = 5.5 Hz, J_2 = 2.5 Hz), 4.28

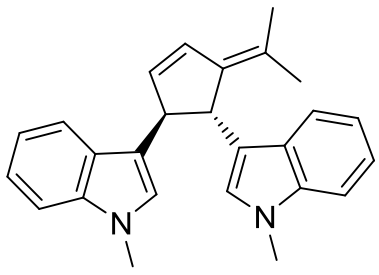
(s, 1H), 4.22 (s, 1H), 1.93 (s, 3H), 1.61 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 141.9, 137.1, 136.9, 135.8, 130.4, 127.3, 126.8, 125.8,125.7, 124.4, 121.5, 121.3, 120.5, 120.3, 120.0, 118.4, 118.2, 117.9, 110.8, 110.7, 52.4, 46.4, 21.3

HRMS (ESI): Calcd for $C_{24}H_{22}N_2Na$: 361.16807; Found: 361.16848

Compound 55eb

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53e** (45 mg, 0.16 mmol), indole **1a** (42 mg, 0.32 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **55eb** (33 mg, 56%) as pale yellow solid along with minor amount the product **54eb** (18 mg, 27%).



R_f : 0.50 (hexane/ethyl acetate = 3:1).

Mp : 162-164 ^oC

IR (Neat) ν_{max}: 2925, 2852, 2371, 1649, 1586, 1523, 1465, 1364, 1254, 1167, 1122, 1042 cm^{-1}.

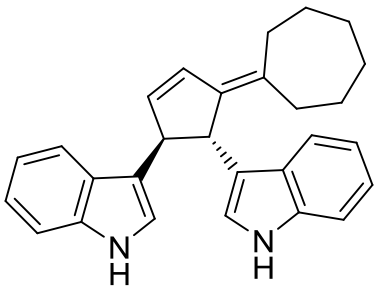
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.66-7.61 (m, 2H), 7.38-7.31 (m, 2H), 7.29- 7.27 (m, 2H), 7.14-7.09 (m, 2H), 6.90 (s, 1H), 6.83 (s, 1H), 6.78 (dd, 1H, J_1 = 5.5 Hz, J_2 = 2 Hz,) 6.09 (dd, H, J_1 = 5.5 Hz, J_2 = 2.5 Hz), 4.32 (s, 1H), 4.25 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 1.99 (s, 3H), 1.60 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 142.2, 137.6, 137.5, 135.9, 130.5, 127.1, 127.0, 125.9, 125.7, 124.4, 121.5, 121.3, 120.3, 120.2, 119.9, 118.8, 118.7, 118.4, 109.2, 109.1, 52.6, 46.6, 31.7, 21.4.

HRMS (ESI): Calcd for $C_{26}H_{26}N_2Na$: 389.19937; Found: 389.19969.

Compound 55fa

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53f** (50 mg, 0.15 mmol), indole **1a** (35 mg, 0.30 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **55fa** (31 mg, 53%) as colourless viscous liquid along with minor amount the product **54fa** (17 mg, 25%).



R_f : 0.43 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3408, 3056, 2923, 2853, 1703, 1619, 1583, 1517, 1485, 1455, 1338, 1227, 1095, 1012, 741 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.97 (s, 1H), 7.89 (s, 1H),7.59-7.57 (d, J= 8Hz, 2H), 7.37-7.34 (m, 2H), 7.21-7.16 (m, 2H), 7.07-7.05 (m, 2H), 6.98-6.93 (m, 2H), 6.76 (dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 1H), 6.04 (dd, J_1 = 5.5 Hz, J_2 = 3 Hz, 1H), 4.27 (s, 1H), 4.18 (brs, 1H), 2.57-2.51 (m, 2H), 2.25-2.19 (m, 1H), 2.07-2.06 (m, 1H), 1.72-1.29 (m, 8H).

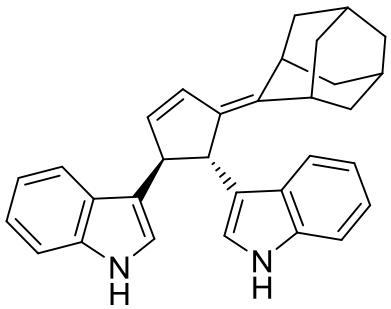
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 142.1, 136.9, 136.7, 135.9, 134.3, 130.4, 129.0, 128.2, 126.7, 126.6, 121.9, 121.5,120.8, 120.7,120.2,

120.1, 119.2,119.0, 111.0, 110.9, 52.5, 46.1, 32.8, 32.5, 29.8, 28.8, 27.2, 26.9.

HRMS (ESI): Calcd for $C_{28}H_{28}N_2Na$: 415.21502; Found: 415.21538.

Compound 55ga

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53g** (50 mg, 0.13 mmol), indole **1a** (31 mg, 0.27 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **55ga** (34 mg, 58%) as colourless viscous liquid along with minor amount the product **54ga** (20 mg, 30%).



R_f : 0.43 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3289, 3066, 2931, 2857, 1668, 1620, 1582, 1520, 1455, 1304, 1238, 933, 744 cm^{-1}.

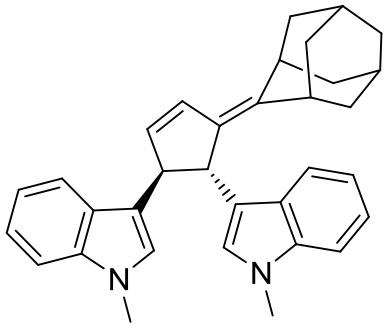
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.88 (s, 1H), 7.79 (s, 1H), 7.62 (d, *J* = 8 Hz, 1H), 7.55 (d, *J* = 8 Hz, 1H), 7.54-7.21 (m, 2H), 7.19-7.13 (m, 2H), 7.05- 6.93 (m, 4H), 6.72-6.71 (m, 1H), 5.94 (dd, J_1 = 5.5 Hz, J_2 = 3 Hz, 1H), 4.30 (s, 1H), 4.11 (brs, 1H), 3.12 (brs, 1H), 2.49 (brs, 1H), 2.04-1.68 (m, 9H), 1.53-1.43 (m, 2H), 0.88-0.84 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 140.8, 137.8, 137.0, 136.9, 135.4, 135.2, 129.5, 129.1, 128.3, 126.8, 126.5, 125.4, 122.0, 121.8, 120.9, 120.4, 119.2, 118.9, 111.2, 111.1, 52.4, 45.2, 39.8, 39.4, 38.2, 37.3, 35.1, 34.8, 28.4, 21.6.

HRMS (ESI): Calcd for $C_{31}H_{30}N_2Na$: 453.23067; Found: 453.23101.

Compound 55gb

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53g** (50 mg, 0.13 mmol), indole **1b** (35 mg, 0.27 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **55gb** (34 mg, 55%) as colourless viscous liquid along with minor amount the product **54gb** (22 mg, 32%).



R_f : 0.48 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3090, 2950, 2932, 2857, 1688, 1621, 1583, 1514, 1462, 1380, 1304, 1238, 1108, 1042, 957, 931, 743 cm^{-1}.

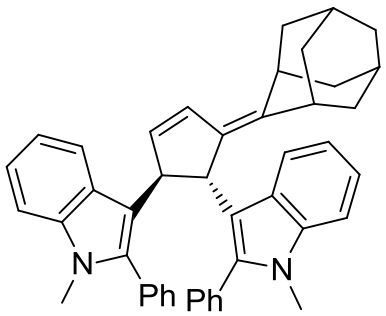
^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.65 (d, *J* = 8 Hz, 1H), 7.58 (d, *J* = 8 Hz, 1H), 7.33-7.20 (m, 6H), 7.08-7.02 (m, 2H), 6.89 (s, 1H), 6.83 (s, 1H), 6.73 (d, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 1H), 5.95 (t, *J* = 2.5 Hz, 1H), 4.32 (s, 1H), 4.13 (s, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.17 (s, 1H), 2.53 (s, 1H), 2.01-1.58 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 140.6, 137.6, 135.6, 135.2, 129.2, 127.2, 127.0, 125.6, 125.5, 121.5, 120.5, 120.3, 118.8, 118.8, 118.6, 109.1, 108.9, 52.5, 45.2, 39.8, 39.3, 38.2, 37.3, 35.0, 34.4, 32.6, 32.5, 28.4, 28.3.

HRMS (ESI): Calcd for $C_{33}H_{34}N_2Na$: 481.26197; Found: 481.26141

Compound 55gc

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53g** (50 mg, 0.13 mmol), indole **1c** (52 mg, 0.27 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **55gc** (58 mg, 74%) as colourless viscous liquid along with minor amount the product **54gc** (10 mg, 13%).



R_f : 0.55 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 2981, 2915, 2833, 1671, 1621, 1586, 1542, 1380, 1300, 1238, 1042, 957, 931, 743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.62-7.47 (m, 6H), 7.38-6.96 (m, 12H), 6.66 (dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 1H), 6.04 (dd, J_1 = 5.5 Hz, J_2 = 2.5 Hz, 1H), 4.41 (brs, 1H), 4.22 (brs, 1H), 3.61 (s, 3H), 3.57 (s, 3H), 2.98 (brs, 1H), 2.32 (brs, 1H), 1.83-1.50 (m, 12H).

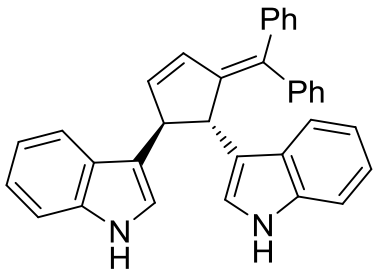
^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 140.2, 137.9, 137.4, 136.2, 135.8, 134.6, 133.9, 133.4, 131.3, 130.5, 129.7, 128.7, 128.2, 127.7, 127.5, 126.6, 125.3, 122.3, 121.4, 120.3, 119.5, 119.1, 119.0, 117.5, 115.2, 108.9, 108.7, 51.0, 45.3, 39.3, 38.9, 37.8, 37.4, 34.9, 33.1, 30.9, 28.1.

HRMS (ESI): Calcd for $C_{45}H_{42}N_2Na$: 633.32457; Found: 633.32486.

Compound 55ha

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53h** (45 mg, 0.11 mmol), indole **1a** (26 mg, 0.22 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere

for 4 hours gave the product **55ha** (43 mg, 84%) as pale yellow solid along with minor amount the product **54ha** (5 mg, 8%).



R_f : 0.43 (hexane/ethyl acetate = 3:1).

Mp : 154-156 ^oC.

IR (Neat) ν_{max}: 3294, 2857, 2366, 2335, 1647, 1590, 1369, 1120, 1037, 702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.90 (s, 1H), 7.67-7.51 (m, 3H), 7.37-7.06 (m, 9H), 6.98-6.78 (m, 9H), 6.40 (d, *J* = 4 Hz, 1H), 6.24 (brs, 1H), 4.51-4.49 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 148.1, 143.2, 142.6, 140.4, 136.8, 136.5, 135.0, 133.1, 129.8, 129.3, 127.9, 127.4, 126.7, 126.5, 126.2, 125.9, 122.0, 121.5, 120.8, 120.1, 119.8, 119.5, 119.3, 119.0, 118.9, 111.1, 110.9, 57.7, 48.5.

HRMS (ESI): Calcd for $C_{34}H_{26}N_2Na$: 485.19937; Found: 485.19969.

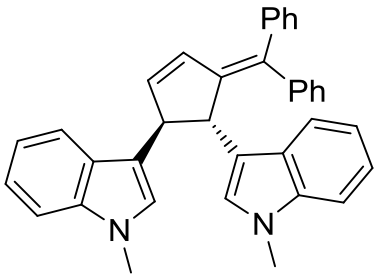
Compound 55hb

Following the general experimental procedure, the pentafulvene derived bicyclic hydrazine **53h** (45 mg, 0.11 mmol), indole **1a** (29 mg, 0.22 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL acetonitrile at room temperature under argon atmosphere for 4 hours gave the product **55hb** (44 mg, 81%) as yellow solid along with minor amount the product **54hb** (6 mg, 10%).

R_f : 0.48 (hexane/ethyl acetate = 3:1).

Mp : 160-162 ^oC.

IR (Neat) ν_{max}: 3053, 2927, 1709, 1688, 1613, 1513, 1469, 1427, 1372, 1328, 1242, 1156, 1130, 1013, 740 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$, TMS): **δ** 7.78-7.76 (m,2H), 7.72-7.30 (m, 9H), 7.20-6.99 (m, 6H), 6.87 (brs, 3H), 6.52 (t, J = 3 Hz, 1H), 6.09 (dd, J_1 = 4 Hz, J_2 = 2.5 Hz, 1H), 4.66 (brs, 1H), 4.57-4.54 (m, 1H), 3.81 (s, 3H), 3.58 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): **δ** 148.8, 143.3, 143.0, 140.8, 137.6, 137.3, 134.9, 132.9, 129.9, 129.3,129.2, 128.4, 128.0, 127.4, 127.2, 127.2, 126.8, 126.5, 125.8, 125.7, 121.7, 121.1, 120.3, 120.0, 118.9, 118.4, 118.1, 117.6, 109.3, 109.1, 51.8, 48.9, 32.6, 32.2.

MS (ESI): Calcd for $C_{36}H_{30}N_2Na$: 513.23067; Found: 513.23098.

3.8. References

1 G. Bartoli, G. Bencivenni and R. Dalpozzo, *Chem. Soc. Rev.*, 2010, **39**, 4449–4465.

2 S. Lancianesi, A. Palmieri and M. Petrini, *Chem. Rev.*, 2014, **114**, 7108–49.

3 M. Berger, J. A. Gray and B. L. Roth, *Annu. Rev. Med.*, 2009, **60**, 355–66.

4 H. D. King, Z. Meng, J. A. Deskus, C. P. Sloan, Q. Gao, B. R. Beno, E. S. Kozlowski, M. A. Lapaglia, G. K. Mattson, T. F. Molski, M. T. Taber, N. J. Lodge, R. J. Mattson and J. E. Macor, *J. Med. Chem.*, 2010, **53**, 7564–7572.

5 J. S. Beer, K. Clarke, H. K. Khorana and A. Robertson, *J. Chem. Soc.*, 1948, 885–889.

6 F. Meggio, A. D. Deana, M. Ruzzene, A. M. Brunati, L. Cesaro, B. Guerra, T. Meyer, H. Mett, D. Fabbro, P. Furet, G. Dobrowolska and L. A. Pinna, *Eur. J. Biochem.*, 1995, **234**, 317–322.

7 M. Prudhomme, *Eur. J. Med. Chem.*, 2003, **38**, 123–140.

8 K. S. Ryan and C. L. Drennan, *Chem. Biol.*, 2009, **16**, 351–364.

9 S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873–2920.

10 M. Bandini and A. Eichholzer, *Angew. Chem. Int. Ed.*, 2009, **48**, 9608–9644.

11 K. B. Jensen, J. Thorhauge, R. G. Hazell and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2001, **40**, 160–163.

12 D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam and J. Wu, *J. Am. Chem. Soc.*, 2003, **125**, 10780–10781.

13 W. Zhuang, T. Hansen and K. A. Jørgensen, *Chem. Commun.*, 2001, 347–348.

14 C. Palomo, M. Oiarbide, B. G. Kardak, J. M. García and A. Linden, *J. Am. Chem. Soc.*, 2005, **127**, 4154–4155.

15 D. A. Evans, K. R. Fandrick and H.-J. Song, *J. Am. Chem. Soc.*, 2005, **127**, 8942–8943.

16 W. Zhuang, R. G. Hazell and K. A. Jørgensen, *Org. Biomol. Chem.*, 2005, **3**, 2566–2571.

17 J. Szmuszkovicz, *J. Am. Chem. Soc.*, 1957, **79**, 2819–2821.

18 A. Taheri, B. Lai, C. Cheng and Y. Gu, *Green Chem.*, 2015, **17**, 812–816.

19 C.-W. Cai, X.-L. Zhu, S. Wu, Z.-L. Zuo, L.-L. Yu, D.-B. Qin, Q.-Z. Liu and L.-H. Jing, *Eur. J. Org. Chem.*, 2013, 456–459.

20 N. P. Grimster, C. Gauntlett, C. R. A. Godfrey and M. J. Gaunt, *Angew. Chem. Int. Ed.*, 2005, **44**, 3125–3529.

21 R. J. Phipps, N. P. Grimster and M. J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130**, 8172–8174.

22 G. Yan, C. Kuang, Y. Zhang and J. Wang, *Org. Lett.*, 2010, **12**, 1052–1055.

23 M. Tobisu, S. Yamaguchi and N. Chatani, *Org. Lett.*, 2007, **9**, 3351–3353.

24 X.-Y. Liu, P. Gao, Y.-W. Shen and Y.-M. Liang, *Org. Lett.*, 2011, **13**, 4196–4199.

25 P. M. Habib, V. Kavala, C.-W. Kuo and C.-F. Yao, *Tetrahedron Lett.*, 2008, **49**, 7005–7007.

26 M. Shiri, M. A. Zolfigol, H. G. Kruger and Z. Tanbakouchian, *Chem. Rev.*, 2010, **110**, 2250–2293.

27 M. Chakrabarty, R. Basak, N. Ghosh and Y. Harigaya, *Tetrahedron*, 2004, **60**, 1941–1949.

28 G. Bartoli, M. Bosco, S. Giuli, A. Giuliani, L. Lucarelli, E. Marcantoni, L. Sambri and E. Torregiani, *J. Org. Chem.*, 2005, **70**, 1941–1944.

29 R. P. Herrera, V. Sgarzani, L. Bernardi and A. Ricci, *Angew. Chem. Int. Ed.*, 2005, **44**, 6576–6579.

30 R. Ballini, R. R. Clemente and A. Palmieri, *Adv. Synth. Catal.*, 2006, **348**, 191–196.

31 N. P. Marullo and J. A. Alford, *J. Org. Chem.*, 1968, **33**, 2368–2370.

CHAPTER 4

Palladium/Lewis acid mediated domino reaction of pentafulvene derived diazabicyclic olefins: Efficient access to spiropentacyclic motif with an indoline and pyrazolidine fused to cyclopentene

4.1. Introduction

The construction of carbon-carbon bonds with concomitant formation of multi stereogenic carbon centers have acquired much attention in the current organic synthesis.[1] The ability to perform multiple reactions on a single substrate in a complex chemical environment is a grand challenge in many different aspects of chemistry and materials science. In this scenario, catalytic domino transformation offers a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step.[2,3] Furthermore, the increase in efficiency favours the economic and ecological feasibility of this type of process towards the synthesis of complex polyheterocycles. Among the self-evident domino reactions, skeletal rearrangements of simple precursors are powerful processes for generating molecular diversity with atom economy.[4,5]

A polyheterocyclic system with rigid conformation *via* restriction of three dimensional relationships of multiple functional groups often renders specific and promising pharmacological properties.[6,7] Owing to their structural rigidity, cyclopentane-annulated heterocycles are important cores of biologically active molecules. Among these cores, nitrogen heterocycles such as indole,[8] indoline[9] and

pyrazolidine[10,11] motifs are very common. Some of the important molecules with fused indole/indoline framework are shown in figure 4.1.

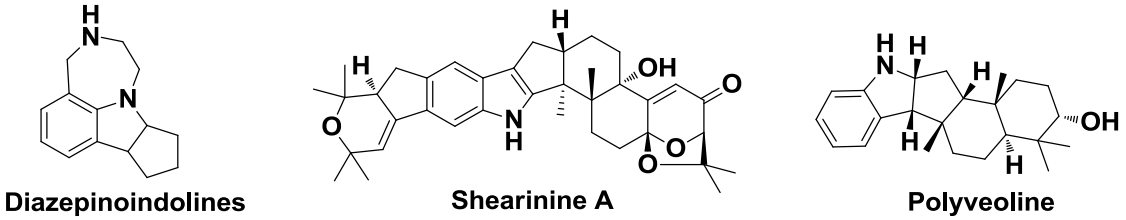


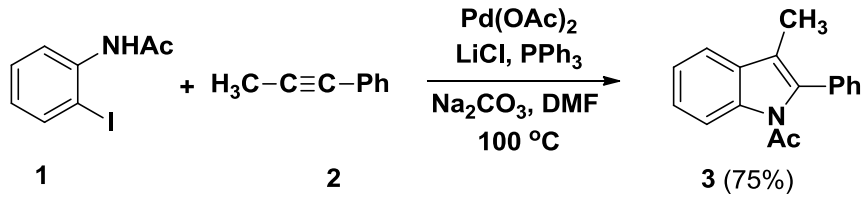
Figure 4.1

A number of stereoselective transformations were performed on *meso* bicyclic hydrazines, most of them being reported in the last decade by the research groups of Kaufmann,[12] Micouin,[13] Pineschi,[14–17] Lautens,[18–20] and Miller[21] describing the access of cyclopentanoids and cyclopentannulated ring systems. Our laboratory has contributed significantly in this area towards the synthesis of pharmaceutically important cyclopentanoids.[22] The present chapter discloses a facile methodology for the stepwise and one pot strategy for the synthetic transformation of pentafulvene derived diazabicyclic olefins to spiropentacyclic motifs with indoline and pyrazolidine fused to the cyclopentene core. Before going to the details a brief discussion on the palladium catalyzed annulation reaction of 2-iodophenols and 2-iodoanilines is outlined below.

4.2. Transition metal catalyzed annulation reactions of *o*-substituted aryl halides

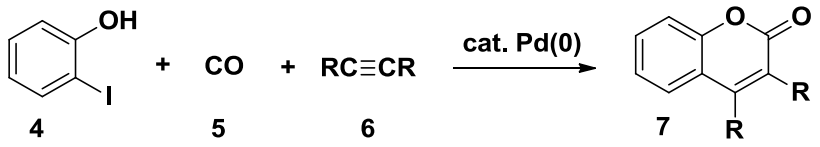
4.2.1. Annulation with alkynes

Annulation in organic chemistry is a chemical reaction in which a new ring is constructed on another molecule (often another ring). In 1991, the research group of Larock reported a conceptually simple approach to indoles involving the palladium catalyzed heteroannulation of internal alkynes using *o*-iodoanilines (Scheme 4.1).[23]



Scheme 4.1

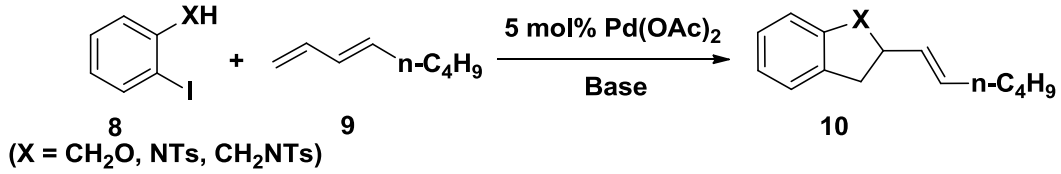
They have also demonstrated the synthesis of substituted coumarins in reasonable yields through the simultaneous insertion of both alkynes and carbon monoxide under the suitable reaction conditions (Scheme 4.2).[24]



Scheme 4.2

4.2.2. Annulation with 1,3-dienes

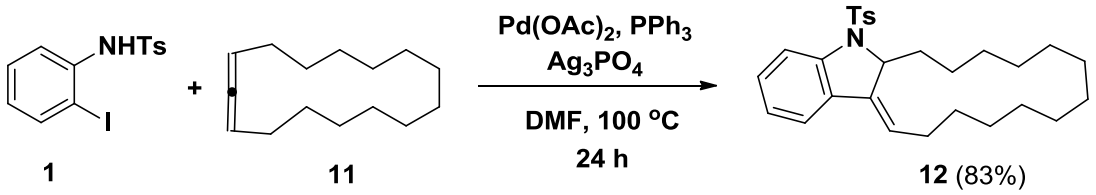
1,3-dienes readily undergo heteroannulation with appropriately functionalized aryl iodides and a suitable Pd catalyst (Scheme 2.1). The *ortho*- functionalized aryl halides afforded the corresponding heterocycle derivatives on reaction with 1,3-dienes (Scheme 4.3).[25]



Scheme 4.3

4.2.3. Annulation with allenes

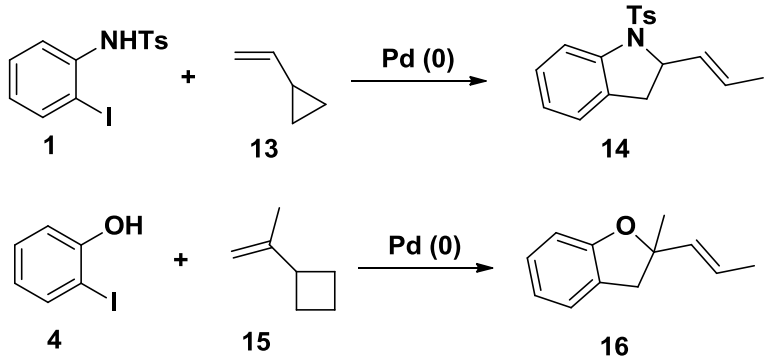
Since organopalladium compounds add to 1,2-dienes to produce π-allylpalladium compounds, allenes readily undergo annulation with a wide variety of functionalized aryl halides. Variety of acyclic and cyclic allenes have been successfully annulated by functionalized aryl iodides as depicted in Scheme 4.4.[26]



Scheme 4.4

4.2.4. Annulation with vinyl cyclopropanes and vinyl cyclobutanes

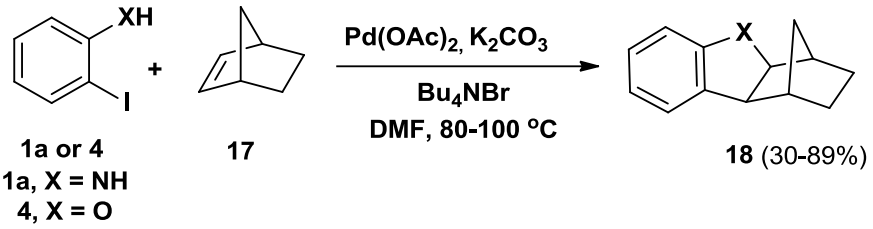
The pioneering work of Larock in the area of annulations also include unsaturated cyclopropanes and cyclobutanes with different *o*-functionalized aryl halides.[27,28] They have shown that aryl iodide substituted in the *ortho* position by OH, NH_2, NHTs, CH_2OH and $CH(CO_2Et)$ groups reacts with vinyl cyclopropanes and cyclobutanes in presence of palladium catalyst and appropriate base to afford heterocycles and carbocycles in good yields (Scheme 4.5).



Scheme 4.5

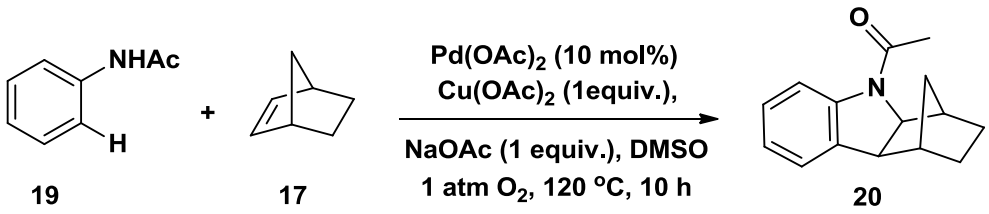
4.3. Annulation reactions of norbornene and its derivatives

Catellani and coworkers used the palladium catalysis in the heteroannulation of strained olefin such as norbornene.[29,30] They trapped the aryl norbornylpalladium complexes derived from norbornene, palladium catalyst and aryl halides, towards the synthesis of fused dihydro-furans or -pyrroles (Scheme 4.6).



Scheme 4.6

Very recently Jiang *et al.* developed an efficient Pd-catalyzed oxidative cyclization reaction for the synthesis of functionalized indolines by direct C-H activation of acetanilide (Scheme 4.7).[31]



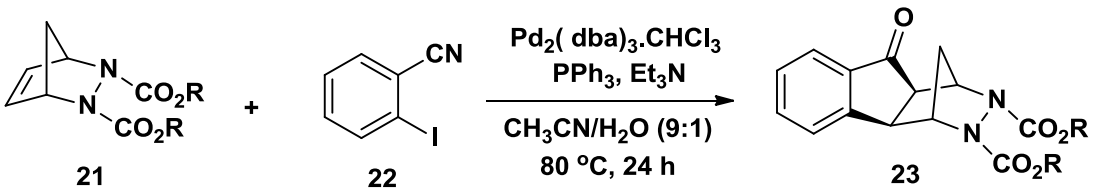
Scheme 4.7

4.4. Annulation reactions of diazanorbornenes

4.4.1. Annulation with diethyl(2-iodophenyl)malonate

In 2011, we have developed a one pot strategy for the synthesis of highly functionalized indanones **23** through the palladium-catalyzed annulation of 2-iodobenzonitrile **22** with various bicyclic olefins **21**. The methodology provides an

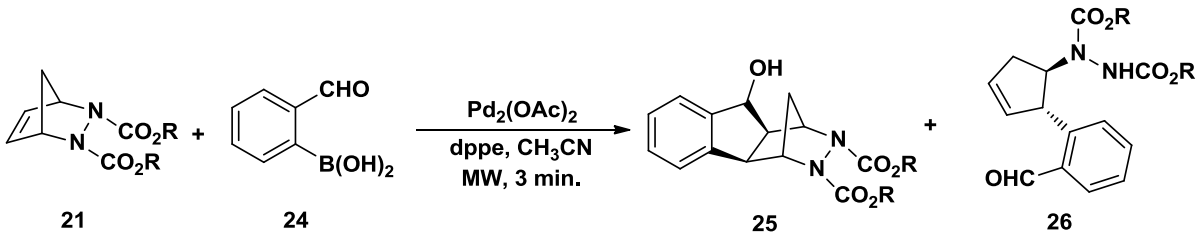
easy access to indanones which constitute the core structures of many biologically active compounds, synthetic intermediates for pharmaceuticals and ligands for olefin polymerization catalysts (Scheme 4.8).[32]



Scheme 4.8

4.4.2. Annulation with 2-formylphenylboronic acid

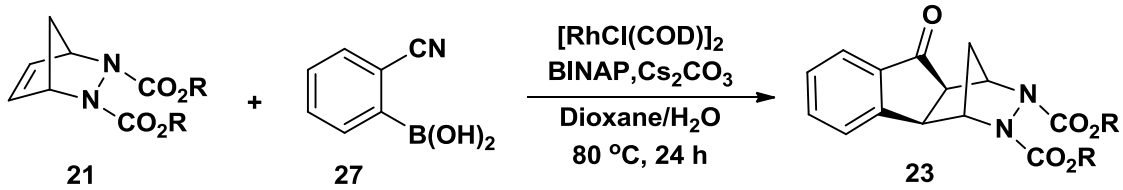
The protocol of ring annulation was then extended to the carbonylative cyclization of bicyclic hydrazines **21** with 2-formylphenylboronic acid **24** under microwave irradiation. The reaction afforded 3,4-disubstituted cyclopentenes **26** as a minor product along with indanols **25** (Scheme 4.9).[32]



Scheme 4.9

4.4.3. Annulation with 2-cyanophenylboronic acid

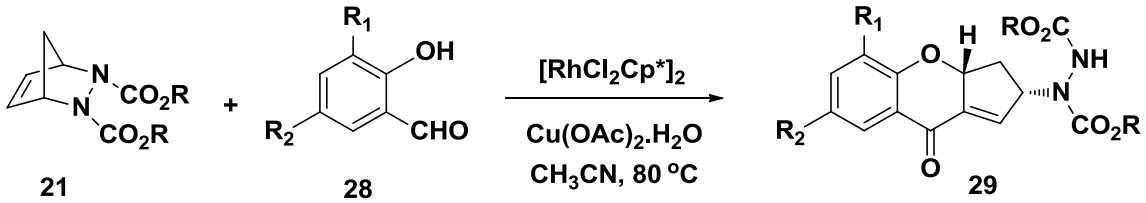
We have also demonstrated an alternative and efficient method for the synthesis of highly functionalized indanone **23** using 2-cyanophenylboronic acid **27** under rhodium catalysis (Scheme 4.10).[32]



Scheme 4.10

4.4.4. Oxidative coupling of salicylaldehydes with diazabicyclic olefins

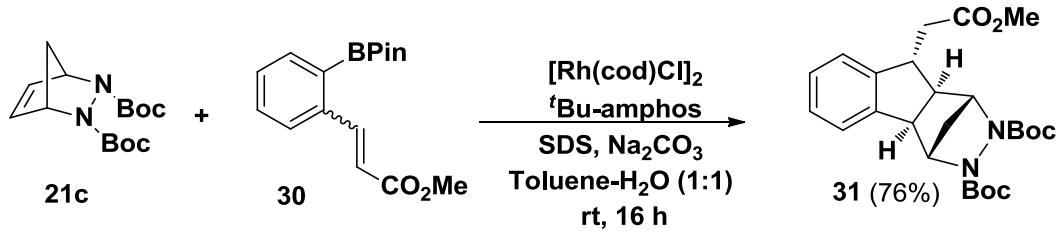
An efficient one pot strategy has been developed for the synthesis of cyclopentene fused chromanone derivatives **29** through the direct oxidative coupling of salicylaldehydes **28** with bicyclic olefins (Scheme 4.11).[33]



Scheme 4.11

4.4.5. Carboannulation with arylboronic esters

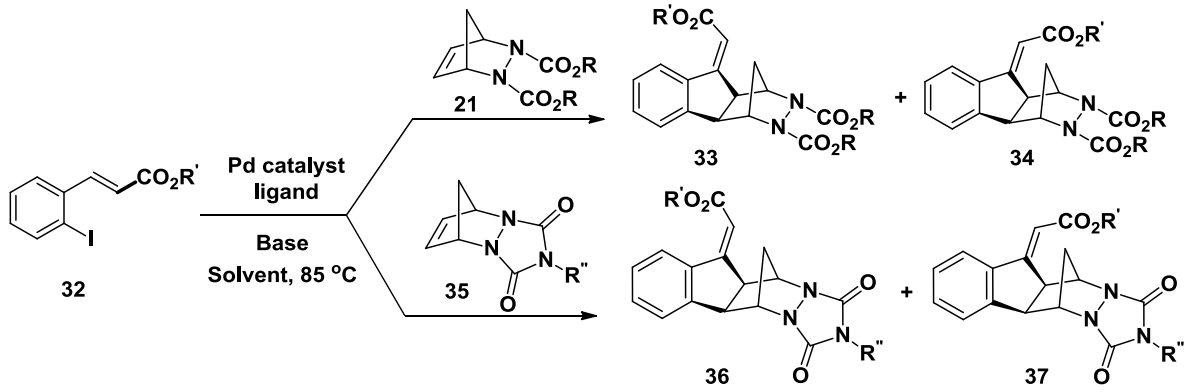
Lautens and Mancuso reported a rhodium-catalyzed tandem carbocyclization of arylboronic esters bearing a pendant Michael-acceptor alkene **30** and azabicyclic olefin **21c** to produce highly functionalized indanes **31**. The reaction gives access to highly functionalized polycyclic systems with the generation of three asymmetric centers in a single step and fully diastereoselective manner (Scheme 4.12).[34]



Scheme 4.12

4.4.6. Carboannulation with 2-iodostyrenes

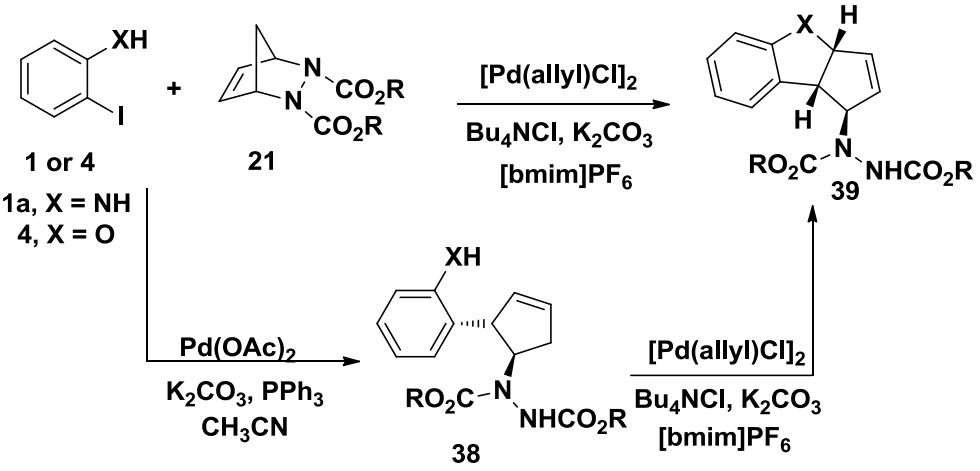
Functionalized indanes were synthesized efficiently by the palladium catalyzed carboannulation of *o*-iodostyrenes with diazabicyclic olefins. Variety of functional groups such as esters, ketone and nitrile as substituents on the iodostyrenes well tolerated the reaction, which explains the synthetic potential of the product for further transformations (Scheme 4.13).[35]



Scheme 4.13

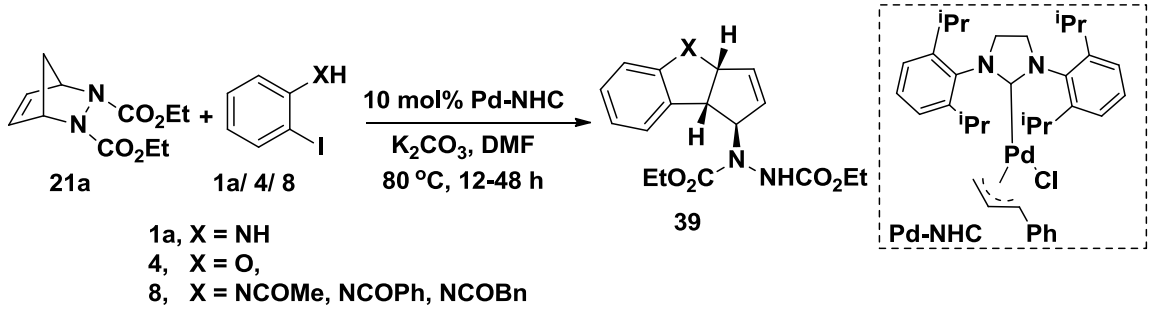
4.5. Domino ring annulation of diazanorbornenes

Domino transformations, as multi-step one-pot processes, are effective tools in organic synthesis, allowing the formation of several new bonds in a simple and elegant one-pot synthetic operation, thereby providing access to various types of molecular entities. Recently, we have reported a very promising palladium catalyzed ring opening of diazabicyclic alkenes **56** with subsequent ring closure to give cyclopentene annulated benzofuran and indole derivatives (Scheme 4.14).[36]



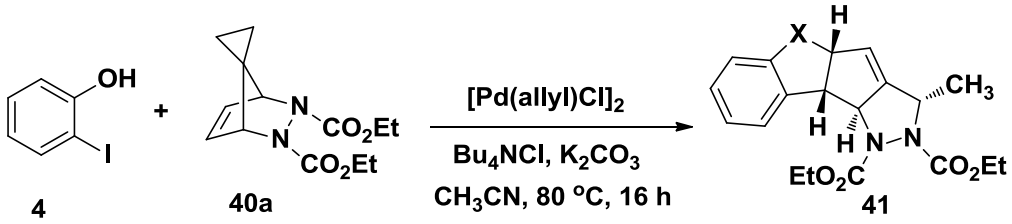
Scheme 4.14

A palladium-NHC catalyzed cyclopentannulation of diazabicyclic alkenes with *ortho*-functionalized aryl halides was also reported by Gilberston *et al.* (Scheme 4.15).[37]



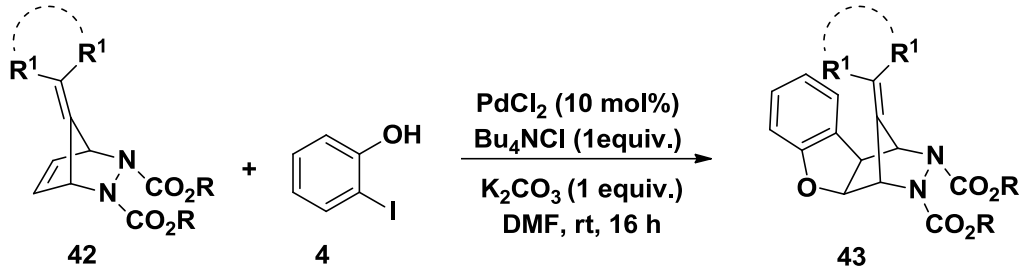
Scheme 4.15

In 2013, we extended the scope of the reaction with cyclopropane appended spirotricyclic olefins **40a** with 2-iodophenol **4** towards the formation of a tetracyclic framework **41** with multiple stereocenters (Scheme 4.16).[38]



Scheme 4.16

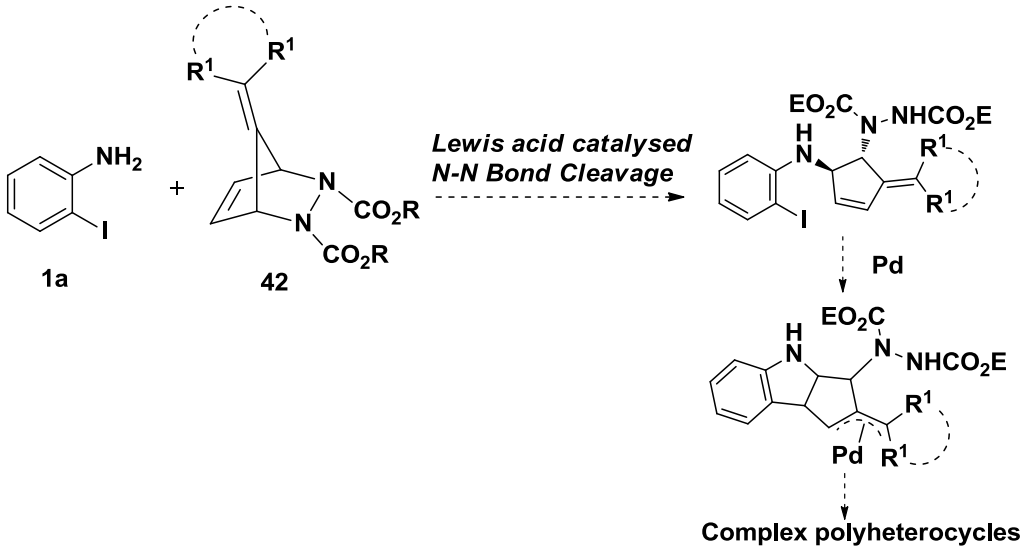
After a while, we carried out a palladium catalysed reaction of fulvene derived azabicyclic olefins and *o*-iodophenol envisaging a domino reaction leading to a polycyclic framework with multiple stereocentres. But the reaction ended up with the formation of a highly functionalized dihydrobenzofuran fused azabicycles instead of the expected complex polyheteocycle (Scheme 4.17).[39]



Scheme 4.17

4.6. Statement of the Problem

Encouraged by these results we extended the palladium catalysis towards the synthesis of indoline derivatives using 2-iodoaniline, but the reaction failed to afford the product. Considering the wide applicability of nitrogen heterocycles in various aspects of life we tried alternate methods to achieve the reaction. Eventually we have accomplished our target with a Lewis acid catalysed ring opening of **42** followed by an intramolecular Heck reaction towards the construction of complex polyheterocyclic molecules (Scheme 4.18).

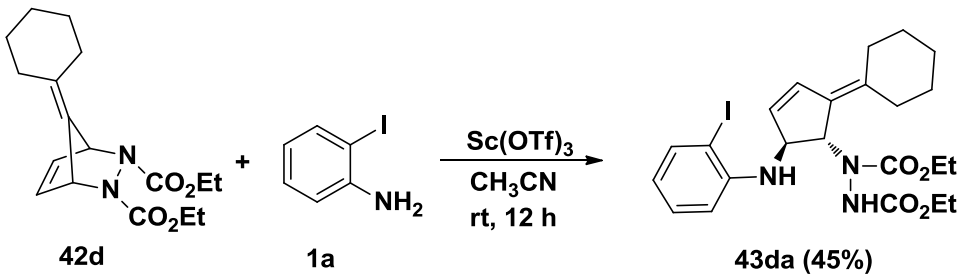


Scheme 4.18

The results of the Lewis acid/Pd catalyzed step-wise and one pot synthesis of the spiropentacyclic motif with an indoline and pyrazolidine fused to cyclopentene are presented in the following sections.

4.7. Results and discussion

Our experiments started with the reaction of **42d** and 2-iodoaniline **1a** using $Sc(OTf)_3$ as the Lewis acid in acetonitrile at room temperature, trans-3,4-Disubstituted alkylidene cyclopentene **43da** was formed exclusively in 45% yield (Scheme 19).



Scheme 4.19

The structure of the compound **43da** was established by various spectroscopic studies. In the IR spectrum, the signals at 3387, 3284 cm^{-1} were diagnostic of the NH absorption whereas the carbethoxy groups were discernible at 1709 cm^{-1}. In the ^{1}H NMR spectrum (Figure 4.2), the two ring olefinic protons were observed as a doublet at δ 6.65 ppm (d, J = 5 Hz) and a broad singlet at δ 5.95 ppm respectively. A broad peak in the range of δ 6.21-6.17 ppm represents the NH proton of the hydrazine moiety. The multiplet in the range δ 5.10-4.92 ppm was assigned as the proton attached to the C-3 carbon atom. The proton at C-4 carbon atom resonated as a multiplet in the range of δ 4.92-4.68 ppm. The two CH_2 protons from the carbethoxy group along with the NH proton (exchangeable with deuterium) of aniline resonated in the range of δ 4.23-4.08 ppm as multiplet.

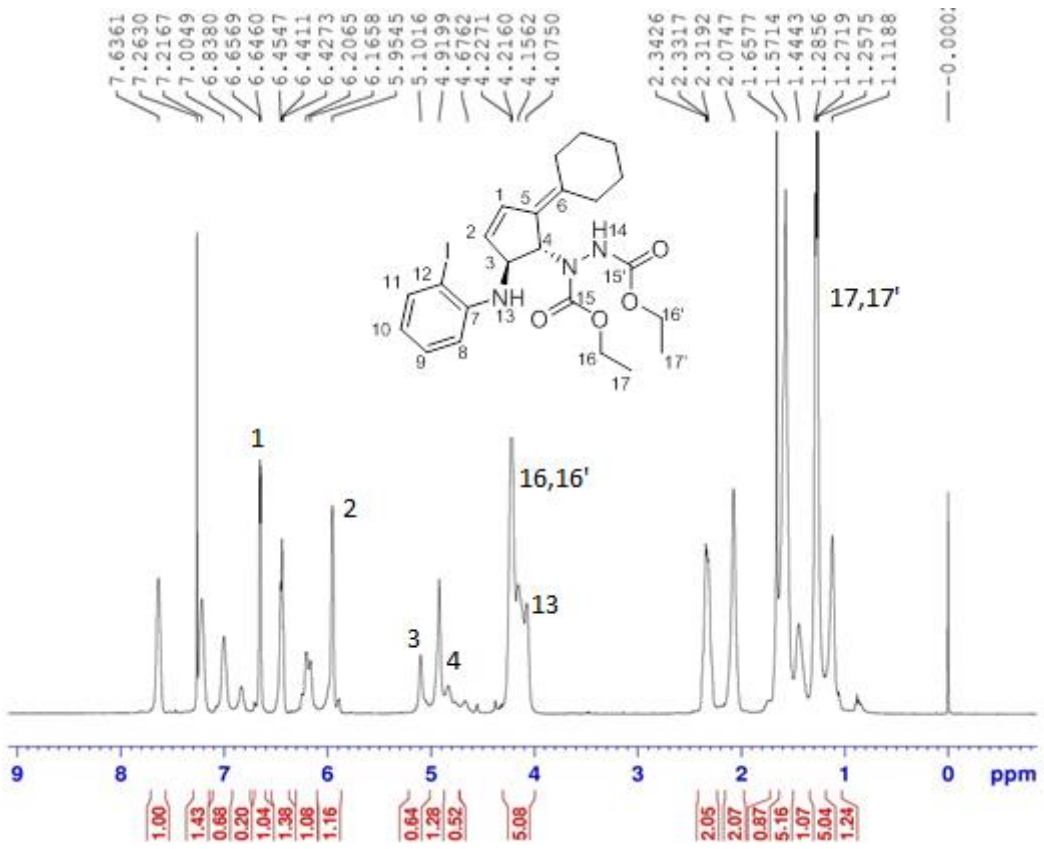


Figure 4.2. ^{1}H NMR spectrum of compound **43da**

The ^{13}C NMR spectrum (Figure 4.3) of **43da** showed peaks at δ 156.4 and 155.2 ppm which correspond to the carbonyl carbons. The two olefinic protons were found to resonate at δ 134.2 and 132.3 ppm respectively. The aromatic carbon (C-12) attached to iodine resonated at δ 85.5 ppm. The peaks at δ 64.7 and 63.4 ppm were assigned to the C-4 and C-3 respectively. The methylene carbons of the ester groups resonated at δ 62.8 and 62.1 ppm. The methylene carbons of the ester groups resonated at δ 62.7 and 62.2 ppm. The methyl carbons of the carbethoxy group showed sharp peak at δ 14.6 ppm.

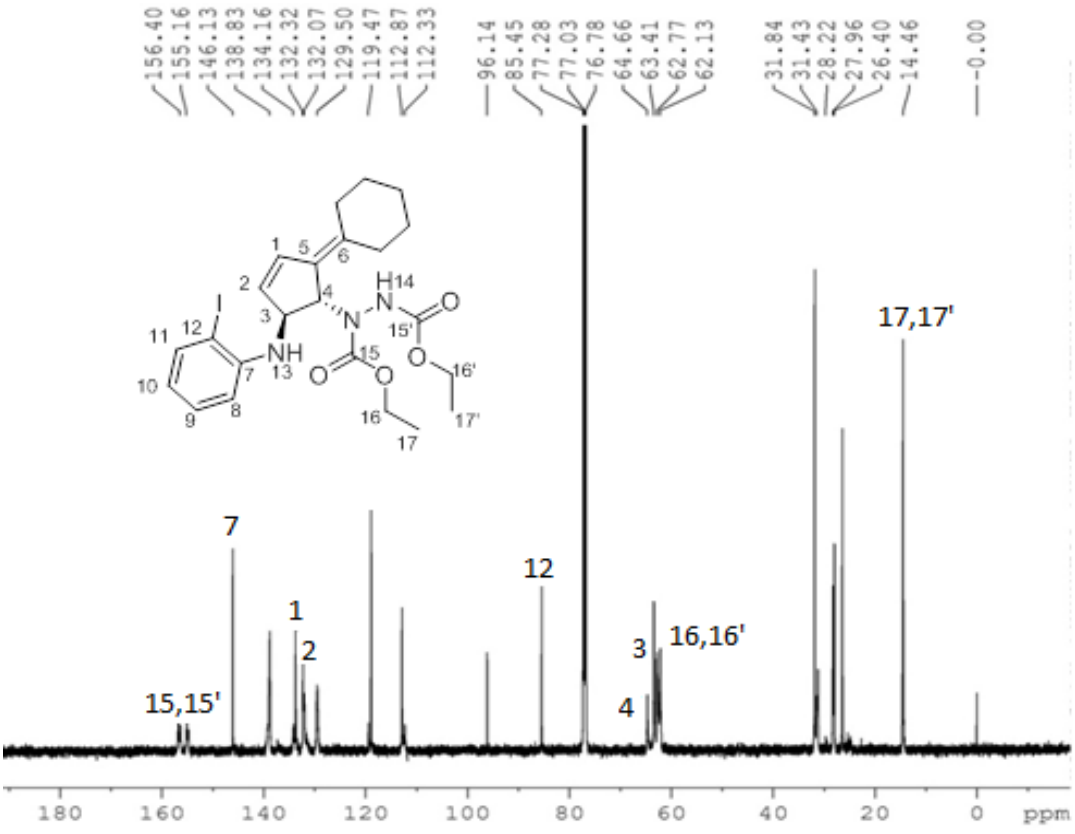


Figure 4.3. ^{13}C NMR spectrum of compound **43da**

Further evidence for the structure was obtained from high resolution mass spectral analysis of **43da** which showed the molecular ion peak at *m/z* = 562.1148

($C_{23}H_{30}IN_3O_4Na$). Finally the structure and stereochemistry of the compound **43da** was unambiguously confirmed by single crystal X-ray analysis (Figure 4.4).

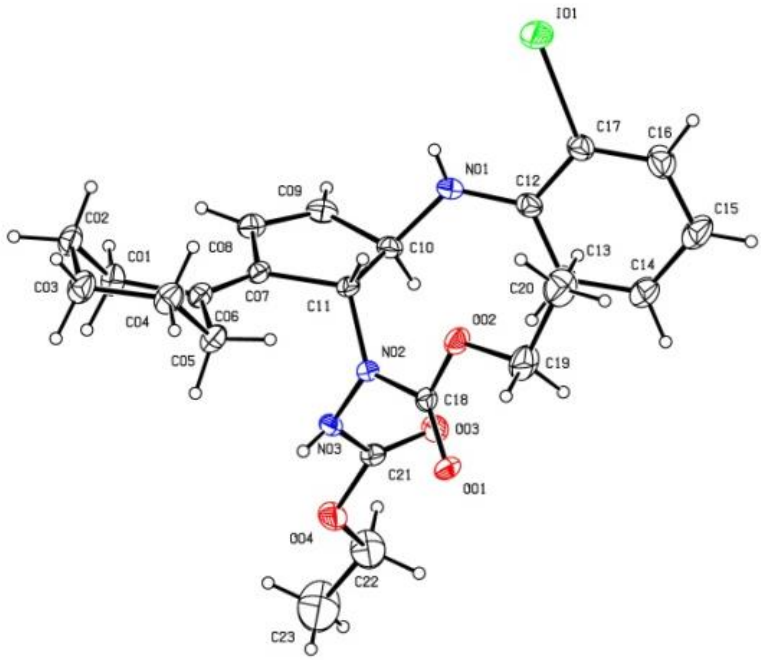
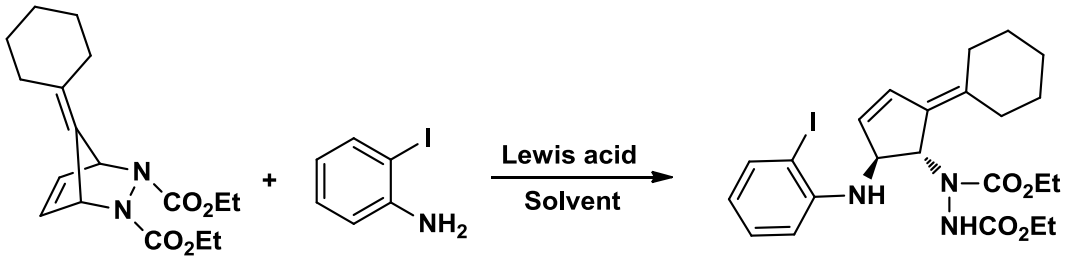


Figure 4.4. Single Crystal X-ray of **43da**

Detailed optimization studies were carried out to find the best conditions for this transformation. Screening of various Lewis acids revealed that $Sc(OTf)_3$ is the best catalyst for this transformation. From an extensive screening of reaction parameters, the best yield was obtained with 3 equiv. of bicyclic olefin and 1 equiv. of 2-iodoaniline in the presence of 2 mol% $Sc(OTf)_3$ in toluene at room temperature (Table 4.1). Under the optimized conditions, **43da** was obtained in 93% yield.

Table 4.1. Optimization for a suitable catalyst system



Entry	Lewis acid	Solvent	Yield (%)
1	$Sc(OTf)_3$	CH_3CN	45
2	$Sc(OTf)_3$	DMF	29
3	$Sc(OTf)_3$	THF	48
4	$Sc(OTf)_3$	Toluene	93
5	$Yb(OTf)_3$	Toluene	85
6	$Zn(OTf)_2$	Toluene	80
7	$La(OTf)_3$	Toluene	83
8	$Cu(OTf)_2$	Toluene	27
9	$AlCl_3$	Toluene	49

Reaction Conditions: alkene (3 equiv), *o*-iodoaniline(1 equiv), catalyst (2 mol%), solvent (2 mL), at rt

The diazabicyclic olefins derived from different pentafulvenes gave substituted alkylidenecyclopentenes in good to excellent yields (Table 4.2). To investigate the reactivity of substituted 2-iodoanilines, we carried out the reaction of 2-iodoanilines bearing $–NO_2$ and $-CF_3$ substituents. Both $-NO_2$ and $-CF_3$ substituted 2-iodoanilines afforded alkylidenecyclopentenes in moderate to good yields.

Table 4.2 Substrate Scope for Lewis acid catalyzed desymmetrization

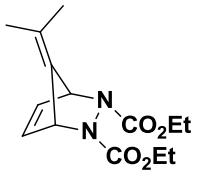
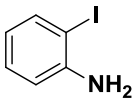
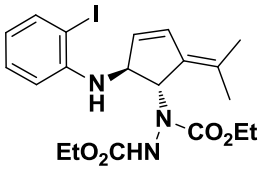
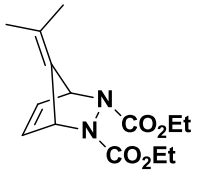
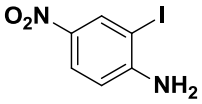
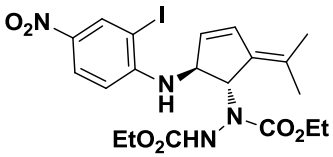
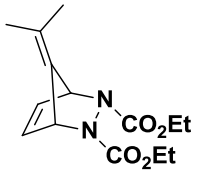
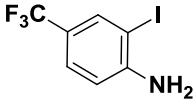
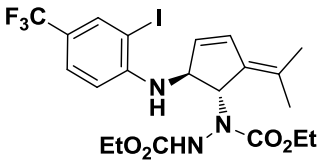
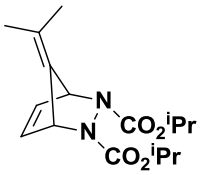
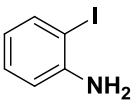
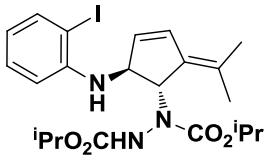
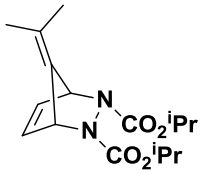
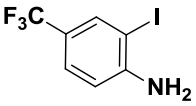
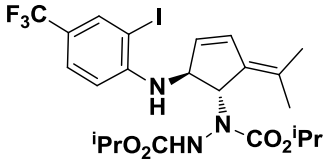
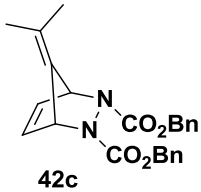
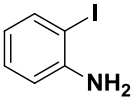
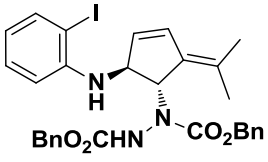
Entry	Bicyclic olefin	2-Iodoaniline	Product
1	 **42a**	 **1a**	 **43aa** (90%)
2	 **42a**	 **1b**	 **43ab** (73%)
3	 **42a**	 **1c**	 **43ac** (67%)
4	 **42b**	 **1a**	 **43ba** (84%)
5	 **42b**	 **1c**	 **43bc** (66%)
6	 **42c**	 **1a**	 **43ca** (72%)

Table 4.2 continues...

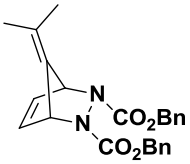
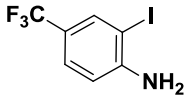
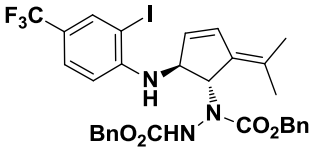
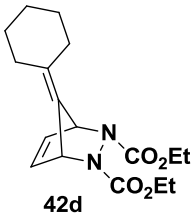
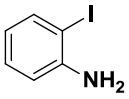
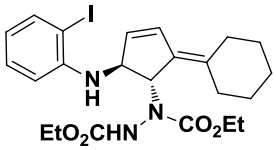
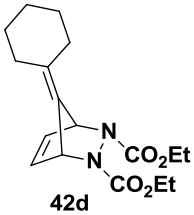
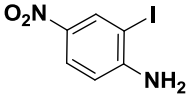
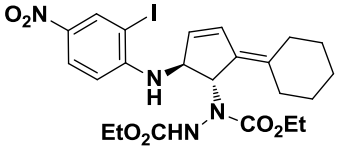
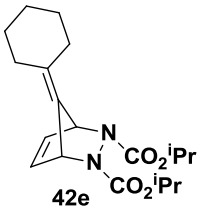
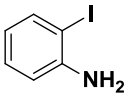
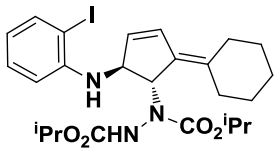
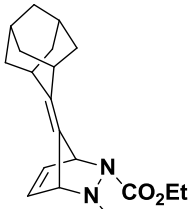
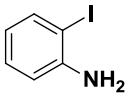
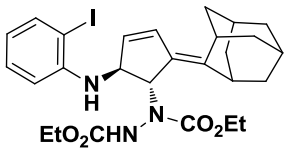
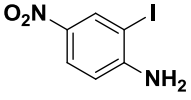
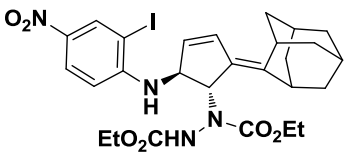
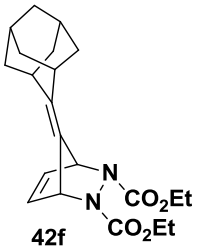
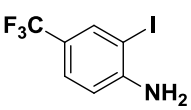
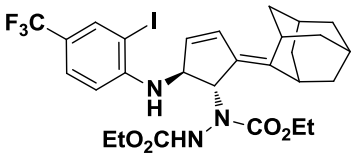
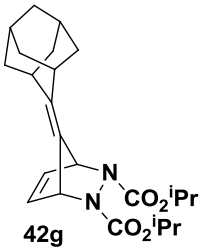
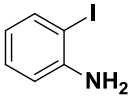
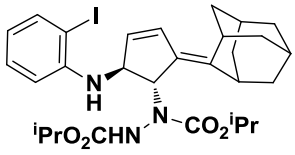
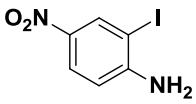
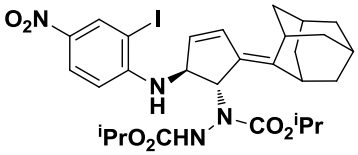
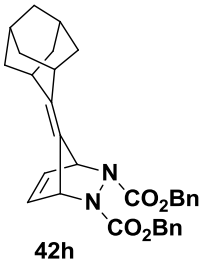
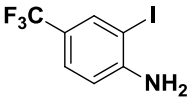
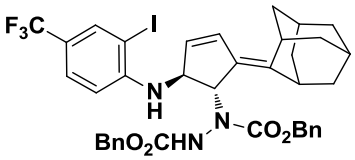
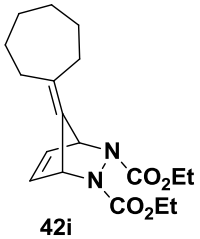
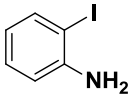
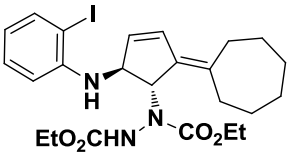
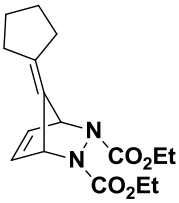
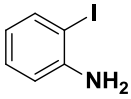
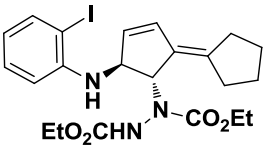
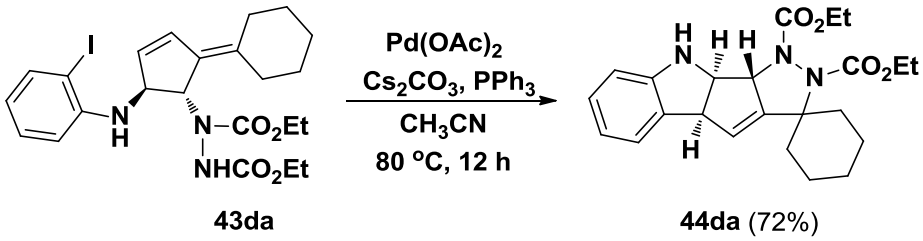
Entry	Bicyclic olefin	2-Iodoaniline	Product
7	 **42c**	 **1c**	 **43cc** (68%)
8	 **42d**	 **1a**	 **43da** (93%)
9	 **42d**	 **1b**	 **43db** (78%)
10	 **42e**	 **1a**	 **43ea** (84%)
11	 **42f**	 **1a**	 **43fa** (78%)
12	**42f**	 **1b**	 **43fb** (62%)

Table 4.2 continues...

Entry	Bicyclic olefin	2-Iodoaniline	Product
13	 **42f**	 **1c**	 **43fc** (72%)
14	 **42g**	 **1a**	 **43ga** (80%)
15	**42g**	 **1b**	 **43gb** (64%)
16	 **42h**	 **1c**	 **43hc** (64%)
17	 **42i**	 **1a**	 **43ia** (67%)
18	 **42j**	 **1a**	 **43ja** (68%)

Reaction conditions: alkene (3 equiv.), *o*-iodoaniline (1equiv.), $Sc(OTf)_3$ (2 mol%), Toluene (2 mL), 2 h at rt.

To explore the synthetic utility of the alkylidenecyclopentenes, the intramolecular Heck cyclization of **43da** was conducted in the presence of $Pd(OAc)_2$ (5 mol%), PPh_3 and Cs_2CO_3 in acetonitrile at 80 ^oC. Gratifyingly, the indoline-pyrazolidine fused cyclopentene **44da** was obtained in 72% yield (Scheme 4.20).



43da **44da** (72%)

Scheme 4.20 Syntheis of derivatized indoline by intramolecular Heck cyclization

The structure of **44da** was established by IR, ^1H, ^{13}C and mass spectrometry. The IR spectrum showed characteristic NH absorption at 3375 cm^{-1} whereas the carbethoxy groups show a sharp signal at 1698 cm^{-1}. The ^1H NMR spectrum showed the aromatic protons as two multiplets at δ 7.71-7.04 (m, 2H) and 6.74-6.68 (m, 2H). The olefin proton was observed as broad singlet at δ 6.06 ppm. The proton attached to the C-3 carbon atom resonated as broad singlet at δ 4.66 ppm. The proton on the ring junction carbon (C-4) resonated as a multiplet in the range of δ 4.53-4.52 ppm. The proton attached to the neighboring carbon (C-5) shows a broad singlet at δ 4.37 ppm. The multiplet in the region δ 4.27- 4.13 ppm was assigned to the -CH_2- protons of two carbethoxy groups. The methyl protons of the carboethoxy groups resonated as multiplets at δ 1.29-1.20 ppm along with the methylene protons of cyclohexyl ring. The ^1H NMR spectrum of the compound **44da** is shown in Figure 4.5.

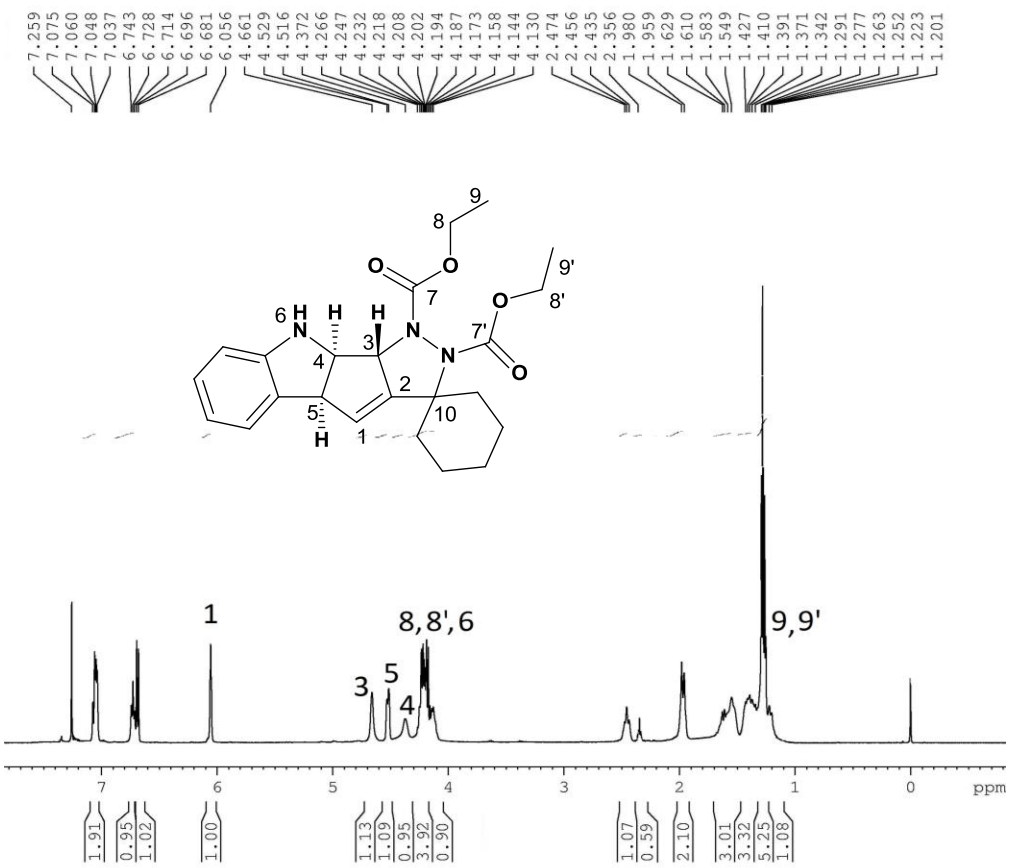


Figure 4.5 ^{1}H NMR spectrum of compound **44da**

The ^{13}C NMR spectrum (Figure 4.6) of **44da** showed peaks at δ 155.6 and 155.0 ppm which correspond to the carbonyl carbons. The signals of the olefinic carbons could be found along with the aromatic carbons in the region δ 148.8-109.2 ppm. The peak at δ 74.9 ppm was assigned to the C-10 carbon atom. The signal of ring junction carbon (C-4) was observed at δ 71.6 ppm. The signal at δ 64.3 was attributed to the carbon C-4 which is attached to the nitrogen atom of the indoline ring. The methylene carbons of the ester groups resonated at δ 61.3 and 61.1 ppm. The carbon atom (C-5) bonded to the aromatic ring displayed its signal at δ 56.0 ppm. The methyl carbons of the carboethoxy group showed sharp peaks at δ 13.6 and 13.4 ppm. The assigned structure of **44da** was well supported by mass spectra, showing the molecular ion peak at *m/z* 434.20336 ($C_{23}H_{29}N_3O_4Na$).

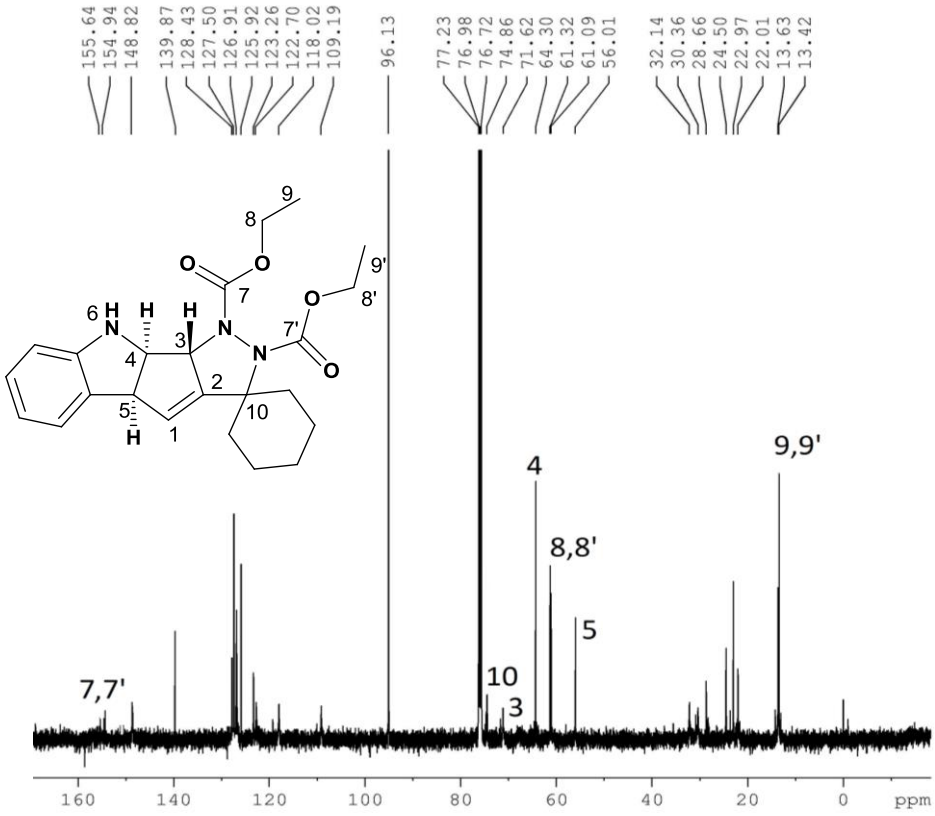


Figure 4.6 ^{13}C NMR spectrum of compound **44da**

Finally the structure and stereochemistry of the compound was unambiguously confirmed by single crystal X-ray analysis of the compound **44fa** (Figure 4.7).

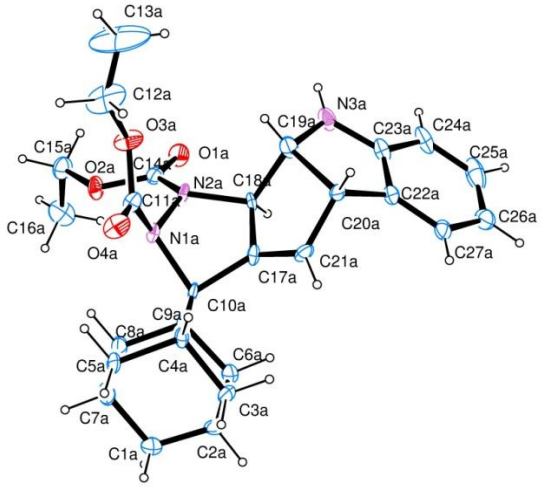
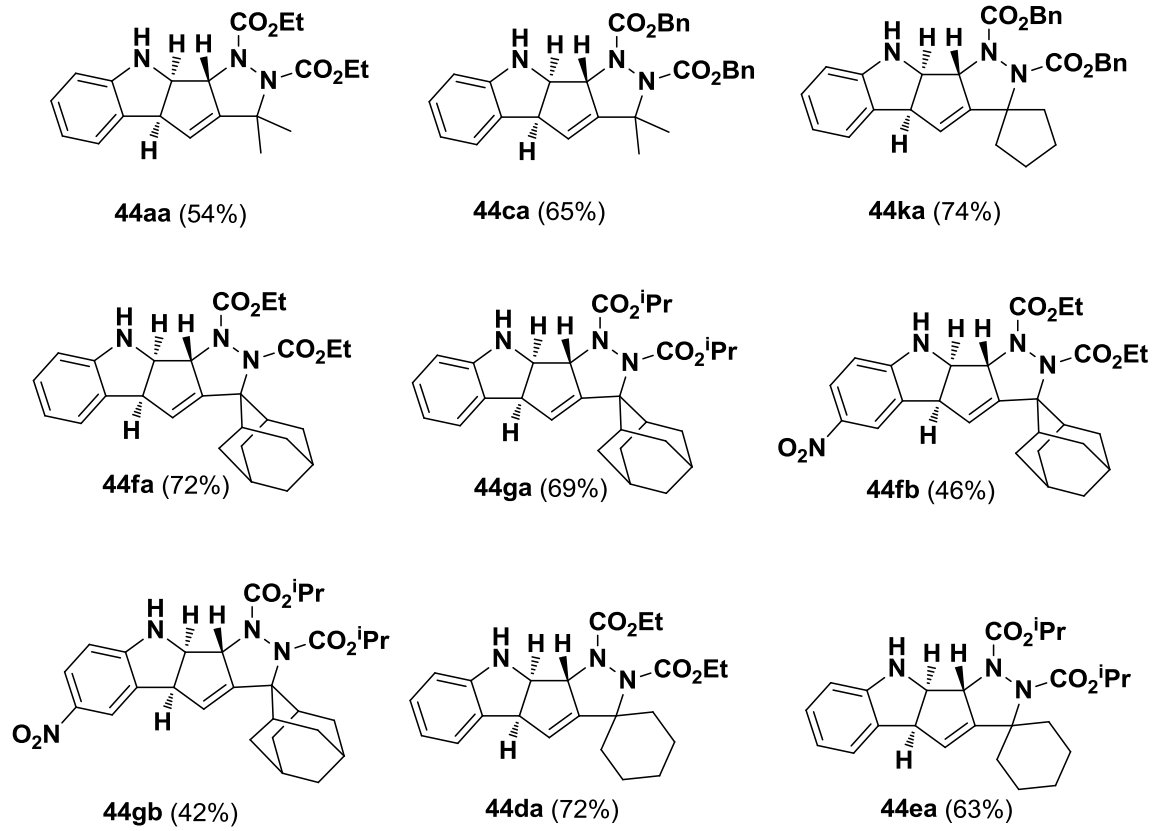


Figure 4.7. Single Crystal X-ray of **44fa**

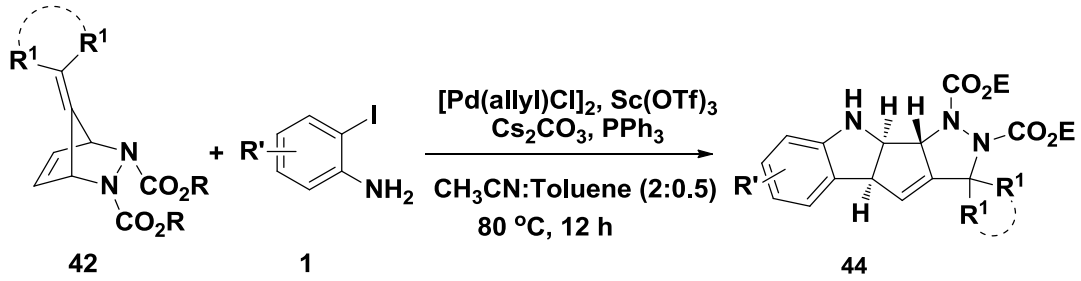
The intramolecular Heck cyclization of various alkylidenecyclopentenes was next examined, and the tandem palladium catalyzed cyclization smoothly afforded the corresponding indoline-pyrazolidine fused cyclopentenes in moderate to good yields (Table 4.3).

Table 4.3. Substrate Scope for Intramolecular Heck Cyclization



Reaction Conditions: 1 (3 equiv.), *o*-iodoaniline (1 equiv.), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), Cs_2CO_3 (1.5 equiv.) CH_3CN (2 mL), 12 h at 80 °C

Finally, in order to evaluate the one pot efficiency of this method, a tandem reaction was performed in the presence of a Lewis acid and palladium catalyst (Scheme 4.21).



Scheme 4.21

Interestingly, indoline-pyrazolidine fused cyclopentene was obtained in moderate to good yield. The reaction was found to be general with various pentafulvene derived bicyclic hydrazines. Detailed optimization studies were carried out to find the best conditions for the one-pot reaction (Table 4.4). The use of 5 mol% $[Pd(allyl)Cl]_2$, 2 mol% $Sc(OTf)_3$, 10 mol% PPh_3 and 1.5 equiv. Cs_2CO_3 in 2:0.5 mixture of acetonitrile-toluene for 12 hours at 80 ^oC resulted in the exclusive formation of spiropentacyclic molecule.

Table 4.4. Optimization for the one pot synthesis of indoline-pyrazolidine fused cyclopentene

Entry	Lewis acid	Pd Catalyst	Ligand	Base	Solvent	Temperature (°C)	Yield % 3	4
1	$Sc(OTf)_3$	$Pd(OAc)_2$	PPh_3	K_2CO_3	CH_3CN	80	10	21
2	$Sc(OTf)_3$	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	CH_3CN	80	20	28
3	$Sc(OTf)_3$	$Pd(OAc)_2$	PPh_3	KOAc	CH_3CN	60	trace amount	
4	$Sc(OTf)_3$	$Pd(OAc)_2$	PPh_3	Et_3N	CH_3CN	60	15	trace
5	$Sc(OTf)_3$	$PdCl_2$	PPh_3	Cs_2CO_3	CH_3CN	60	25	trace
6	$Sc(OTf)_3$	$[Pd(allyl)Cl]_2$	PPh_3	Cs_2CO_3	CH_3CN	60	–	28
7	$Sc(OTf)_3$	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	CH_3CN	80	trace	42
8	$Sc(OTf)_3$	$PdCl_2$	PPh_3	Cs_2CO_3	CH_3CN	80	trace amount	
9	$Sc(OTf)_3$	$Pd(PPh_3)_4$	PPh_3	Cs_2CO_3	CH_3CN	80	trace amount	
10	$Sc(OTf)_3$	$[Pd(allyl)Cl]_2$	PPh_3	Cs_2CO_3	CH_3CN	80	–	51
11	$Sc(OTf)_3$	$Pd(dba)_3CHCl_3$	PPh_3	Cs_2CO_3	CH_3CN	80	–	12
12	$Sc(OTf)_3$	$[Pd(allyl)Cl]_2$	PPh_3	Cs_2CO_3	CH_3CN	80	–	55
13[a]	$Sc(OTf)_3$	$[Pd(allyl)Cl]_2$	PPh_3	Cs_2CO_3	CH_3CN + Toluene	80	–	58
14[a]	$Sc(OTf)_3$	$[Pd(allyl)Cl]_2$	PPh_3	Cs_2CO_3	CH_3CN + Toluene	70	–	14
15[a]	$Sc(OTf)_3$	$[Pd(allyl)Cl]_2$	dppe	Cs_2CO_3	CH_3CN + Toluene	70	–	18

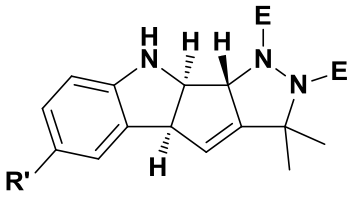
Reaction Conditions: alkene (3 equiv.), *o*-iodoaniline (1 equiv.), catalyst (5 mol%), base(1.5 equiv.), ligand (10 mol%), Lewis acid (2 mol%), solvent (2.5 mL) 12 hours at 80 °C

[a] CH_3CN:Toluene(2:0.5)

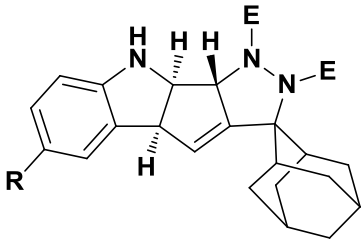
To explore the scope and generality of the one-pot reaction, the above reaction was repeated using differently substituted bicyclic hydrazine and *o*-iodoanilines. The

reaction was found to be general with various pentafulvene derived bicyclic hydrazines (Table 4.5).

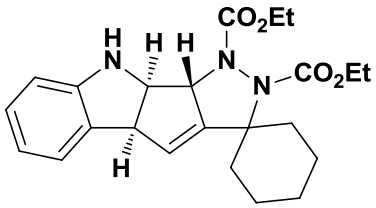
Table 4.5. One-pot synthesis of indoline derivative



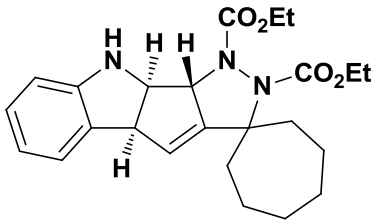
44aa, E = CO_2Et, R' = H, 54%
44ba, E = $CO_2{}^iPr$, R' = H, 74%
44ac, E = CO_2Et, R' = CF_3, 40%



44fa, E = CO_2Et, R' = H, 72%
44ga, E = $CO_2{}^iPr$, R' = H, 75%
69fb, E = CO_2Et, R' = NO_2, 46%
69gb, E = $CO_2{}^iPr$, R' = NO_2, 72%



44da (58%)

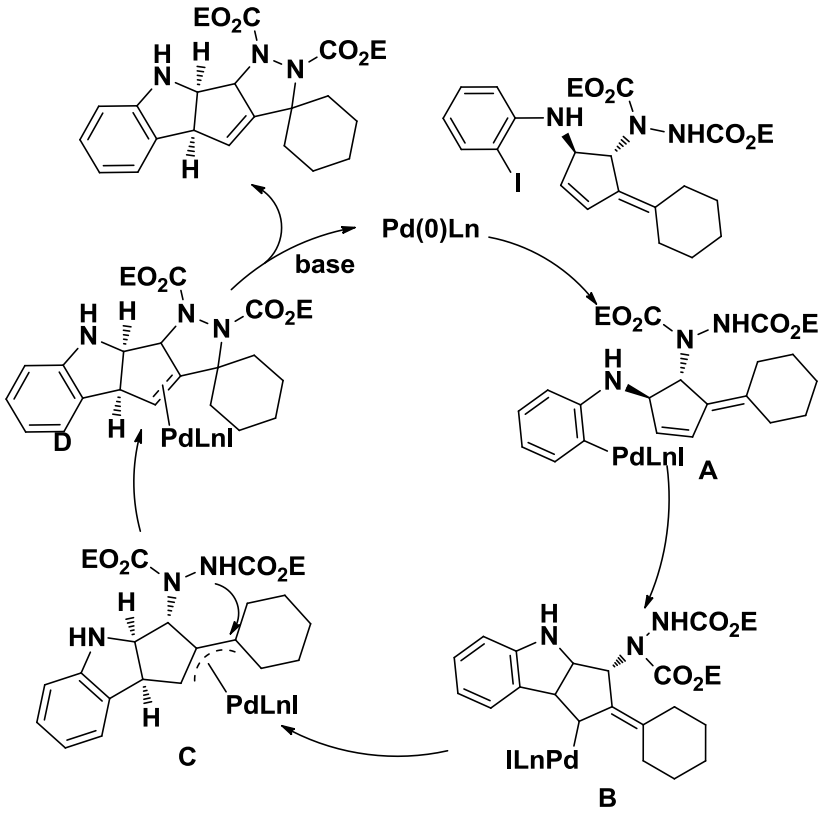


44ia (40%)

Reaction conditons: alkene (3 equiv.), *o*-iodoaniline (1 equiv.), $Pd[(allyl)Cl]_2$ (5 mol%), $Sc(OTf)_3$ (2 mol%), PPh_3 (10 mol%), Cs_2CO_3 (1.5 equiv.), CH_3CN (2 mL), toluene (0.5 mL), 12 h at 80 ^oC

4.8. Mechanistic pathway

A plausible mechanism for the formation of indoline-pyrazolidine fused cyclopentene is illustrated in Scheme 4.22. The first step of the catalytic cycle is the oxidative addition of Pd(0) to the aryl iodide, which lead to the formation of **A**. Coordination of species A to the double bond followed by the generation of π-allylpalladium complex affords the key intermediate **C**. Finally the base assisted intramolecular nucleophilic attack furnished the desired product.



Scheme 4.22 Proposed catalytic cycle underlying the mechanism of tandem cyclization

4.9. Conclusion

In summary, we have developed a Lewis acid/ Pd mediated strategy for the synthesis of a new spiropentacyclic motif having indoline and pyrazolidine fused to the cyclopentene core. The reaction involves multiple bond formations. It also shows that the proper positioning of "palladium active" functional groups in the diazabicyclic olefins helps in passing the palladium baton from initial organopalladium addition to the strained olefin, ultimately delivering complex polycycles in a one pot transformation.

4.10. Experimental section

General methods

All chemicals were of the best grade commercially available and are used without further purification. All solvents were purified according to standard procedure; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin layer chromatography was performed on glass plates coated with silica gel containing calcium sulfate binder. Gravity column chromatography was performed using 60-120 or 100-200 mesh silica gel and mixtures of hexane-ethyl acetate were used for elution.

Melting points were determined on a Buchi melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker Avance DPX 300 and Bruker AMX 500 spectrophotometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.25, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (double doublet); m (multiplet). Coupling constants are reported as *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). Mass spectra were recorded under EI/HRMS at 60,000 resolution using Thermo Scientific Exactive Mass Spectrometer. IR spectra were recorded on Bruker FTIR spectrometer.

General procedure for the lewis acid catalyzed reaction of pentafulvene derived bicyclic hydrazines with *o*-iodoaniline

A mixture of pentafulvene derived bicyclic hydrazine (3.0 eqiuv.), *o*-iodoaniline (1.0 equiv.) and $Sc(OTf)_3$ (2 mol %) were weighed in a schlenk tube and degassed for

10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at room temperature for 2 hours. The solvent was evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography yielded *trans*-3,4-disubstituted alkylidenecyclopentene.

General procedure for the intramolecular Heck reaction

A mixture of *trans*-3,4-disubstituted alkylidenecyclopentene. (1.0 eqiuv.), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%) and Cs_2CO_3 (1.5 equiv.) were weighed in a schlenk tube and degassed for 10 minutes. Dry acetonitrile (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 80 ^oC for 12 hours. The solvent was evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography yielded indoline-pyrazolidine fused cyclopentene.

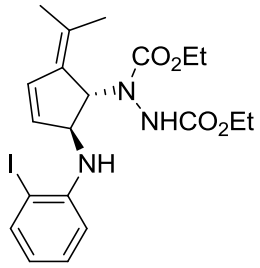
General procedure for the one pot synthesis of indoline-pyrazolidine fused cyclopentene

A mixture of pentafulvene derived bicyclic hydrazine (3.0 eqiuv.), *o*-iodoaniline (1.0 equiv.), $[Pd(allyl)Cl]_2$ (5 mol%), PPh_3 (10 mol%) and $Sc(OTf)_3$ (2 mol%) and Cs_2CO_3 (1.5 equiv.) were weighed in a schlenk tube and degassed for 10 minutes. Dry acetonitrile (2 mL) and toluene (0.5 mL) were added and the reaction mixture was purged with argon and allowed to stir at 80 ^oC for 12 hours. The solvent was evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography yielded indoline-pyrazolidine fused cyclopentene.

Compound 43aa

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42a** (130 mg, 0.46 mmol), *o*-iodoaniline **1a** (34 mg, 0.15 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43aa** (69 mg, 90%) as as colourless viscous

liquid.



R_f : 0.31 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3383, 3280, 3054, 2976, 2928, 2853, 1709, 1586, 1499, 1149, 1410, 1330, 1220, 1120, 1052, 1011, 920, 745 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): 7.61 (s, 1H), 7.20 (s, 1H), 6.99-6.80 (brs, 1H), 6.59 (d, *J* = 3.5 Hz, 1H), 6.42 (t, *J* = 7.5 Hz, 1H), 6.30-6.16 (m, 1H), 5.94 (s, 1H), 5.07-4.80 (m, 2H), 4.22-4.05 (m, 5H), 1.87 (s, 3H), 1.68 (s, 3H), 1.28-1.11 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS): 156.8, 155.2, 146.0, 138.8, 135.5, 134.2, 131.9, 129.4, 118.9, 112.8, 85.5, 65.3, 63.8, 62.8, 62.0, 21.4, 20.6, 14.5.

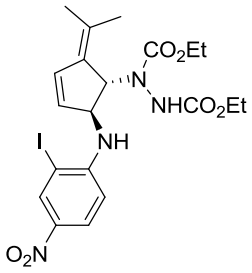
MS (ESI): Calcd for $C_{20}H_{26}IN_3O_4Na$: 522.08657; Found: 522.08608 ($C_{20}H_{26}IN_3O_4Na$).

Compound 43ab

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42a** (130 mg, 0.46 mmol), *o*-iodoaniline **1b** (41 mg, 0.15 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43ab** (61 mg, 73%) as pale yellow viscous liquid.

R_f : 0.43 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3369, 3258, 2921, 1731, 1560, 1418, 1375, 1280, 1213, 1112, 1054, 1002, 751 cm^{-1}.



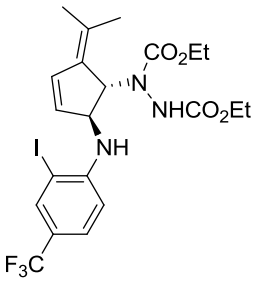
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 8.56 (d, *J* = 10 Hz, 1H), 8.17 (d, *J* = 9 Hz, 1H), 7.05 (m, 1H), 6.67 (d, *J* = 5 Hz, 1H), 6.27-6.19 (m, 1H), 5.92 (s, 1H), 5.01- 4.79 (m, 2H), 4.27-4.09 (m, 5H), 1.89 (s, 3H), 1.69 (s, 3H), 1.29 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 156.6, 154.7, 151.0, 138.6, 135.1, 134.8, 130.4, 126.2, 125.9, 112.2, 110.4, 82.4, 65.6, 64.1, 63.3, 62.2, 21.5, 20.9, 14.6, 14.1.

MS (ESI): Calcd for $C_{20}H_{25}IN_4O_6Na$: 567.07165; Found: 567.07123 ($C_{20}H_{25}IN_4O_6Na$).

Compound 43ac

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42a** (130 mg, 0.46 mmol), *o*-iodoaniline **1c** (44 mg, 0.15 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43ac** (59 mg, 67%) as colourless viscous liquid;



R_f : 0.40 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3379, 3280, 2988, 2920, 2868, 1714, 1580, 1478, 1450, 1368, 1301, 1224, 1129, 931, 749 cm^{-1}.

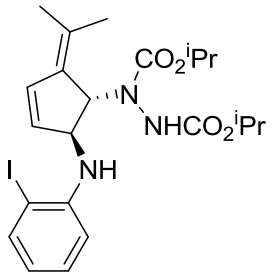
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.85 (d, *J* = 13 Hz, 1H), 7.48 (s, 1H), 7.12-7.02 (m, 1H), 6.63 (s, 1H), 6.19- 6.14 (m, 1H), 5.93 (s, 1H), 5.05 (d, *J* = 15.5 Hz, 1H), 4.87 (s, 1H), 4.40 (d, *J* =11.5 Hz, 1H), 4.41-4.10 (m, 4H), 1.19 (s, 3H), 1.68 (s, 3H), 1.27 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** 156.4, 155.1, 148.5, 135.8, 135.2, 134.8, 131.0, 126.9, 126.7, 120.5, 111.6, 83.7, 63.9, 63.3, 62.9, 62.2, 21.4, 20.5, 14.5.

MS (ESI): Calcd for $C_{21}H_{25}F_3IN_3O_4Na$: 590.07395; Found: 590.07257 ($C_{21}H_{25}F_3IN_3O_4Na$)

Compound 43ba

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42b** (120 mg, 0.39 mmol), *o*-iodoaniline **1a** (29 mg, 0.13 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43ba** (57 mg, 84%) as colourless viscous liquid.



R_f : 0.45 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3375, 3280, 2979, 2934, 2850, 1730, 1580, 1490, 1446, 1403, 1314, 1280, 1220, 1120, 1060, 1000, 931, 741 cm^{-1}.

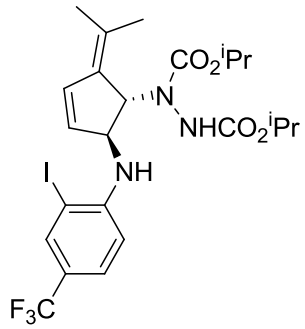
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.61 (d, *J* = 8 Hz, 1H), 7.23-7.19 (m, 1H), 7.02 (brs, 1H), 6.59 (d, *J* = 5.5 Hz, 1H), 6.65-6.41 (m, 1H), 6.16-6.05 (m, 1H), 5.94 (s, 1H), 5.05-4.89 (m, 4H), 4.05 (s, 1H), 1.87 (s, 3H), 1.68 (s, 3H), 1.28-1.09 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 156.1, 154.8, 146.1, 138.9, 135.6, 131.8, 129.7, 127.2, 125.3, 118.8, 112.9, 85.4, 70.8, 70.0, 65.1, 63.6, 26.9, 25.3, 22.1, 21.9, 21.5, 20.7.

MS (ESI): Calcd for $C_{22}H_{30}IN_3O_4Na$: 550.11787; Found: 550.11633 ($C_{22}H_{30}IN_3O_4Na$).

Compound 43bc

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42b** (120 mg, 0.39 mmol), *o*-iodoaniline **1c** (37 mg, 0.13 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43bc** (51 mg, 66%) as colourless viscous liquid.



R_f : 0.43 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3295, 2940, 2850, 1713, 1580, 1481, 1411, 1281, 1220, 1123, 1061, 1001, 920, 741 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.84 (d, *J* = 11 Hz, 1H), 7.48 (d, *J* = 8 Hz, 1H), 7.16-7.06 (m, 1H), 6.63 (s, 1H), 6.14-6.06 (m, 1H), 5.92 (s, 1H), 5.05-4.87 (m, 4H), 4.43-4.38 (m, 1H), 1.88 (s, 3H), 1.68 (s, 3H), 1.32-1.03 (m, 12H).

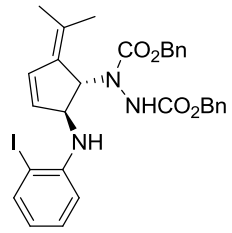
^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 156.8, 154.7, 148.4, 136.1, 135.9, 130.7, 128.9, 126.9, 125.2, 120.2, 113.4, 111.6, 83.7, 70.2, 65.4, 63.7, 63.1, 26.9, 25.2, 22.6, 21.9, 21.4, 20.7.

MS (ESI): Calcd for $C_{23}H_{29}F_3IN_3O_4Na$: 618.10525; Found: 618.10495 ($C_{23}H_{29}F_3IN_3O_4Na$).

Compound 42ca

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42c** (120 mg, 0.31 mmol), *o*-iodoaniline **1a** (22 mg, 0.10 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon

atmosphere for 2 hours gave the product **43ca** (46 mg, 72%) as colourless viscous liquid.



R_f : 0.48 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3386, 3287, 3063, 3032, 2926, 2852, 1716, 1586, 1489, 1450, 1402, 1313, 1283, 1128, 1077, 1050, 1004, 894, 743, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.60 (d, *J* = 6.5 Hz, 1H), 7.52-7.04 (m, 12H), 6.79 (s, 1H), 6.55-6.32 (m, 3H), 5.92-5.86 (m, 1H), 5.29-4.85 (m, 5H), 4.05 (brs, 1H), 1.81 (s, 3H), 1.58 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 156.6, 155.2, 145.9, 145.3, 138.9, 137.4, 135.7, 135.4, 134.2, 131.7, 129.7, 128.6, 128.4, 128.2, 128.1, 119.0, 112.7, 85.5, 68.2, 67.7, 65.8, 63.5, 21.8, 21.4.

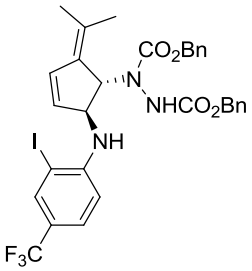
MS (ESI): Calcd for $C_{30}H_{30}IN_3O_4$, M^+: 623.12810; Found: (M+1) 624.13416.

Compound 43cc

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42c** (125 mg, 0.31 mmol), *o*-iodoaniline **1c** (30 mg, 0.10 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43cc** (49 mg, 68%) as colourless viscous liquid.

R_f : 0.51 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3084, 2385, 3060, 3038, 2932, 2850, 1718, 1586, 1494, 1451, 1402, 1284, 1403,



1311, 1280, 1210, 1124, 1051, 1010, 916, 741, 690 cm^{-1}.

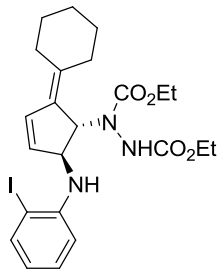
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.81 (s, 1H), 7.32-7.10 (m, 12H), 6.58 (d, *J* = 6 Hz, 1H), 6.36 (s, 1H), 5.87 (d, *J* = 12 Hz, 1H), 5.18-4.92 (m, 6H), 4.38 (brs, 1H), 1.29 (s, 3H), 1.63 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 156.9, 155.2, 148.3, 135.8, 135.1, 128.6, 128.5, 128.1, 127.1, 120.2, 111.5, 83.8, 68.4, 67.8, 64.1, 63.2, 21.5, 20.6.

MS (ESI): Calcd for $C_{31}H_{29}F_3IN_3O_4Na$: 714.10325: Found: 714.10339 ($C_{31}H_{29}F_3IN_3O_4Na$).

Compound 43da

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42d** (130 mg, 0.41 mmol), *o*-iodoaniline **1a** (30 mg, 0.14 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43da** (68 mg, 93%) as pale yellow coloured solid.



R_f : 0.46 (hexane/ethyl acetate = 3:1).

Mp : 132-134 ^oC

IR (Neat) ν_{max}: 3387, 3284, 3063, 2980, 2928, 2853, 1709, 1586, 1499, 1449, 1410, 1381, 1313, 1281, 1228, 1171, 1123, 1061, 1007, 928, 741cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.64 (s, 1H), 7.22 (s, 1H), 7.00-6.84 (m, 1H), 6.65 (d, *J* =

5 Hz, 1H), 6.44 (t, *J* = 7 Hz, 1H), 6.21-6.17 (m, 1H), 5.95 (s, 1H), 5.10-4.92 (m, 2H), 4.23-4.08 (m, 5H), 2.33 (t, *J* = 5.5 Hz, 2H), 2.07 (s, 2H), 1.66-1.44 (m, 6H), 1.29-1.12 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 156.4, 155.2, 146.1, 138.8, 134.2, 132.3, 132.1, 129.5, 119.5, 112.9, 112.3, 85.5, 64.7, 63.4, 62.8, 62.1, 31.8, 31.4, 28.2, 27.9, 26.4, 14.5.

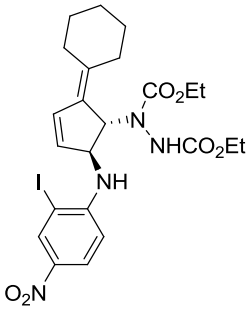
MS (ESI): Calcd for $C_{23}H_{30}IN_3O_4Na$: 562.11787; Found: 562.11481 ($C_{23}H_{30}IN_3O_4Na$).

Compound 43db

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42d** (130 mg, 0.41 mmol), *o*-iodoaniline **1b** (34 mg, 0.28 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43db** (62 mg, 78%) as yellow viscous liquid.

R_f : 0.53 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3464, 3365, 3071, 2920, 2852, 1705, 1623, 1582, 1469, 1410, 1380, 1318, 1173, 1115, 1058, 743 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 8.58 (m, 1H), 8.17 (m, 1H), 7.07-7.01 (m, 1H), 6.74-6.69 (m, 1H), 6.24-6.19 (m, 1H), 5.93 (s, 1H), 5.10-4.83 (m, 3H), 4.26-4.12 (m, 4H), 2.39-2.34 (m, 2H), 2.07-2.05 (m, 2H), 1.59 (brs, 6H), 1.30-1.16 (m, 6H).

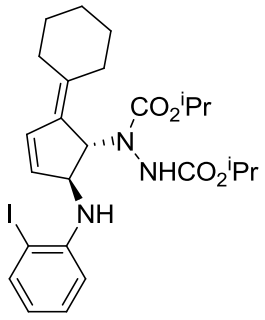
^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 156.8, 154.8, 150.9, 138.5, 135.2, 131.7, 130.5, 126.3, 125.7, 112.3, 110.4, 82.5, 64.9, 63.5, 62.9, 62.4,

31.9, 30.9, 29.7, 28.3, 26.3, 14.6, 14.1.

MS (ESI): Calcd for $C_{23}H_{29}IN_4O_6Na$: 607.10295; Found: 607.10139 ($C_{23}H_{29}IN_4O_6Na$).

Compound 43ea

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42e** (120 mg, 0.34 mmol), *o*-iodoaniline **1a** (25 mg, 0.11 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43ea** (55 mg, 84%) as colourless viscous liquid.



R_f : 0.48 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3387, 3285, 2979, 2927, 2853, 1721, 1706, 1587, 1497, 1451, 1384, 1316, 1282, 1107, 1037, 1005, 743 cm^{-1}.

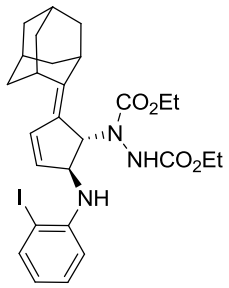
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.61 (d, *J* = 7.5 Hz, 1H), 7.23-7.16 (m, 1H), 7.31-6.84 (m, 1H), 6.64 (d, *J* = 5.5 Hz, 1H), 6.42 (t, *J* = 7.5 Hz, 1H), 6.11-6.03 (m, 1H), 5.95 (s,1H), 5.07-4.82 (m, 4H), 4.07 (brs, 1H), 2.34 (brs, 2H), 2.09 (s, 2H), 1.57 (brs, 6H), 1.28-1.17 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 155.9, 154.5, 146.0, 138.7, 133.7, 132.8, 129.7, 129.4, 118.8, 118.3, 110.3, 85.4, 70.7, 69.9, 63.8, 57.9, 32.1, 31.9, 28.2, 27.8, 26.4, 22.7, 22.2, 22.1, 21.9.

MS (ESI): Calcd for $C_{25}H_{34}IN_3O_4Na$: 590.14917: Found: 590.14721 ($C_{25}H_{34}IN_3O_4Na$).

Compound 43fa

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42f** (130 mg, 0.35 mmol), *o*-iodoaniline **1a** (26 mg, 0.12 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43fa** (54 mg, 78%) as colourless viscous liquid.



R_f : 0.48 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3389, 3293, 3062, 2912, 2849, 1750, 1712, 1586, 1498, 1449, 1406, 1316, 1281, 1220, 1116, 1061, 929, 802, 743 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, TMS)**:** δ 7.62 (s,1H), 7.24-7.21 (m, 1H), 6.99 (d, *J* = 14 Hz, 1H), 6.64 (d, *J* = 5 Hz, 1H), 6.43 (t, *J* =5 Hz, 1H), 6.15 (m, 1H), 5.94 (s, 1H), 5.08-4.83 (m, 2H), 4.23- 4.09 (m, 5H), 2.98 (s, 1H), 2.55 (d, *J* = 16.5Hz, 1H), 1.98-1.74 (m, 12H), 1.29-1.14 (m, 6H).

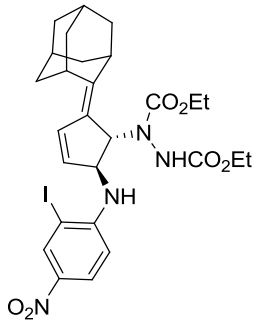
^{13}C NMR (75 MHz, $CDCl_3$, TMS)**:** δ 156.2, 154.6, 147.2, 146.1, 138.8, 133.4, 131.9, 129.5, 128.5, 118.9, 112.9, 85.5, 64.2, 63.2, 62.6, 62.1, 40.3, 39.6, 38.9, 38.8, 36.9, 35.1, 34.5, 28.0, 27.9, 14.6, 14.5.

MS (ESI): Calcd for $C_{27}H_{34}IN_3O_4Na$: 614.14917: Found: 614.14694 ($C_{27}H_{34}IN_3O_4Na$).

Compound 43fb

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42f** (130 mg, 0.35 mmol), *o*-iodoaniline **1b** (31 mg, 0.12 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon

atmosphere for 2 hours gave the product **43fb** (46 mg, 62%) as colourless viscous liquid.



R_f : 0.51 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3382, 2955, 2919, 2851, 1736, 1654, 1584, 1499, 1463, 1379, 1324, 1183, 1116, 1054, 853 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, TMS)**:** δ 8.54 (s, 1H), 8.16 (d, *J* =14 Hz, 1H),7.03-7.00 (m, 1H), 6.72 (d, *J* = 9 Hz, 1H), 6.14 (s, 1H), 5.90 (s, 1H), 5.07-4.82 (m, 2H), 4.23-4.14 (m, 5H), 2.98 (s, 1H), 2.51 (s, 1H), 2.03-1.84 (m, 12H), 1.31-1.14 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$, TMS)**:** δ 154.6, 150.9, 138.7, 134.7, 130.1, 128.9, 128.2, 126.2, 110.6, 82.5, 63.1, 62.9, 62.3, 40.4, 39.7, 38.9, 36.8, 35.2, 34.6, 31.6, 28.0, 26.9, 22.7, 14.7, 14.5.

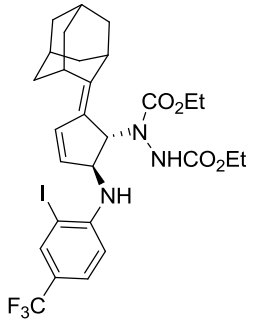
MS (ESI): Calcd for $C_{27}H_{33}IN_4O_6Na$: 659.13425: Found: 659.13192 ($C_{27}H_{33}IN_4O_6Na$).

Compound 43fc

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42f** (130 mg, 0.35 mmol), *o*-iodoaniline **1c** (34 mg, 0.12 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43fc** (55 mg, 72%) as colourless viscous liquid.

R_f : 0.51 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3380, 3280, 2981, 2924, 2853, 1718, 1601, 1583, 1490, 1450, 1412, 1228, 1120, 1062, 1004, 928, 740 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.87 (d, *J* = 14.5 Hz, 1H), 7.49 (d, *J* = 9 Hz, 1H), 7.11-7.00 (m, 1H), 6.68 (s, 1H), 6.13 (d, *J* = 5 Hz, 1H), 5.92 (s, 1H), 5.07-5.00 (m, 1H), 4.86 (s, 1H), 4.44-4.38 (m, 1H), 4.24-4.14 (m, 4H), 2.98 (s, 1H), 2.53 (d, *J* = 17.5 Hz, 1H), 1.99-1.76 (m, 12H), 1.33-1.12 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 156.4, 154.8, 148.4, 135.8, 134.0, 131.1, 128.2, 127.0, 126.8, 120.5, 111.6, 83.7, 63.1, 62.8, 62.7, 62.2, 40.2, 39.7, 38.9, 36.8, 35.1, 34.6, 29.7, 29.4, 28.0, 27.8, 14.6, 14.5.

MS (ESI): Calcd for $C_{28}H_{33}F_3IN_3O_4Na$: 682.13655; Found: 682.13652 ($C_{28}H_{33}F_3IN_3O_4Na$).

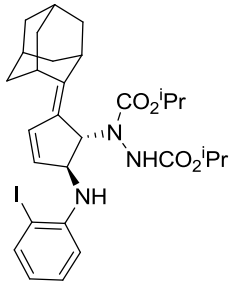
Compound 43ga

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42g** (110 mg, 0.40 mmol), *o*-iodoaniline **1a** (20 mg, 0.09 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43ga** (46 mg, 80%) as colourless viscous liquid.

R_f : 0.46 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3297, 3032, 2920, 2856, 1736, 1601, 1498, 1453, 1400, 1314, 1280, 1214, 1124, 1046, 1014, 848, 749, 697, 648 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.62 (s, 1H), 7.22 (brs, 1H), 7.11 (brs, 1H), 6.74-6.64 (m,



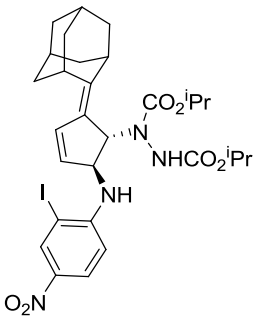
1H), 6.43 (t, *J* = 11.5 Hz, 1H), 6.07-5.94 (m, 2H), 5.06-4.88 (m, 4H), 4.07 (s, 1H), 2.97 (s, 1H), 2.57 (s, 1H), 1.98-1.83 (m, 1H), 1.25-1.16 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 156.1, 154.5, 146.2, 138.9, 133.9, 131.8, 129.7, 128.7, 118.9, 114.7, 112.5, 85.4, 70.4, 69.8, 63.9, 63.1, 40.3, 39.7, 38.8, 36.9, 35.1, 34.5, 28.0, 27.9, 22.1, 21.9.

MS (ESI): Calcd for $C_{29}H_{38}IN_3O_6Na$: 642.18047; Found: 642.18722 ($C_{29}H_{38}IN_3O_6Na$).

Compound 43gb

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42g** (110 mg, 0.40 mmol), *o*-iodoaniline **1b** (24 mg, 0.09 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43gb** (39 mg, 64%) as yellow viscous liquid.



R_f : 0.54 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3389, 3285, 3059, 2990, 2926, 2850, 1718, 1583, 1492, 1443, 1410, 1380, 1281, 1227, 1170, 1120, 1059, 1014, 928, 741, 689 cm^{-1}.

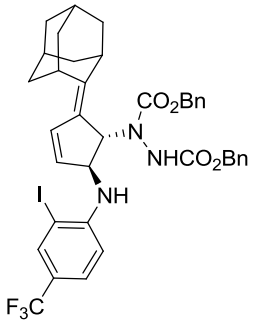
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 8.53 (s, 1H), 8.16 (d, *J* = 15 Hz, 1H), 7.15-7.04 (m, 1H), 6.72 (d, *J* = 9 Hz, 1H), 6.09-6.04 (m, 1H), 5.89 (s, 1H), 5.06-4.83 (m, 5H), 2.97 (s, 1H), 2.61 (s, 1H), 1.98-1.42 (m, 12H), 1.30-1.11 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 156.4, 154.1, 150.9, 148.1, 138.7, 134.8, 128.9, 128.2, 126.2, 110.7, 82.4, 70.4, 70.1, 63.0, 40.4, 39.7, 38.8, 36.8, 35.2, 34.6, 29.3, 28.0, 27.8, 26.9, 22.1, 21.9.

MS (ESI): Calcd for $C_{29}H_{37}IN_4O_6Na$: 687.16555: Found: 687.16336 ($C_{29}H_{37}IN_4O_6Na$).

Compound 43hc

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42h** (120 mg, 0.24 mmol), *o*-iodoaniline **1c** (23 mg, 0.08 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43hc** (40 mg, 64%) as yellow viscous liquid.



R_f : 0.46 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3378, 3281, 3059, 3027, 2920, 2858, 1719, 1580, 1489, 1449, 1400, 1311, 1281, 1050, 1000, 743cm^{-1}.

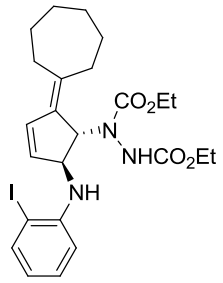
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.83(s, 1H), 7.35-7.29 (m, 11H), 6.96-6.94 (m, 1H), 6.65-6.63 (m, 1H), 6.28-6.24 (m, 1H), 5.83 (brs, 1H), 5.29-4.99 (m, 6H), 4.40-4.37 (m, 1H), 2.93 (brs, 1H), 2.49 (s, 1H), 2.30 (brs, 1H), 1.97-1.66 (m, 11H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 156.2, 154.4, 148.4, 135.8, 135.4, 134.1, 128.6, 128.5, 128.2, 111.5, 83.7, 68.4, 67.9, 62.9, 62.8, 40.3, 40.1, 39.5, 38.7, 36.7, 35.1, 34.6, 34.1, 31.9, 29.7, 27.7.

MS (ESI): Calcd for $C_{38}H_{37}F_3IN_3O_4Na$: 806.16785: Found: 806.16628 ($C_{38}H_{37}F_3IN_3O_4Na$).

Compound 43ia

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42i** (135 mg, 0.40 mmol), *o*-iodoaniline **1c** (30 mg, 0.13 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43ia** (50 mg, 67%) as colourless viscous liquid.



R_f : 0.40 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3384, 3295, 3062, 2979, 2928, 2855, 1745, 1710, 1586, 1500, 1409, 1228, 1061, 1008, 743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7 .65 (s, 1H), 7.24 (brs, 1H), 7.07 (s, 1H), 6.65 (d, *J* = 10 Hz, 1H), 6.48 (d, *J* = 11 Hz, 1H), 6.25 (brs, 1H), 5.98 (s, 1H), 5.11-4.69 (m, 2H), 4.25-4.11 (m, 5H), 2.49 (s, 2H), 2.23 (s, 2H), 1.85-1.14 (m, 14H).

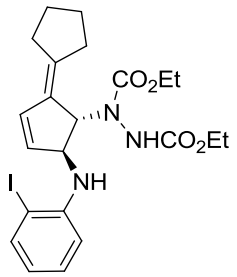
^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 156.4, 155.1, 146.0, 140.4, 138.7, 135.0, 134.1, 131.9, 129.4, 118.8, 112.3, 85.4, 64.9, 63.3, 62.7, 62.0, 32.5, 32.3, 29.7, 29.1, 27.8, 27.4, 26.8, 14.4.

MS (ESI): Calcd for $C_{24}H_{32}IN_3O_4Na$: 576.13352; Found: 576.13131 ($C_{24}H_{32}IN_3O_4Na$).

Compound 43ja

Following general experimental procedure, the pentafulvene derived bicyclic hydrazine **42j** (140 mg, 0.46 mmol), *o*-iodoaniline **51a** (33 mg, 0.15 mmol) and

$Sc(OTf)_3$ (2 mg, 0.003 mmol), in 2 mL toluene at room temperature under argon atmosphere for 2 hours gave the product **43ja** (54 mg, 68%) as colourless viscous liquid.



R_f : 0.37 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3388, 3289, 2978, 2955, 2926, 2869, 1714, 1587, 1499, 1453, 1385, 1315, 1280, 1231, 1180, 1107, 1037, 956, 743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.60 (s, 1H), 7.20 (brs, 1H), 7.08 (brs, 1H), 6.43 (d, *J* = 10 Hz, 2H), 6.18 (brs, 1H), 5.93 (s, 1H), 5.05 (m, 2H), 4.17 (m, 5H), 2.43 (s, 2H), 2.15-2.06 (m, 2H), 1.75-1.57 (m, 4H), 1.30-1.10 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 156.7, 155.6, 146.1, 140.7, 138.8, 134.9, 131.8, 129.5, 118.9, 112.9, 85.4, 66.2, 64.9, 63.3, 62.7, 31.9, 31.6, 30.5, 26.7, 26.4, 14.5.

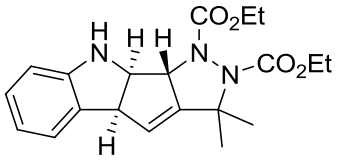
MS (ESI): Calcd for $C_{22}H_{28}IN_3O_4Na$: 548.10222; Found: 548.09994 ($C_{22}H_{28}IN_3O_4Na$).

Compound 44aa

Following the general procedure of the intramolecular Heck Reaction, the *trans*-3,4-disubstituted alkylidene cyclopentene **43aa** (40 mg, 0.08 mmol), $Pd(OAc)_2$ (1 mg, 0.004 mmol), PPh_3 (2 mg, 0.008 mmol) and Cs_2CO_3 (39 mg, 0.12 mmol) in acetonitrile (2 mL) at 80 ^oC under argon atmosphere for 12 hours gave the product **44aa** (16 mg, 54%) as colourless viscous liquid.

R_f : 0.31 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3388, 3263, 2969, 2919, 2848, 1708, 1605, 1558, 1490, 1410, 1389, 1313, 1289, 1218, 1120, 1071, 938, 731 cm^{-1}.



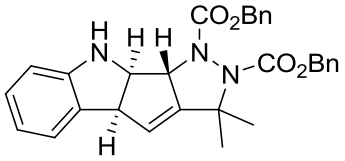
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.07-7.00 (m, 2H), 6.74-6.67 (m, 2H), 5.91 (t, *J* = 3 Hz, 1H), 4.69 (s, 1H), 4.55 (s, 1H), 4.54 (brs, 1H), 4.27-4.11 (m, 5H), 1.71 (s, 3H), 1.32-1.24 (m, 9H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 155.6, 154.8, 148.9, 139.8, 127.5, 126.9, 125.9, 123.2, 118.0, 109.2, 64.4, 61.4, 61.0, 56.1, 21.4, 20.9, 14.5, 14.1.

MS (ESI): Calcd for $C_{20}H_{25}N_3O_4$, M^+: 371.18451; Found, (M+1): 372.19001.

Compound 44ca

Following the general procedure of the intramolecular Heck Reaction, the *trans*-3,4-disubstituted alkylidene cyclopentene **43ca** (40 mg, 0.06 mmol), $Pd(OAc)_2$ (1 mg, 0.003 mmol), PPh_3 (2 mg, 0.006 mmol) and Cs_2CO_3 (31 mg, 0.10 mmol) in acetonitrile (2 mL) at 80 ^oC under argon atmosphere for 12 hours gave the product **44ca** (24 mg, 65%) as colourless viscous liquid.



R_f : 0.54 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3390, 3288, 3060, 3038, 297, 2849, 1717, 1594, 1498, 1454, 1404, 1318, 1279, 1218, 1131, 1056, 1011, 916, 748, 670 cm^{-1}.

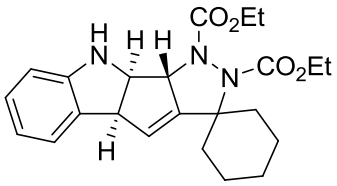
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.34-7.25 (m, 12H), 7.02-6.97 (m, 2H), 6.69 (t, *J* = 7 Hz, 1H), 5.85 (s,1H), 5.17-5.09 (m, 4H), 4.69 (brs, 1H), 4.49 (brs, 1H), 4.40 (brs,1H), 1.79-1.552 (m, 3H), 1.25-1.20 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 157.7, 156.1, 149.8, 136.0, 128.6, 128.5, 128.1, 127.9, 127.7, 127.3, 126.9, 124.3, 119.0, 70.1, 68.2, 57.2, 39.4, 23.3, 23.2.

MS (ESI): Calcd for $C_{30}H_{29}N_3O_4Na$: 518.20558; Found: 518.20322 ($C_{30}H_{29}N_3O_4Na$).

Compound 44da

Following the general procedure of the intramolecular Heck Reaction, the *trans*-3,4-disubstituted alkylidene cyclopentene **43da** (50 mg, 0.09 mmol), $Pd(OAc)_2$ (1 mg, 0.005 mmol), PPh_3 (2 mg, 0.01 mmol) and Cs_2CO_3 (45 mg, 0.14 mmol) in acetonitrile (2 mL) at 80 ^oC under argon atmosphere for 12 hours gave the product **44da** (27 mg, 72%) as colourless viscous liquid.



R_f : 0.34 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3375, 3051, 2933, 2861, 1698, 1605, 1459, 1407, 1377, 1334, 1287, 1171, 1131, 1098, 1032, 897, 870, 750 cm^{-1}.

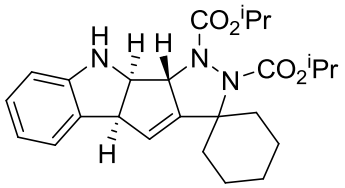
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.71-7.04 (m, 2H), 6.74-6.68 (m, 2H), 6.06 (s, 1H), 4.66 (s, 1H), 4.54 (d, *J* = 6.5 Hz, 1H), 4.37 (brs, 1H), 4.23-4.13 (m, 5H), 2.46 (t, *J* = 10 Hz, 1H), 2.36 (s, 1H), 1.97 (d, *J* = 10.5 Hz, 2H), 1.63-1.20 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 155.6, 154.9, 148.8, 139.9, 128.4, 127.5, 126.1, 125.9, 123.3, 122.7, 118.0, 109.2, 64.3, 61.3, 56.0, 32.1, 30.4, 28.7, 24.5, 22.9, 22.0, 13.6, 13.4.

MS (ESI): Calcd for $C_{23}H_{29}N_3O_4Na$: 434.20558; Found: 434.20336 ($C_{23}H_{29}N_3O_4Na$).

Compound 44ea

Following the general procedure of the intramolecular Heck Reaction, the *trans*-3,4-disubstituted alkylidene cyclopentene **43ea** (50 mg, 0.09 mmol), $Pd(OAc)_2$ (1 mg, 0.005 mmol), PPh_3 (2 mg, 0.01 mmol) and Cs_2CO_3 (43 mg, 0.13 mmol) in acetonitrile (2 mL) at 80 ^oC under argon atmosphere for 12 hours gave the product **44ea** (27 mg, 72%) as colourless viscous liquid.



R_f : 0.43 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3377, 3051, 2928, 2856, 2670, 1708, 1694, 1606, 1462, 1379, 1232, 1107, 1022, 916, 748 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.08-7.03 (m, 2H), 6.75-6.68 (m, 2H), 6.03 (s, 1H), 4.99-4.86 (m, 2H), 6.46 (s, 1H), 4.50 (s, 1H), 4.36 (s, 1H), 2.43 (m, 1H), 2.17 (brs, 1H), 1.99-1.91 (m, 2H), 1.60-1.25 (m, 18H).

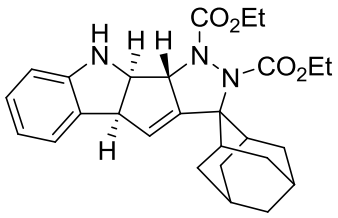
^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 156.1, 154.7, 145.9, 138.7, 133.6, 132.8, 129.6, 129.3, 118.8, 118.2, 110.2, 69.9, 63.2, 57.8, 32.0, 31.8, 28.2, 27.8, 26.4, 22.6, 22.1.

MS (EI): Calcd for $C_{25}H_{33}N_3O_4$, M^+: 439.24711; Found, (M+1): 440.25259 ($C_{25}H_{34}N_3O_4$).

Compound 44fa

Following the general procedure of the intramolecular Heck Reaction, the *trans*-3,4-disubstituted alkylidene cyclopentene **43fa** (50 mg, 0.08 mmol), $Pd(OAc)_2$ (1 mg, 0.004 mmol), PPh_3 (2 mg, 0.008 mmol) and Cs_2CO_3 (42 mg, 0.13 mmol) in

acetonitrile (2 mL) at 80 ^{o}C under argon atmosphere for 12 hours gave the product **44fa** (28 mg, 72%) as pale yellow solid.



R_f : 0.31 (hexane/ethyl acetate = 3:1).

Mp :136-139 ^{o}C.

IR (Neat) ν_{max}: 3368, 3268, 2990, 2931, 2860, 1718, 1588, 1410, 1282, 1228, 1124, 1056, 1016, 746, 694 cm^{-1}.

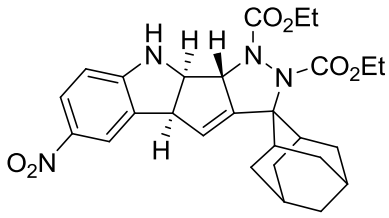
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.05 (m, 2H), 6.73-6.66 (m, 2H), 6.11 (s, 1H), 4.64 (brs, 1H), 4.48 (brs, 1H), 4.37-4.35 (m, 1H), 4.23-4.12 (m, 5H), 2.80 (s, 1H), 2.55-2.51 (m, 1H), 2.21-2.12 (m, 2H), 1.90-1.54 (m, 6H), 1.59-1.54 (m, 4H), 1.29-1.22 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 157.9, 157.1, 154.5, 149.5, 127.9, 124.2, 123.8, 119.3, 119.0, 110.2, 109.9, 71.4, 62.1, 57.0, 37.2, 35.7, 35.4, 34.6, 32.5, 32.2, 32.0, 27.1, 27.0, 14.7, 14.5.

MS (ESI): Calcd for $C_{27}H_{33}N_3O_4$, M^+: 463.24711; Found, (M+1): 464.25262 ($C_{27}H_{34}N_3O_4$).

Compound 44fb

Following the general procedure of the intramolecular Heck Reaction, the *trans*-3,4-disubstituted alkylidene cyclopentene **43fb** (50 mg, 0.08 mmol), $Pd(OAc)_2$ (1 mg, 0.004 mmol), PPh_3 (2 mg, 0.008 mmol) and Cs_2CO_3 (38 mg, 0.12 mmol) in acetonitrile (2 mL) at 80 ^{o}C under argon atmosphere for 12 hours gave the product **44fb** (18 mg, 46%) as colourless viscous liquid.



R_f: 0.37 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3381, 980, 2938, 2861, 1738, 1712, 1594, 1499, 1451, 1410, 1284, 1230, 1126, 1062, 1007, 746, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 8.03 (d, *J* = 14.5 Hz, 1H), 7.95 (s, 1H), 6.57 (d, *J* = 14.5 Hz, 1H), 6.09 (s, 1H), 5.33 (s, 1H), 4.62-4.56 (m, 2H), 4.23-4.12 (m, 5H), 2.76 (s, 1H), 2.50-2.03 (m, 4H), 1.91-1.42 (m, 9H), 1.29-1.24 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 155.9, 154.3, 147.2, 138.8, 133.4, 131.9, 129.5, 128.5, 118.9, 112.9, 75.6, 64.3, 63.3, 62.4, 56.1, 40.1, 39.5, 38.9, 38.8, 36.8, 35.0, 34.5, 28.1, 27.9, 14.6, 14.4.

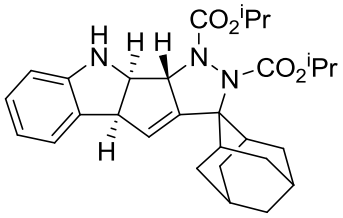
MS (ESI): Calcd for $C_{27}H_{32}N_4O_6$, M^+: 508.23218; Found (M+1): 509.23765 ($C_{27}H_{33}N_4O_6$).

Compound 44ga

Following the general procedure of the intramolecular Heck Reaction, the *trans*-3,4-disubstituted alkylidene cyclopentene **43ga** (50 mg, 0.08 mmol), $Pd(OAc)_2$ (1 mg, 0.004 mmol), PPh_3 (2 mg, 0.008 mmol) and Cs_2CO_3 (40 mg, 0.12 mmol) in acetonitrile (2 mL) at 80 ^oC under argon atmosphere for 12 hours gave the product **44ga** (27 mg, 69%) as colourless viscous liquid.

R_f : 0.36 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3380, 3051, 2978, 2920, 2856, 2666, 1704, 1683, 1606, 1460, 1277, 1106, 956, 912, 746 cm^{-1}.



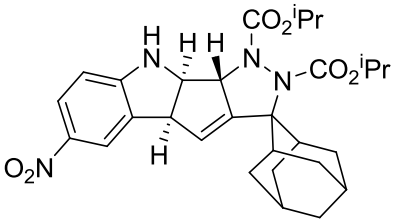
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.06-7.02 (m, 2H), 6.72-6.65 (m, 2H), 6.10 (d, *J* = 5.5Hz, 1H), 5.02-4.87 (m, 2H), 4.62-4.06 (m, 4H), 2.83 (brs, 1H), 2.61-2.51 (m, 1H), 2.35-2.11 (m, 2H), 1.89-1.37 (m, 10H), 1.25-1.21 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 157.4, 156.8, 149.8, 129.0, 128.2, 127.9, 125.3, 124.2, 118.9, 110.1, 75.6, 71.4, 69.5, 56.9, 37.2, 35.8, 35.4, 34.6, 32.6, 32.3, 32.0, 27.2, 22.2, 22.1.

MS (ESI): Calcd for $C_{29}H_{37}N_3O_4$, M^+: 491.27841; Found (M+1): 492.28394 ($C_{29}H_{38}N_3O_4$).

Compound 44gb

Following the general procedure of the intramolecular Heck Reaction, the *trans*-3,4-disubstituted alkylidene cyclopentene **43gb** (50 mg, 0.08 mmol), $Pd(OAc)_2$ (1 mg, 0.004 mmol), PPh_3 (2 mg, 0.008 mmol) and Cs_2CO_3 (37 mg, 0.11 mmol) in acetonitrile (2 mL) at 80 ^oC under argon atmosphere for 12 hours gave the product **44gb** (17 mg, 42%) as colourless viscous liquid.



R_f : 0.40 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3293, 2922, 2852, 1716, 1587, 1499, 1456, 1381, 1316, 1282, 1178, 1109, 1038, 743 cm^{-1}.

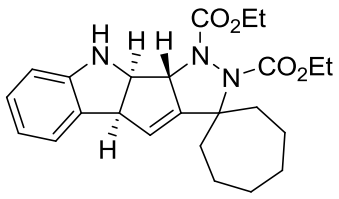
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 8.05 (d, *J* = 9 Hz, 1H), 7.95 (s, 1H), 6.57 (d, *J* = 8.5 Hz, 1H), 6.10 (s, 1H), 5.01-4.89 (m, 2H), 4.62 (s, 1H), 4.57-4.52 (m, 3H), 2.80 (s, 1H), 2.53 (d, *J* = 13.5 Hz, 1H), 2.21-2.11 (m, 2H), 1.92-1.53 (m, 10H), 1.31-1.24 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 155.6, 155.1, 153.3, 148.9, 138.1, 126.2, 124.7, 121.2, 119.3, 105.7, 69.8, 68.2, 68.1, 54.5, 35.4, 34.0, 33.6, 32.5, 30.9, 30.7, 30.3, 27.7, 25.4, 25.2, 20.5, 20.4.

MS (ESI): Calcd for $C_{29}H_{36}N_4O_6$, (M^+): 536.26348; Found (M+1): 537.26905 ($C_{29}H_{37}N_4O_6$).

Compound 44ia

Following the general procedure of the intramolecular Heck Reaction, the *trans*-3,4-disubstituted alkylidene cyclopentene **43ia** (50 mg, 0.09 mmol), $Pd(OAc)_2$ (1 mg, 0.004 mmol), PPh_3 (2 mg, 0.008 mmol) and Cs_2CO_3 (43 mg, 0.13 mmol) in acetonitrile (2 mL) at 80 ^oC under argon atmosphere for 12 hours gave the product **44ia** (24 mg, 63%) as colourless viscous liquid.



IR (Neat) ν_{max}: 3376, 2983, 2924, 2857, 2359, 1706, 1597, 1468, 1410, 1379, 1307, 1230, 1172, 1132, 1061, 939, 868 cm^{-1}.

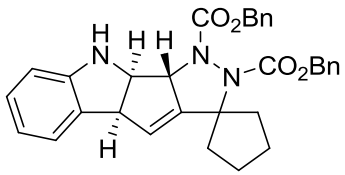
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.07-7.02 (m, 2H), 6.74-6.67 (m, 2H), 5.95 (t, J = 3 Hz, 1H), 4.64 (s, 1H), 4.52 (s, 1H), 4.39-4.38 (m, 1H), 4.22-4.17 (m, 5H), 2.52-2.46 (m, 2H), 2.19-2.16 (m, 2H), 1.59 (m, 8H), 1.29-1.26 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 155.5, 155.2, 145.2, 135.5, 128.0, 127.9, 124.4, 122.7, 119.1, 110.6, 62.4, 62.0, 61.9, 56.8, 34.6, 32.3, 29.8, 29.1, 24.5, 14.5.

MS (ESI): Calcd for $C_{24}H_{31}N_3NaO_4$, M^+: 448.22123; Found: 448.22079 ($C_{23}H_{29}N_3O_4Na$).

Compound 44ka

Following the general procedure of the intramolecular Heck Reaction, the *trans*-3,4-disubstituted alkylidene cyclopentene **43ka** (40 mg, 0.06 mmol), $Pd(OAc)_2$ (1 mg, 0.003 mmol), PPh_3 (2 mg, 0.006 mmol) and Cs_2CO_3 (30 mg, 0.09 mmol) in acetonitrile (2 mL) at 80 ^oC under argon atmosphere for 12 hours gave the product **44ka** (24 mg, 74%) as colourless viscous liquid.



R_f : 0.31 (hexane/ethyl acetate = 3:1).

IR (Neat) ν_{max}: 3377, 3058, 2918, 2851, 1729, 1604, 1461, 1403, 1118, 1050, 740, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.36-7.31 (m, 12H), 7.00 (t, *J* = 12.5 Hz, 1H), 6.69 (t, *J* = 12 Hz, 1H), 5.89 (s, 1H), 5.20-5.12 (m, 4H), 4.69 (s, 2H), 4.46 (brs, 1H), 4.35 (brs, 1H), 2.71 (brs, 1H), 2.48 (brs, 1H), 1.97-1.54 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 154.9, 152.1, 149.8, 136.0, 128.6, 128.5, 128.1, 127.9, 127.7, 127.3, 126.9, 124.3, 119.0, 76.1, 67.8, 65.2, 56.9, 46.2, 31.9, 29.3, 27.4, 23.9.

MS (ESI): Calcd for $C_{32}H_{31}N_3O_4$, M^+: 521.23146; Found (M+1): 522.23688 ($C_{32}H_{32}N_3O_4$).

4.12. Reference

1 A. De Meijere, P. Von Zezschwitz and S. Brase, *Acc. Chem. Res.*, 2005, **38**, 413–422.

2 K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem. Int. Ed.*, 2006, **45**, 7134–7186.

3 L. J. Sebren, J. J. Devery and C. R. J. Stephenson, *ACS Catal.*, 2014, **4**, 703–716.

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

5 C. M. R. Volla, I. Atodiresei and M. Rueping, *Chem. Rev.*, 2014, **114**, 2390–431.

6 R. Dua, S. Shrivastava, S. K. Sonwane and S. K. Srivastava, *Adv. Biol. Res. (Rennes).*, 2011, **5**, 120–144.

7 B. Prasad, B. Y. Sreenivas, G. R. Krishna, R. Kapavarapu and M. Pal, *Chem. Commun.*, 2013, **49**, 6716–6718.

8 A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489–97.

9 D. L. Boger, C. W. Boyce, R. M. Garbaccio, J. A. Goldberg and B. A. Duocarmycin, *Chem. Rev.*, 1997, **97**, 787–828.

10 J. H. Ahn, J. A. Kim, H.-M. Kim, H.-M. Kwon, S.-C. Huh, S. D. Rhee, K. R. Kim, S.-D. Yang, S. D. Park, J. M. Lee, S. S. Kim and H. G. Cheon, *Bioorganic Med. Chem. Lett.*, 2005, **15**, 1337–1340.

11 S. Lemaire, G. Giambastiani, G. Prestat and G. Poli, *Eur. J. Org. Chem.*, 2004,

2840–2847.

12 J. Storsberg, M. V Nandakumar, S. Sankaranarayanan and D. E. Kaufmann, *Adv. Synth. Catal.*, 2001, **343**, 177–180.

13 C. Bournaud, F. Chung, A. Luna, M. Pasco, G. Errasti, T. Lecourt and L. Micouin, *Synthesis*, 2009, **6**, 869–887.

14 S. Crotti, F. Bertolini, F. Macchia and M. Pineschi, *Adv. Synth. Catal.*, 2009, **351**, 869–873.

15 M. Pineschi, F. Del Moro, P. Crotti and F. Macchia, *Org. Lett.*, 2005, **7**, 3605–3607.

16 F. Bertolini, F. Macchia and M. Pineschi, *Tetrahedron Lett.*, 2006, **47**, 9173–9176.

17 S. Crotti, F. Bertolini, F. Macchia and M. Pineschi, *Chem. Commun.*, 2008, 3127–3129.

18 F. Menard and M. Lautens, *Angew. Chem. Int. Ed.*, 2008, **47**, 2085–2088.

19 J. Panteleev, F. Menard and M. Lautens, *Adv. Synth. Catal.*, 2008, **350**, 2893–2902.

20 M. J. Fleming, H. a. McManus, A. Rudolph, W. H. Chan, J. Ruiz, C. Dockendorff and M. Lautens, *Chem. - Eur. J.*, 2008, **14**, 2112–2124.

21 C. Cesario and M. J. Miller, *Org. Lett.*, 2009, **11**, 1293–1295.

22 V. S. Sajisha, S. Anas, J. John and K. V. Radhakrishnan, *Synlett*, 2009, 2885–2895.

23 R. C. Larock and E. K. Yum, *J. Am. Chem. Soc.*, 1991, **113**, 6689–6690.

24 D. V. Kadnikov and R. C. Larock, *Org. Lett.*, 2000, **2**, 3643–3646.

25 R. C. Larock, N. Berrios-Pena and K. Narayanan, *J. Org. Chem.*, 1990, **55**, 3447–3450.

26 R. C. Larock and C. A. Fried, *J. Am. Chem. Soc.*, 1990, **112**, 5882–5884.

27 R. C. Larock and E. K. Yum, *Synlett*, 1990, **1990**, 529–530.

28 R. C. Larock and E. K. Yum, *Tetrahedron*, 1996, **52**, 2743–2758.

29 M. Catellani and A. Del Rio, *Russ. Chem. Bull.*, 1998, **47**, 928–931.

30 M. Catellani, F. Fringnani and A. Rangoni, *Angew. Chem. Int. Ed.*, 1997, **36**, 119–122.

31 Y. Gao, Y. Huang, W. Wu, K. Huang and H. Jiang, *Chem. Commun.*, 2014, **50**, 8370–8373.

32 N. Joseph, J. John, R. Rajan, S. Thulasi, A. Mohan, E. Suresh and K. V. Radhakrishnan, *Tetrahedron*, 2011, **67**, 4905–4913.

33 E. Jijy, P. Prakash, M. Shimi, P. M. Pihko, N. Joseph and K. V. Radhakrishnan, *Chem. Commun.*, 2013, **49**, 7349–51.

34 M. Lautens and J. Mancuso, *J. Org. Chem.*, 2004, **69**, 3478–3487.

35 E. Jijy, P. Prakash, S. Saranya, E. Suresh and K. Radhakrishnan, *Synthesis*, 2013, **45**, 2583–2592.

36 J. John, U. Indu, E. Suresh and K. V. Radhakrishnan, *J. Am. Chem. Soc.*, 2009, **131**, 5042–5043.

37 B. A. B. Prasad, A. E. Buechele and S. R. Gilbertson, 2010, 2410–2411.

38 P. Prakash, E. Jijy, P. Preethanuj, P. M. Pihko, S. Sarath Chand and K. V Radhakrishnan, *Chem. - Eur. J.*, 2013, **19**, 10473–10477.

39 J. John, R. Rajan, S. Sarath Chand, P. Prakash, N. Joseph, E. Suresh and K. V. Radhakrishnan, *Tetrahedron*, 2013, **69**, 152–159.

SUMMARY

The thesis entitled "**Lewis acid/palladium catalyzed synthetic transformations of pentafulvenes and its derivatives: Facile synthesis of indole appended carbocycles and heterocycles**" embodies the results of the investigations carried out in the area of Lewis acid and/or transition metal catalysis toward indole/bis-indole/*o*-iodoaniline appended alkylidenecyclopentenes and complex azapolyheterocycles.

The introductory chapter of the thesis gives an overview of the intriguing reactivity parameters and the synthetic applications of pentafulvenes and its derivatives (Figure 1). A definition of the present work is also incorporated in the chapter.

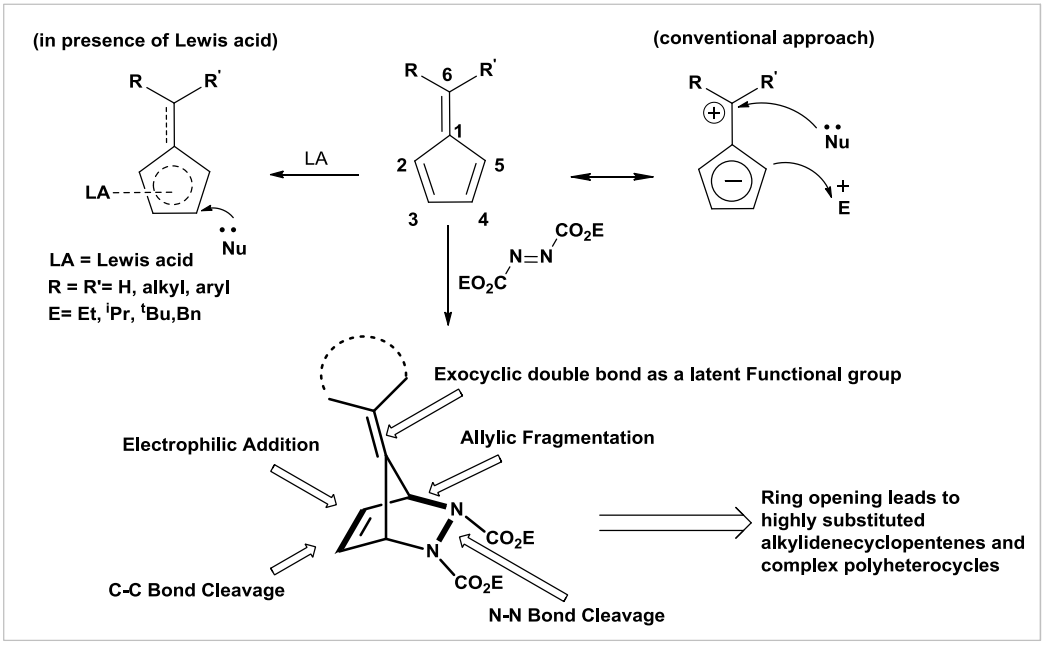
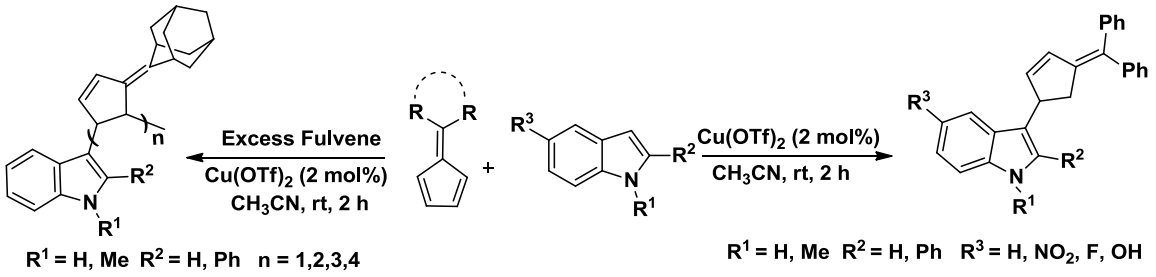


Figure 1

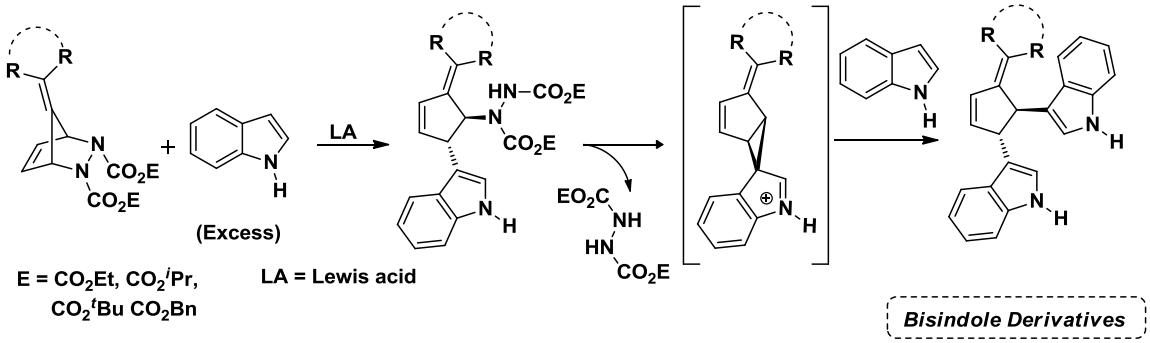
The second chapter describes the Lewis acid-catalysed regioselective nucleophilic addition of indoles and pyrrole to the endocyclic ring of pentafulvenes. Here we utilized the cross conjugated triene, pentafulvene as an unsaturated alkene for the

Lewis acid catalyzed hydroheteroarylation reaction. The method has provided the C-3 alkylidenecyclopentenylated indole and is the first example for the acid catalyzed endo-selective 1,2-addition of nucleophile to fulvenes (Scheme 1).



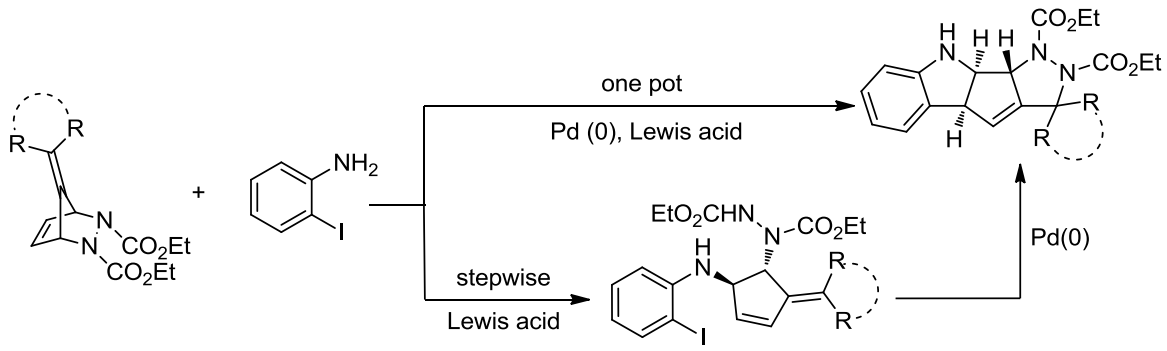
Scheme 1

Encouraged by these unusual results, we extended the scope of the Lewis acid catalyzed transformation of pentafulvene derived azabicyclic olefins. The Lewis acid catalysis led to the ring opening of bicyclic olefins and provided an efficient synthetic route to furnish pharmaceutically valuable indole and bis-indole derivatives of alkylidenecyclopentenes. The results of the detailed investigation of trapping the Lewis acid generated allylic carbocation derived from pentafulvene derived azabicyclic olefins by indole and its subsequent transformation to bis-indole analogues (Schme 2) are described in the second chapter.



Scheme 2

In conjunction with our interest in the chemistry of pentafulvenes and transition metal catalyzed synthetic transformations of heterobicyclic olefins, we have explored the Lewis acid/Pd mediated transformation of pentafulvene derived bicyclic hydrazines, which led to the formation of a new spiropentacyclic framework having cyclopentene fused to indoline and pyrazolidine. The reaction proceeded through Lewis acid catalyzed C-N bond cleavage followed by Pd catalyzed C-C and C-N bond formations in a domino fashion. The results of the Lewis acid/Pd catalyzed step-wise and one pot synthesis of so formed complex polyheterocycles with multiple stereocenters (Scheme 3) are embodied in the fourth chapter of the thesis.



Scheme 3

In conclusion, we have introduced pentafulvenes as non-symmetrical alkenes for the regioselective Lewis acid-catalysed hydroheteroarylation reaction. The Lewis acid catalysis of pentafulvene and it derivatives provide proficient routes toward the synthesis of alkylidenecyclopentenyl functionalized indole and bis-indole units that are valuable motifs for drug design. It is remarkable that, we have developed a Lewis acid/ palladium mediated strategy for the synthesis of complex polyheterocyclic molecules. In short, the thesis describes of the methodologies towards the synthesis of *N*-heterocycle appended alkylidenecyclopentenes with biological importance.

List of publications

1. Palladium catalyzed reaction of *ortho*-functionalized aryl iodides with bicyclic hydrazines: facile route toward heteroannulated cyclopentenes and azabicycles. J. John, R. Rajan, **S. Sarath Chand**, P. Prakash, N. Joseph, E. Suresh and K. V. Radhakrishnan, *Tetrahedron*, 2013, **69**, 152–159.
2. Palladium Catalyzed Skeletal Rearrangement of Spirotricyclic Olefins: A facile One Pot Strategy for the Synthesis of a Novel Motif with Cyclopentene Fused to Benzofuran and Pyrazolidine, P. Prakash, E. Jijy, P. Preethanuj, P. M. Pihko, **S. Sarath Chand** and K. V. Radhakrishnan, *Chem. - Eur. J.*, 2013, **19**, 10473–10477
3. Palladium/Lewis Acid Mediated Domino Reaction of Pentafulvene Derived Diazabicyclic Olefins: Efficient Access to Spiropentacyclic Motif with an Indoline and Pyrazolidine fused to Cyclopentene, **S. Sarath Chand**, E. Jijy, P. Prakash, J. Szymoniak, P. Preethanuj, B. P. Dhanya and K. V Radhakrishnan, *Org. Lett.*, 2013, **15**, 3338–41.
4. An exclusive approach to 3,4-disubstituted cyclopentenes and alkylidene cyclopentenes via the palladium catalyzed ring opening of azabicyclic olefins with aryl halides, N. Joseph, R. Rajan, J. John, N. V. Devika, **S. Sarath Chand**, E. Suresh, P. M. Pihko and K. V. Radhakrishnan, *RSC Adv.*, 2013, **3**, 7751.
5. Trapping the Lewis acid generated transient species from pentafulvene derived diazanorbornenes with *ortho*-functionalized aryl iodides and aliphatic alcohols, **S. Sarath Chand**, S. Saranya, P. Preethanuj, B. P. Dhanya, E. Jijy, P. Prakash, B. S. Sasidhar, J. Szymoniak, P. V Santhini and K. V Radhakrishnan, *Org. Biomol. Chem.*, 2014, **12**, 3045–61.
6. Lewis Acid Catalyzed C-3 Alkylidenecyclopentenylation of Indoles: An Easy Access to Functionalized Indoles and Bisindoles, **S. Sarath Chand**, B. S. Sasidhar, P. Prakash, P. Sasikumar, P. Preethanuj, F. Jaroschik, D. Harakat, J.-L.

Vasse and K. V. Radhakrishnan, *RSC Adv.*, 2015, **5**, 38075–38084.

7. Lewis Acid-Catalysed Regioselective Hydroheteroarylation of Pentafulvenes, **S. Sarath Chand**, Greeshma Gopalan, P. V. Santhini, P. Preethanuj, Jubi John, Dominique Harakat, Florian Jaroschik, and K. V. Radhakrishnan (To be submitted to *Org. Lett.)*
8. Palladium mediated strain release of pentafulvene derived diazanorbornenes with o-iodoanilines: A strategic approch toward the synthesis of complex polyheterocycles with indoline, pyrazolidine and 1,3-oxazinan-2-one scaffolds. P. Preethanuj, Ajesh Vijayan, **S. Sarath Chand**, Dominique Harakat, Florian Jaroschik, and K. V. Radhakrishnan (manuscript under preparation).

Papers presented at conferences

9. Palladium catalyzed desymmetrization of pentafulvene derived bicyclic hydrazine with soft nucleophiles. **S. Sarath Chand,** Rani Rajan and K. V. Radhakrishnan, a poster presented at 8th J-NOST Conference held at Indian Institute of Technology, Guwahati, Assam, December **2012**.
10. Palladium catalyzed heteroannulation of 2-iodophenols with fulvene derived bicyclic hydrazines: facile route towards dihydrobenzofuran derivatives; **S. Sarath Chand**, Rani Rajan and K. V. Radhakrishnan, a poster presented at CTDDR-2013: International Symposium on Drug Development for Orphan/Neglected Diseases, CDRI, Lucknow, February **2013**.
11. Palladium/Lewis acid mediated reaction of pentafulvene derived diazabicyclic olefins: efficient access to indoline-pyrazolidine fused cyclopentenes. **S. Sarath Chand**, and K. V. Radhakrishnan, a poster presented at the 16th CRSI National Symposium in Chemistry (NSC-16), held at Indian Institute of Technology, Bombay, February **2014**.

12. Palladium/Lewis Acid Catalyzed Synthetic Transformation of Pentafulvene Derived Diazabicyclic Olefins: An Efficient Access to Complex Heterocyclic Indoline-Pyrazolidine Ring System. **S. Sarath Chand** and K. V. Radhakrishnan, a paper presented at National Seminar on 'Current Trends in Chemistry' (CTriC), held at Cochin University of Science and Technology, Kochi, January **2014**.
13. Trapping the Lewis acid generated transient species from pentafulvene derived diazanorbornenes with *ortho*-functionalized aryl iodides and aliphatic alcohols. **S. Sarath Chand**, and K. V. Radhakrishnan, 8th Mid-Year CRSI National Symposium in Chemistry (NSC-16), held at CSIR-North East Institute of Science and Technology, Jorhat, Assam, July **2014**.
14. Rhodium(III)-catalyzed ring-opening of strained olefins through C–H activation of O-acetyl ketoximes: an efficient synthesis of transfunctionalized cyclopentenes and spiro[2.4]heptenes. **S. Sarath Chand**, E. Jijy and K. V. Radhakrishnan, a poster presented at the National Symposium on Transcending Frontiers in Organic Chemistry (TFOC- 2014) held at CSIR-National Institute for Interdisciplinary Science and Technology, Trivandrum, October **2014**.