Development of Synthetic Methods for Selected Indole-Based Heterocyclic Compounds from Indole, Isatin and Indoline-2-thione

THESIS

Submitted in partial fulfillment

of the requirements for the degree of

DOCTOR OF PHILOSOPHY

by

GANESH MAHADEORAO SHELKE

ID. NO. 2011PHXF015P

Under the guidance of supervisor

Prof. Anil Kumar

and Co-supervisor

Dr. Mukund Jha

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE
PILANI (RAJASTHAN) INDIA
2016

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE
PILANI (RAJASTHAN)

CERTIFICATE

This is to certify that the thesis entitled **"Development of Synthetic Methods for Selected Indole-Based Heterocyclic Compounds from Indole, Isatin and Indoline-2-thione"** and submitted by **Mr. Ganesh Mahadeorao Shelke** ID No **2011PHXF015P** for award of Ph.D. of the Institute embodies original work done by him under our supervision.

Signature in full of the Supervisors:

Name in capital block letters: **Prof. ANIL KUMAR**
Designation: Associate Professor, Birla Institute of Technology and Science Pilani, Pilani Campus, Rajasthan India.

Date:

Name in capital block letters: **Dr. MUKUND JHA**
Designation: Professor, Nipissing University, North Bay, Ontario, Canada.

Date: Nov 21, 2016

Dedicated to

My Parents,

Family Members

and

Teachers

ACKNOWLEDGEMENTS

I take this opportunity as an advantage to put my gratitude and thanks to many people who are responsible one or another way for supporting me to reach this point of my life. Although words are inadequate, first and foremost, I would like to express my sincere and everlasting gratitude to my supervisors Professor Anil Kumar and co-supervisor Dr. Mukund Jha for their excellent guidance throughout my research. Without their trust and constant support, successful achievement of this work would have remained a dream. I am indebted to Professor Anil Kumar for mentoring me and teaching me the necessary things to become a successful researcher. Without him, it would have been really difficult for me to reach the position where I am today. I will never forget our endless chemistry discussions with no time boundaries. His supportive discussions and enthusiasm for chemistry always replenished my energy to work. His inspiring hard work and constant motivation have helped me to understand better and remain optimistic during the course of my study. His forensic scrutiny of my technical writing has been invaluable. His continued encouragement and suggestions resulted in the form of high-quality publications which are unprecedented in such a less time period.

I am immensely thankful to the Vice-Chancellor, Director, Deputy Directors and Deans of Birla Institute of Technology & Science, Pilani (BITS Pilani) for giving me the opportunity to pursue my doctoral studies by providing necessary facilities and financial support.

My whole-hearted gratitude to Prof. Sanjay Kumar Verma, Dean, Academic Research Division (ARD), BITS Pilani and Dr. Saumi Ray, Convener, Departmental Research Committee (DRC), Department of Chemistry, BITS Pilani, Pilani Campus for their official support and encouragement. I owe my sincere thanks to Dr. Hemant R. Jadhav, Dr. Prasanta Das, Dr. Angshuman Sarkar and Dr. Anjan Chattopadhyay nucleus members of ARD. I overwhelmingly acknowledge the office staff of ARD, whose secretarial assistance helped me in submitting the various evaluation documents in time. I am grateful to the members of my Doctoral Advisory Committee, Prof. Ajay Kumar Sah and Dr. Madhushree Sarkar for their great cooperation in refining my thesis. I also would like to extend my sincere gratitude to Prof. Ajay Kumar Sah, Prof. Bharti Khungar, Dr. Madhushree Sarkar, Dr. Prashant U. Manohar and Dr. Indresh Kumar members of DRC and also Prof. S. C. Sivasubramanian, Prof. S. K. Saha, Prof. R. K. Roy, Prof. Dalip Kumar, Prof. I. R. Laskar, Dr. Paritosh Shukla, Dr. Surojit Pande, Dr. Rajeev Sakhuja,

Dr. S. Chakraborthy and Dr. B. R. Sarkar faculty members of Department of Chemistry, BITS Pilani, Pilani Campus for their constant guidance. I am thankful to all the respectable faculty members of the Department of Chemistry, BITS Pilani for their generous help and support along with fruitful discussions during the different stages of my doctoral study. Thanks are also due to all the office staff of the Department for their help during my work. My sincere thanks to Mr. Giridhar Kunkur, Librarian, BITS Pilani and other staff of library for their support and help rendered while utilizing the library services.

I am grateful to Dr. Mukund Jha for giving me opportunity to visit his lab at Nipissing University, Canada and allowing me to work with their group for a period of six months with the financial support from Natural Sciences and Engineering Research Council of Canada (NSERC) and the Canada Foundation for Innovation (CFI). I am thankful to Prof. Keykavous Parang, Chapman University, in extending his support for analytical data and valuable suggestions. I would like to thank Dr. Rakesh Tiwari and Dr. Bhupender Chhikara for their generous help in this work.

I would like to extend my gratitude to emeritus Retd. Prof. M. S. Shingare (F.R.S.C, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad) for his continuous support. Without his initiation, I would not have joined BITS Pilani. I am highly delighted to acknowledge Dr. Ramrao Mane (Retd. Professor, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad) and Dr. B. B. Shingate (Assistant Professor, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad) for their constant motivation to reach this point quickly. I can't restrict myself to thank my close friends Mrs. Sunita Choudhary and Mr. Veer Reddy for their never-ending support.

The great inspiring and congenial atmosphere along with the achievements made in Lab 3145 are one of the most memorable things in my life. I am delighted to work with my lovely colleagues. My sincere thanks to Dr. Sudershan Rao, Dr. Kameswara Rao, Dr. Manoj Kumar Muthyala, Dr. Kasiviswanadharaju Pericherla for their friendly guidance. My special thanks to Dr. Kamesh and Dr. Manoj for their continuous support in my professional as well as personal life in BITS Pilani. Without these two guys, my life would have been monotonous during these years. My sincere thanks to Mr. Mukund, Mr. Santosh and Mr. Arun for their continuous support. Here comes my favorite group members Mrs. Poonam, Mrs. Pinku, Mr. Hitesh, Ms. Khima, Ms. Saroj, Mr. Shiv, Mr. Nitesh, Mr. Vikki special thanks to you all for your untiring and continued support during

my thesis work. My research life in BITS Pilani would have been imperfect without your support. My sincere thanks to other group members Dr. Noorullah, Ms. Meenakshi and Ms. Vaishali. I am thankful to graduate students Mr. Yash Kothari, with whom I have worked. I extend my heartfelt thanks to my best friends Dr. Veer Reddy (Postdoctoral Fellow, University of Cape Town, South Africa), Mr. Panjab Arde (PhD Student, IISER Mohali), Mr. Badrinath Kakde (Postdoctoral Fellow, Shanghai Institute of Organic Chemistry, China), Mr. Satish Dighe (PhD Student, The University of Queensland, Australia), Mrs. Jane Agnew (Undergraduate Student, Nipissing University, Canada), Ms. Ashley Ryan (Graduate Student, Nipissing University, Canada) and BITS research scholars Dr. Amrith, Dr. Rituparna, Dr. Parvej Alam, Dr. Sonu Kumar, Mr. Santosh Khandagale, Mrs. Santosh Kumari, Ms. Pallavi Rao, Dr. Ramaraju, Dr. Nisar Ahmed, Mr. Sachin Choudhary, Mr. Saleem Pasha, Mr. Ashok Sharma, Mr. Anoop Singh, Ms. Sunita, Ms. Pragati, Ms. Bijoya, Ms. Moyna, Mr. Abdul, Mr. Saleem, Mr. Vishal, Mr. Vimal, Mr. Manish, Mr. Devesh, Mrs. Archana, Mrs. Suman, Ms. Sonam, Mrs. Rajinder, Mr. Roshan, Mr. Abid, Mr. Emil, Mr. Prashant, Mr. Yash, Mr. Arpit, Mr. Arghya, Mr. Muthu, Mr. Sourab Mundra, Mr. Rajnish for their help and charming company.

It would be an understatement to say that I would not be the person I am today without my family. A special gratitude to my father (Mr. Mahadev) and my mother (Mrs. Parvati) for always believing me and encouraging me over the years. Their visions, ethical principles, moral support, endless patience and eternal inspiration to face any situation in life have guided me to the successful completion of this work. A special thanks to my brother (Mr. Mahesh), who always considered my success as his own which gave me immense pleasure to achieve the best in my life. In most of my successful stints, he celebrated louder than me and I feel confident that he is always there for me. He always sacrificed his personal life for my convenience and I truly do appreciate it. Last but not least, I deeply acknowledge the special person who recently gave entry to my life and will continue the journey with me, my wife (Mrs. Pooja). Completion of this thesis in anticipated time would have been difficult for me without her support. Finally, I thank my God, for letting me through all the difficulties. Thanks, Deva !!

I duly acknowledge valuable support in the form of Research Fellowship from BITS Pilani, UGC and CSIR New Delhi.

Ganesh Mahadeorao Shelke

ABSTRACT

Nitrogen-containing heterocyclic compounds show a wide range of biological activities, so their syntheses have always been an attractive area in organic chemistry. The thesis entitled "**Development of Synthetic Methods for Selected Indole-Based Heterocyclic Compounds from Indole, Isatin and Indoline-2-thione**" deals with the synthesis of some selected indole derivatives and indole-fused heterocycles by employing Lewis acid such as metal triflates and utilizing transition metal catalyzed C−H functionalizations. The thesis is divided into four chapters.

The first chapter of the thesis describes the synthesis of bisindolyl compounds using metal triflate as a catalyst. This chapter is divided into two parts. **Part A** described the reaction of different substituted indoles with acetone using $Bi(OTf)_3$ as a catalyst. An efficient protocol was developed for the synthesis of spirobicyclopenta[*b*]indoles, 1-methylindolyl-cyclopenta[*b*]indoles and bis(1-methylindolyl)propanes through the reaction of indole with acetone in the presence of $Bi(OTf)_3$ in dichloromethane. The reaction conditions were benign, required shorter reaction time and furnished good yields. The structure of 1-methylindolyl-cyclopenta[*b*]indole **119a** was unambiguously confirmed by X-ray crystallographic data. In **part B**, we have studied the polymerization of indole using $Sc(OTf)_3$ as a Lewis acid catalyst in dichloromethane and found that the product indole-3,3′-trimer or indole-dimer formation was dependent on the substituent present on the indole ring. A plausible mechanism has been proposed based on the product distribution.

The second chapter of the thesis describes the classical and advanced methods for synthesis of oxindole derivatives based on the type of bond formation and use of starting materials. Here, we significantly expand the scope of the Wolff-Kishner reduction method for the synthesis of substituted 2-oxindoles. We have developed one-pot tandem reduction of oxo and *N*-ene/-yne functional group of substituted isatins into *N*-alkyl-2-oxindoles in excellent yields using hydrazine hydrate (25% in H_2O). A gram-scale reaction has been performed to demonstrate the potency of optimized procedure for the scale-up processes.

The third chapter of the thesis deals with the synthesis of benzo-thiazino[3,2-*a*]indoles, 5,7-dihydro-isothiochromeno[3,4-*b*]indoles and dihydro-thiopyrano[2,3-*b*]indoles *via* transition metal catalyzed intramolecular cross-coupling and hydroarylation reactions. The chapter is divided into two parts. In **part A,** firstly we prepared required precursors, substituted 2-(2-bromobenzylthio)indoles by the reaction of substituted indoline-2-thiones with 2-bromobenzyl alcohols in the presence of BF_3.etherate in chloroform. Further, copper-catalyzed intramolecular Ullmann type C-N coupling of 2-(2-bromobenzylthio)-1*H*-indoles and palladium-catalysed intramolecular direct arylation reaction of 2-(2-bromobenzylthio)-1-methyl-1*H* indoles afforded benzo-thiazino[3,2-*a*]indoles and 5,7-dihydro-isothiochromeno[3,4-*b*]indoles, respectively. In **part B,** we used unsaturated aliphatic alcohols in place of 2-bromobenzyl alcohols and prepared substituted 2-(2-alkenylthio)indoles in BF_3.etherate which further on treatment with $AuCl_3$ furnished the dihydrothiopyrano[2,3-*b*]indoles *via* rearrangement of the ene-yne side chain of 2-(2-alkenylthio)-indoles followed by intramolecular hydroarylation at the C-3 position of the indole core. The structure of the product **143k** was unambiguously confirmed by an X-ray crystallographic data.

Finally, overall thesis work is summarized in chapter four. The future scope of the research work has also been highlighted in this chapter.

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS / SYMBOLS

Abbreviation/Symbol	Description
α	Alpha
β	Beta
γ	Gamma
Δ	Delta
°C	Degree centigrade
Å	Angstrom
Ac	Acetyl
Ac_2O	Acetic anhydride
AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
Autoclave	A strong sealed vessel used for chemical reactions at high pressures and temperatures
Aq	Aqueous
Ar	Aryl
[Bmim][BF_4]	1-Butyl-3-methylimidazolium tetrafluoroborate
[Bmim][PF_6]	1-Butyl-3-methylimidazolium hexafluorophosphate
BNPH	Bismuth nitrate pentahydrate
BTEAC	Benzyl triethylammonium chloride
-NTf	Bis(trifluoromethanesulfonyl)imide [$(CF_3SO_2)_2N^-$]
Bu	Butyl
bn	Billion
t-BuOK	Potassium *tert*-butoxide
Calcd.	Calculated

^{13}C	Carbon-13
δ	Chemical shift
Cat.	Catalyst
cm	Centimeter
CNS	Central nervous system
$CDCl_3$	Deuterated chloroform
m-CPBA	*meta*-Chloroperoxybenzoic acid
CHDA	*trans*-1,2-Diaminocyclohexane
Conc	Concentration
COSY	Correlation spectroscopy (NMR)
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical,
dd	Doublet of doublet
DNBS	2,4-Dinitrobenzenesulfonyl
DCE	Dichloroethane
DEG	Diethylene glycol
DCM	Dichloromethane
DMA	*N,N*-Dimethylacetamide
DMEDA	*N,N'*-Dimethylethylenediamine
DMF	*N,N*-Dimethylformamide
DMSO-d_6	Deuterated dimethylsulfoxide
DMSO	Dimethylsulfoxide
EI	Electron ionization

ESI	Electron-spray ionization
EDDA	Ethylenediamine-*N,N′*-diacetic acid
EtOAc	Ethyl acetate
equiv	Equivalent
ESI-MS	Electrospray ionization mass spectrometry
FMN	Flavin mononucleotide
g	Gram
h	Hours
HDNIB	[Hydroxy-(2,4-dinitrobenzenesulfonyloxy)iodo]benzene,
HMBC	Heteronuclear multiple bond coherence
HRMS	High resolution mass spectra
HSQC	Heteronuclear single quantum correlation
HTIB	(Hydroxy(tosyloxy)iodo)benzene
IBX	2-Iodoxybenzoic acid
ILs	Ionic liquids
IR	Infra-red
Hz	Hertz
J	Coupling constant
Lit.	Literature
LDA	Lithium diisopropylamide
MCR	Multicomponent reaction
Me	Methyl
MS	Molecular sieve
mp	Melting point
m	Multiplet

mg	Milligram
MHz	Mega hertz
min	Minutes
mmol	Millimole
MW	Microwave
N_2	Nitrogen
Nu	Nucleophile
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect
NOESY	Nuclear overhauser effect spectroscopy
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NCS	*N*-Chlorosuccinimide
NMI	*N*-Methylimidazole
O_2	Oxygen
[Omim] PF_6^-	1-Methyl-3-octylimidazolium hexafluorophosphate
PEG	Polyethylene glycol
PIDA	Phenyl iodonium diacetate
Ph	Phenyl
Py	Pyridine
PBPB	Pyridinium bromide perbromide
P-Zr	Phosphate zirconia
ppm	Parts per million
π	Pi
PPA	Polyphosphoric acid

%	Percentage
psi	Per square inch
p-TSA or *p*-TsOH	*p*-Toluenesulfonic acid
rt	Room temperature
s	Singlet
$	Dollar sign
SDS	Sodium dodecyl sulfate
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
t	Triplet
TBAI	Tetrabutylammonium iodide
TBAB	Tetrabutylammonium bromide
TBHP	*tert*-Butyl hydroperoxide
qTOF	Quadrupole time-of-flight
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TMSCl	Trimethylsilyl chloride
-OTf	Triflouromethanesulfonate

TABLE OF CONTENTS

Chapter I

Metal Triflate Catalyzed Reactions of Indoles

1.1 Introduction

Heterocyclic compounds are those cyclic molecules where one or more of the ring carbons are replaced by nitrogen, oxygen, sulfur etc. Heterocycles containing nitrogen atoms such as quinolines, isoquinolines, indoles etc. show a range of biological activities, so their syntheses have always been an attractive area in organic chemistry. In particular indole and its derivatives, have occupied a unique place in the chemistry of nitrogen-containing heterocyclic compounds because of their varied biodynamic properties.[1] The significance of indole can be documented both by ever increasing number of publications (more than 80,000 publications in the 20th century) targeting indole chemistry[2] and with its presence in pharmaceuticals, fragrances, agrochemicals, pigments, material science, organic electronics and natural products.[3, 4] Some of the known naturally occurring indole derivatives includes, Reserpine one of the first drug for the treatment of diseases of the central nervous system (CNS) such as anxiety and mental disorders, which was isolated from the dried root of *Rauwolfia serpentina* (Indian snakeroot).[5, 6] Vincristine is a mitotic inhibitor which inhibits mitosis or cell division and used in cancer chemotherapy.[7, 8] This can be isolated and extracted from the Madagascar periwinkle (*Catharanthus roseus*). Another example is an essential amino acid Tryptophan, which is necessary for normal growth in infants and for nitrogen balance in adults. This amino acid can not be synthesized by the organisms but must be obtained from the daily diet. Additionally, tryptophan can be used as a biochemical precursor for the synthesis of Serotonin (chemically called as 5-hydroxytryptamine) which act as an antidepressant drug. It can be converted to Melatonin (chemically known as *N*-acetyl-5-methoxytryptamine) which act as a medication for insomnia. The indole-3-acetic acid is one of the naturally occurring basic auxin (a phytohormone) synthesized by plants (**Figure 1.1**). To date, over ten thousand biologically active indole derivatives have been identified[9] and from those, over 200 are currently marked as drugs or undergoing clinical trials.[10] Moreover, a number of vital synthetic drugs including sumatriptan, tadalafil, rizatriptan and fluvastatin contain indole motif (**Figure 1.2**). The prominence of indole and its extensive applications justifies it being addressed as “The Lord of the Rings” of heteroaromatic compounds.[11]

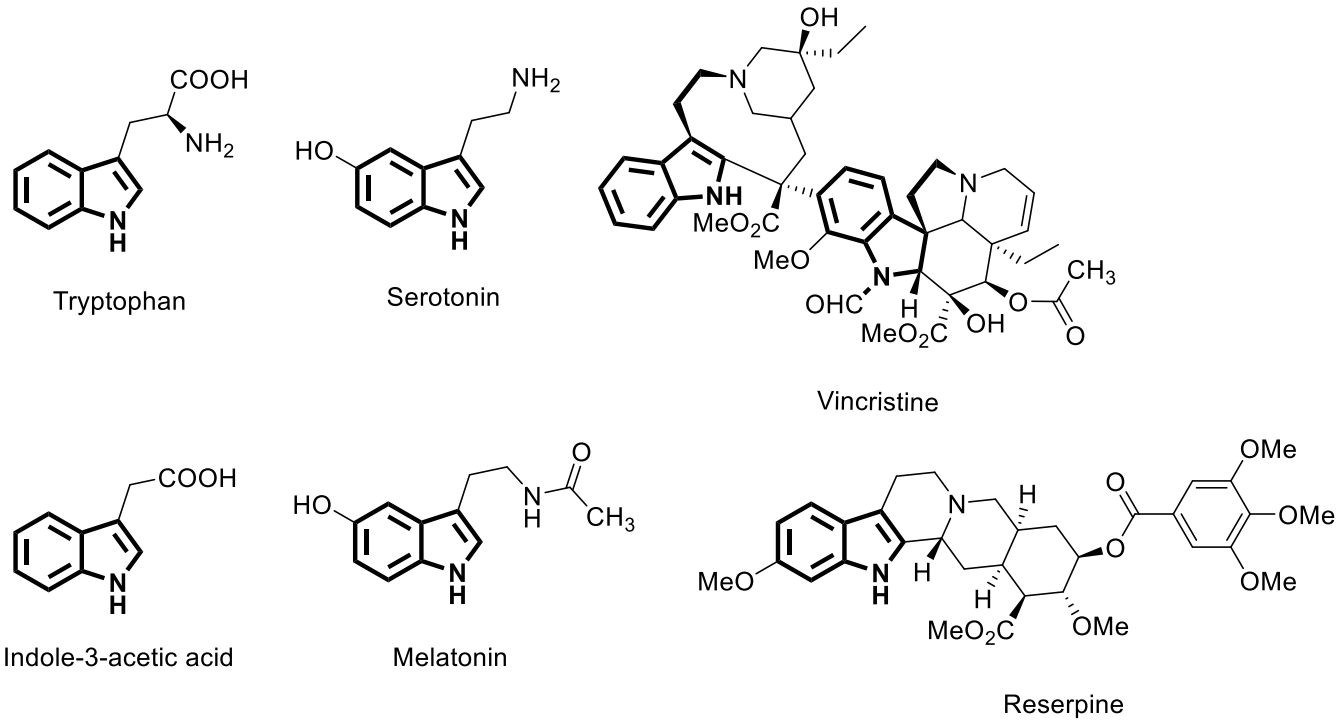


Figure 1.1: Selected examples of naturally occurring indole derivatives

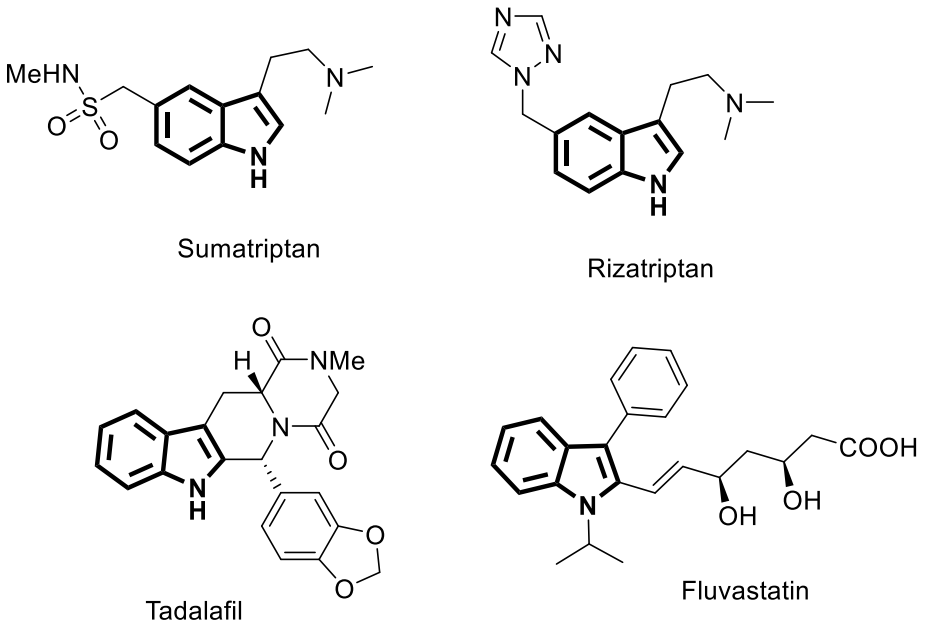
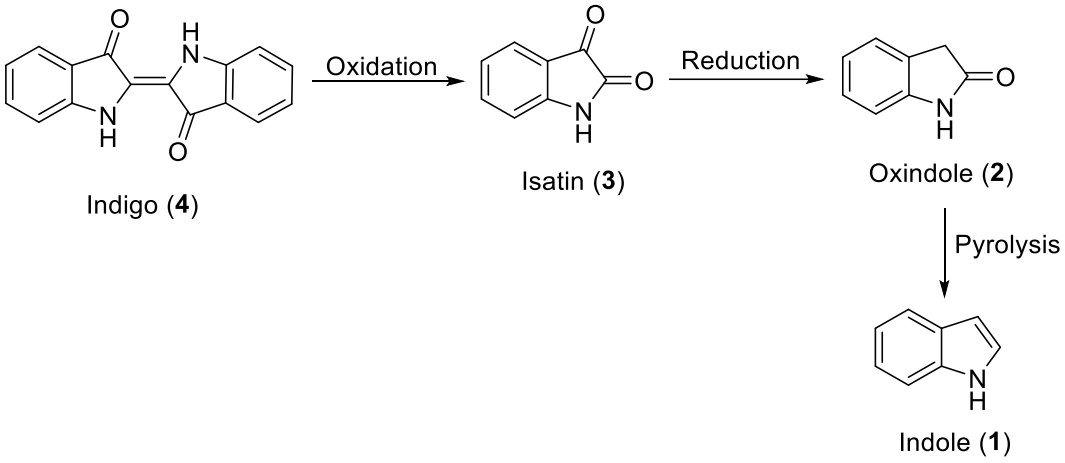


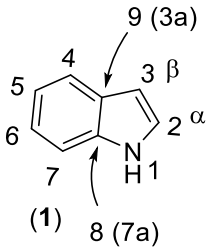
Figure 1.2: Clinically used indole derivatives

The attention in the chemistry of indole (**1**) began in the mid of the 19th century with extensive research on the natural blue dye indigo (**4**), imported to Europe mainly from India. Indigo (**4**) (species of *Indigofera*) is an example of simple bisindole, which was converted into isatin (**3**) on oxidation[12] and further on reduction[13] afforded oxindole (**2**). In 1866, Adolf Von Baeyer discovered the conversion of oxindole (**2**) into indole (**1**) by a pyrolytic technique using zinc dust[14] (**Scheme 1.1**).



Scheme 1.1: First synthetic method of indole (**1**)

Indole (**1**) (or 1*H*-benzo[*b*]pyrrole or 1-benzazole or 1-azaindene or ketole) is a planer bicyclic heteroaromatic molecule in which benzene ring is fused with 2 and 3 positions of pyrrole ring also known as 2, 3-benzopyrrole. It is a colorless crystalline solid and melts at 52 °C, soluble in most organic solvents such as alcohol, benzene and ether. It can be recrystallized from water. It has a musty odor which is very persistent and its derivatives have plenty of applications in the formulation of fragrances. The numbering of the atoms of 1*H*-benzo[*b*]pyrrole (**1**) starts at the nitrogen and 2- and 3-positions are also referred to as the α and β-positions, respectively (**Figure 1.3**)



Chemical formula: C_8H_7N
Molecular weight:117.1510 g

Figure 1.3 : Structure and numbering of atoms of indole [1*H*-benzo[*b*]pyrrole] (**1**)

The isomer **1A** of 1*H*-benzo[*b*]pyrrole (**1**) in which the nitrogen atom takes part in the double bond is termed as 3*H*-benzo[*b*]pyrrole (**1A**) (also known as 3-pseudoindole or indolenin or 3*H*-indole). Here, 1*H*-benzo[*b*]pyrrole (**1**) is more stable than the isomeric benzo[*c*] pyrroles **1B** and **1C**, which are also called 2*H*-isoindole and 1*H*-isoindole, respectively. There are some other oxygenated derivatives of 1*H*-indole that include indole-2,3-dione or isatin (**3**), oxindole (**2**), indoxyl (**5**) and dioxindole (**6**) (**Figure 1.4**).

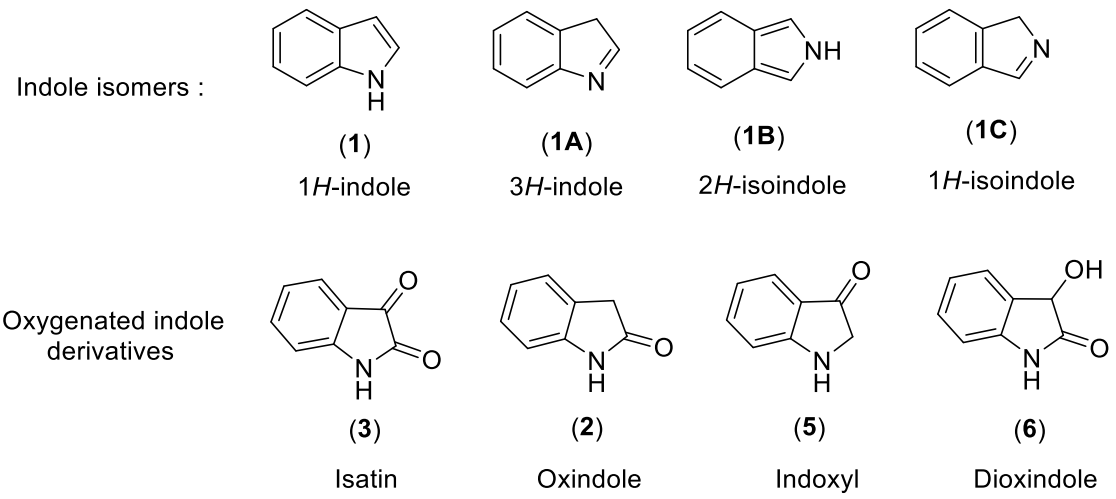


Figure 1.4: Indole isomers and some other oxygenated indole derivatives

1.2 Preparation and reactivity of indoles

There are numerous synthetic methods available for the preparation of indole and its derivatives, some of them are summarized in table 1.1 and are broadly classified in three categories.

a) Through terminal C-C bond formation: The first practical synthesis of substituted indole **10** was proposed by Fischer and Jourdan based on the [3,3]-sigmatropic rearrangement of an arylhydrazone **9** under acidic condition (Table 1.1, entry 1).[15] The Bischler-Möhlau reported that α-bromoketones **12** with an excess of aniline **11** undergo electrophilic aromatic substitution and dehydration when treated with acid, to produce substituted indoles **10** (Table 1.1, entry 2).[16] Later, Madelung disclosed that *ortho*-alkyl anilides **14** undergo intramolecular cyclization in the presence of amide bases at a higher temperature to afford indole derivatives **10** (Table 1.1, entry 3).[17] Gassman developed a one-pot synthesis of 3-thioindoles **16** *via* [2,3]-sigmatropic rearrangement of sulfonium intermediate formed by the reaction of alkyl anilines **11** with α-sulfidoketones **15** in the presence of an oxidant NaOCl. Further reduction of **16** with Raney-Ni yielded indole

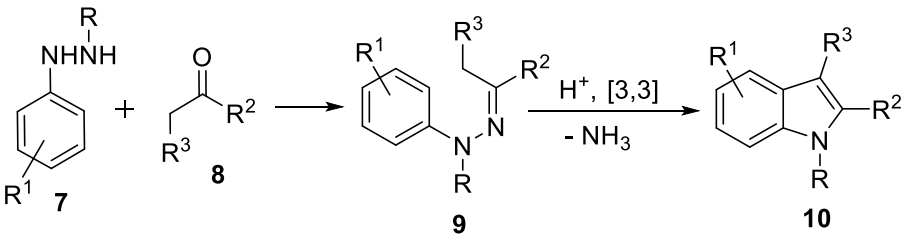
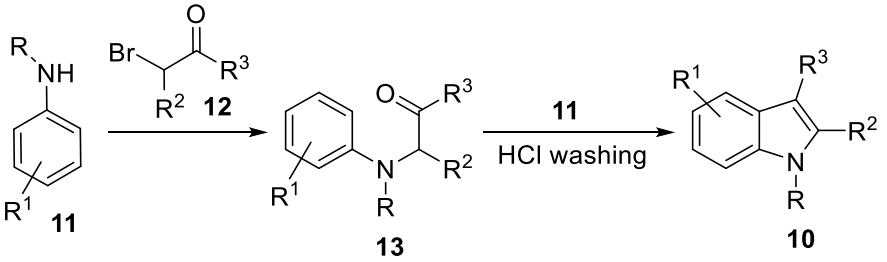
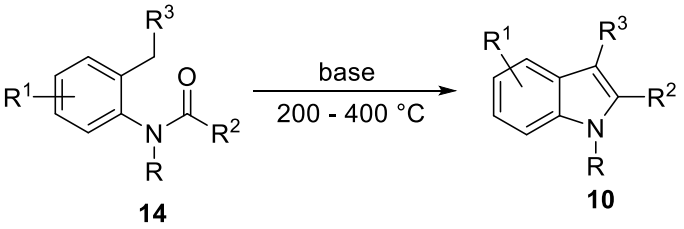
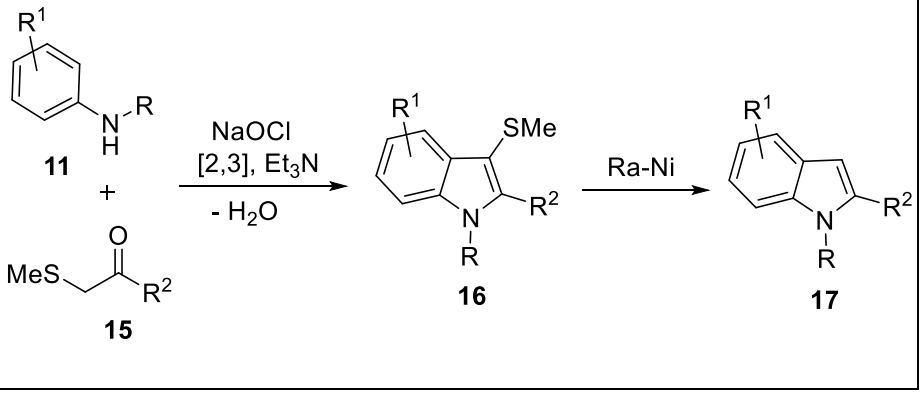
derivatives **17** (Table 1.1, entry 4).[18, 19] In organometallic approach, Bartoli discovered the synthesis of 7-substituted indole derivatives **21** by successive reduction of *ortho*-substituted nitrobenzenes **18** with excess vinyl Grignard reagent **19** followed by an acid workup. The intermediate alkoxy aniline **20** undergoes a [3,3]-sigmatropic rearrangement and consequent condensation to afford the product **21** (Table 1.1, entry 5).[20, 21]

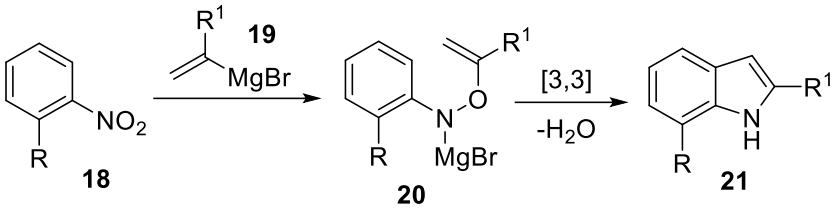
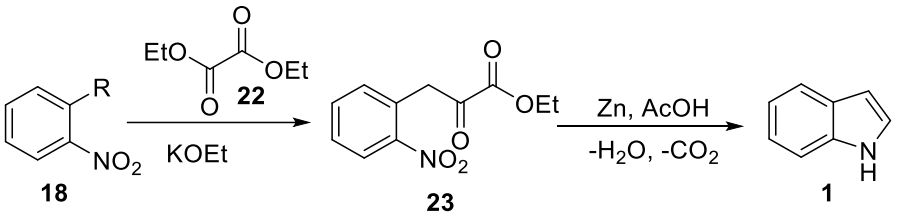
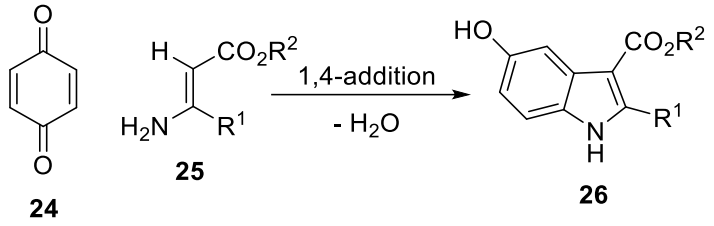
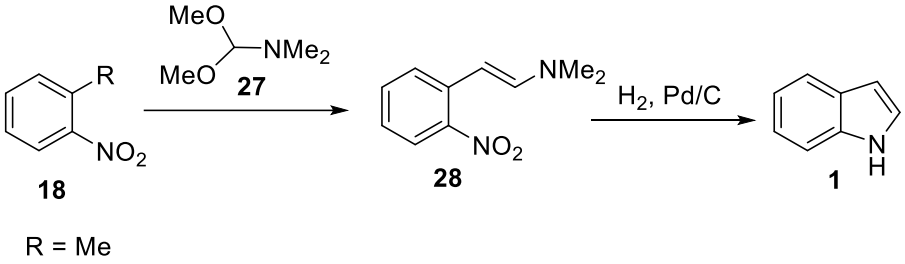
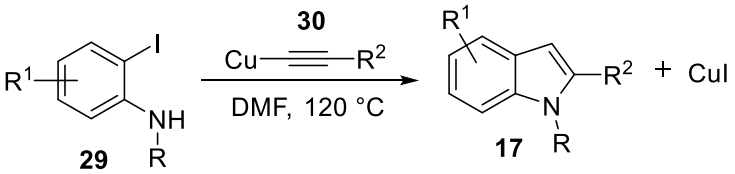
b) Through terminal C-N bond formation: Reissert demonstrated synthesis of indole (**1**) by the condensation of *o*-nitrotoluene (**18**) with ethyl oxalate (**22**) under basic condition (KOEt), with the formation of ethyl *o*-nitrophenyl pyruvate (**23**) as intermediate followed by subsequent reductive cyclization and decarboxylation (Table 1.1, entry 6).[22, 23] Nenitzescu reported a unique approach for the preparation of 5-hydroxyindole derivatives **26** by coupling benzoquinone (**24**) with β-aminocrotonic esters (**25**) (Table 1.1, entry 7).[24] In analogy to the Reissert synthesis, Leimgruber and Batcho developed a two-step reaction that produces indole (**1**) by the condensation of *o*-nitrotoluene (**18**) with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) (**27**) followed by the reductive cyclization of *trans*-β-dimethylamino-2-nitrostyrene (**28**) (Table 1.1, entry 8).[25]

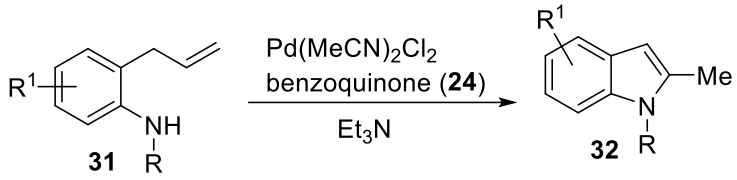
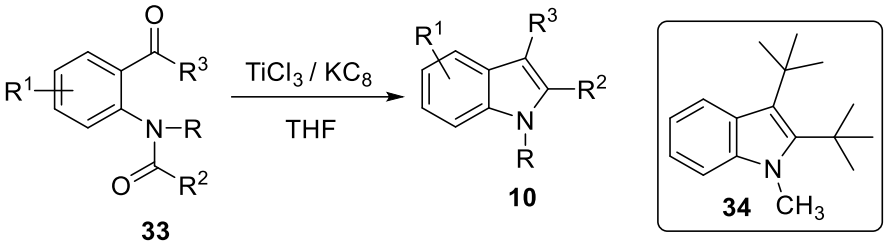
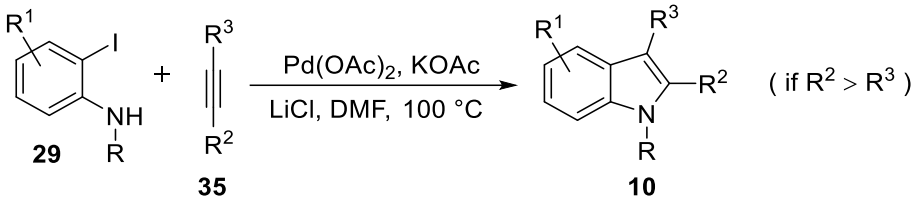
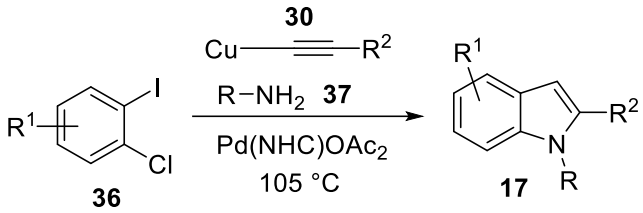
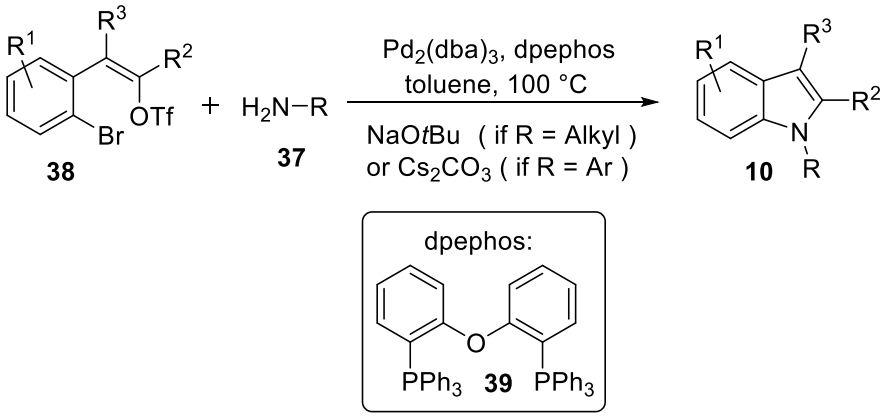
c) Transition metal catalyzed indole synthesis: Castro and co-workers reported a detailed study of the copper-mediated synthesis of substituted indoles **17** by the coupling between *o*-iodoaniline (**29**) and cuprous mono-substituted acetylides (**30**) (Table 1.1, entry 9).[26] In 1976, Hegedus *et al.* described an intramolecular cyclization of *o*-allylaniline **31** assisted by $PdCl_2$ (generated *in situ* by $PdCl_2(MeCN)_2)/NEt_3$), in the presence of benzoquinone (**24**) to afford 2-methylindole (**32**) (Table 1.1, entry 10).[27, 28] Fürstner and co-workers revealed low-valent Ti-mediated intramolecular reductive cyclization of oxo-amides **33** to furnish 2,3-disubstituted indoles **10** (Table 1.1, entry 11).[29-31] This methodology is not only used for the preparation of simple indoles but also includes highly strained examples such as 2,3-di-*tert*-butyl-1-methyl-indole (**34**). In 1991, Larock disclosed an alternative method for the synthesis of 2,3-substitutedindoles **10** *via* one pot intermolecular palladium-catalyzed hetero annulation of *o*-iodoanilines (**29**) and internal alkynes **35** (Table 1.1, entry 12).[32, 33] Later, Ackermann has extended Larock's general strategy to one pot, multicomponent synthesis of indoles **17** from *ortho*-chloroiodobenzene (**36**), alkynyl cuprates **30**, and alkylamines **37** (Table 1.1, entry 13).[34] In the case of an unsymmetrical alkyne, the C-2 position of indole is occupied with the bulkiest substituent. Similarly, Willis and co-workers constructed 1,2,3-trisubstituted indoles **10** by double coupling of styrene derivatives **38** with a single alkyl amine **37** (Table 1.1, entry 14).[35] These seminal studies encouraged various syntheses

of indoles, which have used stoichiometric and progressively catalytic amounts of various metals such as ruthenium, rhodium, platinum, iron or gold and improved protocols involving copper or palladium.

Table 1.1: Classical methods for the synthesis of indoles

(Entry) Name reactions[ref]	**Reactions**
Indole synthesis employing terminal C-C bond formation	
(1) Fischer-Jourdan[15]	
(2) Bischler-Möhlau[16]	
(3) Madelung[17]	
(4) Gassman[18, 19]	

(5) Bartoli[20, 21]	
Indole synthesis employing terminal C-N bond formation	
(6) Reissert[22, 23]	
(7) Nenitzescu[24]	
(8) Leimgruber-Batcho[25]	
Transition metal-catalyzed indole syntheses	
(9) Castro[26]	

(10) Hegedus[27, 28]	
(11) Fürstner[29-31]	
(12) Larock[32, 33]	
(13) Ackermann[34]	
(14) Willis[35]	

Reactivity of indoles

Indole has 10 π electrons, two from the lone pair of nitrogen and eight from the four carbon-carbon double bonds (C=C) and is thus a π-excessive heterocycle.[4] Due to the delocalization of nitrogen lone pair around the indole ring, it is considered a resonance hybrid of the following cannonical forms (**Figure 1.5**).

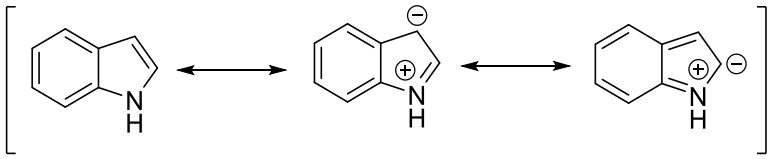
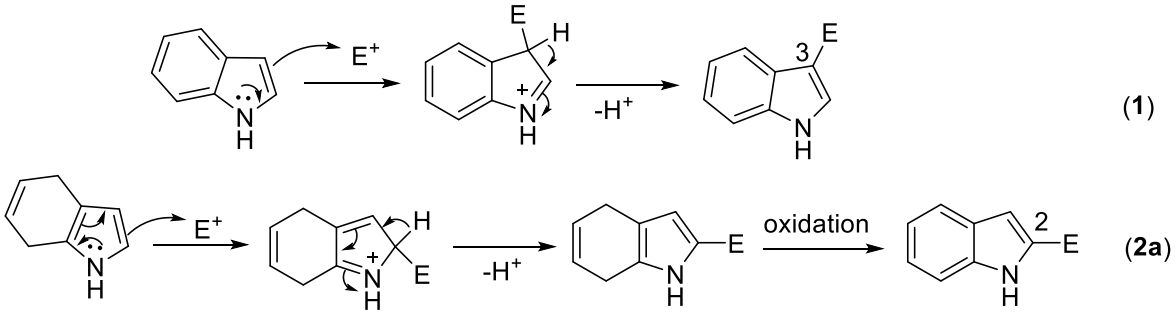


Figure 1.5: Cannonical structures of 1*H*-indole

Its resonance energy is 47-49 kcal/mol. It is a very weak base with pK_a value -3.63.[36] Because of the π-excessive property, indole shows enhanced reactivity compared to benzene, in electrophilic aromatic substitution.[37] Molecular orbital calculations show that the C-3 site of indole has the highest electron density and it is the most reactive position on indole for the electrophilic aromatic substitution which is 10^{13} times more reactive than benzene positions (**Figure 1.6**, Eq. (**1**)). The C-2 position is the second most reactive site of indole toward electrophiles and it can occur only if the pyrrole core is electronically isolated: i.e. on 4,7-dihydroderivatives (**Figure 1.6**, Eq. (**2a**)). However, electrophilic substitution at C-2 of a C-3 unsubstituted indole is possible by using *N*-protected indole, followed by directed metallation at C-2 and subsequent introduction of the electrophile. The most commonly used *N*-protecting groups are benzenesulfonyl, *p*-toluenesulfonyl (Tosyl), *t*-butoxycarbonyl (Boc) etc. Katritzky and co-workers developed a practical, one-pot protocol for the preparation of 2-substituted indoles even in the absence of C-3 substituent.[38] After the introduction of an electrophile, the temporary protecting group was removed during acidic workup (**Figure 1.6**, Eq. (**2b**)).



(**1**)

(**2a**)

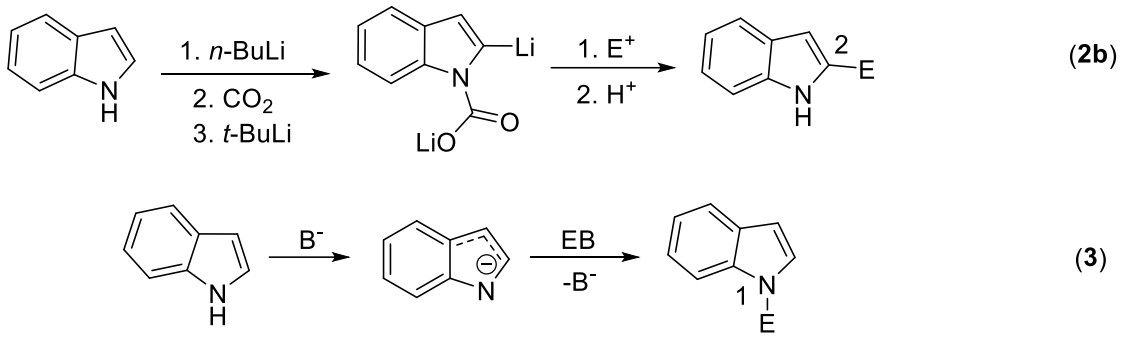


Figure 1.6: Electrophilic attacks on C-3 [Eq. (**1**)], C-2 followed by oxidation [Eq. (**2a**)], C-2 followed by directed metallation [Eq. (**2b**)] and deprotonated *N*-1 [Eq. (**3**)]

The N-H bond in the indole skeleton is weakly acidic hence *N*-substitution reactions such as alkylations, acylations and transition metal catalyzed arylations can occur only when N-H proton of indole was removed to generate charged nucleophile under strongly basic conditions (**Figure 1.6**, Eq. (**3**)). When N-1, C-2, and C-3 positions are occupied by a substituent other than hydrogen, then electrophilic substitution of the carbocyclic ring can take place and to achieve this, benzene ring functionalization is generally obtained by *de novo* ring syntheses.[39] Moreover, in the case of 3-substituted indole, electrophilic substitution at C-2 position can take place in two different ways, either the first attack at the C-3 position and subsequent 1, 2-migration to the C-2 position or *via* direct attack at the C-2 position (**Figure 1.7**).

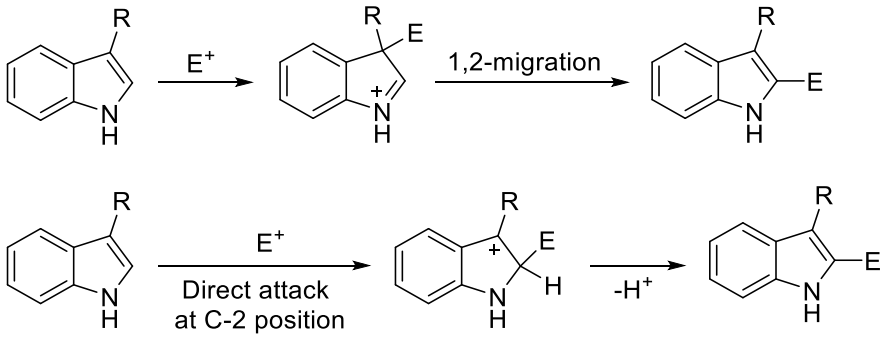


Figure 1.7: Two pathways for electrophile to attack on C-3 substituted indole

1.3 Metal triflates

In this section the discussion is focused on recent progress in metal triflates based catalytic systems for indole synthesis and its functionalization. In the past few decades, metal triflates catalyzed organic transformations has received growing interest due to their unique reactivity, selectivities and mild reaction conditions. Unlike the traditional Lewis acid catalyst (such as $AlCl_3$, BF_3, $TiCl_4$, $SnCl_4$ etc.), metal triflates are stable and can work as Lewis acid in aqueous media. They can be used in catalytic amounts rather than stoichiometric and can be recovered, reused without loss of activity.[40, 41]

Metal triflates consist of a metal cation (M^{+n}) and triflate anion (known as trifluoromethanesulfonate $CF_3SO_3^-$). The triflate group is often represented by -OTf, as opposed to -Tf (triflyl known as trifluoromethanesulfonyl $CF_3SO_2^-$). They are readily obtained by heating the corresponding metal chlorides or oxides in an aqueous trifluoromethanesulfonic acid (TfOH) (also known as triflic acid CF_3SO_3H) solution. Alternatively, they can be obtained from reaction of metal chlorides with silver triflate as shown below[42-44]

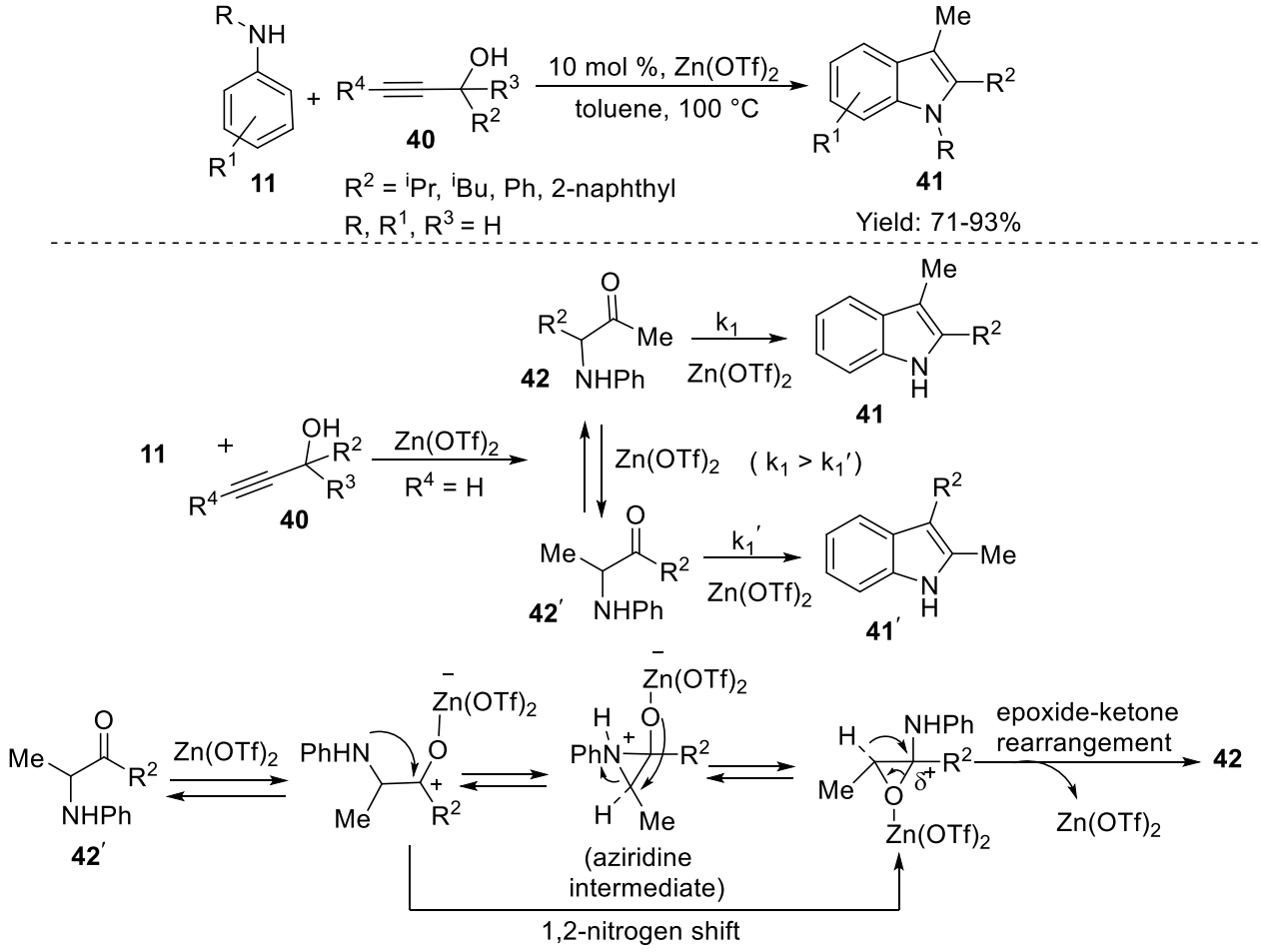
$$MCl_n + nHOTf \rightarrow M(OTf)_n + nHCl$$

$$MCl_n + nAgOTf \rightarrow M(OTf)_n + nAgCl \downarrow$$

Due to the presence of strong electron withdrawing nature of the triflate group (-OTf), metal triflates can act as strong Lewis acid compared to the metal halides and therefore, they show strong oxophilic character (a strong affinity towards oxygen-containing functional groups). Metal triflates retain their superior catalytic activity even in the presence of multiple Lewis bases containing nitrogen, oxygen, sulfur and phosphorous atoms, and therefore, these Lewis acids have found application in carbon-hetero and carbon-carbon bond formation reactions, oxidation-reduction reactions, rearrangements as well as protection-deprotection reactions.[45] Because of their low toxicity, easy handling, moderate cost and ease of availability, moisture, and air stability, possibility of recycling/reuse, high chemo-, regio- and stereoselectivities in organic transformations make these reagents environmentally friendly promoter in modern organic synthesis.

1.3.1 Metal triflate catalyzed synthesis of substituted indoles

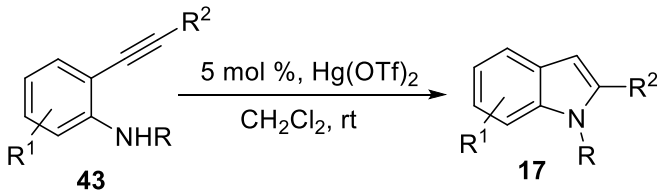
Liu group reported $Zn(OTf)_2$ catalyzed synthesis of indole derivatives **41** by the reaction of propargyl alcohols (**40**) (as a two-carbon building unit) with aniline **(11)** in toluene at 100 °C *via* α-amino ketone intermediate **42**. This catalytic process produces only one regioisomeric product **41** over the other one **41′** (**Scheme 1.2**).[46] This was observed due to the rate of formation of indole **41** is faster in cyclization of ketone **42** relative to that of its regioisomer **42′** ($k_1 > k_1'$). The $Zn(OTf)_2$ catalyzed isomerization between species **42′** and **42** occurs through 1,2-nitrogen shift followed by epoxide-ketone rearrangement.



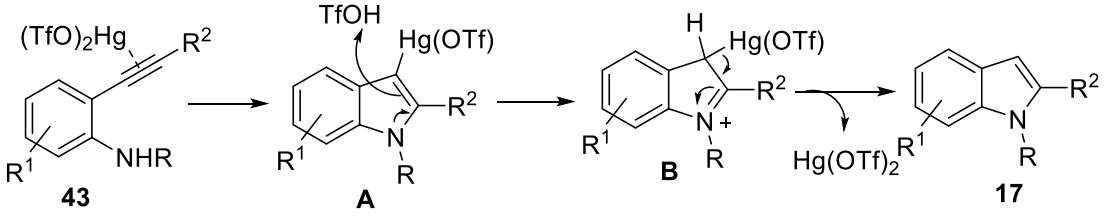
Scheme 1.2: $Zn(OTf)_2$ catalyzed synthesis of indole derivatives **41**

Nishizawa and co-workers developed $Hg(OTf)_2$ catalyzed highly efficient cycloisomerization of 2-ethynylaniline derivatives **48** to afford *N*-substituted indole derivatives **17** in excellent yield under mild reaction conditions (**Scheme 1.3**).[47] In the case of unprotected nitrogen of 2-

ethynylaniline (R = H) and its *N*-acetyl derivatives (R = Ac), the desired products were not detected at all.

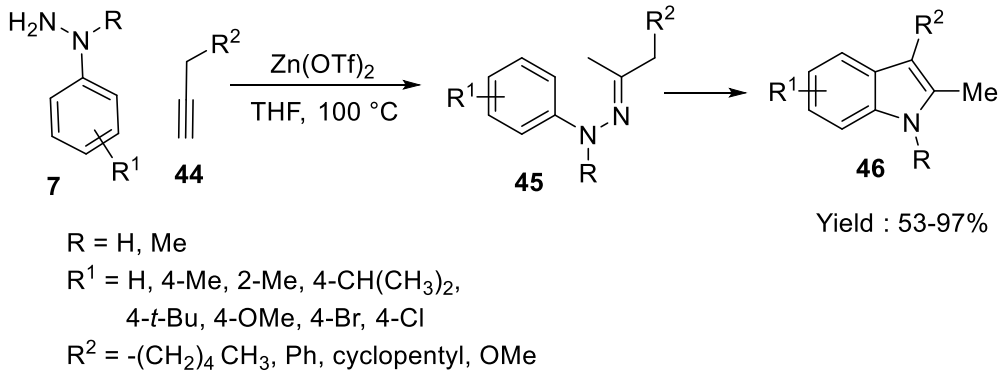


R	R^2	Yield
H, Ac	H	0%
$SO_2C_6H_4NO_2$-*o*	H	78%
$SO_2C_6H_4NO_2$-*p*	H	89%
$SO_2C_6H_4CH_3$-*p*	H	93%
$SO_2C_6H_4CH_3$-*p*	C_4H_9, $CH(CH_3)_2$, $CH(CH_3)_3$, Ph, C_6H_4OMe-*p*	88 - 97%



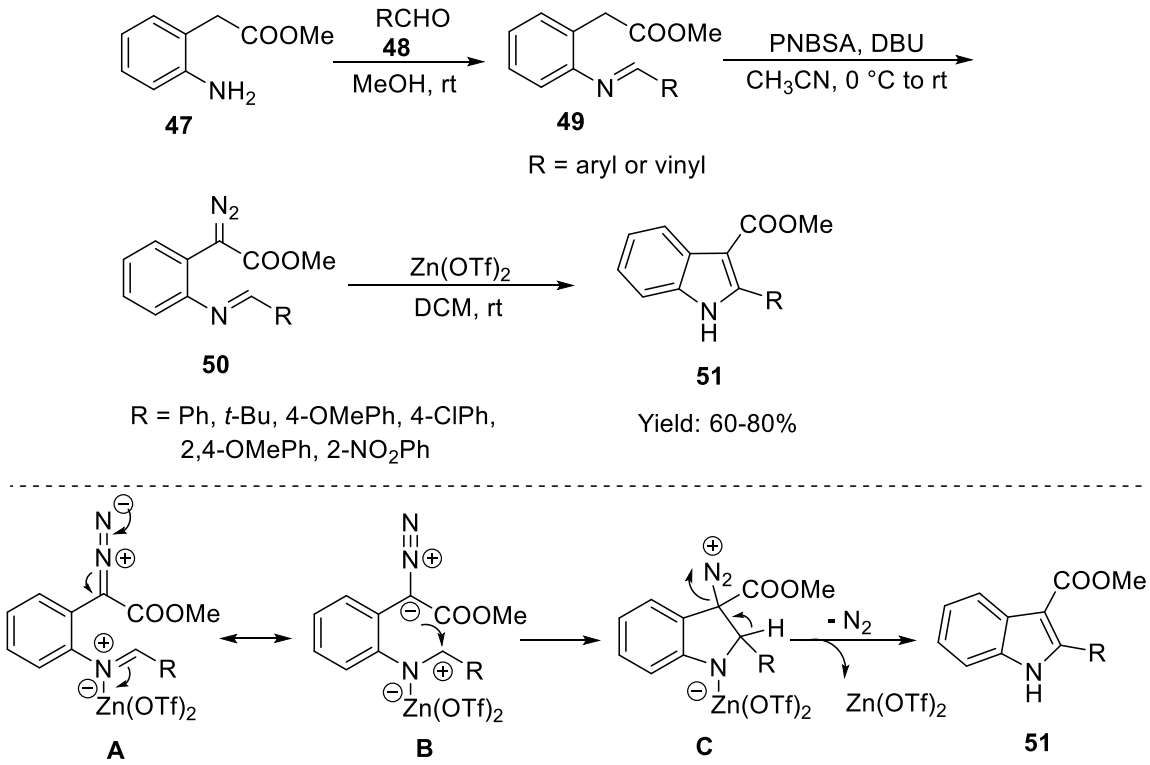
Scheme 1.3: $Hg(OTf)_2$ catalyzed cycloisomerization of **43**

Matthias Beller and co-workers demonstrated one-pot domino synthesis of various substituted indoles **55** from the reaction of arylhydrazines **7** and terminal alkynes **44** in the presence of $Zn(OTf)_2$ (**Scheme 1.4**).[48] In this method, $Zn(OTf)_2$ promoted both the intermolecular hydroamination of arylhydrazines **7** with terminal alkynes **44** to form corresponding arylhydrazones **45** and subsequently [3,3]-sigmatropic cyclization to furnish the corresponding indole derivatives **46**. When internal alkynes such as 1-phenyl-propyne and diphenylacetylene were used, trace amounts of respective indoles were obtained under the optimized conditions.



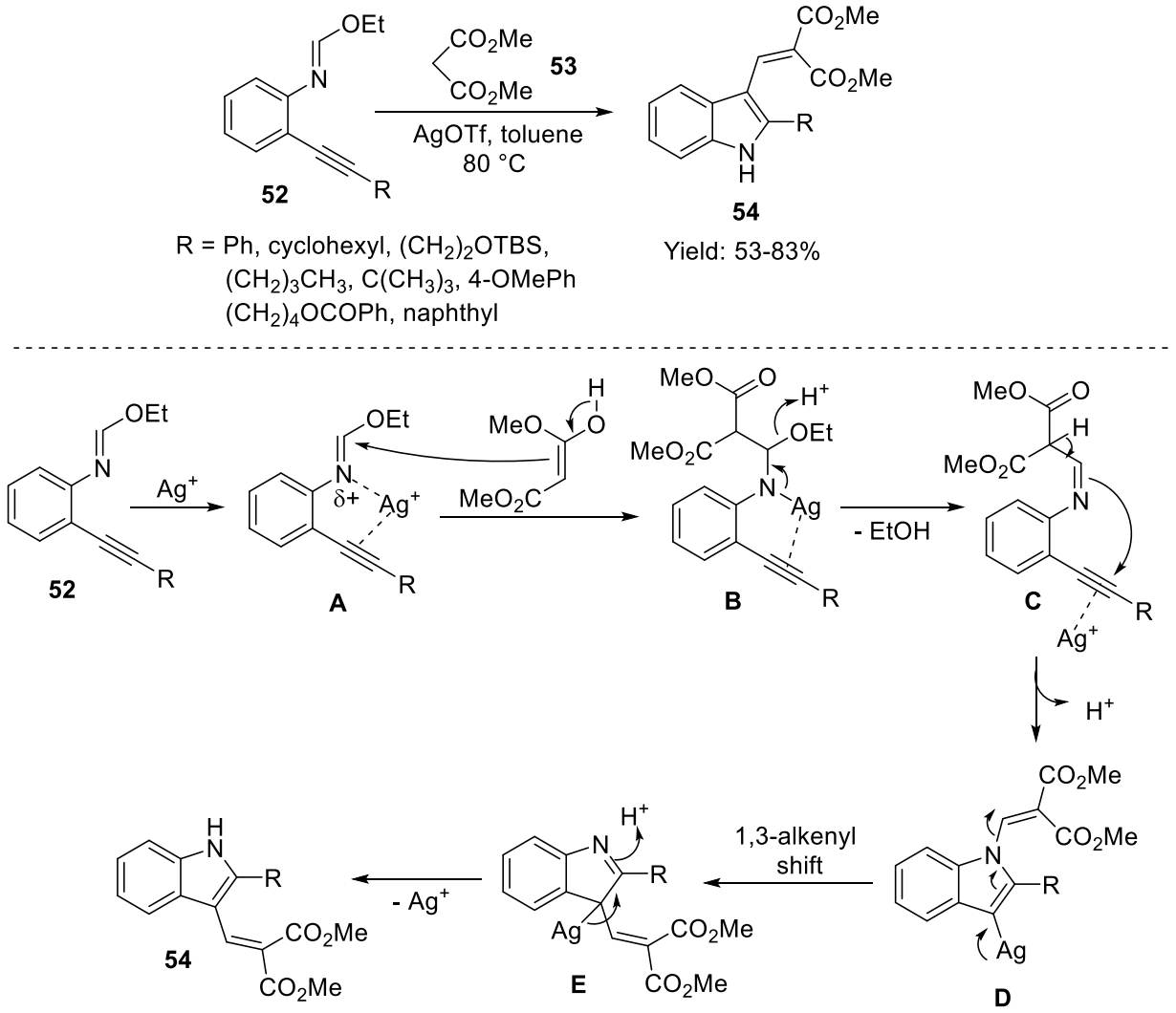
Scheme 1.4: $Zn(OTf)_2$ catalyzed reaction of arylhydrazines **7** with terminal alkynes **44**

Doyle group described the synthesis of functionalized indoles **51** *via* $Zn(OTf)_2$ catalyzed intramolecular cyclization of methyl phenyldiazoacetates with an *ortho*-imino group of **50**, prepared from methyl 2-(2-aminophenyl)acetate **47** according to **Scheme 1.5**.[49] The mechanism of the cyclization involves activation of the imine by $Zn(OTf)_2$ for nucleophilic attack by phenyldiazoacetates to form a diazonium ion intermediate **C**, subsequently expulsion of N_2 and dissociation of the $Zn(OTf)_2$ furnishes the product **51**.



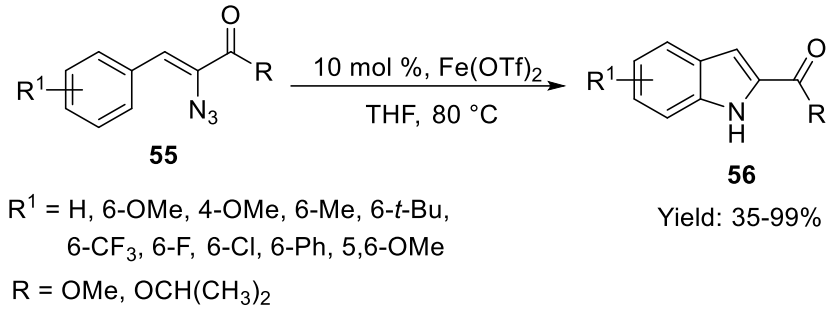
Scheme 1.5: Synthesis of indole derivatives **51** *via* $Zn(OTf)_2$ catalyzed cyclization of **50**

Oh and co-workers disclosed an unusual highly efficient approach for the construction of 2,3-disubstituted indoles **54** by AgOTf catalyzed condensation of *N*-arylformimidates **52** with active methylene compound (dimethyl malonate) **53** followed by a tandem Ag-induced cycloisomerization and unprecedented 1,3-alkenyl shift (**Scheme 1.6**).[50]



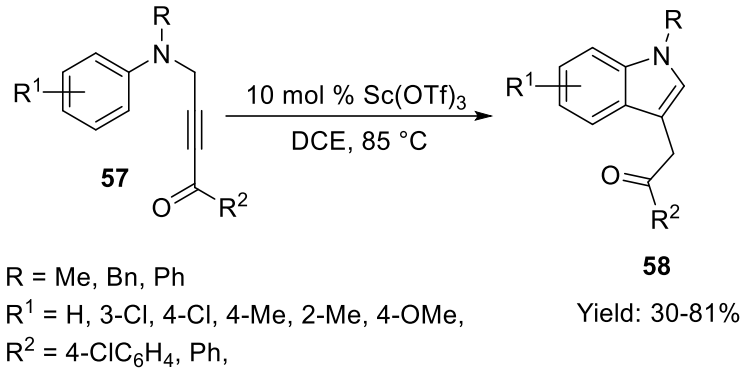
Scheme 1.6: AgOTf catalyzed synthesis of 2,3-disubstituted indole

Bolm *et al.* reported $Fe(OTf)_2$ catalyzed synthesis of a variety of indole derivatives **56** from corresponding arylazidoacrylate **55** *via* intramolecular C-H amination reaction **(Scheme 1.7)**.[51] In the absence of the catalyst, no product was observed. However, both triflic acid and copper (I/II) triflate were also unable to convert **55** into the product **56**. Therefore, $Fe(OTf)_2$ was chosen as highly suitable catalyst for this transformation.



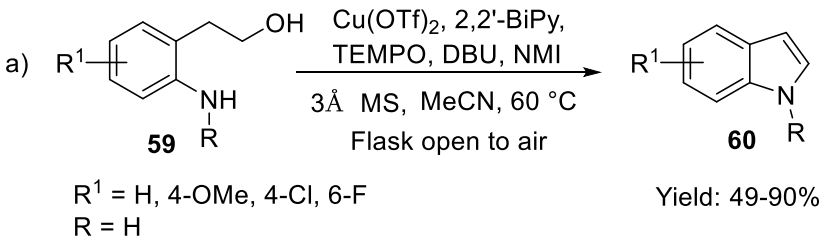
Scheme 1.7: $Fe(OTf)_2$ catalyzed synthesis of indole derivatives **56**

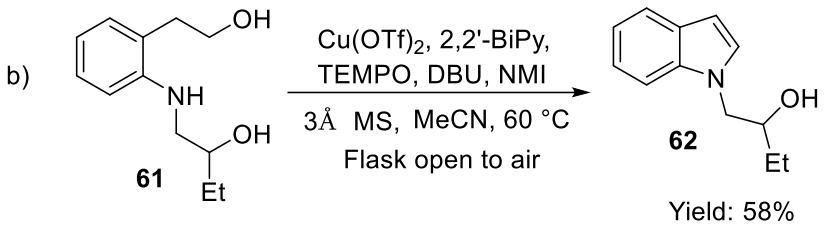
Liang and co-workers introduced synthesis of indole derivatives **58** by $Sc(OTf)_3$ catalyzed intramolecular Friedel-Crafts alkenylation of 5-(arylamino)pent-3-yn-2-ones **57** in 1,2-dichloroethane (DCE) at 85 °C **(Scheme 1.8)**.[52]



Scheme 1.8: $Sc(OTf)_3$ catalyzed Friedel-Crafts reaction for the synthesis of **58**

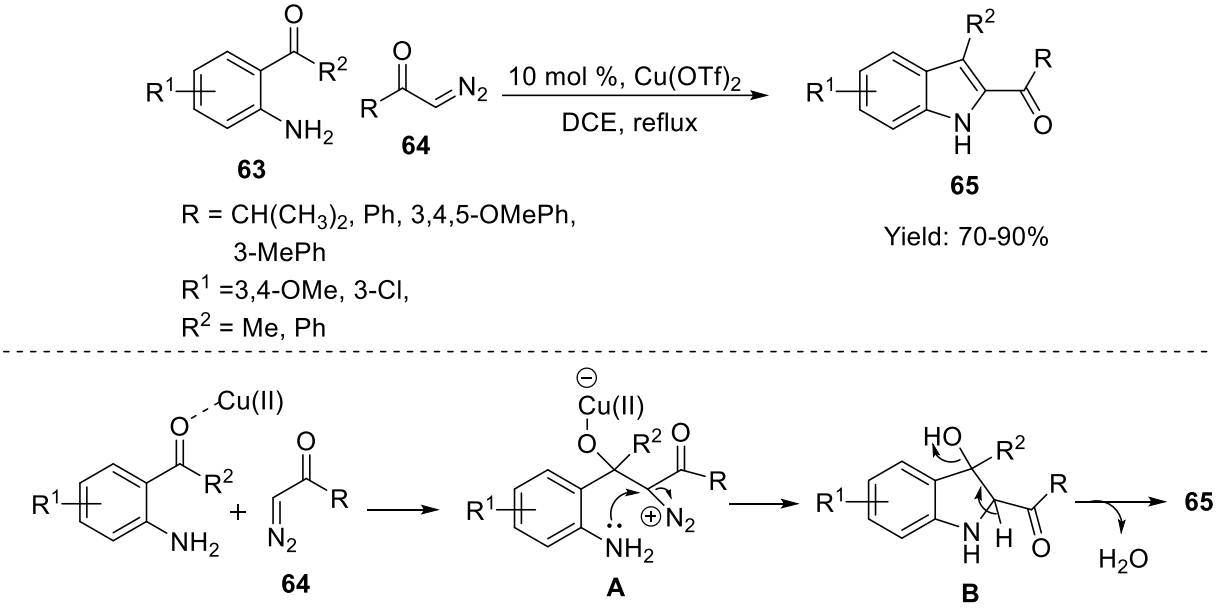
Cook and Muldoon group discovered the synthesis of indole derivatives **60** by the intramolecular oxidative cyclization of amino alcohols **59** using $Cu(OTf)_2$/TEMPO/O_2 catalytic system, which primarily executed the oxidation of an alcohol to an aldehyde to cyclize the product **(Scheme 1.9a)**.[53] The $Cu(OTf)_2$/TEMPO/O_2 catalytic system selectively oxidized the primary alcohol of **61**, without affecting secondary alcoholic group into the product **62** (**Scheme 1.9b**).





Scheme 1.9: $Cu(OTf)_2$/TEMPO catalyzed synthesis of indole derivatives **60** and **62**

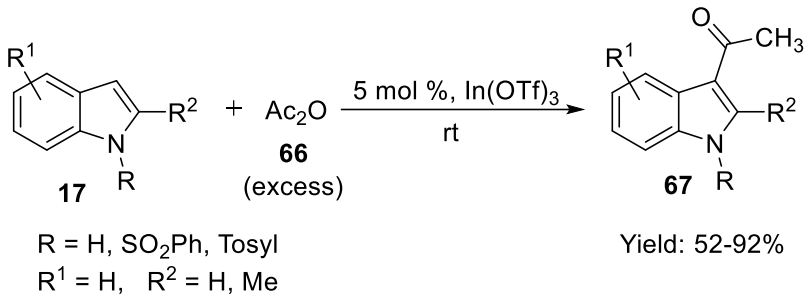
Recently, Reddy and co-workers reported $Cu(OTf)_2$ catalyzed synthesis of 2,3-disubstituted indoles **65** *via* the coupling of α-diazoketones **64** with 2-aminoaryl ketones **63** in 1,2-dichloroethane at reflux conditions (**Scheme 1.10**).[54]



Scheme 1.10: $Cu(OTf)_2$ catalyzed synthesis of indole derivatives **65** from α-diazoketones **64** with 2-aminoaryl ketones **63**

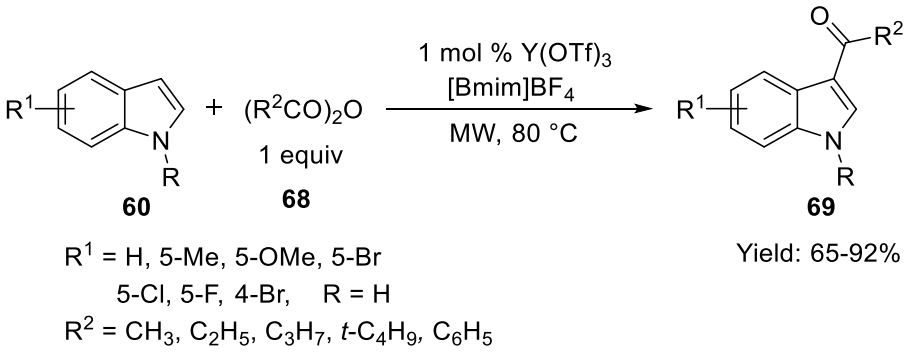
1.3.2 Metal triflate catalyzed functionalization of indoles

Perumal group first time reported $In(OTf)_3$ catalyzed synthesis of acetylation of indole using excess acetic anhydride (**66**) as an acetylating agent at room temperature. In this methodology, excess reagent and NH-protection were required to obtain 3-acylated indoles **67** in good yields (**Scheme 1.11**).[55]



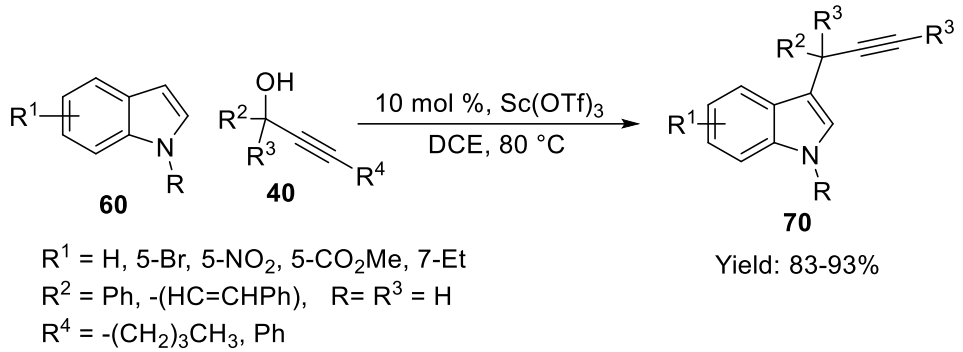
Scheme 1.11: $In(OTf)_3$ catalyzed synthesis of 3-acetylindoles **67**

To overcome the problem of the use of excess reagent and NH-protection of indole recently, Hansen and co-workers developed a green method for the regioselective Friedel-Crafts acylation of indoles **60** at C-3 with several acid anhydrides **68** using 1 mol % $Y(OTf)_3$ in ionic liquid $[Bmim]BF_4$ under microwave irradiation (**Scheme 1.12**).[56] Another advantage of this methodology is the reusability of catalyst for up to four times without significant loss of activity.



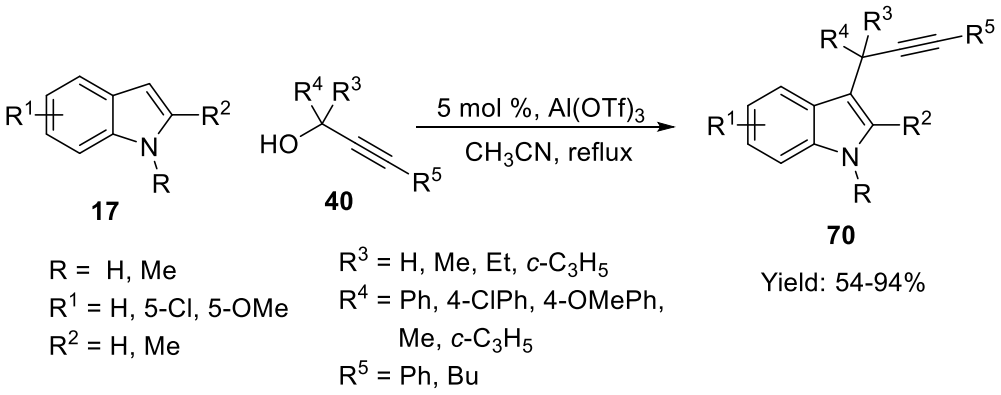
Scheme 1.12: $Y(OTf)_3$ catalyzed regioselective synthesis of 3-acylatedindoles **69**

Yadav and co-workers reported Friedel-Crafts alkylation of indoles **60** with propargyl alcohols **40** using 10 mol % $Sc(OTf)_3$ as catalyst (**Scheme 1.13**).[57] The reaction failed with simple propargylic and homopropargylic alcohols under similar reaction conditions. In addition, 1-cyclohexylhept-2-yn-1-ol did not afford the desired product. Therefore, this method was effective only with propargyl alcohols **40**.



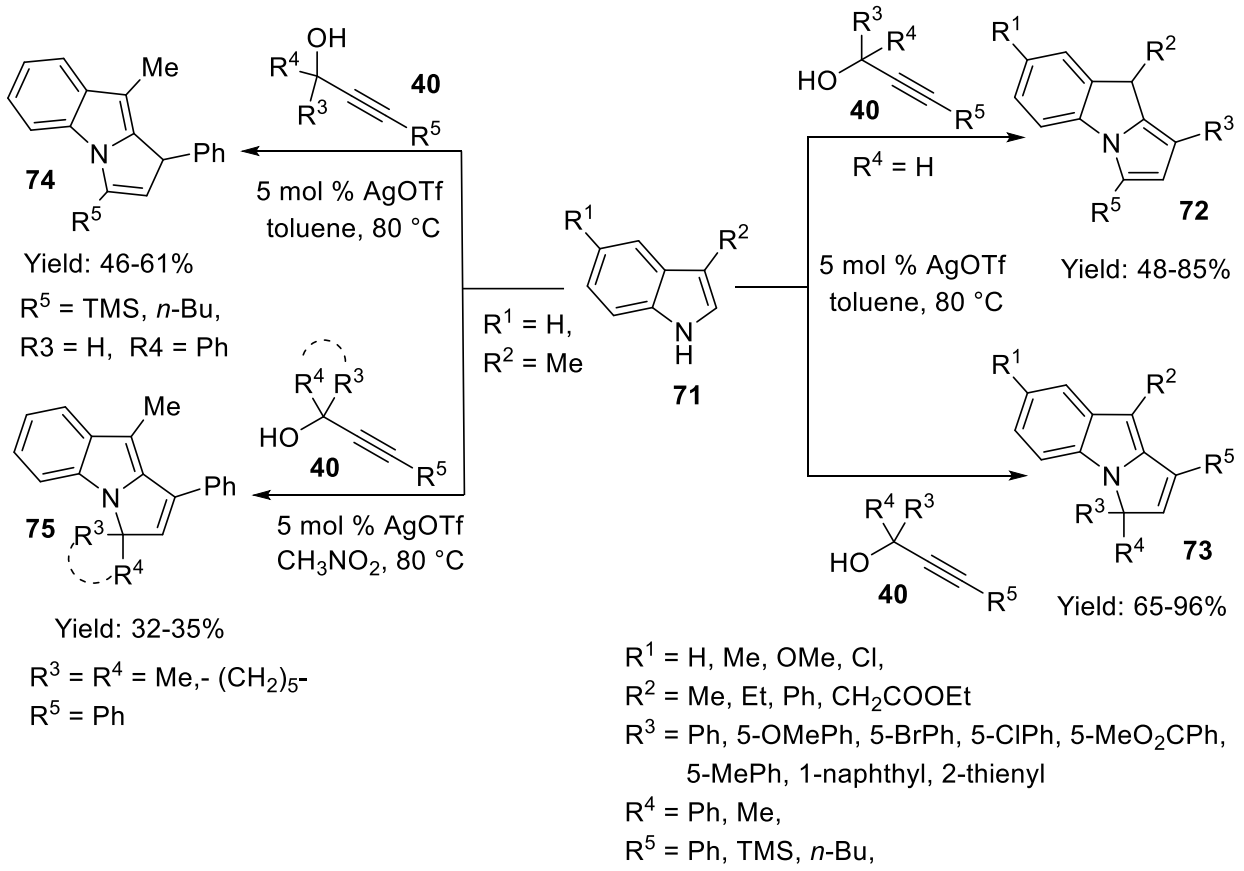
Scheme 1.13: $Sc(OTf)_3$ catalyzed alkylation of indoles **60** with propargylic alcohols **40**

In an extension of Yadav's work, Bezuidenhoudt groupdemonstrated $Al(OTf)_3$ catalyzed synthesis of C3-propargylated indoles **70** in excellent yields using both 3° and 2° propargylic alcohols **40** in acetonitrile solvent at reflux condition **(Scheme 1.14)**.[58] In this methodology, the aromatic or aliphatic substituent at both the terminal (R^5) and propargylic positions (R^3 and R^4) furnished the desired products **70** in good to moderate yields.



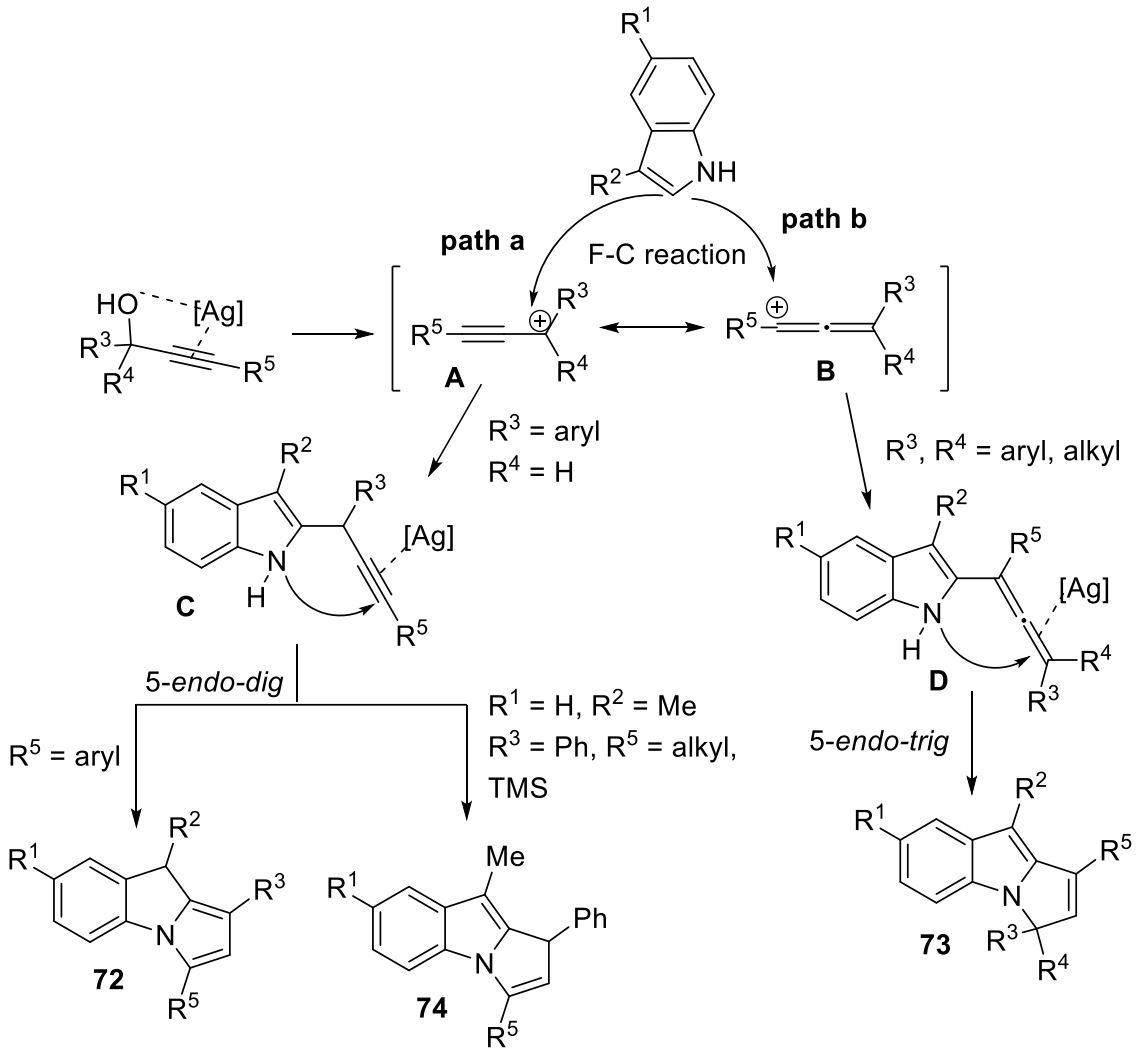
Scheme 1.14: $Al(OTf)_3$ catalyzed Friedel-Crafts alkylation of indoles **17** with propargylic alcohols **40**

Zhan and co-workers developed an efficient cascade Friedel-Crafts reaction/N-C bond formation protocol for the chemoselective synthesis of *N*-fused indole derivatives **72, 73** and **74** *via* AgOTf catalyzed the reaction of 3-substituted 1*H*-indoles **71** with propargylic alcohols (**40**) (**Scheme 1.15a**).[59] This is the first report, where the single metallic AgOTf catalyzed the nucleophilic addition of 1*H*-indole-NH to alkyne-C and allene-C without the presence of any base and ligand.



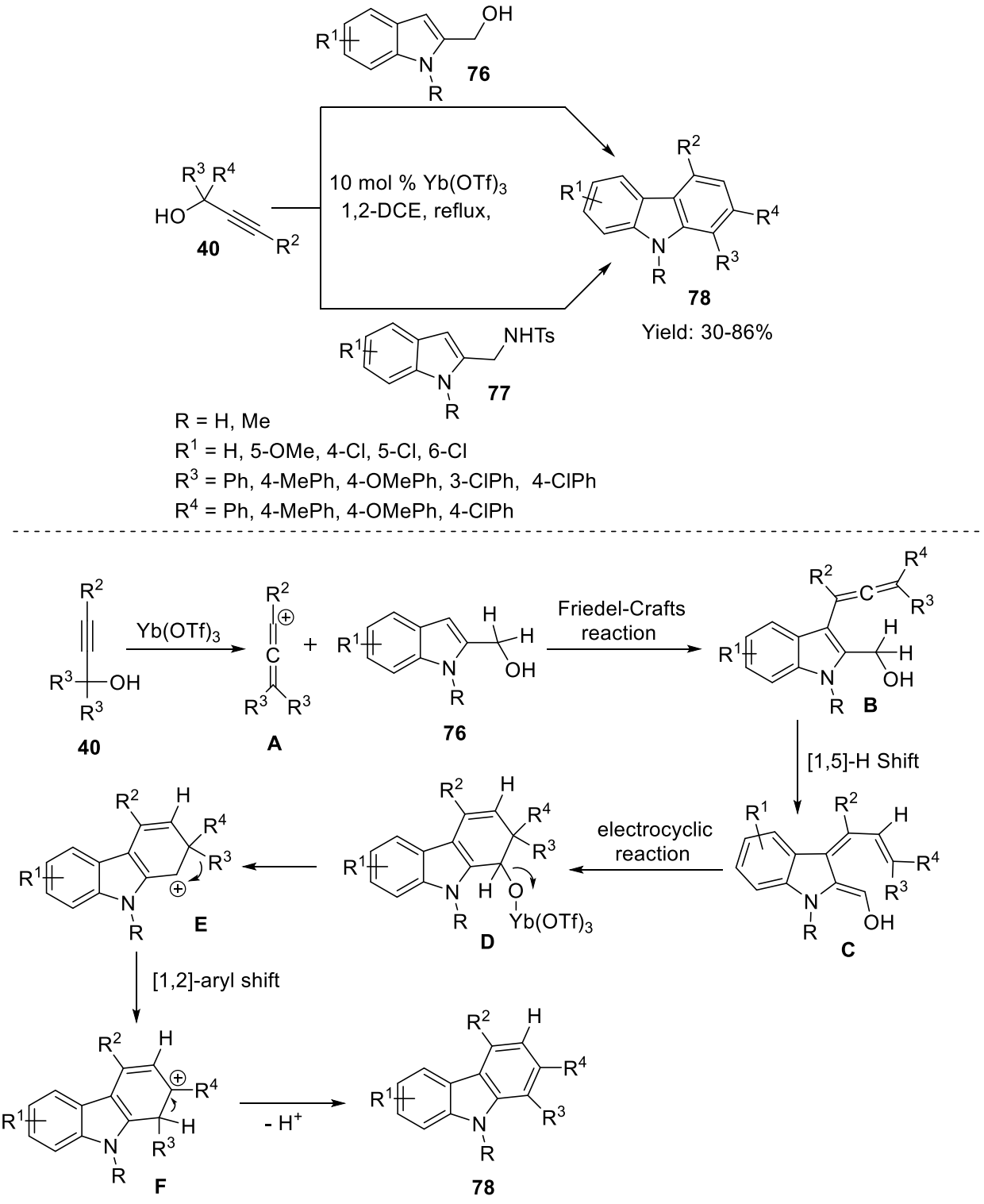
Scheme 1.15a: AgOTf catalyzed synthesis of *N*-fused indole derivatives **72, 73** and **74**

The formation of *N*-fused indole derivatives depended on the substituent and the type of propargyl alcohols (2° or 3°) used for the reaction. When aryl-substituted secondary propargyl alcohols (R^3 = Aryl, R^4 = H) were used, the reaction proceeded very well to offered an easy access to *N*-fused skeleton **72** whereas Trimethylsilyl (TMS) and an alkyl group substituted propargyl alcohols **40** gives *N*-fused skeleton **74** under the similar reaction conditions. However, when triaryl-substituted tertiary propargyl alcohols ($R^3 = R^4 = R^5$ = Aryl) were used, the reaction proceeded very well to affords *N*-fused skeleton **73** in good yield. In the case of dialkyl-substituted tertiary propargyl alcohols, the desired products were not obtained but the use of nitromethane in place of toluene as the solvent afforded *N*-fused skeleton **75** in low yields. The proposed mechanism for the formation of *N*-fused indole derivatives **72, 73** and **74** included two routes-a) C2-propargylation/N-C cyclization (5-*endo*-*dig*), and b) C2-allenation/N-C cyclization (5-*endo*-*trig*) (**Scheme 1.15b**).



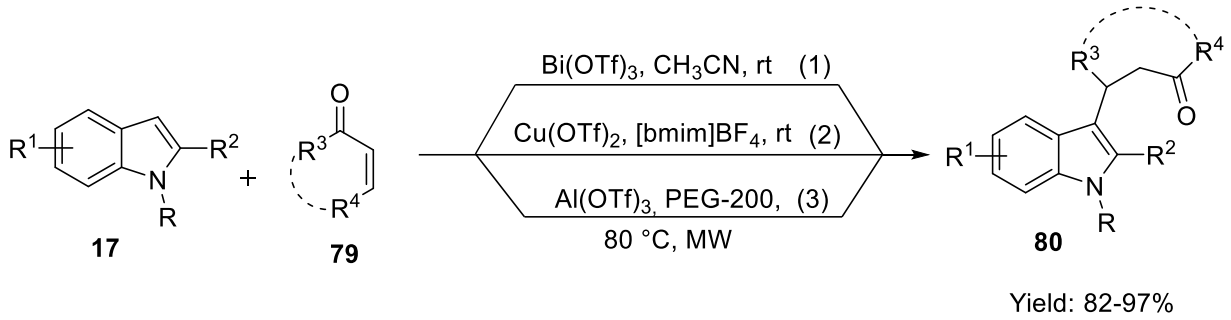
Scheme 1.15b: Proposed mechanism for the formation of indole derivatives **72, 73** and **74**

Wang *et al.* revealed $Yb(OTf)_3$ catalyzed dehydrative [3+3]-annulation of propargylic alcohols **40** and 2-indolyl methanols **76** or 2-indolyl sulfonamides **77** for the construction of carbazoles in moderate to good yields. The reaction was presumed to proceed through a cascade process consisting of Friedel-Crafts-type allenylation, 1,5-hydride shift, 6π-electrocyclization and Wagner-Meerwein rearrangement (**Scheme 1.16**).[60]



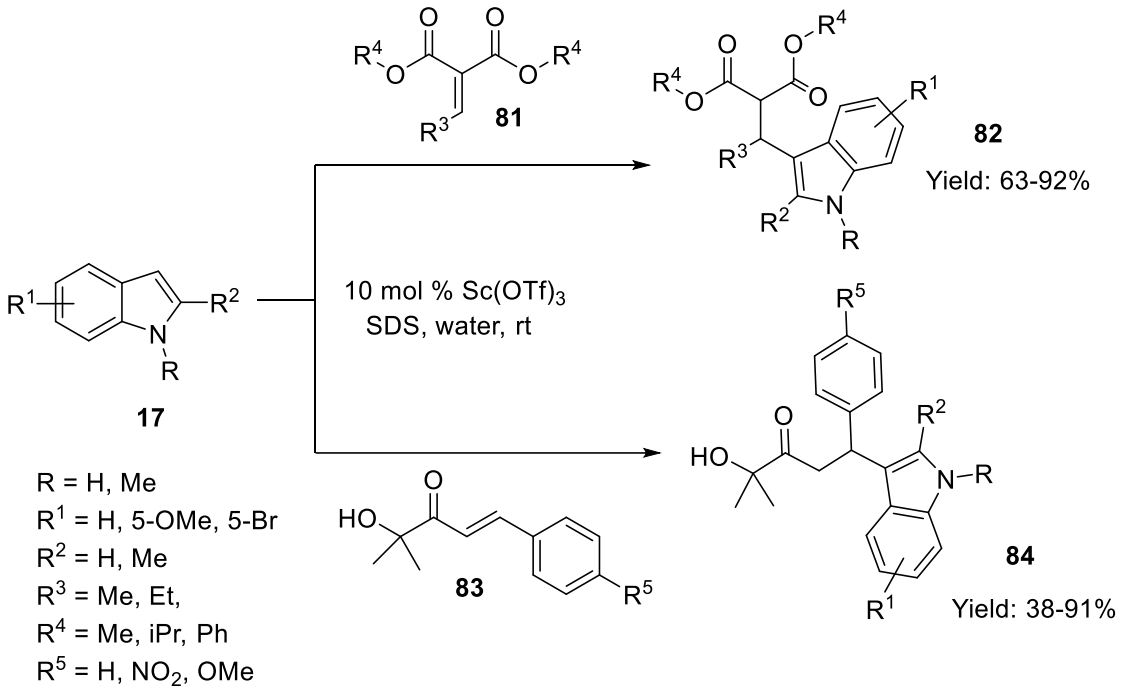
Scheme 1.16: $Yb(OTf)_3$ catalyzed reaction of 2-indolylmethanols **76** or 2-indolylsulfonamides **77** with propargylic alcohols **40**

Venkateswarlu and co-workers reported $Bi(OTf)_3$ catalyzed synthesis of 3-substituted indoles **80** in high yields *via* Friedel-Crafts Michael type addition of indoles **17** to α,β-unsaturated ketones **79** in acetonitrile at room temperature (**Scheme 1.17** Eq. (**1**)).[61] Later, Yadav group replaced the use of acetonitrile by ionic liquid $[Bmim]BF_4$ as a recyclable solvent and developed $Cu(OTf)_2$-$[Bmim]BF_4$ recyclable catalytic system for the synthesis of 3-substituted indoles **80** (**Scheme 1.17** Eq. (**2**)).[62] Afterward, Bezuidenhoudt *et al.* revealed the microwave assisted $Al(OTf)_3$ catalyzed synthesis of **80** using PEG-200 as recyclable solvent at 80 °C in 10-120 min (**Scheme 1.17** Eq. (**3**)).[63]



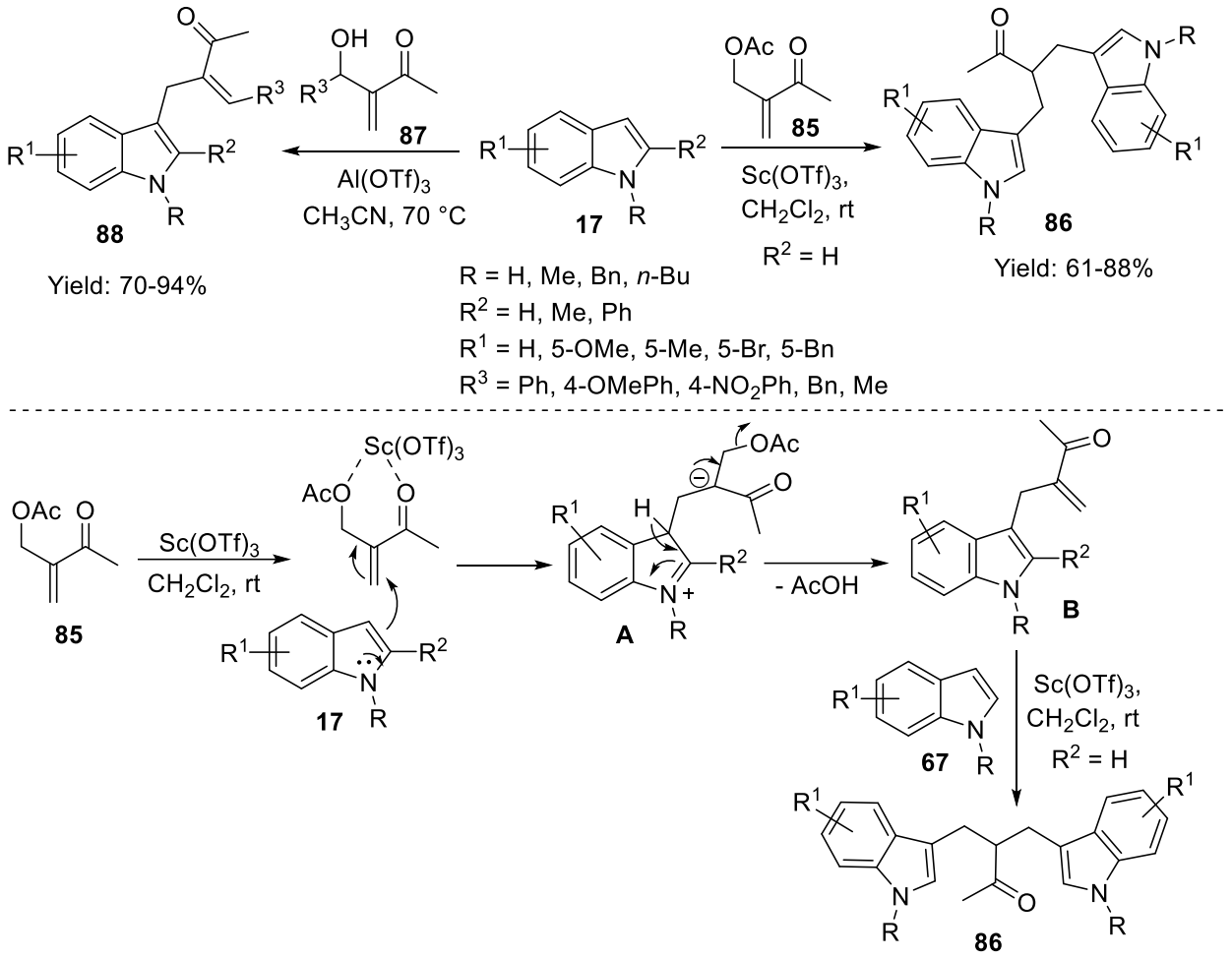
Scheme 1.17: Metal triflate $[M(OTf)_n]$ catalyzed conjugate addition of indoles **17** to α,β-unsaturated ketones **79**

Roelfes group discovered $Sc(OTf)_3$/sodium dodecyl sulfate (SDS) catalytic system for the preparation of 3-substituted indoles **82** and **84** through vinylogous Friedel-Crafts alkylation of indoles **17** with alkylidene/benzylidene malonates **81** and α,β-unsaturated α′-hydroxy ketones **83**, respectively in water at room temperature (**Scheme 1.18**).[64] The conjugate addition reactions of indoles **17** were facilitated through the formation of chelate between two carbonyl groups of **81**/carbonyl and the α′-hydroxy oxygen atom of **83** and $Sc(OTf)_3$ Lewis acid catalyst.



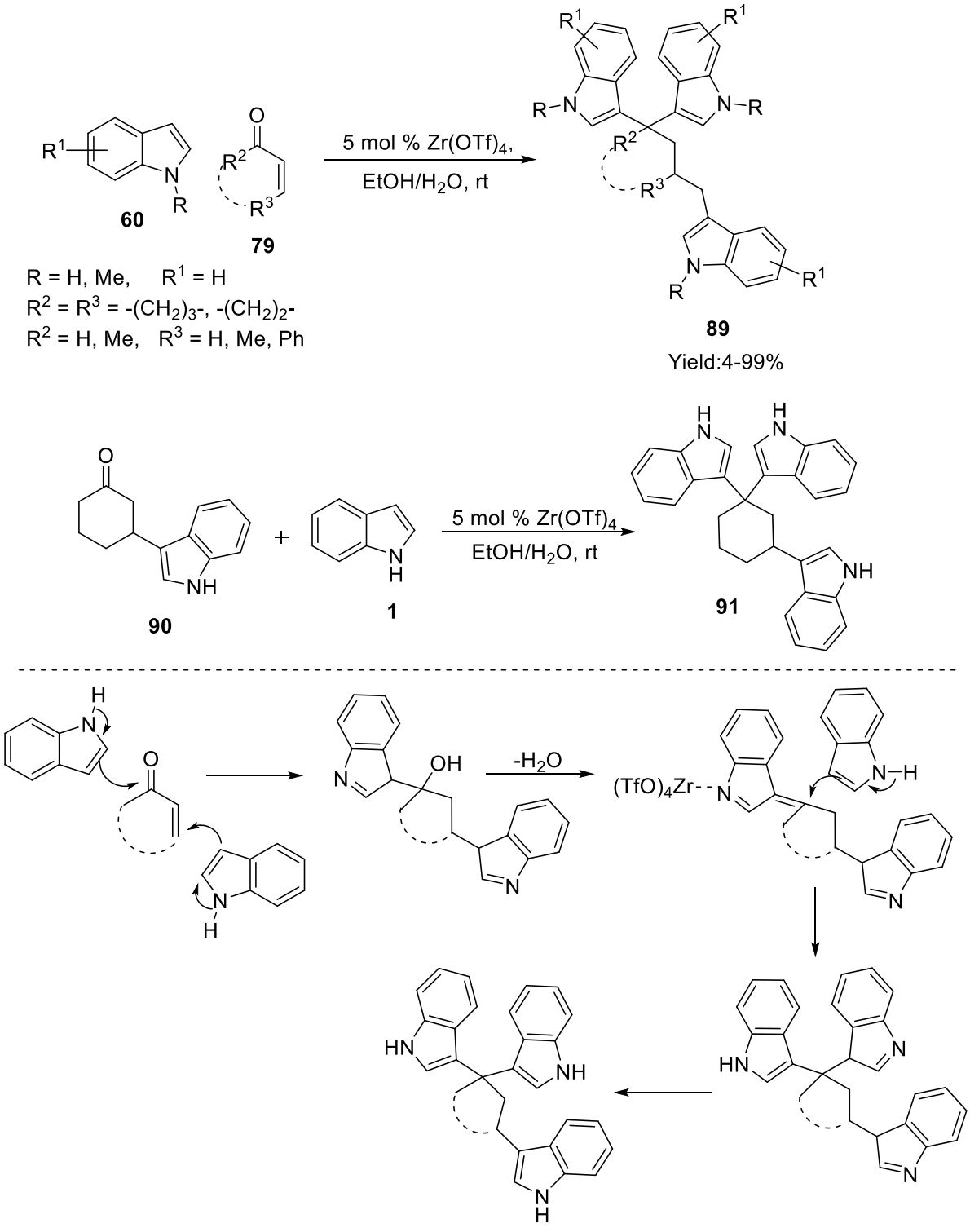
Scheme 1.18: $Sc(OTf)_3$/SDS catalyzed vinylogous Friedel-Crafts alkylation reaction of indoles **17** in water

Ma group reported the formation of *bis*(indolyl) ketones **86** using $Sc(OTf)_3$ catalyzed reaction of substituted indoles **17** with 2-methylene-3-oxobutyl acetate **85** (analogous to α,β-enones) in dichloromethane at room temperature. In this method, synthesis of *bis*(indolyl)ketone **86** was achieved through S_N2' substitution of acetoxy group in **85** with substituted indoles **17** as shown in **Scheme 1.19**.[65] A similar mechanism was also observed in the case of β-hydroxyketones **87** when it was treated with substituted indoles **17**, to afford C3-alkylated indole derivatives **88** in the presence of $Al(OTf)_3$ as catalyst and acetonitrile as solvent at reflux condition. In this methodology, Bezuidenhoudt group obtained 3-substituted indole derivatives **88** instead of *bis*(indolyl) ketones **86,** but only in case of β-hydroxyketones **87** (where R^3 = H), the *bis*(indolyl) ketone **86** (Where R = R^1 = H) was obtained as the major product along with the desired product **86**. However, when the excess indole was used in this reaction only *bis*(indolyl) ketone **86** (Where R = R^1 = H) was obtained (**Scheme 1.19**).[66]



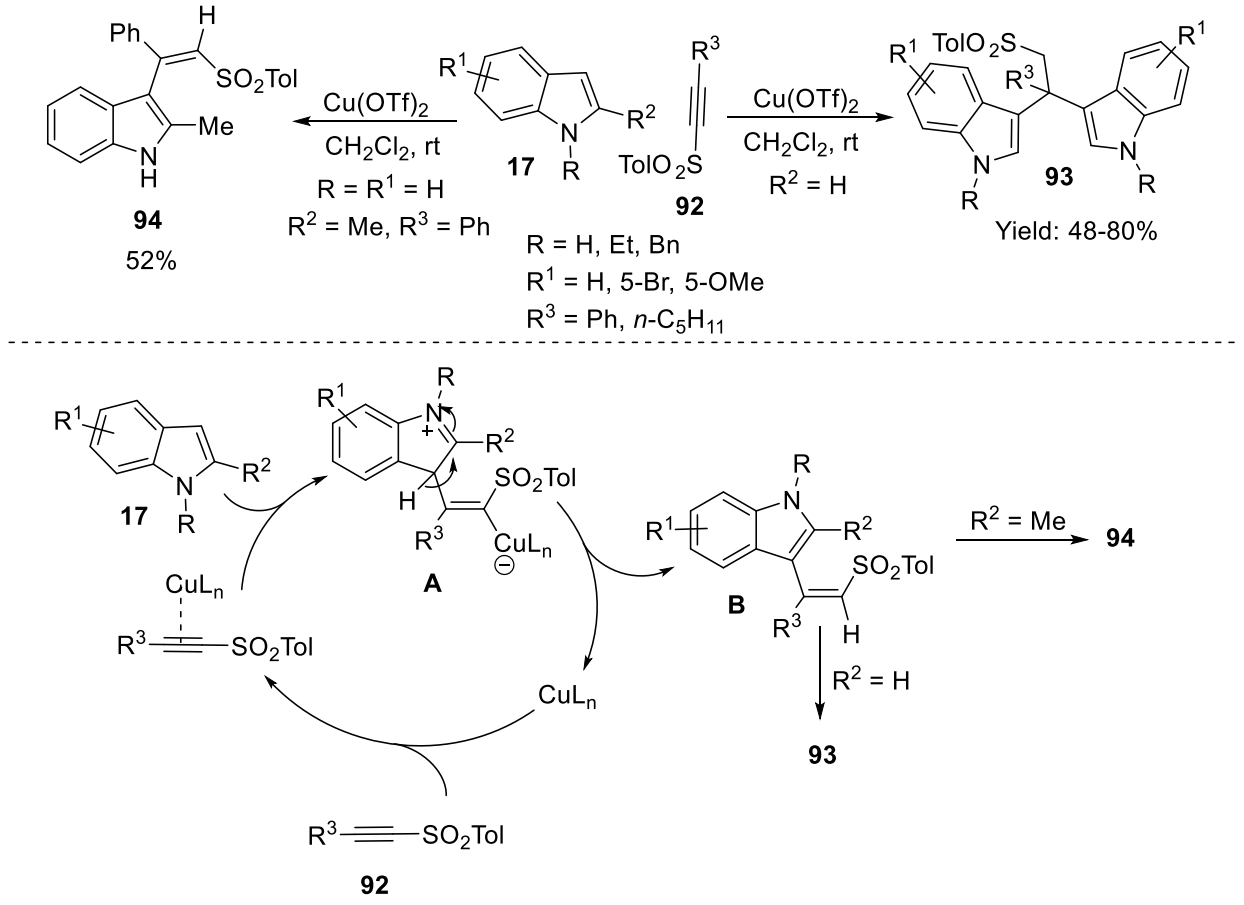
Scheme 1.19: Metal triflate catalyzed reaction of **81** with substrate **103** and **105**

Shi and co-workers disclosed $Zr(OTf)_4$ catalyzed the synthesis of *tris*(indolyl) alkanes **89** by the reaction of an excess of indoles **60** (5 equiv.) with α,β-unsaturated ketones **79** (1 equiv.) in the mixed polar solvent EtOH/H_2O (2/1) at room temperature in 1-3 days. The proposed mechanism for the synthesis of **89** is shown in **Scheme 1.20**[67] and it was supported by the formation of **91** from the reaction of **90** and indole **1** under the same conditions.



Scheme 1.20: $Zr(OTf)_4$ catalyzed synthesis of *tris*(indolyl) alkanes **89** with proposed mechanism

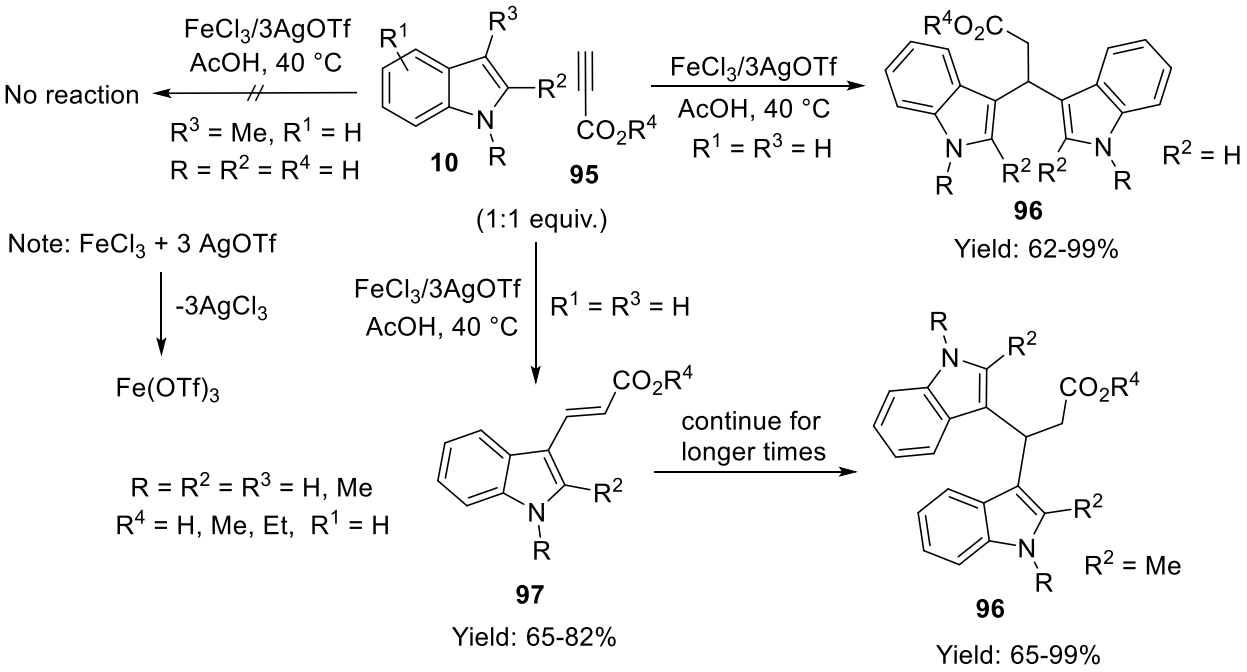
Xie and co-workers demonstrated $Cu(OTf)_2$ catalyzed synthesis of sulfonyl-containing *bis*(indolyl)alkanes **93** in good yield by double Michael addition of substituted indoles **17** with acetylenic sulfones **92** in dichloromethane at room temperature. However, in the case of 2-methylindole only mono-adduct **94** was obtained in 52% yield under standard reaction conditions and no desired *bis*(indolyl)alkane was observed, which supported the formation of the indolyl alkene **B** as an intermediate of the reaction (**Scheme 1.21**).[68] Remarkably, 2-phenyl and *N*-tosyl indole are inert under the same reaction conditions due to the large steric effect of phenyl and strong electron-withdrawing effect of tosyl groups respectively.



Scheme 1.21: $Cu(OTf)_2$ catalyzed synthesis of sulfonyl-containing *bis*(indolyl)alkanes **93**

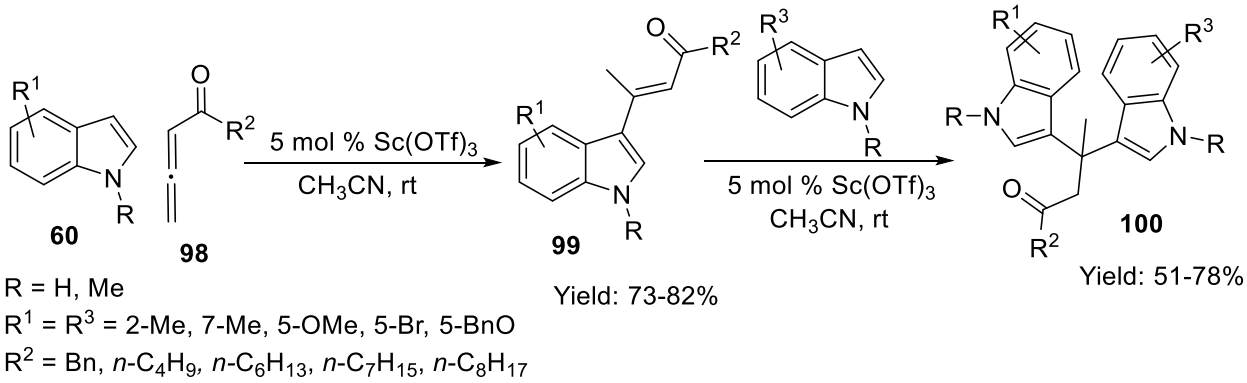
Kitamura group reported $Fe(OTf)_3$ catalyzed regioselective synthesis of *bis*(indol-3-yl)alkanoic acid derivatives **117** and **119** by the reaction between indole derivatives **47** and alkynoic acid derivatives **116** in acetic acid at 40 °C. Here, it was noticed that the reaction of 3-methylindole with propynoic acid did not afford any product and starting materials were recovered. Therefore,

this hydroarylation reaction shows a high regioselectivity at C3-position of indole (**Scheme 1.22**).[69]



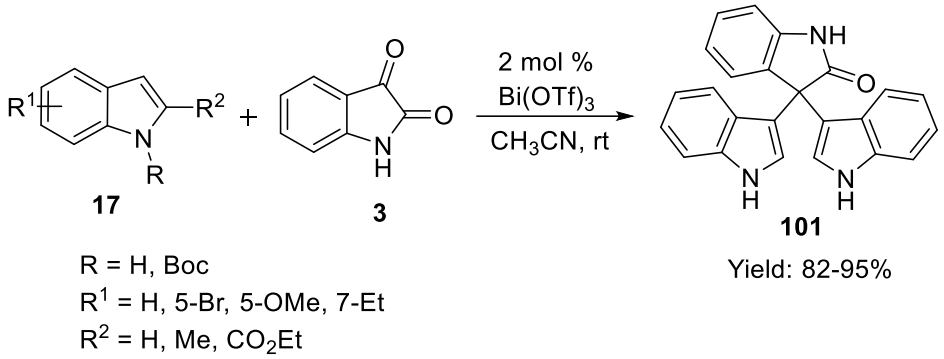
Scheme 1.22: $Fe(OTf)_3$ catalyzed regioselective synthesis of bis(indol-3-yl)alkanoic acid derivatives **96**

Ma *et al.* revealed $Sc(OTf)_3$ catalyzed highly stereoselective synthesis of β-indolyl-α,β-unsaturated (E)-enones **99** by the reaction of substituted indoles **60** with terminal carbon-carbon double bond of 1,2-allenic ketones **98**, which was subsequently treated with same or different indoles to produce simple or mixed β,β-indolyl ketones **100** in moderate yields (**Scheme 1.23**).[70]



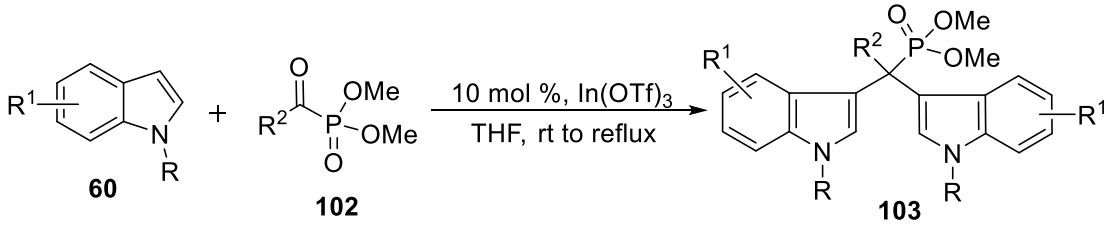
Scheme 1.23: $Sc(OTf)_3$ catalyzed stepwise double addition of indoles **60** with 1,2-allenic ketone **98** to synthesize β,β-indolyl ketones **100**

Yadav and co-workers introduced $Bi(OTf)_3$ catalyzed synthesis of 3,3-diindolyl oxindoles **101** by the condensation of isatin (**3**) with substituted indoles **17** (**Scheme 1.24**).[71] This methodology also worked well in case of Boc-protected 2-methylindole to affords the corresponding Boc-protected *bis*(indolyl)oxindole without cleavage of the Boc group.



Scheme 1.24: $Bi(OTf)_3$ catalyzed synthesis of 3,3-diindolyl oxindoles **101**

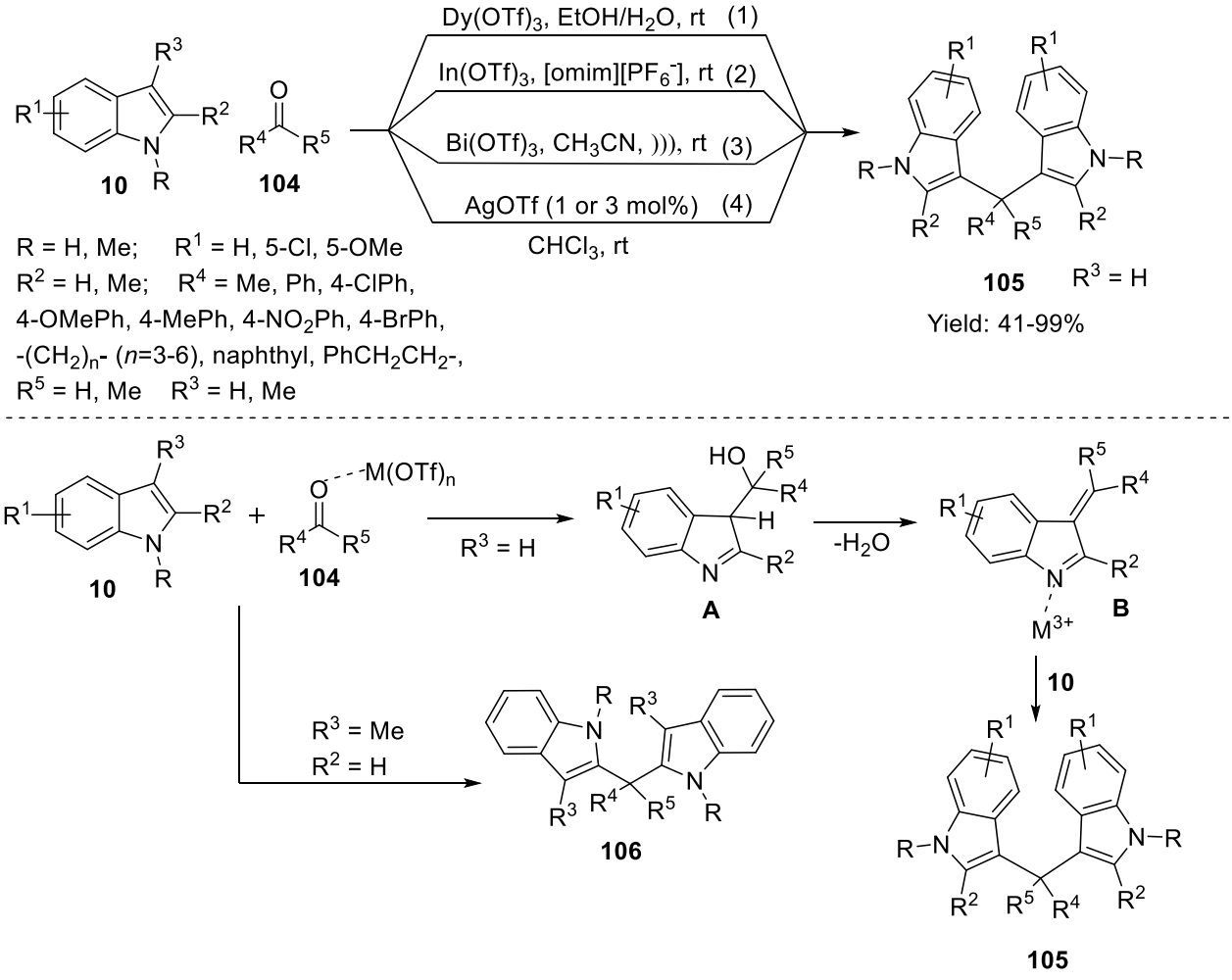
Dasbasi group reported $In(OTf)_3$ catalyzed synthesis of *bis*(indolyl)methane phosphonates **103** from *N*-methylindole **60** and acyl phosphonates **102** in THF (tetrahydrofuran) as solvent at 50 °C. In this methodology, both aliphatic and aromatic phosphonates coupled with *N*-methylindole **60** to furnish the corresponding *bis*(indolyl)methane phosphonates **103**. However, in the case of unsubstituted indole **1**, a trace amount (<9%) of the *bis*(indolyl)methane phosphonate was observed (**Scheme 1.25**).[72]



Scheme 1.25: $In(OTf)_3$ catalyzed synthesis of *bis*(indolyl)methane phosphonates **102**

Wang and co-workers demonstrated $Dy(OTf)_3$ catalyzed synthesis of *bis*(indolyl)methanes (BIMs) **105** by the reaction substituted indoles **10** and aldehydes (R^4 = H) or ketones (R^4 = Me) **104** in aqueous solution ($EtOH/H_2O$:3/1) at room temperature (**Scheme 1.26** Eq. (**1**)).[73] In the case of

C3-substituted indoles, the corresponding C2-substituted *bis*(indolyl)methanes **106** were obtained in chloroform solvent. Later, Ji group developed $In(OTf)_3$-$[Omim]PF_6$ recyclable catalytic system for the synthesis of *bis*(indolyl)methanes (BIMs) **105** in short reaction time with high yields (**Scheme 1.26** Eq. (**2**)).[74] Baltork and co-workers reported ultrasound assisted $Bi(OTf)_3$ catalyzed synthesis of *bis*(indolyl)methanes (BIMs) **105** in acetonitrile as solvent at room temperature (**Scheme 1.26** Eq. (**3**)).[75] Recently, Beltra group disclosed the synthesis of *bis*(indolyl)methanes (BIMs) **105** from corresponding aldehydes and indoles by using 1-3 mol % AgOTf as the catalytic system. Both aliphatic and aromatic aldehydes **104** underwent smooth reaction with substituted indoles **10** to afford the corresponding *bis*(indolyl)methanes **105** in good yields (**Scheme 1.26** Eq. (**4**)).[76]



Scheme 1.26: Metal triflate [$M(OTf)_n$] catalyzed synthesis of *bis*(indolyl)methanes (**BIMs**)

Chapter I

PART A

Bismuth Triflate Catalyzed Condensation of Indoles with Acetone

1.4 Introduction

The indole scaffold is an important structural motif due to its significant biological activities as discussed in the introduction section **Figures 1.1** and **1.2**. The *bis*(indolyl)methanes (BIMs), *bis*(indolyl)propanes (BIPs) and cyclopenta[*b*]indoles (CPIs) constitute an important classes of indole derivatives derived from acetone and indoles.[77-79] Various methods have been reported for the synthesis of BIMs and BIPs.[80-84] They are antineoplastic agents[85-89] and are also used for the synthesis of various dyes.[90, 91] Yuehchukene, a bisindole alkaloid structural analogous to CPIs, possesses strong anti-implantation activity in rats as well as in mice.[92] Although the reaction of simple indole with acetone has been reported, there are limited reports for the synthesis of different BIPs and CPIs by using various substituted indoles and ketone.[93-96] Spiro-heterocyclic compounds containing one carbon atom common to two rings are structurally attractive because of their distinct biological properties.[97, 98] Among various spiro-heterocyclic systems, spiro-indoles have attracted great attention because of their varied biological activities,[99-101] spiro[cyclohexane-1,3′-[3*H*]indole] and spiro[cyclopentane-1,3′-[3*H*]indole] are used as analgesics, fungicides, and antidepressants, spiro [pyrrolidine-3,3′-oxindole] alkaloids e.g. (-) horsfiline exhibits local anaesthetic activity; 2′,3′,5′,6′ tetrahydrospiro[indoline- 3,4′-pyran]-2-one are used as anti-inflammatory agents and spiro[3*H*-indole-3,3′-pyrazolin]-2-one is used as antiphlogistics and blood platelet aggregators.

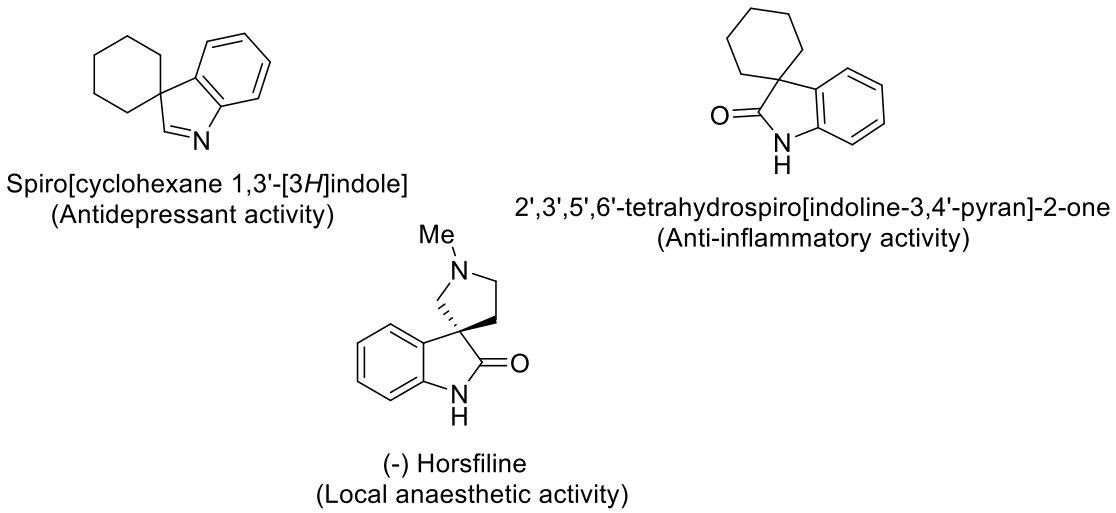


Figure 1.8: Biologically active spiro-indole based compounds.

It has always been a challenge for the organic chemist to synthesize spiro-heterocyclic compounds as it involves the generation of quaternary carbon center and fusion of two rings. The general approaches for the synthesis of spiro-heterocyclic compounds involve alkylation methods, transition metal-based processes, rearrangement-based approaches, ring closure of geminally substituted compounds, radical cyclizations, cleavage of bridged ring systems, or cycloaddition reactions.[102, 103]

1.4.1 Acid-catalyzed condensation of indole with carbonyl compounds

The condensation reaction of indole with carbonyl compounds in the presence of both mineral and Lewis acids has proved to be complex in nature due to the formation of the wide variety of products, albeit numerer of the originally proposed structures have later been shown to be incorrect. For instance, in 1913 Scholtz *et al*.[104] reported that the condensation of indole with acetone in the presence of ethanolic hydrochloric acid gave the structure (**107**). Later, in 1961 Noland *et al*.[105, 106] reinvestigated this reaction and reported the revised structure as tetrahydro-carbazole (**110**). Noland also isolated two 2:2 and three 2:3 condensation products of indole and acetone in ethanolic hydrochloric acid conditions. Noland's group performed a few additional experiments to arrive at the correct structures of these isolated compounds and reported the confirmed (**Figure 1.9**), while still some of the isolated compounds are unknown or are in ambiguity.

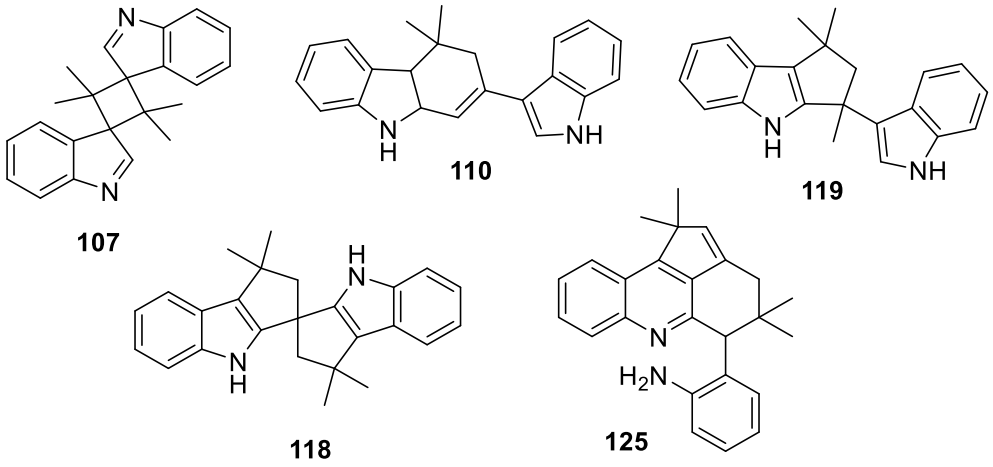
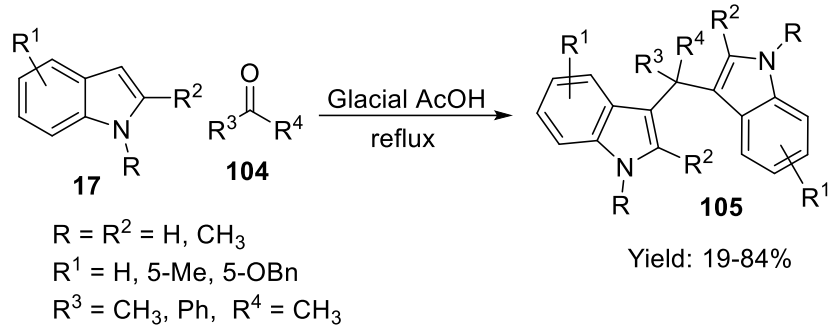


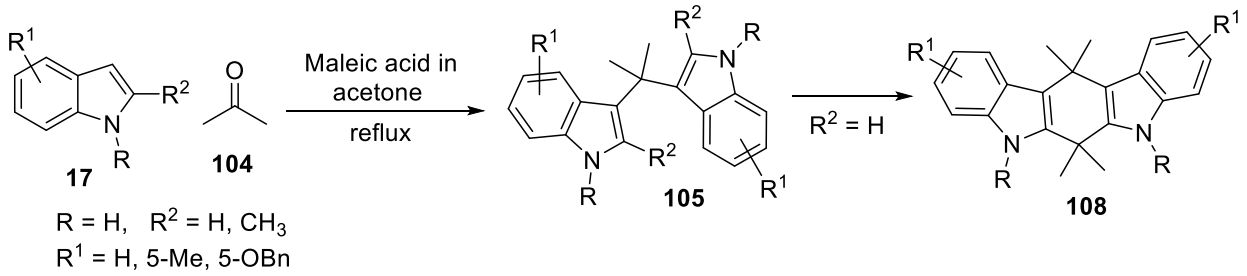
Figure 1.9: Condensation products of indole and acetone

The formation of products from the reaction of indoles and ketones depends on the acidic strength and on position of the substituent in indole. Reaction of substituted indoles **17** with ketone **104** in refluxing acetic acid gave the corresponding bisindoles **105** in moderate to good yield.



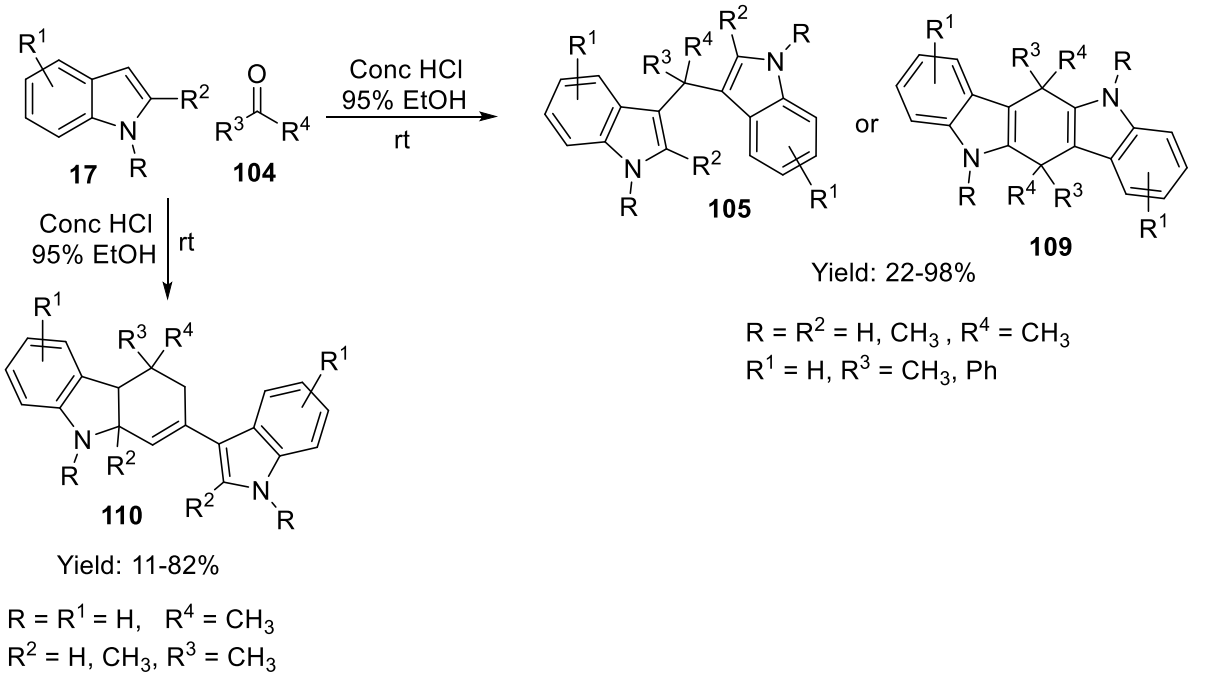
Scheme 1.27: Glacial AcOH catalyzed synthesis of bisindoles **105**

In comparison to indole and 1-methylindole, condensation of 5-methylindole and 5-benzyloxyindole with acetone **104** (R^3 = CH_3, R^4 = CH_3) in refluxing glacial acetic acid gave corresponding bisindole in 84% and 65% yield, respectively (**Scheme 1.27**). However, in the case of 2-methylindole 78% yield was observed and 1,2-dimethylindole did not afford the desired product. Similarly, condensation of indole, 1-methylindole and 2-methylindole with acetophenone (R^3 = Ph, R^4 = CH_3) furnished the corresponding bisindole in 45%, 29% and 64% yield respectively (**Scheme 1.27**). Subsequently, Noland group executed condensation of indole (**1**) and 5-methylindole with acetone (**104**) in refluxing maleic acid solution to give cyclized product indolo[2,3-*b*]carbazole **108** in 54% and 64% yield, respectively (**Scheme 1.28**). Maleic acid provides required acidity for cyclizative condensation compared to glacial acetic acid which stops the reaction at bisindolyl stage. condensation of 5-benzyloxyindole and 2-methylindole with acetone (**104**) under maleic acid conditions did not afford the desired cyclized product **108** (**Scheme 1.28**).

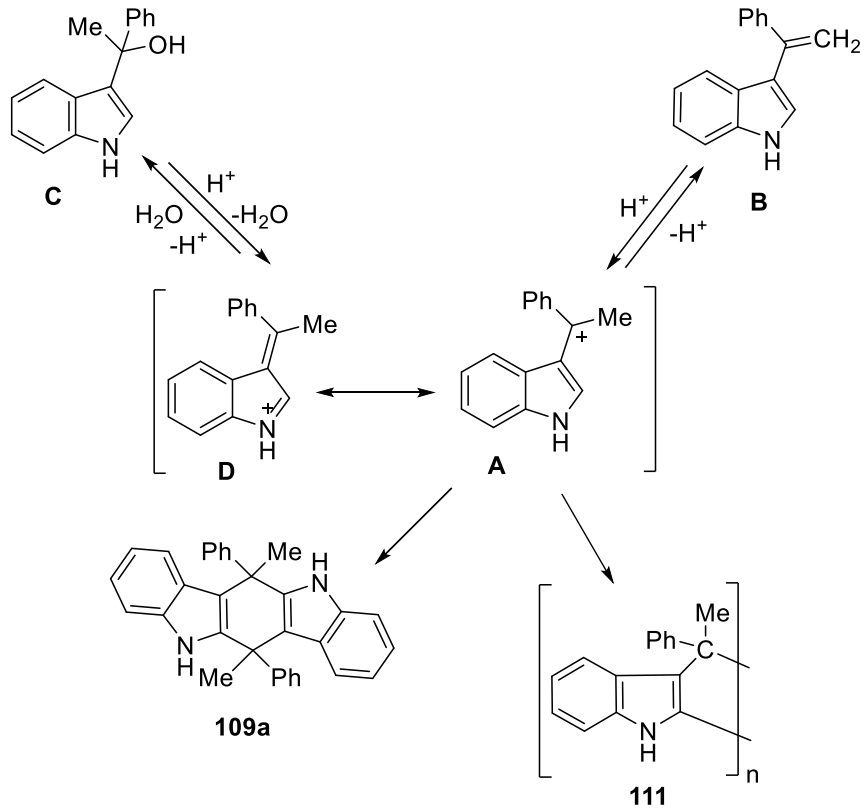


Scheme 1.28: Maleic acid-catalyzed synthesis of indolo[2,3-*b*]carbazole **108**

The condensation of substituted indole **17** and ketone **104** in strongly acidic media such as ethanolic hydrochloric acid gave single or mixture of products depending on the position of the substituent of indoles **17**. Condensation of indole (**1**) and acetone (**104**) in the presence of ethanolic hydrochloric acid afforded five products, one of which was tetrahydro-carbazole **110a** in 11% yield, whereas in the case of 2-methylindole the corresponding tetrahydro-carbazole **110b** was obtained in 82% yield (**Scheme 1.29a**). When 1-methylindole was treated with acetone (**104**) the corresponding bisindolyl product **105** was obtained in 56% yield (higher than the previous 19% yield obtained in glacial AcOH) along with 13% yield of corresponding indolo[2,3-*b*]carbazole **108.** In the case of 1,2-dimethylindole, the corresponding bisindolyl product **105** was obtained in 59% yield (which was not achieved in AcOH). Similarly, condensation of indole **(1)** with acetophenone **104** (R^3 = Ph, R^4 = CH_3) in ethanolic hydrochloric acid gave corresponding cyclic dimer indolo[3,2-*b*]carbazole **109** in 22% yield along with the polymer **111** which could result from alkylation by carbonium ion **A** at the 2-position of its possible precursors, either the vinylogous carbinolamine **C** or the dehydration product, 3-(1-phenylvinyl)indole **B**. The cyclic dimer **109** was, also isolated in 22% yield by the reaction of ethanolic hydrochloric acid on 3-(1-phenylvinyl)indole **B** (**Scheme 1.29b**). Since it is presumed that carbonium ion **A** is also an intermediate for the formation of bisindolyl compounds **105**. Condensation of 1-methylindole with acetophenone **104** (R^3 = Ph, R^4 = CH_3) in ethanolic hydrochloric acid afforded only corresponding bisindolyl compound **105** in 98% yield (**Scheme 1.29a**).

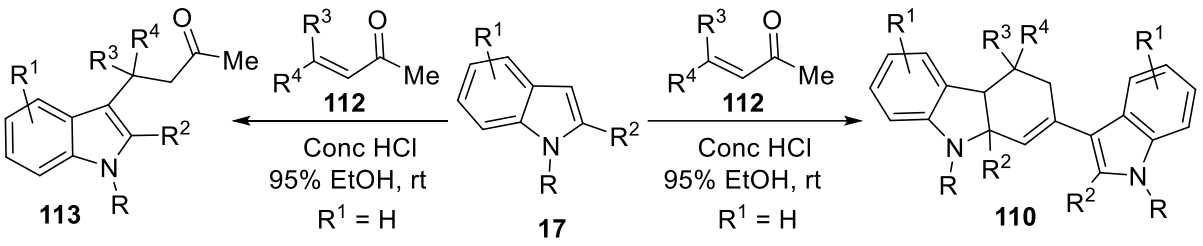


Scheme 1.29a: Ethanolic hydrochloric acid catalyzed condensation of substituted indole **17** and ketone **104**



Scheme 1.29b: Formation of polymer **111** and dimer **109** *via* carbonium ion **A**

Later, Noland group performed the reaction of 2-methylindole with mesityl oxide **112** ($R_3 = R_4 = CH_3$) in ethanolic hydrochloric acid condition and obtained compound **110c** in 67% yield. The same compound was also obtained in 82% yield from the reaction of 2-methylindole with acetone (**Scheme 1.29a**), which was confirmed by both chemical and spectroscopic data. The product **110c** can be formed through intermediate **113a** which is isolable and isolated in 70% yield. This isolated intermediate **113a** was treated with 2-methylindole under same reaction conditions, it afforded compound **110c** with increased 91% yield. However, the condensation of indole, 1-methylindole and 1,2-dimethylindole with mesityl oxide **112** ($R_3 = R_4 = CH_3$) in ethanolic hydrochloric acid solution, furnished the corresponding products **113b, 113c and 113d** respectively in very poor yield (**Scheme 1.30**).

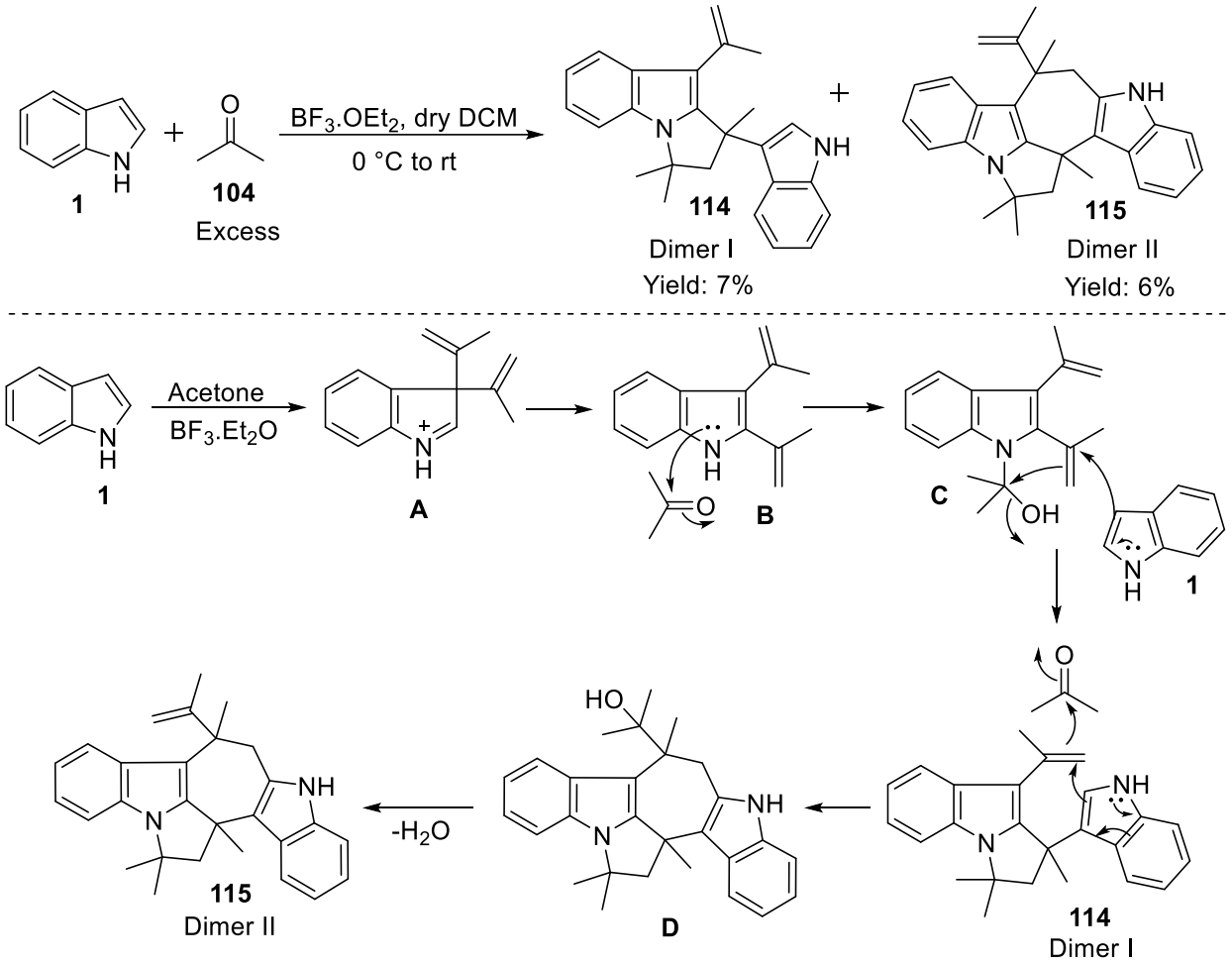


113a	70%	R = H,	$R^2 = CH_3$,	$R^3 = R^4 = CH_3$	R = H,	$R^2 = CH_3$,	$R^3 = R^4 = H$,	30% **110a**
113b	6%	R = H,	R^2 =H,	$R^3 = R^4 = CH_3$	$R = CH_3$,	$R^2 = CH_3$,	$R^3 = R^4 = H$,	52% **110b**
113c	28%	$R = CH_3$,	R^2 =H,	$R^3 = R^4 = CH_3$	R = H,	$R^2 = CH_3$,	$R^3 = R^4 = CH_3$,	67% **110c**
113d	5%	$R = CH_3$,	$R^2 = CH_3$,	$R^3 = R^4 = CH_3$	R = H,	$R^2 = CH_3$,	R^3 = H, R^4 = Ph,	31% **110d**

Scheme 1.30: Condensation reaction of substituted indoles **17** with ketone **112** in presence of ethanolic hydrochloric acid

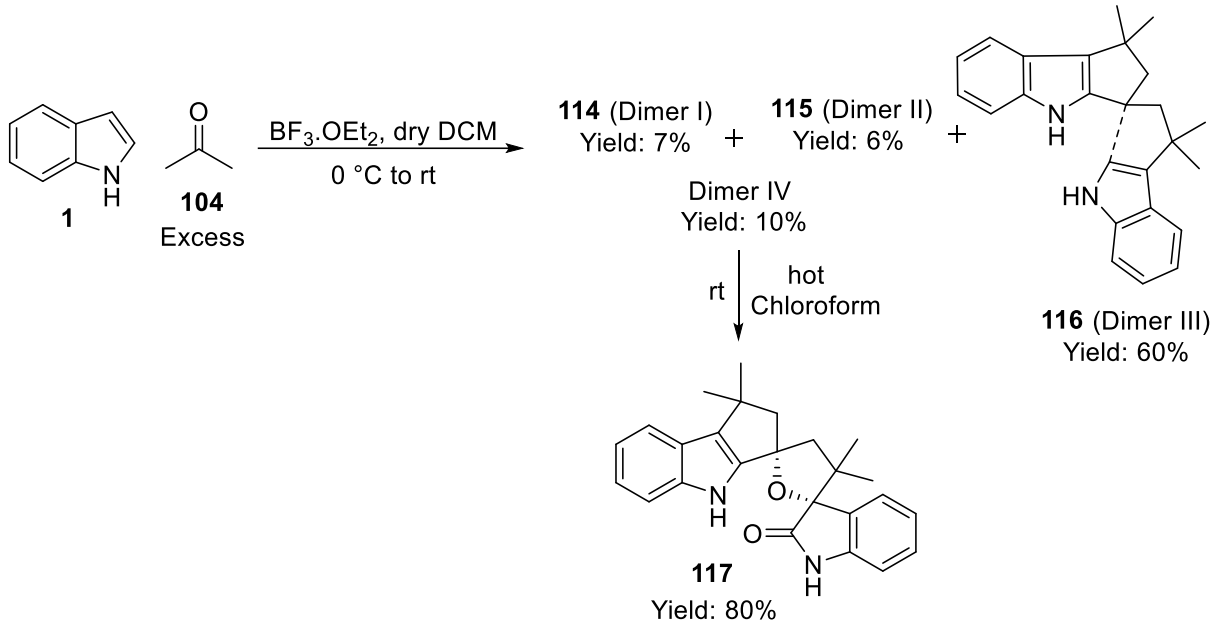
Similarly, condensation of 2-methylindole with methyl vinyl ketone **112** ($R^3 = R^4 = H$) and benzylideneacetone **112 (**R^3 = H, R^4 = Ph) in ethanolic hydrochloric acid afforded corresponding products **110a** and **110d** in 30% and 31% yield, respectively. Subsequently, reaction of 1,2-dimethylindole with methyl vinyl ketone **112** ($R^3 = R^4 = H$) under same reaction conditions gave **110b** in 52% yield. The main advantage of this methodology is to synthesize few more derivatives of the compound **110.**

In 1980, Banerji *et al*. assigned the structure of two dimer products **114** and **115** from three isolated products, which were synthesized by the condensation of indole with acetone *via* boron trifluoride etherate catalyzed reaction in dichloromethane (**Scheme 1.31**).[48, 96] The structures of compound **114 (**dimer I) and **115** (dimer II) were confirmed by NMR and mass spectral data. In addition, the structure of **114** (dimer I) was unambiguously confirmed by X-ray crystallographic data.



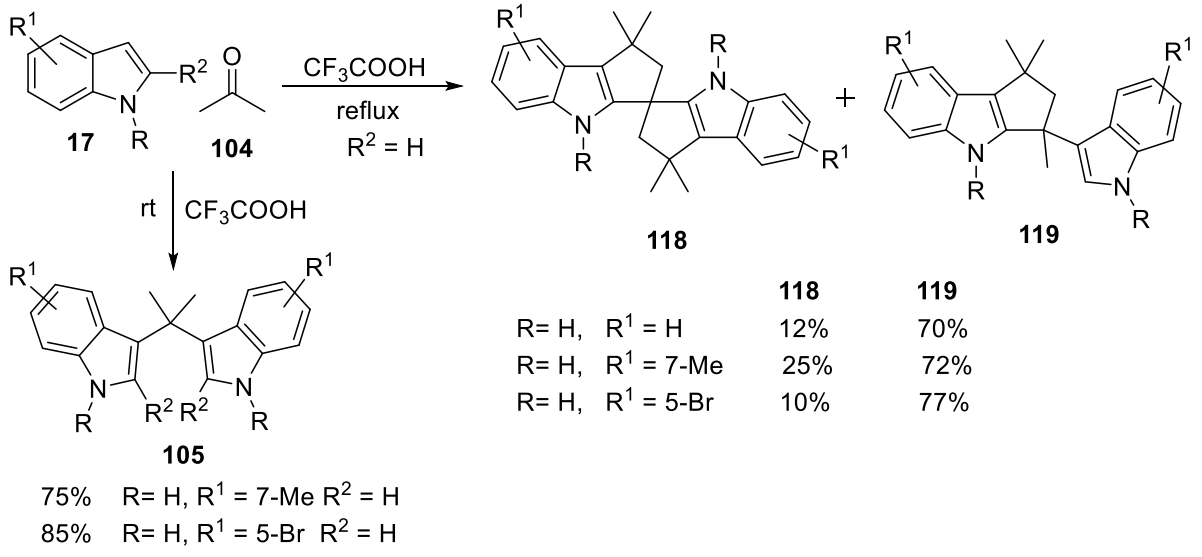
Scheme 1.31: Boron trifluoride etherate catalyzed condensation of indole and acetone with proposed mechanism

In 1981, further studies on this reaction by Banerji group, reported two new dimeric products **116** (dimer III) and the dimer fourth $C_{25}H_{28}N_2O_2$ (M^+ 388.2122) which was highly unstable in hot chloroform and underwent an unusual cyclization (autoxidation) to product **117** $C_{25}H_{26}N_2O_2$ (M^+ 386.1999) (**Scheme 1.32**).[48, 96]



Scheme 1.32: Synthesis of dimer **116** and product **117** in the presence of $BF_3.OEt_2$

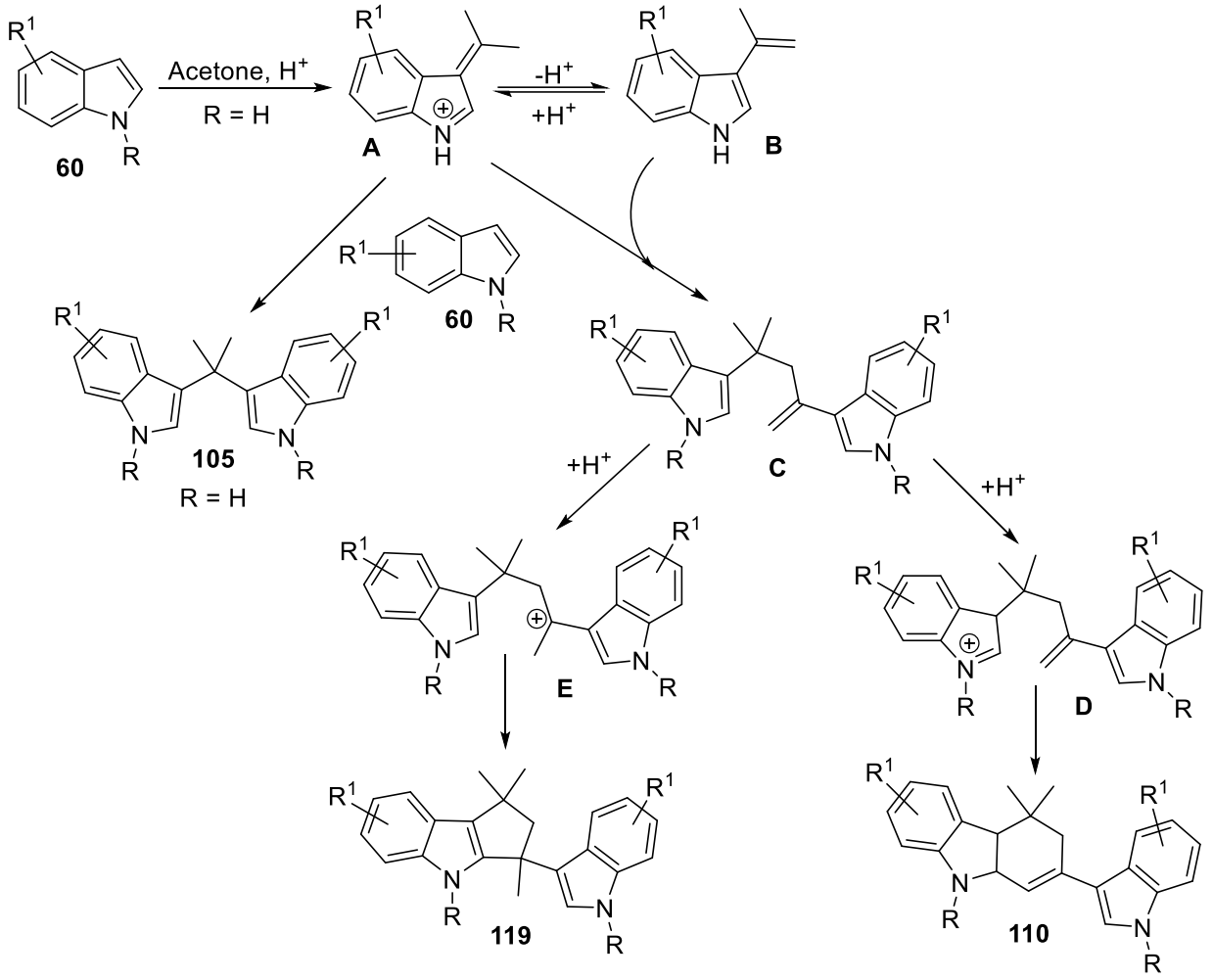
In 1989, Bergman group demonstrated trifluoroacetic acid (TFA) catalyzed synthesis of dimer **118** as the minor product and cyclopenta[*b*]indoles (CPIs) **119** as the major product by the condensation of substituted indole **17** with acetone in refluxing condition, while at room temperature it afforded only *bis*(indolyl)propanes (BIPs) **105** in good yield (**Scheme 1.33a** and **1.33b**).[93]



	118	119
R= H, R^1 = H	12%	70%
R= H, R^1 = 7-Me	25%	72%
R= H, R^1 = 5-Br	10%	77%

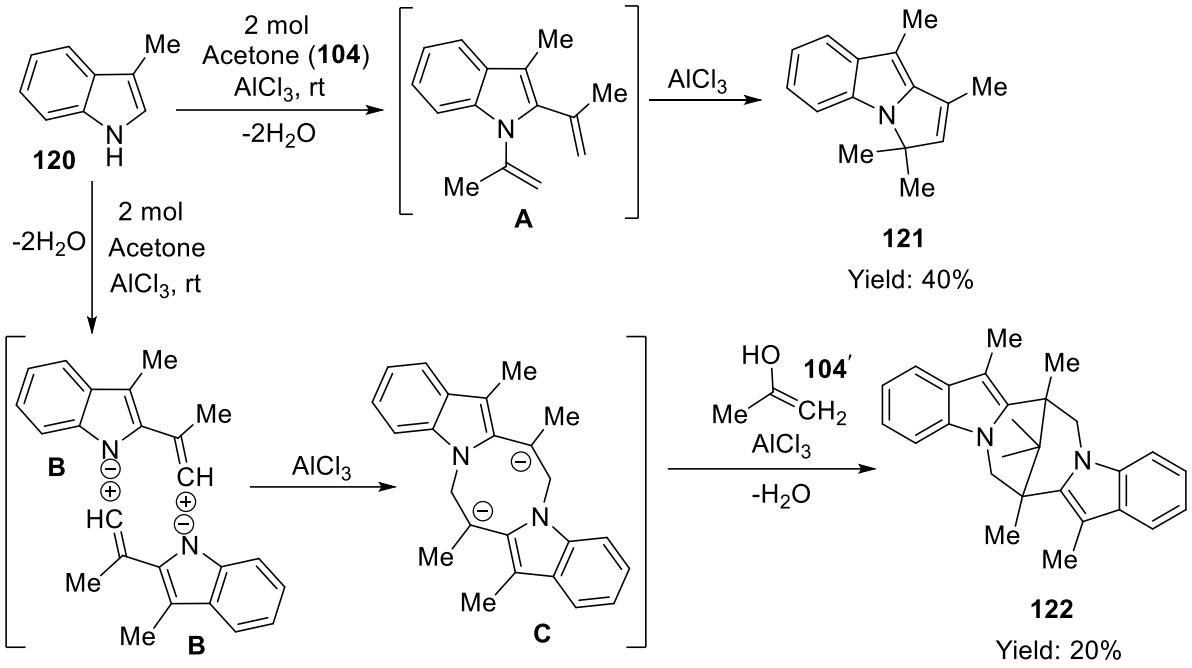
Scheme 1.33a: TFA catalyzed synthesis of dimer **118,** cyclopenta[*b*]indoles **119** at reflux and *bis*(indolyl)propanes **105** at room temperature.

Bergman proposed a mechanism for the synthesis of compounds **119, 105** and also for **110** (R = R^2 = H, R^3 = CH_3) as shown in **Scheme 1.33b**.

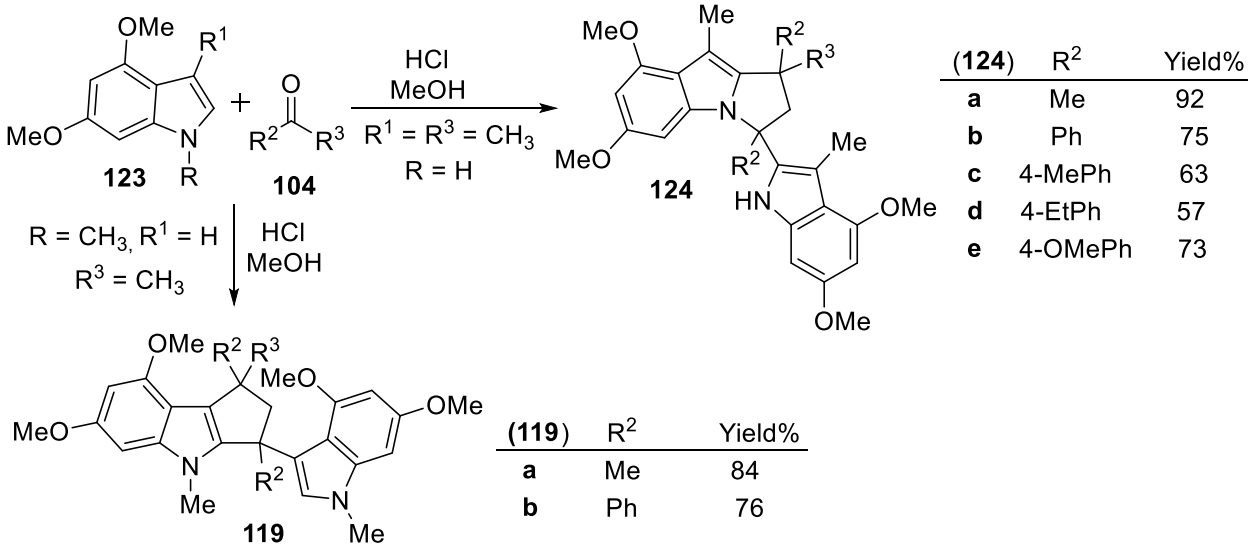


Scheme 1.33b: Proposed mechanism for the synthesis of *bis*(indolyl)propanes (BIPs) **105,** cyclopenta[*b*]indoles (CPIs) **119** and tetrahydro-carbazole **110**

In 1972, Roder[107, 108] reported $AlCl_3$ catalyzed synthesis of 1:2 condensation product pyrrolo[1,2-*a*]indole **121** and 2:3 condensation product diindolo-diaza-bicyclo-nonane derivative **122** from 3-methylindole (**120**) and acetone in 40% and 20% yield, respectively (**Scheme 1.34**).[107, 108] Afterward, David Black group revealed the synthesis of 4,6-dimethoxy-3-methyl(indolyl)-pyrrolo[1,2-*a*]indole derivatives **124 (a-e)** by condensation of 4,6-dimethoxy-3-methylindole with ketone **104** in methanolic hydrochloric acid (**Scheme 1.35**).[95]



Scheme 1.34: $AlCl_3$-catalyzed condensation of 3-methylindole (**120**) with acetone



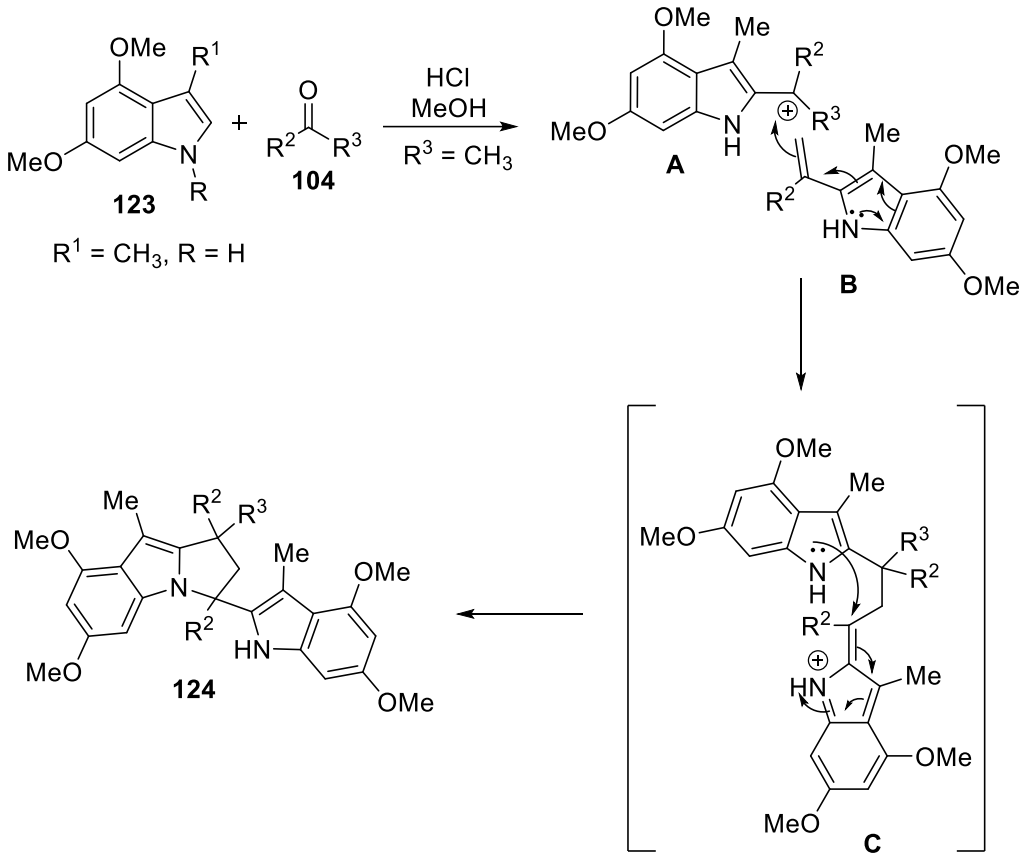
(**124**)	R^2	Yield%
a	Me	92
b	Ph	75
c	4-MePh	63
d	4-EtPh	57
e	4-OMePh	73

(**119**)	R^2	Yield%
a	Me	84
b	Ph	76

Scheme 1.35: Methanolic hydrochloric acid catalyzed condensation of 4,6-dimethoxyindole derivatives **123** and ketone **104**

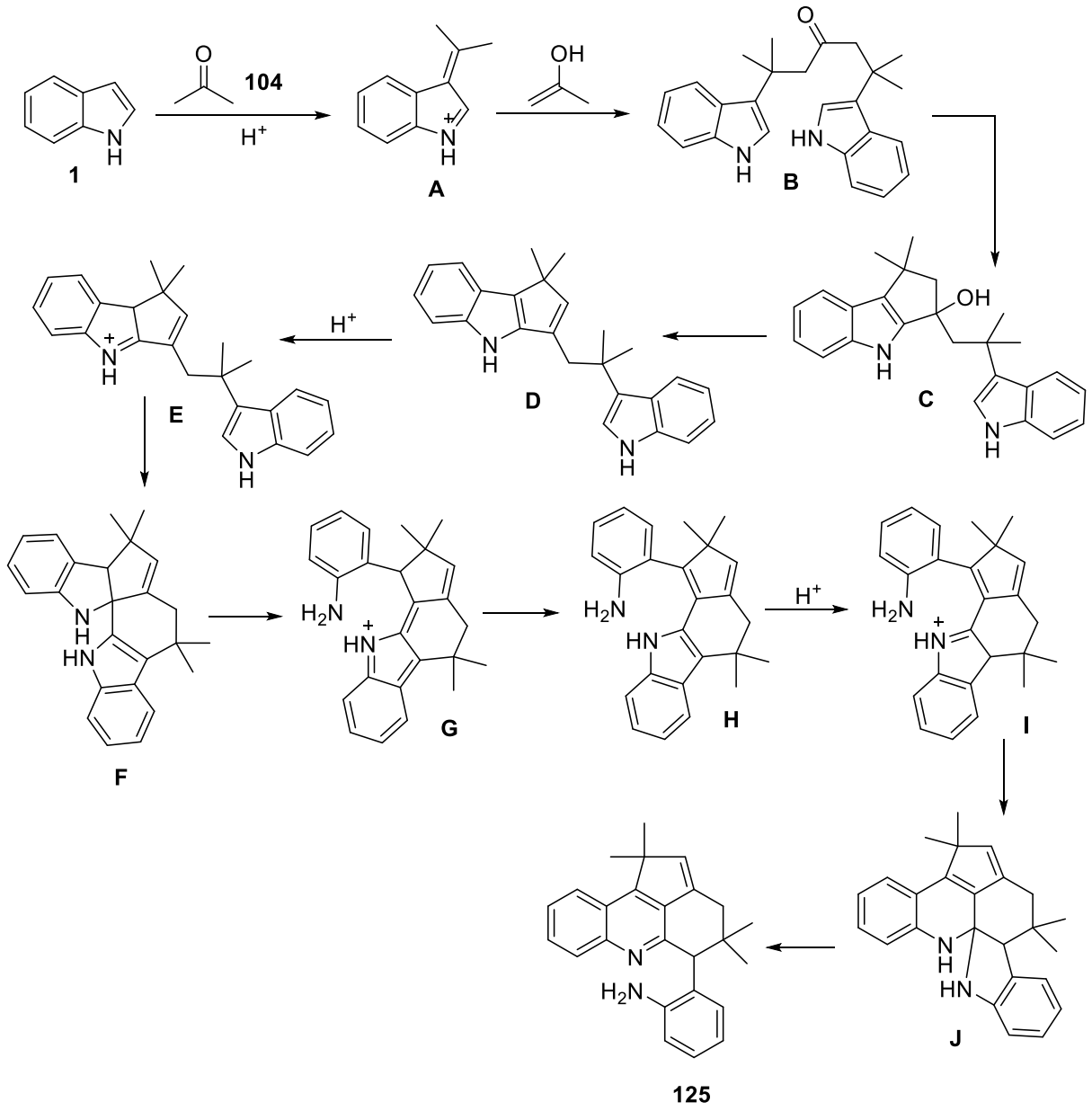
Cyclopenta[*b*]indoles (CPIs) **119 (a-b)** were obtained under same reaction conditions from 4,6-dimethoxy-1-methylindole and ketones **104**. The structure of compound **124b** was confirmed by

X-ray crystallographic data. The formation of ring-fused indoles **124** could be envisaged by intermediate alkenylindole **B** as shown in **Scheme 1.36**.



Scheme 1.36: Proposed mechanism for the synthesis of **124**

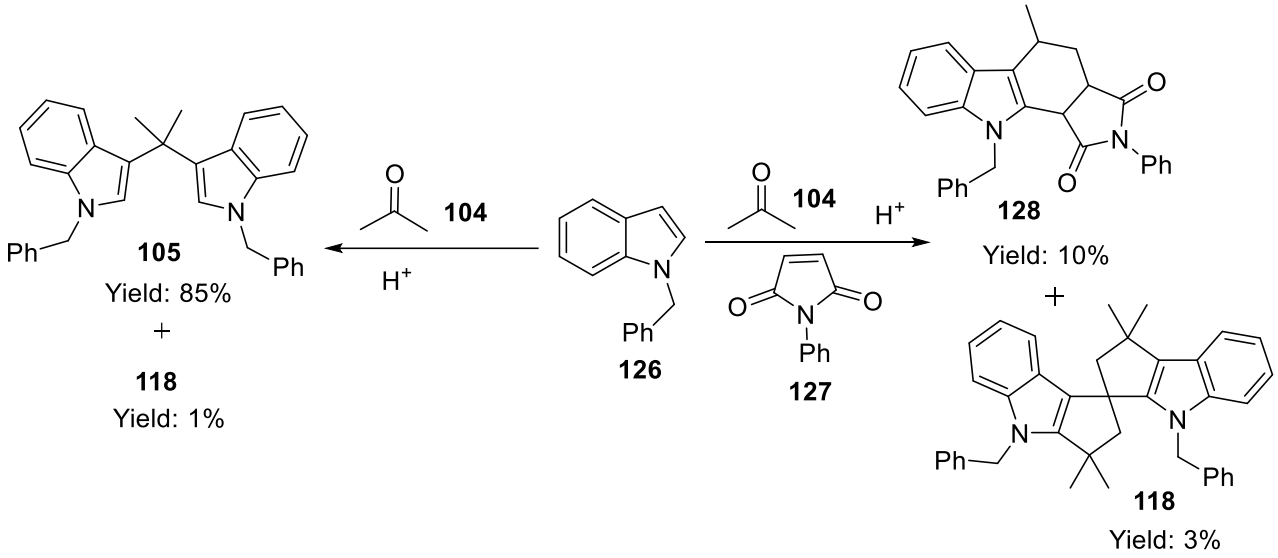
In 1996, Noland group assigned the structure of unknown compound as **125** which was isolated previously from acid catalyzed condensation of indole with acetone. Noland revealed the proposed mechanism for the formation of compound **125** as shown in **Scheme 1.37**[109] and structure was confirmed by X-ray crystal data analysis. Later, in 1999 Nolandperformed conc. HCl catalyzed reaction of 1-benzylindole **(126)** with acetone in the presence of *N*-phenylmaleimide **(127).** Compound **128** was obtained as major compound (10%) along with spiro compound **118** as minor compound (3%) at reflux condition (**Scheme 1.38**),[110] whereas **105** was obtained as major product in 85% yield and dimer spiro compound **118** as the minor product in 1% yield when reaction was performed in absence of **127** under similar conditions (**Scheme 1.38**). The structure of spiro compound **118** was confirmed by X-ray crystallographic data.



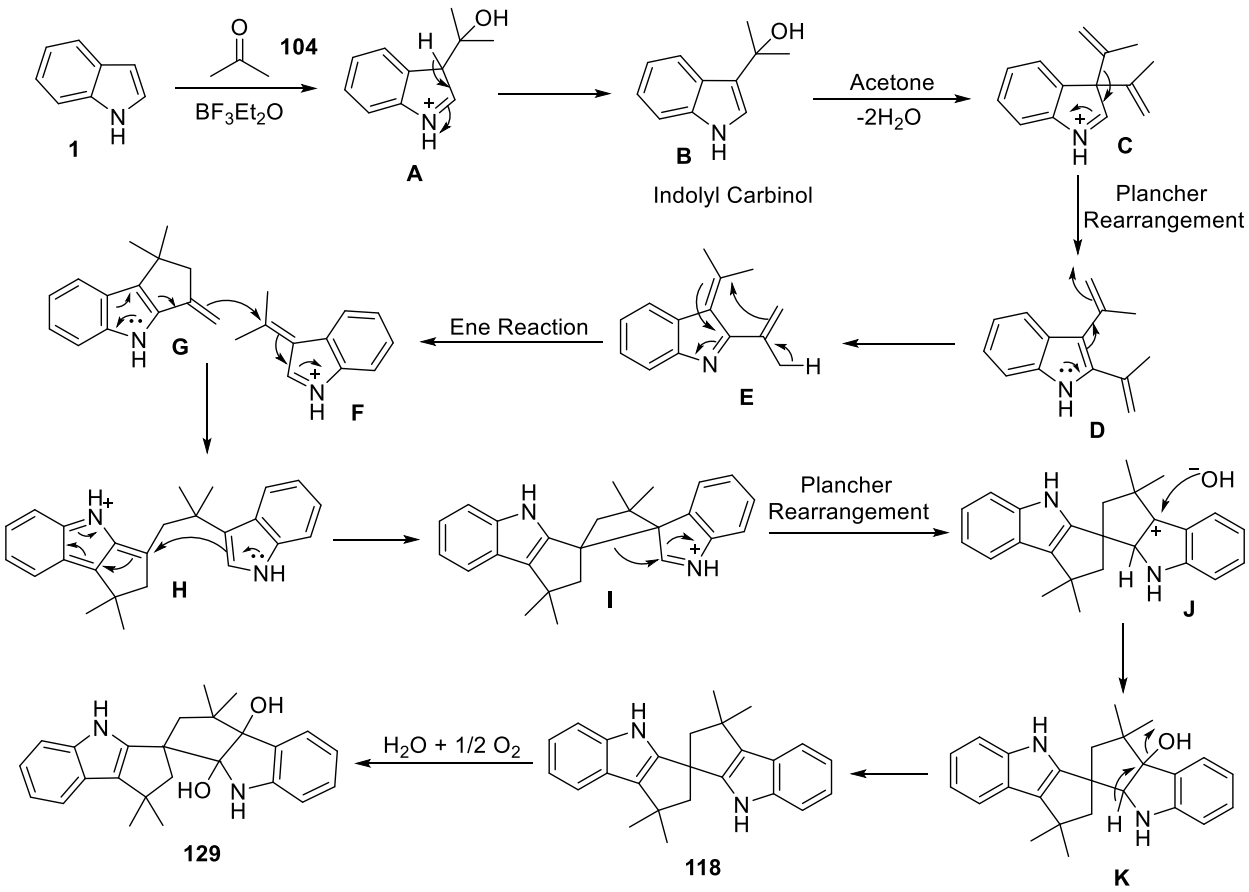
Scheme 1.37: Synthesis of **125** by condensation of indole with acetone in ethanolic hydrochloric acid

In 2008, Banerji *et al.* reported novel spiro heterocyclic compound **129** in 20% yield, procured from the reaction of indole with acetone in the presence of $BF_3.OEt_2$ under a nitrogen atmosphere. The proposed mechanism for the synthesis of compound **129** involves Plancher rearrangement and ene reaction as shown in **Scheme 1.39**.[103]

.

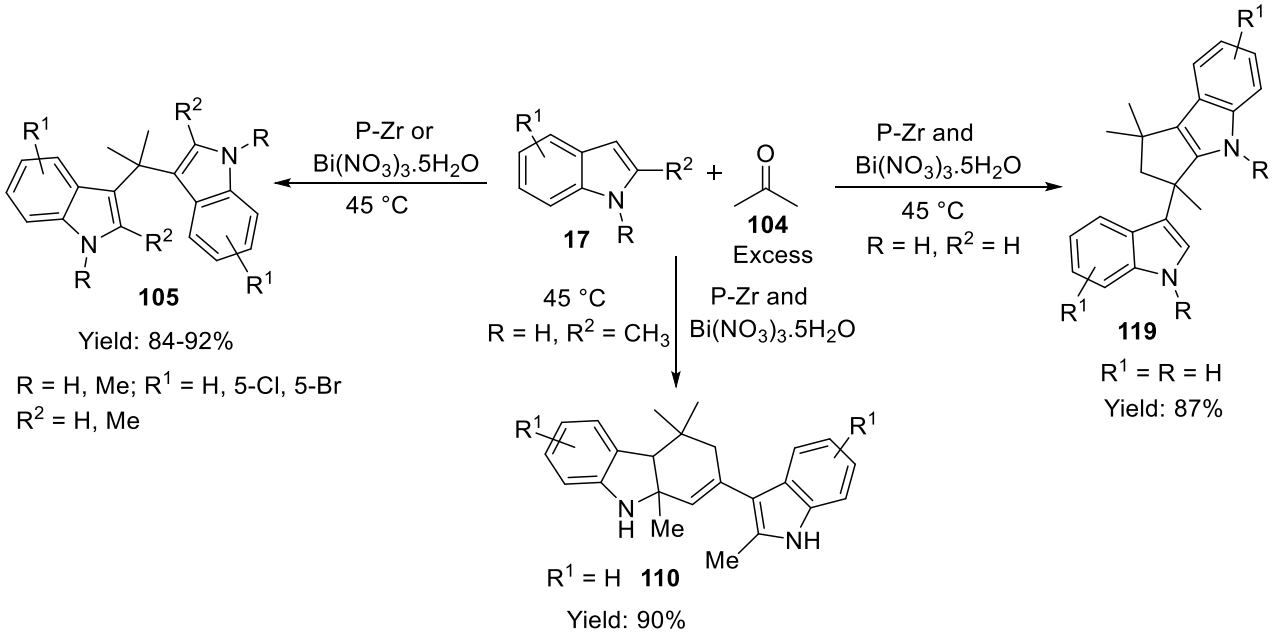


Scheme 1.38: Conc. HCl catalyzed condensation of 1-benzylindole and acetone with and without *N*-phenylmaleimide



Scheme 1.39: BF_3Et_2O catalyzed condensation of indole with acetone

Recently, Nagarkar group demonstrated phosphated zirconia (P-Zr) or bismuth nitrate pentahydrate (BNPH) catalyzed synthesis of *bis*(indolyl)propanes (BIPs) **105** by the condensation of substituted indoles **17** with acetone at 45 °C. 3-Methylindole didn't afford any product under normal conditions but when a combined catalytic system of phosphated zirconia (P-Zr) and bismuth nitrate pentahydrate (BNPH) was used, cyclopenta[*b*]indole **119** was obtained in 87% yield from indole and tetrahydrocarbazole **110** was obtained in 90% yield from 2-methylindole (**Scheme 1.40**).[111]

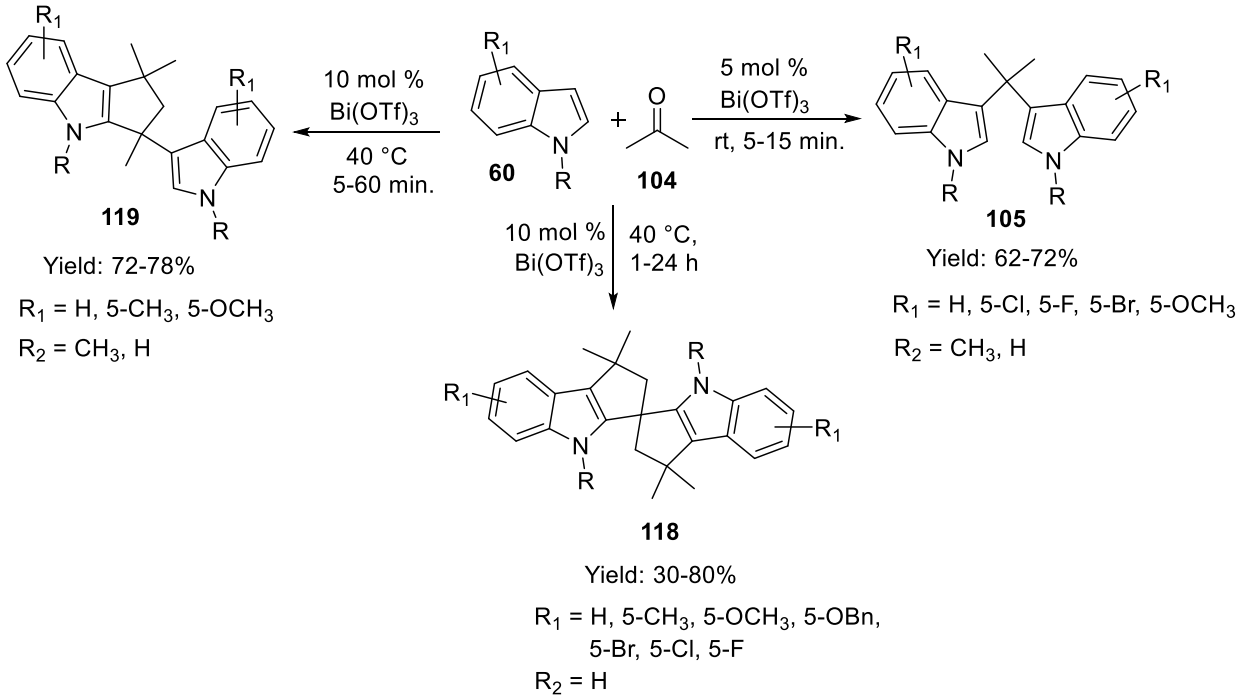


Scheme 1.40: Phosphated zirconia (P-Zr)/$Bi(NO_3)_3.5H_2O$ catalyzed condensation of indole with acetone

Most of the reported studies are based on the reaction of simple indole with acetone and the catalysts used are corrosive, toxic, cause handling problems on a larger scale and their separation from the reaction mixture is difficult. Thus, investigation of the reaction of substituted indoles with acetone using a simple, safe and environmentally friendly catalyst is still desirable. In continuation of our interest in the application of metal triflates as greener catalysts in organic synthesis, herein we report the investigation of $Bi(OTf)_3$ catalyzed condensation of indoles with acetone under different reaction conditions.

1.5 Results and discussion

Initially, we investigated the reaction of indole (1.0 mmol) and acetone (1.5 mL) in the presence of 5 mol % $Bi(OTf)_3$ at room temperature. The color of the reaction mixture changed immediately after the addition of the catalyst (without catalyst, there was no change in the reaction mixture) and the reaction was completed within 5 min as indicated by TLC. The product was isolated and purified by column chromatography and characterized by the ^1H and ^{13}C NMR spectral data. Appearance of singlet at δ 7.76 and δ 1.90 (2 × CH_3) along with multiplet for ten aromatic protons in the region δ 7.41–6.84 in the ^1H NMR spectrum revealed presence of the NH group and in the ^{13}C NMR spectrum, two peaks appeared as δ 30.0 and 34.95 for aliphatic carbons along with peaks for aromatic carbons. A peak at *m/z* 275.1543 was observed in the HRMS corresponding to the molecular formula $C_{19}H_{19}N_2^+$ $[M+H]^+$ ion. These spectral data were in agreement with *bis*(indolyl)propane i.e. 3-(2-(1*H*-indol-3-yl)propan-2-yl)-1*H*-indole **(105a)** (R^1 and R^2 = H) (**Scheme 1.41**). Next, we continued the reaction of indole and acetone under identical conditions for a longer time, the progress of the reaction was monitored by TLC. A new nonpolar spot was formed along with **105a** with increasing reaction time. The reaction was continued for 24 h and this new compound was isolated by column chromatography and characterized by the ^1H and ^{13}C NMR spectral data.



Scheme 1.41: $Bi(OTf)_3$ catalyzed condensation of indole with acetone

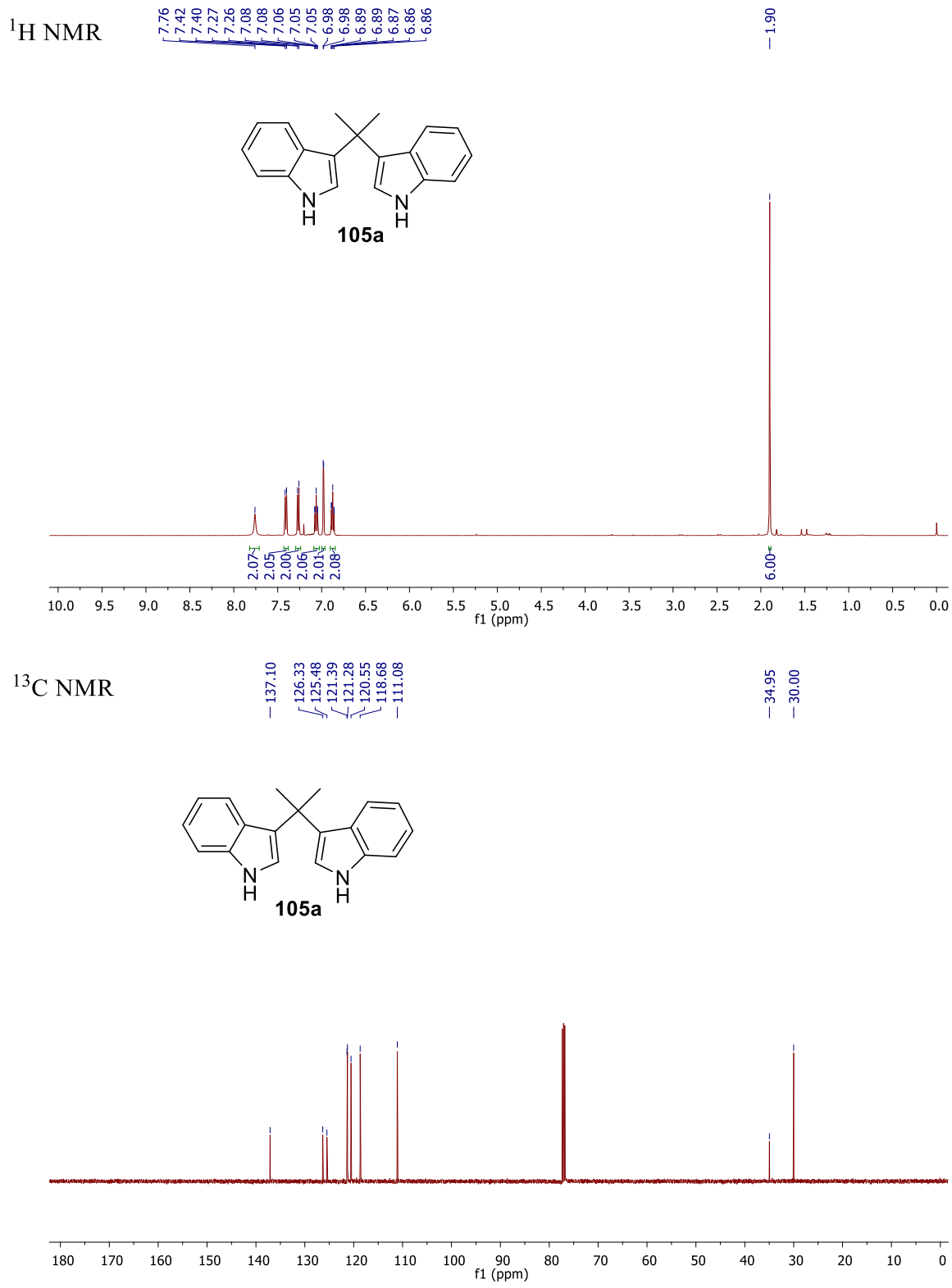
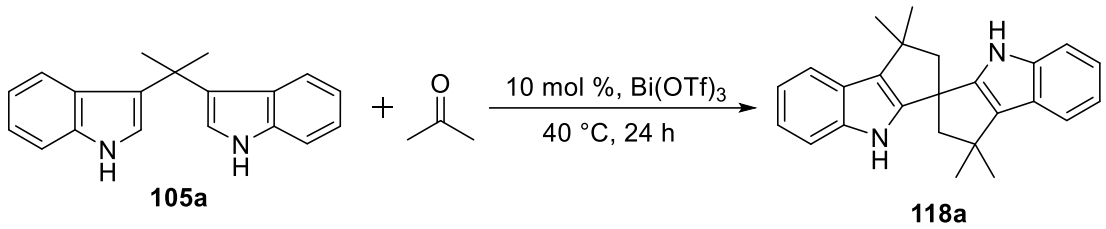


Figure 1.10: ^{1}H and ^{13}C NMR spectra of 3,3'-(propane-2,2-diyl)bis(1*H*-indole) **(105a)** in $CDCl_3$

In the ^{1}H NMR of **118a,** presence of a singlet at δ 7.56 (1H), two doublets at δ 2.76 (2H) and *δ* 2.60 (2H), two singlets at *δ* 1.57 (6H) and *δ* 1.49 (6H) along with eight aromatic protons in the region *δ* 7.45–7.05 indicated presence of NH, two CH_2 and two 2 × CH_3 groups. Peaks for five aliphatic carbons appeared along with aromatic carbons in the ^{13}C NMR and molecular ion peak at *m/z* 354.2224 (M^+) was observed, that corresponds to the molecular formula $C_{25}H_{26}N_2$. Based on these spectral data, the structure of the compound was established as 1,1,1′,1′-tetramethyl 2,2′,4,4′- tetrahydro-1*H*,1′*H*-3,3′-spirobi[cyclopenta[*b*]indole] (**118a**).



Scheme 1.42 : Reaction of **105a** with acetone in presence of $Bi(OTf)_3$

The reaction of indole with acetone furnished *bis*(indolyl)propane (**105a**) in 74% yield after 5 min and on prolonging the reaction **118a** was isolated in 20% yield. It was clear that initially **105a** is formed by condensation of indole and acetone, which further reacts with acetone to gave **118a** (**Scheme 1.42**). To confirm this, we reacted isolated **105a** with acetone under similar condition and found that **105a** gave **118a** in 68% yield after 24 h. Therefore, it was assumed that **105a** is probably intermediate in the synthesis of **118a**.

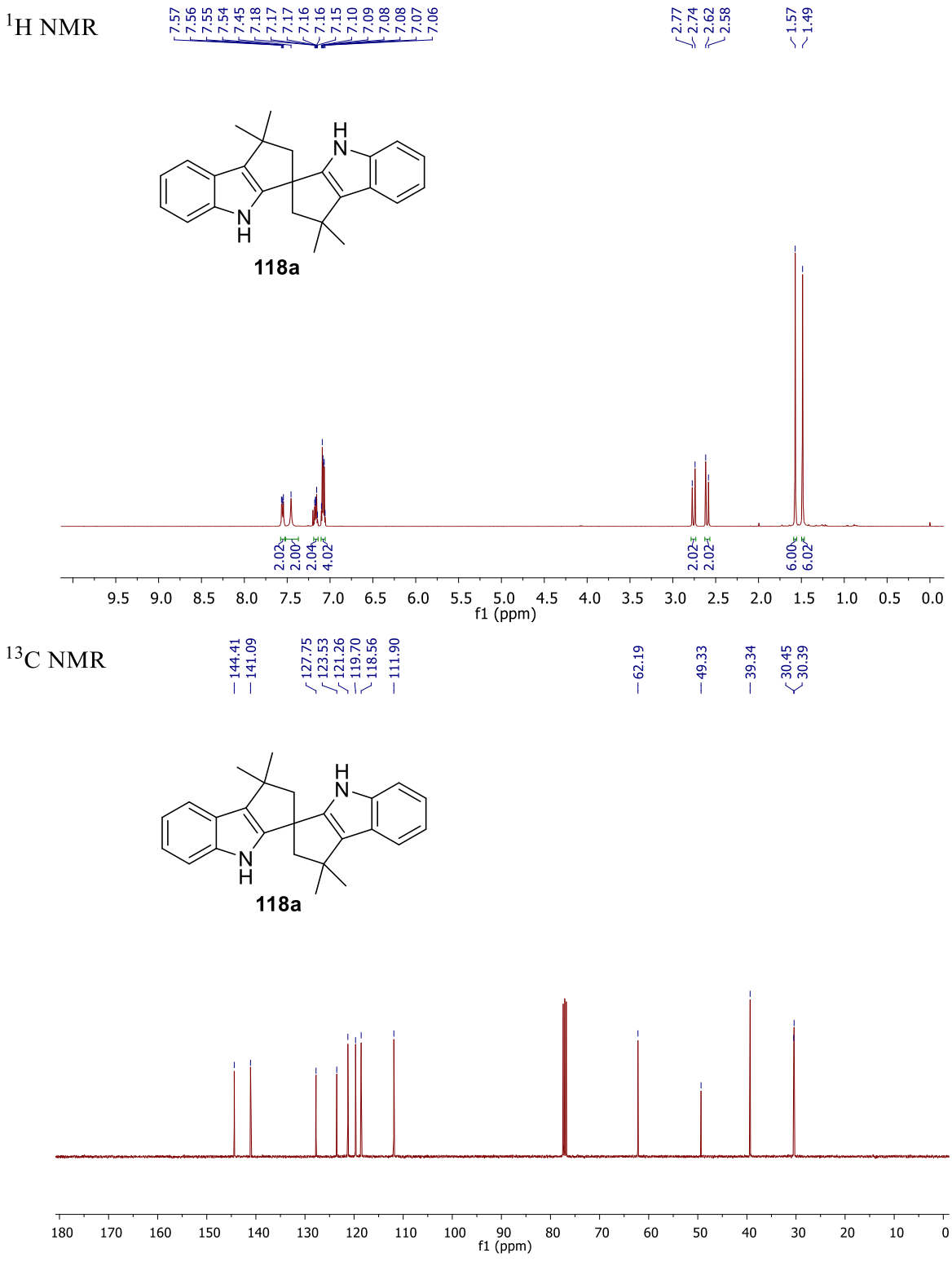


Figure 1.11: ^{1}H and ^{13}C NMR spectra of 1,1,1',1'-tetramethyl-1,1',4,4'-tetrahydro-2*H*,2'*H*-3,3'-spirobi[cyclopenta[*b*]indole] **(118a)** in $CDCl_3$

After obtaining **118a** by increasing the reaction time for condensation of indole with acetone using $Bi(OTf)_3$ as a catalyst, we next optimized the reaction condition for improving the yield of **118a** by varying amount of acetone, reaction time, catalyst, and catalyst loading. The results are summarized in Table 1.2.

Table 1.2: Optimization of reaction conditions for synthesis of **118a** at 40 °C.

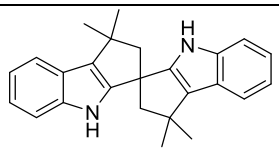
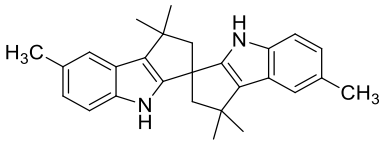
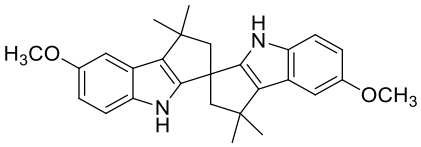
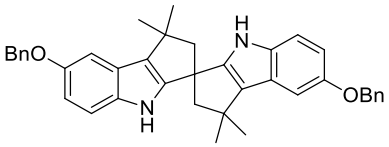
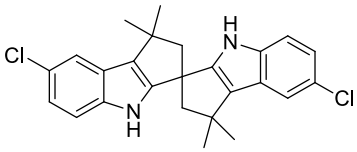
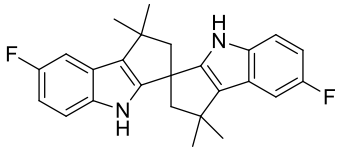
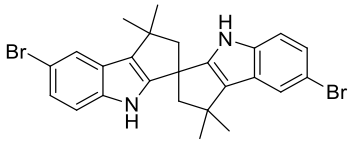
Sr. No	Catalyst	Moles (%)	Solvent (mL)	Time (h)	Yield[a] (%)
1	$Bi(OTf)_3$	5	1.5	24	20
2	$Bi(OTf)_3$	10	1.5	24	56
3	$Bi(OTf)_3$	5	3	24	64
4	**$Bi(OTf)_3$**	**10**	**3**	**24**	**68**
5	$Bi(OTf)_3$	10	3	2	15
6	$Bi(OTf)_3$	10	3	6	35
7	$Bi(OTf)_3$	10	4	24	64
8	$Bi(OTf)_3$	15	3	24	65
9	$Bi(OTf)_3$	20	3	24	58
10	$Sc(OTf)_3$	10	3	24	32
11	$In(OTf)_3$	10	3	24	57
12	AgOTf	10	3	24	66
13	IL-SO_3H	10	3	24	58
14	$Cu(OTf)_2$	10	3	24	NR[b]
15	*p*-TSA	10	3	24	Trace
16	$Yb(OTf)_3$	10	3	24	NA[b]
17	TFA	10	3	24	Trace
18	$InBr_3$	10	3	24	Trace
19	HOTf	10	3	24	—[c]

[a] Isolated yield. [b] No product formed. [c] Reaction was sluggish with a mixture of several compounds.

As indicated in Table 1.2, the yield of **118a** increased from 20% to 68% with increasing catalyst loading to 10 mol % and volume of acetone to 3 mL (Table 1.2, entry 4). Further increase in catalysts loading and amount of acetone did not improve the yield of **118a**. We also screened other catalysts viz. $Sc(OTf)_3$, $Yb(OTf)_3$, $In(OTf)_3$, $Cu(OTf)_2$, $InBr_3$, AgOTf, IL-SO_3H, *p*-TSA, and TFA. Although $Sc(OTf)_3$, $In(OTf)_3$, AgOTf and IL-SO_3H gave good yield of **118a** but $Bi(OTf)_3$ was

found to give the highest yield (68%) under similar conditions. With optimized conditions in hand, we explored the generality of the reaction using substituted indoles. A series of spirobi[cyclopenta[*b*]indole] was prepared and results are shown in Table 1.3. Indole substituted with the electron-donating group afforded comparably better yield than indoles substituted with the electron-withdrawing group. It is noteworthy to mention that 5-nitroindole did not react with acetone under these conditions.

Table 1.3 : Synthesis of spirobi[cyclopenta[*b*]indoles] (**118a-118g**)

Entry	R^1	Product		Time (h)	Yield[a] (%)
1	H		**118a**	24 1	68 65[b]
2	CH_3		**118b**	1	80
3	OCH_3		**118c**	8	75
4	OBn		**118d**	8	71
5	Cl		**118e**	24	52
6	F		**118f**	24	61
7	Br		**118g**	4	30[b]

[a]Isolated yield. [b] At reflux condition.

When *N*-methylindole was reacted with acetone instead of the expected 3,3′-spiro-bi[cyclopenta[*b*]indole] derivative, *N*-methylindolyl-cyclopenta[*b*]indole i.e. 1,2,3,4-tetrahydro-1,1,3,4-tetramethyl-3-(1-methyl-1*H*-indol-3-yl)cyclopenta[*b*]indole (**119a**) was obtained. The structure of **119a** was confirmed by ^{1}H NMR, ^{13}C NMR, and mass spectrometry data. In the ^{1}H NMR spectra, five singlets appeared at δ 1.48, 1.53, 1.88, 3.30, and 3.74 each for three protons, two doublets at δ 2.43 and 2.89 each for one proton and a multiplet in the region δ 6.84–7.62 for nine protons. These data were in agreement with the reported NMR for **119a** by Bergman *et al*.[93] In the ^{13}C NMR, peaks for eight carbons appeared in the aliphatic region along with aromatic carbons. HRMS showed a peak at *m/z* 343.2173 that corresponds to the molecular formula $C_{24}H_{27}N_2^+$ for $[M+H]^+$ ion.

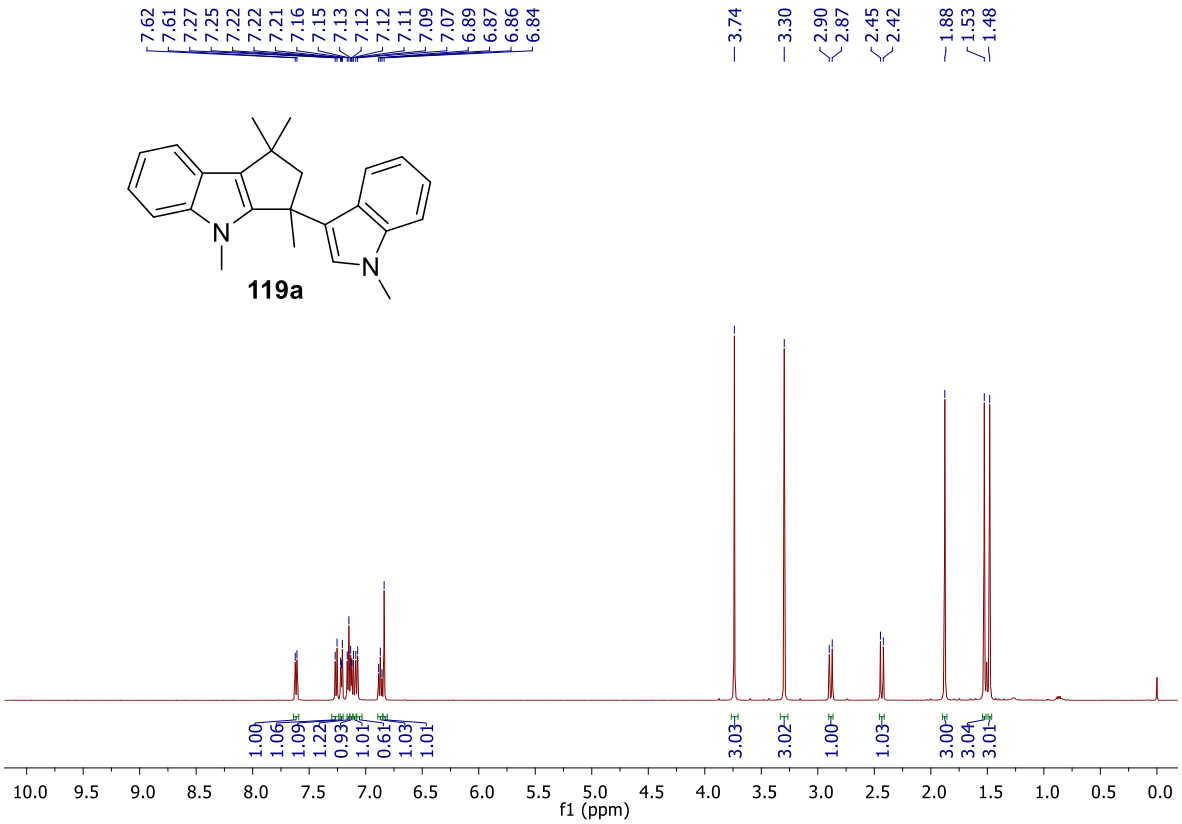


Figure 1.12a: ^{1}H NMR spectra of 1,1,3,4-tetramethyl-3-(1-methyl-1*H*-indol-3-yl)-1,2,3,4-tetrahydrocyclopenta[*b*]indole **(119a)** in $CDCl_3$

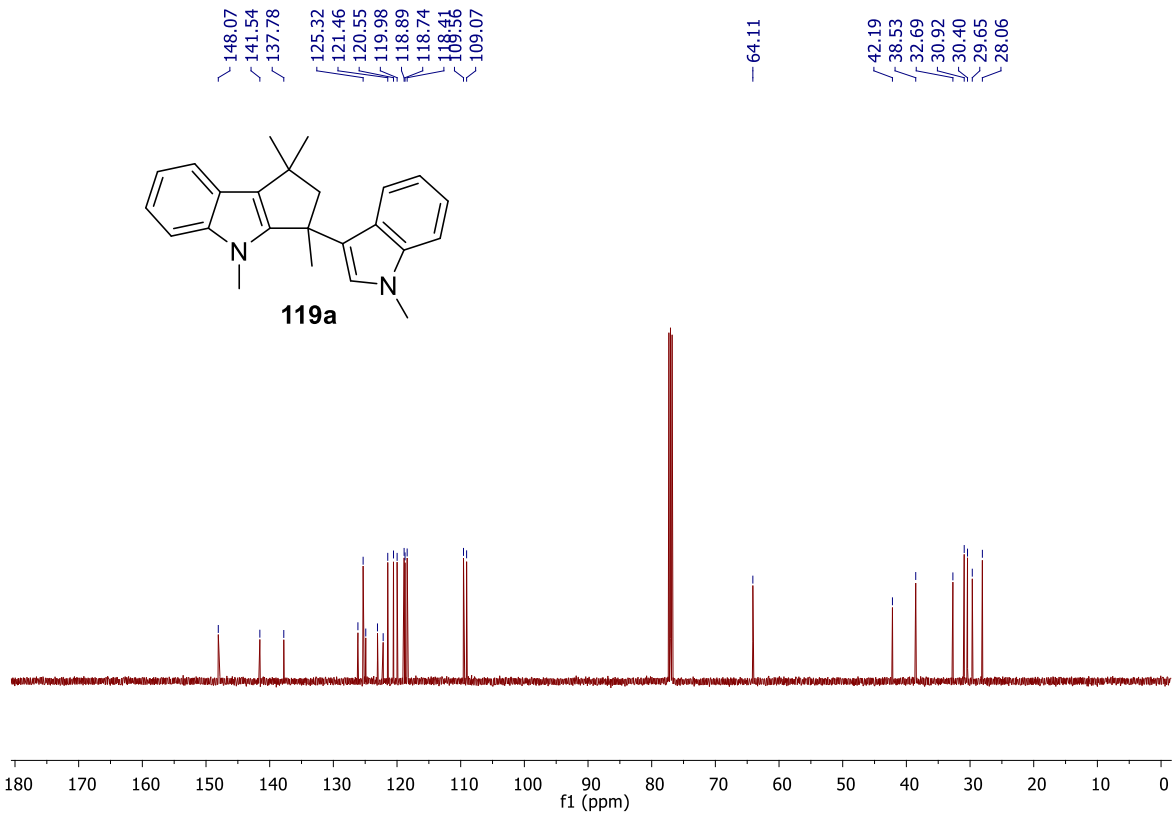


Figure 1.12b: ^{13}C NMR spectra of 1,1,3,4-tetramethyl-3-(1-methyl-1*H*-indol-3-yl)-1,2,3,4-tetrahydrocyclopenta[*b*]indole **(119a)** in $CDCl_3$

Finally, the structure of **119a** was unambiguously confirmed by single crystal X-ray crystallographic analysis (Fig. 1.10). The structure and spectral data of **119a** were in agreement with the earlier reported product of the reaction between *N*-methylindole with acetone (Table 1.4).[93]

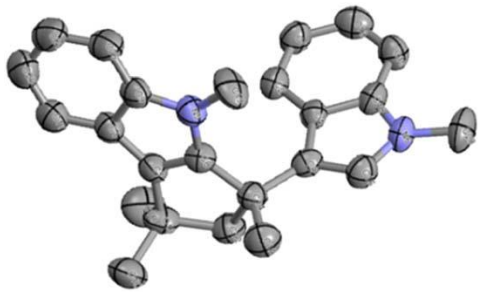


Fig 1.13: A perspective view of **119a** showing 50% thermal ellipsoids and heteroatom (*N*) labels in blue color (CCDC 957557). Hydrogen atoms are omitted for clarity.

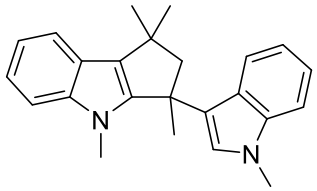
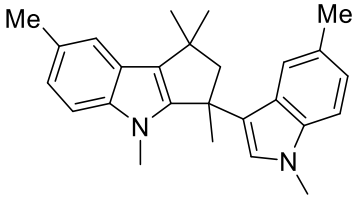
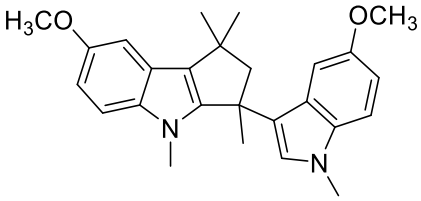
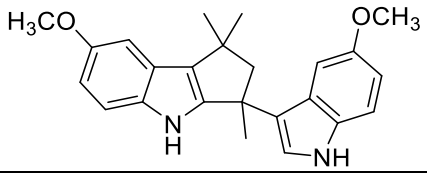
Table 1.4: Crystallographic parameters for **119a**

Formula	$C_{24}H_{26}N_2$	Z	4
Formula wt	342.47	ρ_{calcd} (mg m^{-3})	1.164
Crystal size, colour, shape	0.26 mm × 0.24 mm × 0.21 mm, colourless, block	Absorp. coeff. (mm^{-1})	0.07
Space group	Orthorhombic, *Pna*2_1	Temp, K	293
a, Å	12.8233 (9)	Total no. data	8890
b, Å	16.9231 (15)	No. unique data	3447
c, Å	9.0073 (6)	Obs. data[a]	2125
α, °	90	R,[b] %	0.076
β, °	90	wR_2,[c] %	0.200
γ, °	90	No. of parameters	240
ν, $Å^3$	1954.7 (3)	Max/min peaks, e $Å^{-3}$	0.22/-0.40

[a]Observation criterion : $I > 2\sigma(I)$. [b] $[F^2 > 2\sigma(F^2)]$. [c] $w = 1/[\sigma^2(F_o^2) + (0.0874P)^2$ Where $P = (F_o^2 + 2F_c^2)/3$.

A further variation of the substituent on *N*-methylindole was studied and it was found that *N*-methylindoles with electron donating groups gave corresponding *N*-methylindolyl-cyclopenta[*b*]indole derivatives **(119)**, whereas *N*-methylindoles with electron withdrawing substituted gave bis(*N*-methylindolyl)propane **(105)** instead of *N*-methylindolyl-cyclopenta[*b*]indoles **(119).** Results for the synthesis of cyclopenta[*b*]indole derivatives are given in Table 1.5. It is noteworthy to mention that the reaction of *N*-methylindoles substituted with an electron donating group at 5-position could not be stopped at *bis*(indolyl)propane even by using 5 mol % of $Bi(OTf)_3$ and 1.5 mL acetone. They gave a remarkably good yield of the corresponding cyclopenta[*b*]indoles (Table 1.5, entries 1–3).

Table 1.5: Synthesis of 3-indolyl-1,1,3-trimethyl-cyclopenta[*b*]indoles **(119a-119d)**

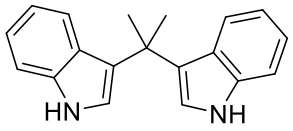
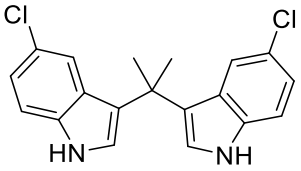
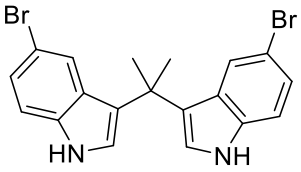
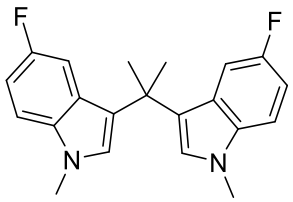
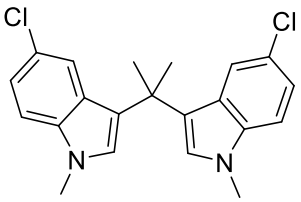
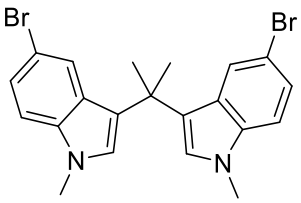
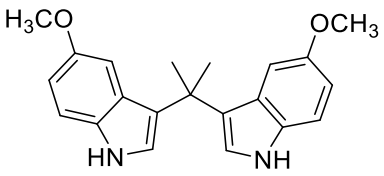
Entry	R^1	R^2	Product		Time (min)	Yield[a] (%)
1	H	CH_3		**119a**	60	74
2	CH_3	CH_3		**119b**	6	78
3	OCH_3	CH_3		**119c**	8	76
4	OCH_3	H		**119d**	6	72

[a]Isolated yield.

It is worth to mention that not only *N*-methylindoles but 5-methoxyindole also resulted in the formation of 3-indolyl-1,1,3-trimethyl-cyclopenta[*b*]indoles derivative (**119d**) on reaction with acetone in the presence of 5 mol % of $Bi(OTf)_3$ in 6 minutes of reaction time. This indicates that the product distribution depends on the electronic effect of indole ring and does not depend on the catalyst loading and amount of acetone used. Very recently, Alcaide *et al*. have synthesized dihydrocyclopenta[*b*]indolone through proton-catalyzed carbocyclization of allenone.[112]

After synthesizing spirobi[cyclopenta[*b*]indole] derivatives and cyclopenta[*b*]indoles, we turned our attention towards synthesis of bis(indolyl)propanes **(105).** The results for the synthesis of bis(indolyl)propanes are shown in Table 1.6.

Table 1.6: Synthesis of bis(indolyl)propanes (BIPs) **(105a-105g)**

Entry	R^1	R^2	Product		Time (min)	Yield[a] (%)
1	H	H		**105a**	5	65
2	Cl	H		**105b**	10	69
3	Br	H		**105c**	10	66
4	F	CH_3		**105d**	5	62
5	Cl	CH_3		**105e**	5	72
6	Br	CH_3		**105f**	5	64
7	OCH_3	H		**105g**	5	48

[a]Isolated yield.

Indoles with both electron donating and electron withdrawing groups in the indole ring as well as *N*-methyl substituted indoles reacted smoothly under these conditions to give corresponding bis(indolyl)-propanes in good (48–72%) yield. The reaction time is very short, and the catalyst can be recovered and reused. The mechanism of the reaction is believed to be similar to that reported by Bergman group[93] with initial formation of indolyl carbinol which may generate vinyl indole as intermediate. Consequent reaction of this with acetone and indole results in the formation of bis(indolyl)propane, 3-indolylcyclopenta[*b*]indoles **(119)** and 3,3′-spirobi[cyclopenta[*b*]indole] **(118)**.

1.6 Conclusions

The products of the reaction between indole derivatives and acetone in the presence of $Bi(OTf)_3$ as a catalyst depends on the reaction conditions and the substituent on the indole ring. By appropriately adjusting the reaction condition and taking suitable indole derivatives we could synthesize 3,3′-spirobi[cyclopenta[*b*]indole], 3-indolylcyclopenta[*b*]indoles and bis(indolyl)propanes. The reaction conditions for the synthesis of spiro-indoles are benign and require less time with improved yield as compared to previously reported methods using protic acids.

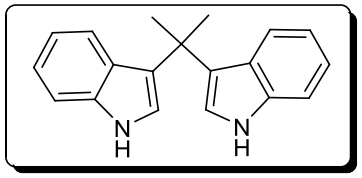
1.7 Experimental

General information

Indole and metal triflates were purchased from Sigma-Aldrich, India and acetone were purchased from Merck, India. All other reagents were purchased from commercial sources and used as received. Melting points were determined by the open capillary tube method using a melting point apparatus (EZ-Melt) and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker (300 MHz & 400 MHz) and Varian 500 MHz NMR spectrometer. High-resolution mass spectra (HRMS) were recorded on a quadrupole time-of-flight (qTOF) mass spectrometer. X-ray crystallographic data were collected on a CCD diffractometer. Thin layer chromatography (TLC) was performed on pre-coated alumina sheets and detected under UV light. Silica gel (100–200 mesh) was used for column chromatography.

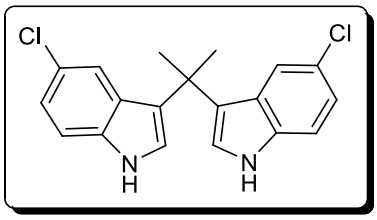
Representative procedure for the synthesis of 5-chloro-1-methyl-1H-indole (105e): A mixture of 5-chloro-1-methyl-1*H*-indole (0.166 g, 1.0 mmol), acetone (1.5 mL) and $Bi(OTf)_3$ (0.066 g, 0.1 mmol) in a round bottom flask of 10 mL was stirred for 5 minutes at room temperature. The progress of the reaction was monitored using TLC (hexane–ethyl acetate 1 : 9 *v/v*). After completion of the reaction, the reaction mixture was diluted with water (5 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography on silica gel (100–200 mesh) to afford the pure product **105e** (0.268 g) as a white solid in 72% yield.

3-(2-(1*H*-Indol-3-yl)propan-2-yl)-5-methyl-1*H*-indole (105a)



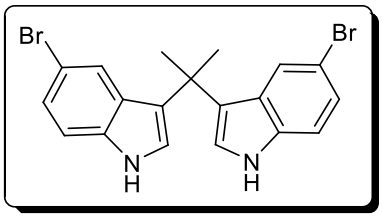
Yield 65%; white solid; mp 158-160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 7.09–7.03 (m, 2H), 6.98 (d, J = 2.4 Hz, 2H), 6.90–6.84 (m, 2H), 1.90 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 126.3, 125.5, 121.4, 121.3, 120.5, 118.7, 111.1, 34.9, 30.0; ESI-MS *m/z* calcd for $C_{19}H_{19}N_2^+$ 275.1543, found 275.1566 $[M+H]^+$.

3,3′-(Propane-2,2-diyl)bis(5-chloro-1*H*-indole) (105b)



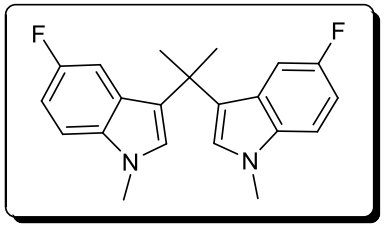
Yield 69%; white solid; mp 146-148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.26 (s, 1H), 7.22 (d, J = 8.6 Hz, 2H), 7.13 (s, 2H), 7.02 (d, J = 8.5 Hz, 2H), 1.85 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 127.2, 124.8, 124.3, 121.9, 121.7, 120.3, 112.1, 34.5, 29.8; ESI-MS *m/z* calcd for $C_{19}H_{16}Cl_2N_2Na^+$ 365.0583, found 365.0565 $[M+Na]^+$.

3,3′-(Propane-2,2-diyl)bis(5-bromo-1*H*-indole) (105c)



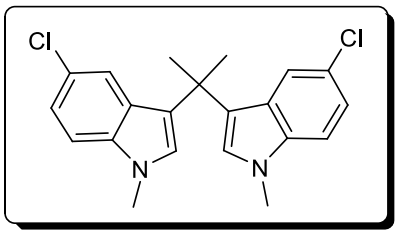
Yield 66%; colorless solid; mp 157-159 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.44 (s, 1H), 7.18 (d, J = 8.6 Hz, 2H), 7.15 (dd, J = 8.6, 1.5 Hz, 2H), 7.09 (d, J = 2.4 Hz, 2H), 1.85 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.7, 127.9, 124.7, 124.4, 123.3, 121.6, 112.6, 112.1, 34.6, 29.8; ESI-MS *m/z* calcd for $C_{19}H_{17}Br_2N_2^+$ 430.9753, found 430.9772 $[M+H]^+$ and 432.9741 $[M+H+2]^+$

3,3′-(Propane-2,2-diyl)bis(5-fluoro-1-methyl-1*H*-indole) (105d)



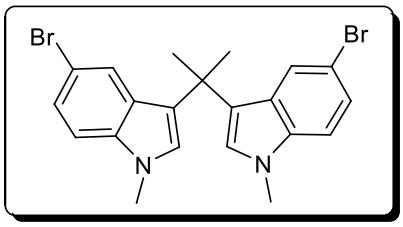
Yield 62%; colorless solid; mp 168-169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (dd, J = 8.9, 4.4 Hz, 2H), 6.98 (s, 2H), 6.92 (dd, J = 10.4, 2.5 Hz, 2H), 6.83 (td, J = 9.0, 2.5 Hz, 2H), 3.74 (s, 6H), 1.81 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7 (d, J = 233.1 Hz) 134.4, 126.7, 126.8 (d, J = 10.08 Hz), 123.5 (d, J = 5.04 Hz), 109.6 (d, J = 10.08 Hz), 109.4 (d, J = 26.46 Hz) 105.9 (d, J = 23.94 Hz), 34.4, 32.1, 30.0; ESI- MS *m/z* calcd for $C_{21}H_{20}F_2N_2Na^+$ 361.1487, found 361.1503 $[M+Na]^+$.

3,3′-(Propane-2,2-diyl)bis(5-chloro-1-methyl-1*H*-indole) (105e)



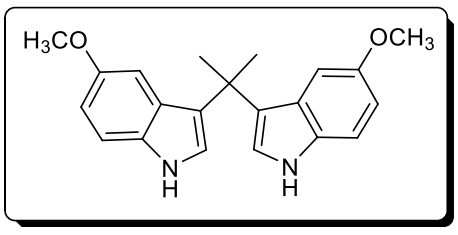
Yield 72%; colourless solid; mp 198-200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.29 (m, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.05 (dd, J = 8.7, 2.0 Hz, 2H), 6.93 (s, 2H), 3.73 (s, 6H), 1.83 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 127.4, 126.6, 123.9, 123.3, 121.3, 120.4, 110.2, 34.5, 32.9, 30.1; ESI-MS *m/z* calcd for $C_{21}H_{21}Cl_2N_2^+$ 371.1076, found 371.1065 $[M+H]^+$.

3,3′-(Propane-2,2-diyl)bis(5-bromo-1-methyl-1*H*-indole) (105f)



Yield 64%; colorless solid; mp 220-222 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 1.5 Hz, 2H), 7.18 (dd, J = 8.7, 1.8 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 6.93 (s, 2H), 3.74 (s, 6H), 1.83 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 131.1, 130.4, 127.7, 127.2, 127.1, 115.4, 114.6, 38.4, 36.6, 33.1; ESI-MS *m/z* calcd for $C_{21}H_{21}Br_2N_2^+$ 459.0066, found 459.0058 $[M+H]^+$, 461.0046 $[M+H+2]^+$, 463.0038 $[M+H+4]^+$.

3,3′-(Propane-2,2-diyl)bis(5-methoxy-1*H*-indole) (105g)

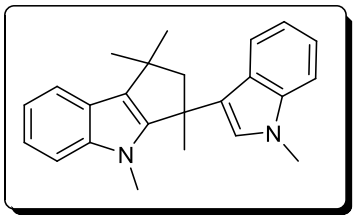


Yield 48%; liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (s, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 2.4 Hz, 2H), 6.84 (d, J = 2.2 Hz, 2H), 6.74 (dd, J = 8.8, 2.4 Hz, 2H), 3.64 (s, 6H), 1.88 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 132.4, 126.8, 124.1, 121.4, 111.5, 111.0, 103.8, 55.8, 34.7, 29.6; ESI-MS *m/z* calcd for $C_{21}H_{23}N_2O_2^+$ 335.1754, found 335.1768 $[M+H]^+$.

Representative procedure for the synthesis of 1,1,3,4-tetra-methyl-3-(1-methyl-1*H*-indol-3-yl)-1,2,3,4-tetra-hydro-cyclopenta-[*b*]indole (119a)

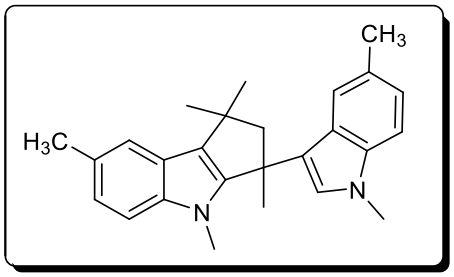
A mixture of 1-methylindole (0.132 g, 1.0 mmol), acetone (3 mL) and $Bi(OTf)_3$ (0.066 g, 0.1 mmol) in a round bottom flask of 10 mL was stirred at 40 °C for 60 min. The progress of the reaction was monitored by TLC (hexane–ethyl acetate 1 : 19 *v/v*). After completion of the reaction, the reaction mixture was diluted with water (5 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography on silica gel (100–200 mesh) to afford the pure product **119a** as a white solid in 74% yield.

1,1,3,4-Tetramethyl-3-(1-methyl-1*H*-indol-3-yl)-1,2,3,4-tetrahydrocyclopenta[*b*]indole (119a)



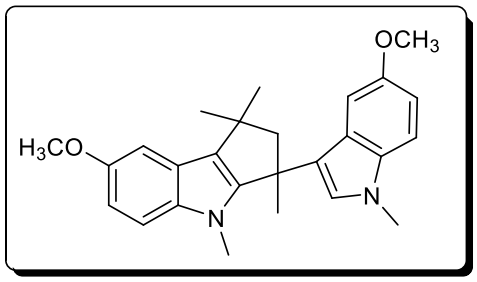
Yield 74%; colorless solid; mp 178-179 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 7.4 Hz, 1H), 7.27 (s, 1H), 7.23–7.20 (m, 1H), 7.16 (d, J = 7.2 Hz, 1H), 7.14–7.12 (m, 1H), 7.10 (d, J = 10.3 Hz, 1H), 7.07 (s, 1H), 6.87 (t, J = 7.5 Hz, 1H), 6.84 (s, 1H), 3.74 (s, 3H), 3.30 (s, 3H), 2.89 (d, J = 13.0 Hz, 1H), 2.43 (d, J = 13.0 Hz, 1H), 1.88 (s, 3H), 1.53 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 141.5, 137.8, 126.1, 125.3, 124.9, 123.1, 122.2, 121.5, 120.5, 119.1, 118.9, 118.7, 118.4, 109.6, 109.1, 64.1, 42.2, 38.5, 32.7, 30.9, 30.4, 29.6, 28.1; ESI-MS *m/z* calcd for $C_{24}H_{27}N_2^+$ 343.2169, found 343.2173 $[M+H]^+$.

3-(1,5-Dimethyl-1*H*-indol-3-yl)-1,1,3,4,7-pentamethyl-1,2,3,4-tetrahydro-cyclopenta-[*b*]indole (119b)



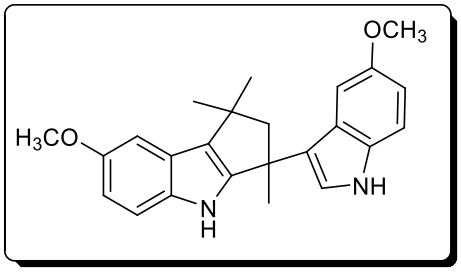
Yield 78%; liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.13 (dd, J = 16.9, 8.1 Hz, 2H), 7.07 (s, 1H), 6.98 (t, J = 8.9 Hz, 2H), 6.68 (s, 1H), 3.67 (s, 3H), 3.36 (s, 3H), 2.90 (d, J = 12.8 Hz, 1H), 2.48 (s, 3H), 2.42 (d, J = 12.8 Hz, 1H), 2.30 (s, 3H), 1.86 (s, 3H), 1.51 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 140.1, 136.3, 127.8, 127.8, 126.3, 125.5, 124.4, 123.0, 122.5, 121.7, 121.4, 120.3, 118.3, 109.2, 108.9, 63.5, 42.4, 38.5, 32.7, 30.9, 30.4, 29.9, 28.2, 21.6, 21.5; ESI-MS *m/z* calcd for $C_{26}H_{31}N_2^+$ 371.2534, found 371.2561 $[M+H]^+$.

7-Methoxy-3-(5-methoxy-1-methyl-1*H*-indol-3-yl)-1,1,3,4-tetramethyl-1,2,3,4 tetrahydrocyclopenta[*b*]indole (119c)



Yield 76%; colorless solid; mp 144-146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16–7.04 (m, 3H), 6.84–6.75 (m, 3H), 6.29 (d, J = 2.2 Hz, 1H), 3.88 (s, 3H), 3.71 (s, 3H), 3.35 (s, 3H), 3.24 (s, 3H), 2.84 (d, J = 13.0 Hz, 1H), 2.44 (d, J = 13.0 Hz, 1H), 1.87 (s, 3H), 1.53 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 153.3, 148.8, 136.1, 133.0, 126.4, 125.6, 124.6, 123.1, 121.7, 111.7, 109.9, 109.8, 109.3, 101.8, 101.3, 64.2, 56.2, 55.3, 41.9, 38.4, 32.8, 31.1, 30.1, 29.6, 27.9; ESI-MS *m/z* calcd for $C_{26}H_{34}N_3O_2^+$ 420.3965, found 420.3946 $[M+NH_4]^+$.

7-Methoxy-3-(5-methoxy-1*H*-indol-3-yl)-1,1,3-trimethyl-1,2,3,4-tetrahydro-cyclopenta-[*b*]indole (119d)

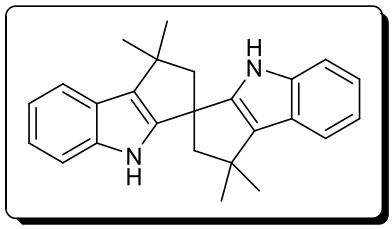


Yield 72%; pale-yellow solid; mp 186-188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.47 (s, 1H), 7.17 (d, J = 8.8 Hz, 1H), 7.07 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 2.4 Hz, 1H), 6.75 (ddd, J = 8.3, 2.4 Hz, 2H), 6.48 (d, J = 2.3 Hz, 1H), 3.86 (s, 3H), 3.43 (s, 3H), 2.87 (d, J = 13.0 Hz, 1H), 2.47 (d, J = 13.0 Hz, 1H), 1.82 (s, 3H), 1.54 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 153.5, 148.5, 136.1, 132.0, 126.1, 124.1, 123.5, 121.3, 112.3, 112.1, 111.8, 109.8, 101.9, 101.3, 65.4, 62.8, 56.1, 55.4, 42.0, 38.1, 30.8, 29.9, 28.3; ESI-MS *m/z* calcd for $C_{24}H_{27}N_2O_2^+$ 375.2067, found 375.2075 $[M+H]^+$.

Representative procedure for the synthesis of 1,1,1′,1′-tetra-methyl-2,2′,4,4′-tetra-hydro-1*H*,1′*H*-3,3′-spiro-bi[cyclopenta-[*b*]indole] (118a)

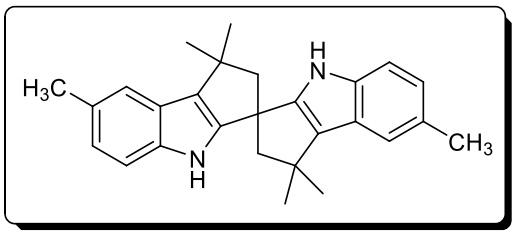
A mixture of indole (0.118 g, 1.0 mmol), acetone (3 mL), and $Bi(OTf)_3$ (0.066 g, 0.1 mmol) in a round bottom flask of 10 mL was stirred at 40 °C for 24 h. The progress of the reaction was monitored by TLC (hexane–ethyl acetate, 15 : 85 *v/v*). After completion of the reaction, the reaction mixture was diluted with water (5 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography on silica gel (100–200 mesh) to afford pure product **118a** as a white solid in 65% yield.

1,1,1′,1′-Tetramethyl-2,2′,4,4′-tetrahydro-1*H*,1′*H*-3,3′-spirobi [cyclopenta[*b*]indole] (118a)



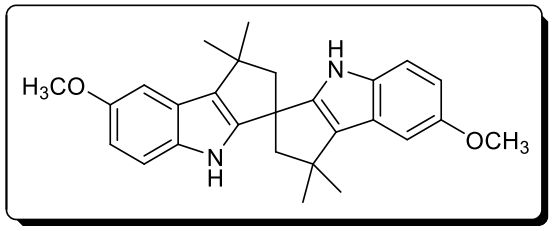
Yield 65%; white solid; mp 246-248 °C (Lit.[113] mp 248 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 5.9, 3.1 Hz, 2H), 7.45 (s, 2H), 7.19–7.15 (m, 2H), 7.11–7.05 (m, 4H), 2.76 (d, J = 13.1 Hz, 2H), 2.60 (d, J = 13.1 Hz, 2H), 1.57 (s, 6H), 1.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 141.1, 127.7, 123.5, 121.3, 119.7, 118.6, 111.9, 62.2, 49.3, 39.3, 30.4, 30.4; ESI-MS *m/z* calcd for $C_{25}H_{27}N_2^+$ 355.2224, found 355.2239 $[M+H]^+$.

1,1,1′,1′,7,7′-Hexamethyl-2,2′,4,4′-tetrahydro-1*H*,1′*H*-3,3′-spirobi[cyclopenta[*b*]indole] (118b)



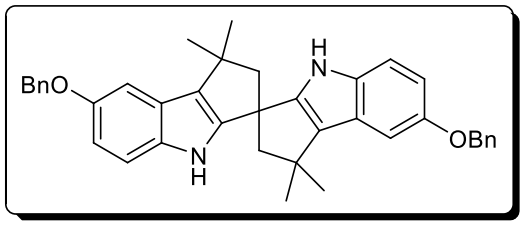
Yield 80%; white solid; mp 160-162 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 2H), 7.34 (s, 2H), 7.09 (d, J = 8.2 Hz, 2H), 6.92 (d, J = 8.3 Hz, 2H), 2.74 (d, J = 13.1 Hz, 2H), 2.57 (d, J = 13.1, 2H), 2.44 (s, 6H), 1.56 (s, 6H), 1.47 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 139.3, 128.9, 127.2, 123.7, 122.6, 118.3, 111.5, 62.1, 49.3, 39.2, 30.4, 30.3, 21.5; ESI-MS *m/z* calcd for $C_{27}H_{31}N_2^+$ 383.2505, found 383.2482 $[M+H]^+$.

7,7′-Dimethoxy-1,1,1′,1′-tetramethyl-2,2′,4,4′-tetrahydro-1*H*,1′*H*-3,3′-spiro-bi[cyclopenta[*b*]indole] (118c)



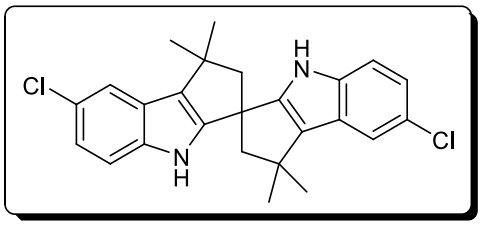
Yield 75%; white solid; mp 238-240 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 2H), 7.12 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 2.4 Hz, 2H), 6.77 (dd, J = 8.8, 2.5 Hz, 2H), 3.86 (s, 6H), 2.75 (d, J = 13.1 Hz, 2H), 2.59 (d, J = 13.1 Hz, 2H), 1.56 (s, 6H), 1.49 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 145.4, 136.2, 127.4, 123.8, 112.3, 110.5, 101.3, 62.1, 56.1, 49.3, 39.1, 30.2, 30.2; ESI-MS *m/z* calcd for $C_{27}H_{31}N_2O_2^+$ 415.2407, found 415.2380 $[M+H]^+$.

7,7′-Bis(benzyloxy)-1,1,1′,1′-tetramethyl-2,2′,4,4′-tetrahydro-1*H*,1′*H*-3,3′-spiro-bi[cyclopenta[*b*]indole] (118d)



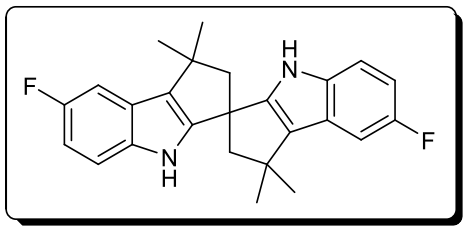
Yield 71%; colorless solid; mp 156-158 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.45 (t, 5H), 7.38 (t, J = 7.4 Hz, 5H), 7.32 (d, J = 7.3 Hz, 2H), 7.11 (d, J = 8.8 Hz, 4H), 6.84 (dd, J = 8.7, 2.4 Hz, 2H), 5.10 (s, 4H), 2.73 (d, J = 13.1 Hz, 2H), 2.57 (d, J = 13.1 Hz, 2H), 1.53 (s, 6H), 1.46 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 145.5, 137.7, 136.4, 128.5, 127.8, 127.6, 127.5, 123.8, 112.3, 111.2, 103.1, 71.2, 62.1, 49.3, 39.1, 30.2, 30.2; ESI-MS *m/z* calcd for $C_{39}H_{41}N_3O_2^+$ 583.2971, found 583.3003 $[M+NH_3]^+$.

7,7′-Dichloro-1,1,1′,1′-tetramethyl-2,2′,4,4′-tetrahydro-1*H*,1′*H*-3,3′-spiro-bi[cyclopenta[*b*]indole] (118e)



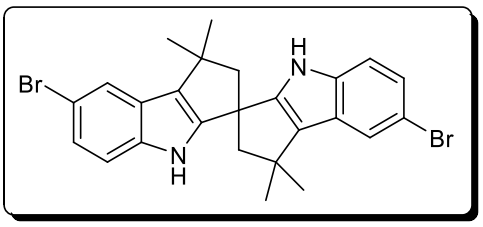
Yield 52%; colorless solid; mp 280-282 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (s, 2H), 7.50 (d, J = 1.7 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 7.06 (dd, J = 8.6, 2.0 Hz, 2H), 2.75 (d, J = 13.1 Hz, 2H), 2.61 (d, J = 13.1 Hz, 2H), 1.54 (s, 6H), 1.47 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 139.4, 127.6, 125.3, 124.3, 121.5, 118.0, 112.7, 61.1, 49.3, 39.2, 30.2, 30.2; ESI-MS *m/z* calcd for $C_{25}H_{24}Cl_2N_2^+$ 422.1344, found 422.1317 $[M]^+$.

7,7′-Difluoro-1,1,1′,1′-tetramethyl-2,2′,4,4′-tetrahydro-1*H*,1′*H*-3,3′-spirobi[cyclopenta[*b*]indole] (118f)



Yield 61%; colorless solid; mp 226-228 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (s, 2H), 7.18 (d, J = 9.2 Hz, 2H), 7.13 (dd, J = 8.6, 4.2 Hz, 2H), 6.85 (t, J = 8.2 Hz, 2H), 2.76 (d, J = 13.1 Hz, 2H), 2.60 (d, J = 13.1 Hz, 2H), 1.54 (s, 6H), 1.47 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7 (d, J = 235.62 Hz), 146.1, 137.5, 127.1 (d, J = 3.78 Hz), 123.6 (d, J = 10.08 Hz), 112.2 (d, J = 10.08 Hz), 109.4 (d, J = 26.48 Hz), 103.7 (d, J = 23.94 Hz), 62.0, 49.3, 39.2, 30.2, 30.1; ESI-MS *m/z* calcd for $C_{25}H_{27}F_2N_3^+$ 407.1965, found 407.1968 $[M+NH_3]^+$.

7,7′-Dibromo-1,1,1′,1′-tetramethyl-2,2′,4,4′-tetrahydro-1*H*,1′*H*-3,3′-spiro-bi[cyclopenta[*b*]indole] (118g)



Yield 30%; colorless solid; mp 216-218 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (s, 2H), 7.61 (s, 2H), 7.19 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H), 2.75 (d, J = 13.1 Hz, 2H), 2.60 (d, J = 13.1 Hz, 2H), 1.54 (s, 6H), 1.47 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 139.7, 127.6, 125.0, 124.1, 121.1, 113.1, 112.1, 61.1, 49.2, 39.2, 30.3, 30.2; ESI-MS *m/z* calcd for $C_{25}H_{24}Br_2N_{22}$ 510.0306, found 510.0332 $[M]^+$ and 512.0317 $[M+2]^+$.

Chapter I

PART B

Scandium Triflate Catalyzed Dimerization and Trimerization of Indoles

1.8 Introduction

Indole is the most ubiquitous heterocycle which is frequently found in natural products, pharmaceuticals, agrochemicals and other synthetic organic compounds.[114-117] Several naturally isolated and synthetically prepared *bis*(indolyl) compounds[118] (**Figure 1.14**) have been found to exhibit various biological activities including antimicrobial, antibiotic, antitumor, anticancer, antiviral, and antiproliferative. 1,1-*Bis*(indolyl)methanes have been found to inhibit colon cancer cell and tumor growth.[119, 120] Due to their diverse biological properties, structural modification of indole nucleus has attracted great attention of synthetic organic chemist in recent years.

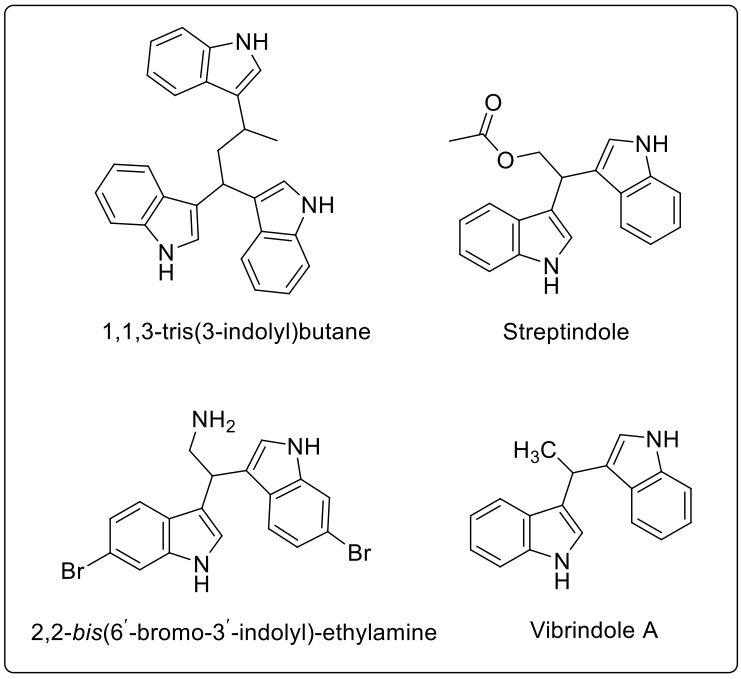


Figure 1.14: Selected compounds containing *bis*(indolyl)methane scaffold

1.8.1 Acid-catalyzed polymerization of indoles

It is well documented that indole itself easily polymerizes to polyindole (dimer or trimer) under various acidic experimental conditions.[121] Early studies on dimerization and trimerization of indoles pointed out that the nature of the polymer formation is affected by the substituent on indole, acid concentration, nature of the solvent, temperature as well as by the nature of the acid.

In 1913, Keller[122] characterized first indole trimer structure, which was further studied by Schmitz-Dumont and co-workers, who proposed structure **130**.[123] This structure failed to explain many of the reactions, for example, formation of monoacyl but not diacyl derivatives under normal conditions; formation of a tetra-acetyl derivative and further hydrolysis by dilute alkali to monoacetyl tri-indole; decomposition occurred instead of formation of tri-*N*-nitroso derivative in presence of nitrous acid (HNO_2). Later in 1954 Smith[39] proposed a structure **132** for indole trimer, accounting all the reactions of this compound so far observed. Further support for this structure is the formation of Schiff base by the condensation of indole trimer **132** with one mol. of benzaldehyde, which indicated the presence of the primary aromatic amino group in the indole trimer **132**.

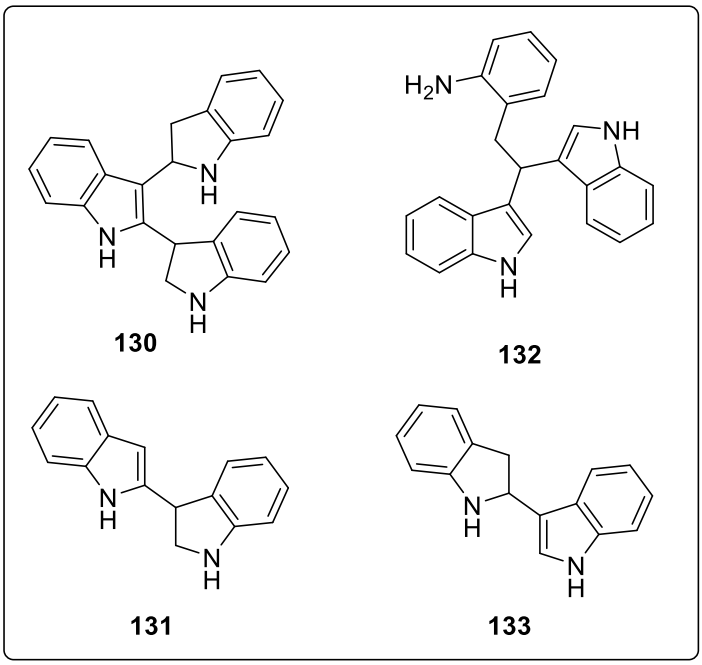
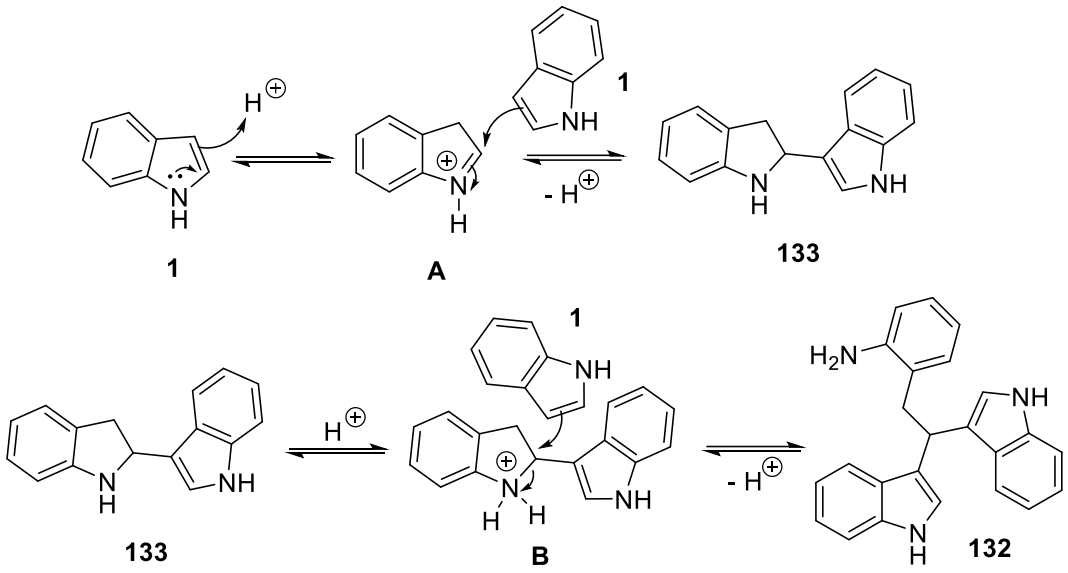


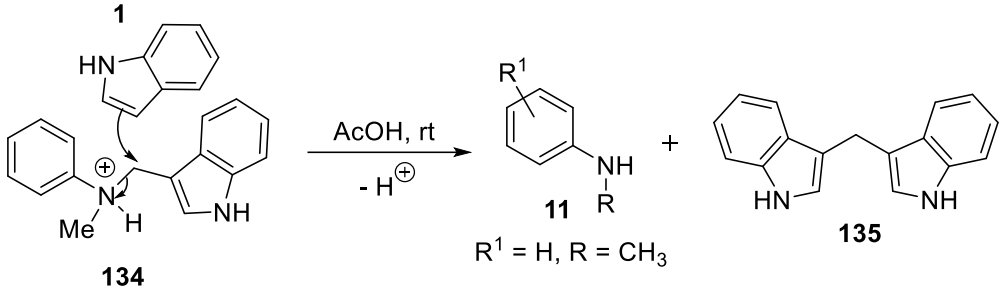
Figure 1.15: Proposed structures for the indole dimer and trimer

The mechanistic pathway for the formation of indole 3,3'-trimer **132** is shown in **Scheme 1.43**. The first step involved protonation of indole at the C-3 position to give cation **A,** which further reacted with another molecule of indole to give indole dimer **133** as intermediate. In the second step, the basic nitrogen (*N*) of intermediate **133** is protonated to give cation **B** which is sufficiently electrophilic to be attacked by the C-3 position of another indole molecule to give the 3.3'-trimer **132**.



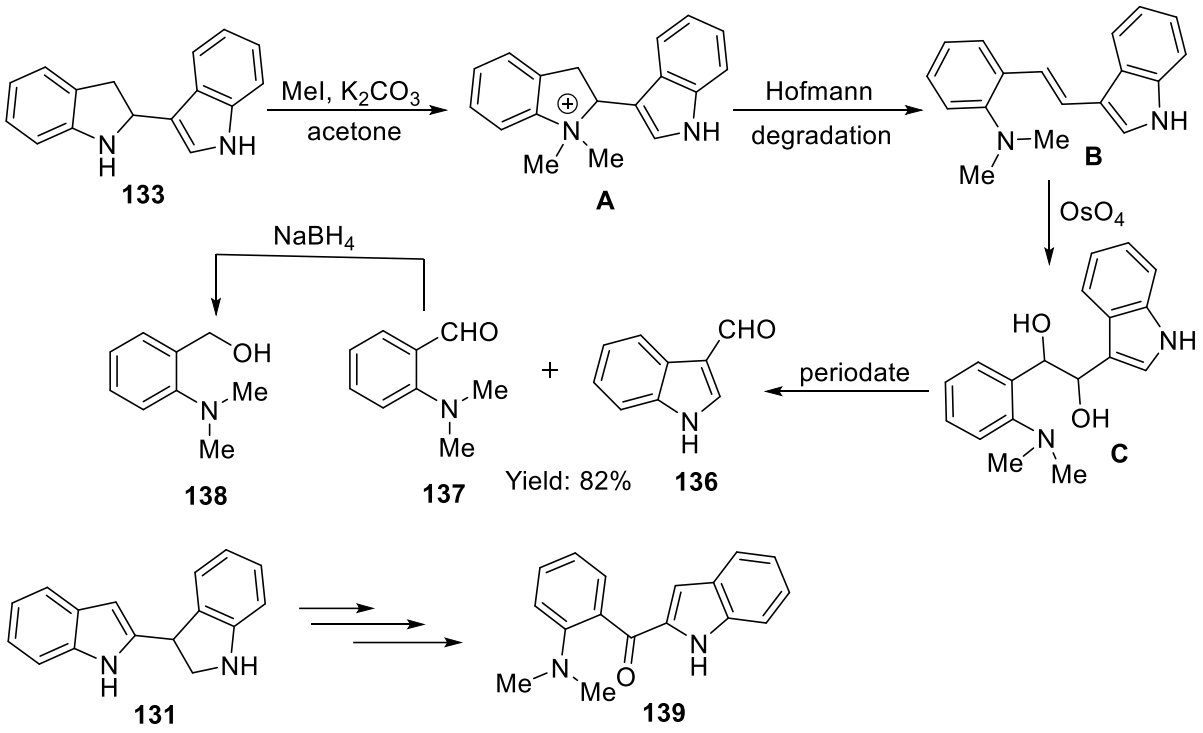
Scheme 1.43: Proposed mechanism for the synthesis of indole dimer **133** and indole trimer **132**

Thesing and Mayer reported acid-catalyzed synthesis of *bis*(indolyl)methane (**135**) and methylaniline (**11**) by the reaction of *N*-indol-3-ylmethyl-*N*-methyl-aniline (**134**) with an excess of indole (**1**) in acetic acid at room temperature (**Scheme 1.44**).[124] This result provided an analogy for the final step in the mechanism proposed for the trimerization of indole.



Scheme 1.44: AcOH catalyzed synthesis of *bis*(indolyl)methane (**135**) from **134** and indole (**1**)

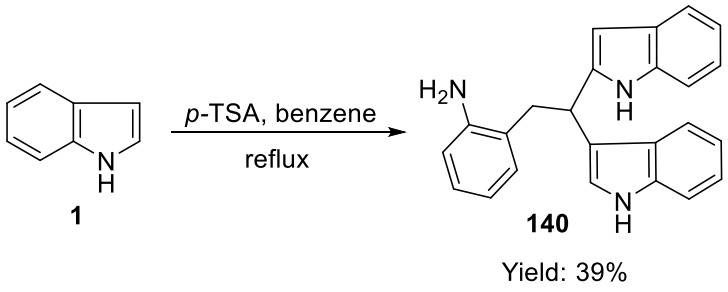
The indole dimer structure **131** proposed by Schmitz-Dumont, Hamann and Geller had no specified possible mechanism but the correct structure of indole dimer **133** was confirmed by Smith[36] through systematic degradation of indole dimer **133** and **131** as shown in **Scheme 1.45**.[125]



Scheme 1.45: Systematic structure correlation of indole dimer **133** and **131**

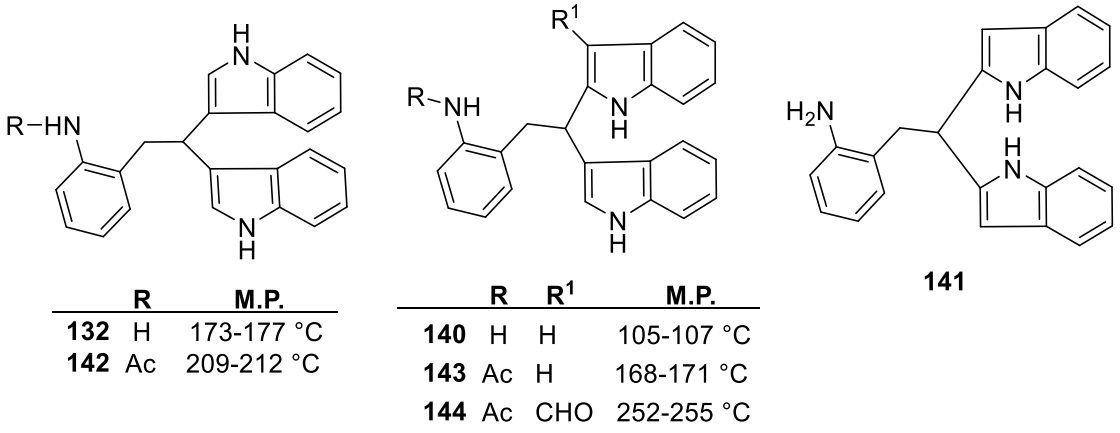
The degradation of indole dimer **131** proposed by Schmitz-DuMont *et al.* lead to the formation of formaldehyde and ketone **139**, whereas **133** proposed by Smith gave 3-formylindole (**136**) and *o*-dimethylaminobenzaldehyde (**137**) in 82% yield. Further, *o*-dimethylaminobenzaldehyde (**137**), was reduced to 2-dimethylaminobenzyl alcohol (**138**) by $NaBH_4$.

In 1977, Ishii and co-workers reported new indole-2,3'-trimer **140** which is different from the known 3,3'-trimer **132** by the self-addition of indole in the presence of *p*-toluenesulfonic acid (*p*-TSA) in benzene at reflux condition (**Scheme 1.46**).[126]



Scheme 1.46: *p*-TSA catalyzed synthesis of indole 2,3'-trimer **140**

The analytical data specified that the two indole trimers **140** and **132** should be assigned to two of three possible isomers **132**, **140**, **141** (**Figure 1.13**). The known 3,3'-trimer **132** and its monoacetate **142** have different melting points than the new 2,3'-trimer **140** and its monoacetate **143** as mentioned in the **Figure 1.13**. In addition, when both trimers **143** and **142** were treated for Vilsmeier reaction using DMF and $POCl_3$, the former **143** gave the monoformyl derivative **144** in 81% yield because of the unsubstituted C-3 position of indole nucleus while the latter **142** did not afford any product. In the NMR spectrum (DMSO-d_6), the presence of singlet for aldehydic proton (1H) at δ 10.04 and absence of singlet for C-3 proton (1H) at δ 6.19 supported for the formation of **144**.

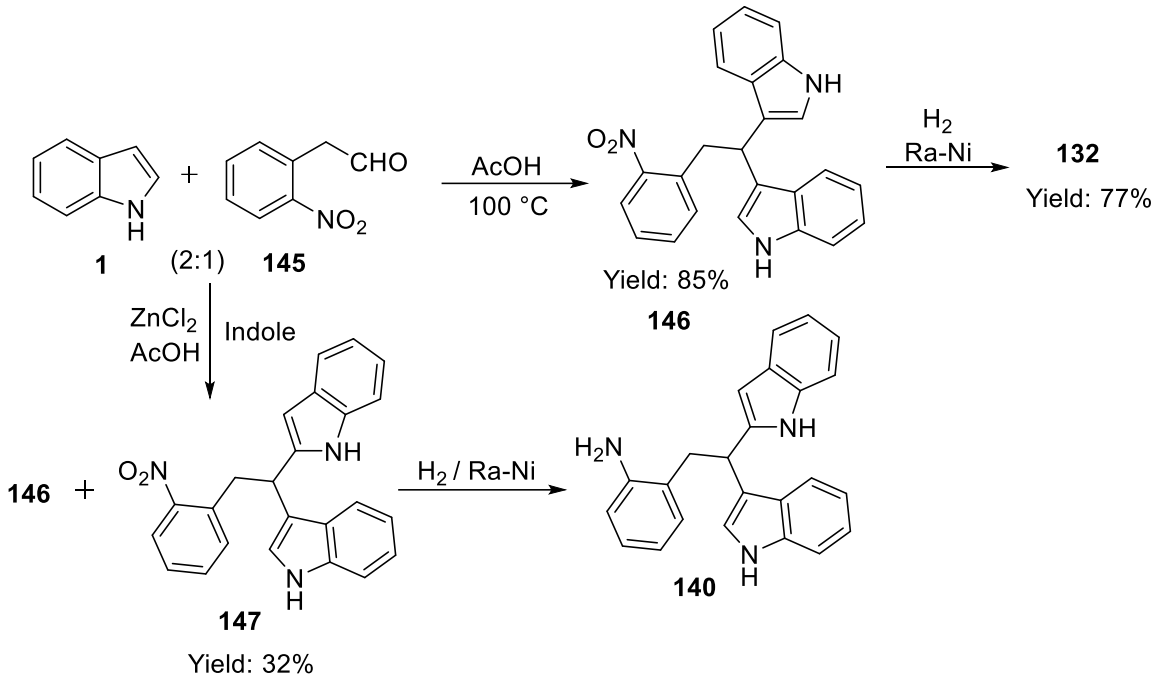


	R	M.P.
132	H	173-177 °C
142	Ac	209-212 °C

	R	R^1	M.P.
140	H	H	105-107 °C
143	Ac	H	168-171 °C
144	Ac	CHO	252-255 °C

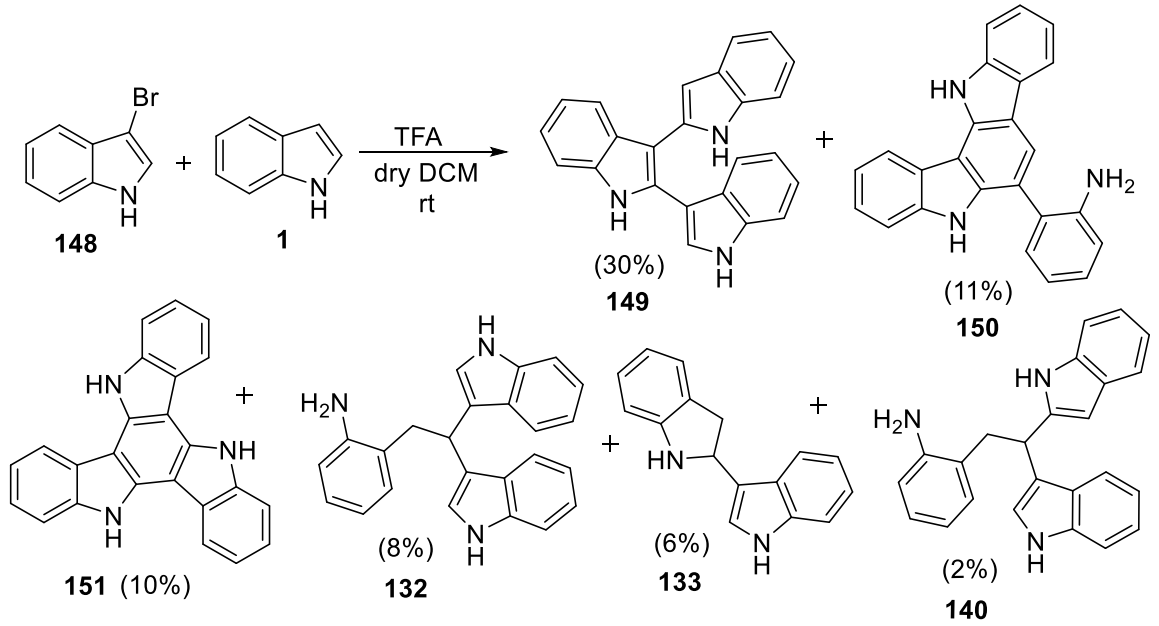
Figure 1.16: Three possible isomers of indole trimers **132, 140** and **141**

In 1960, Noland and Kuryla confirmed the indole trimers **132** and **140** by an independent synthesis. The AcOH-catalyzed condensation reaction of an excess of indole with *o*-nitrophenylacetaldehyde gave *o*-nitro-bisindolyl product **146,** which was converted to indole trimer **132** by the nitro group reduction using hydrogenation over Raney nickel catalyst. The similar treatment of the same reactants in the presence of anhydrous $ZnCl_2$ gave a mixture of **146** and an isomeric nitro derivative **147** in 13% and 32% yields, respectively. Further, catalytic reduction of the nitro group of pure **147** by Raney-Ni provided **140** (**Scheme 1.47**).[127]

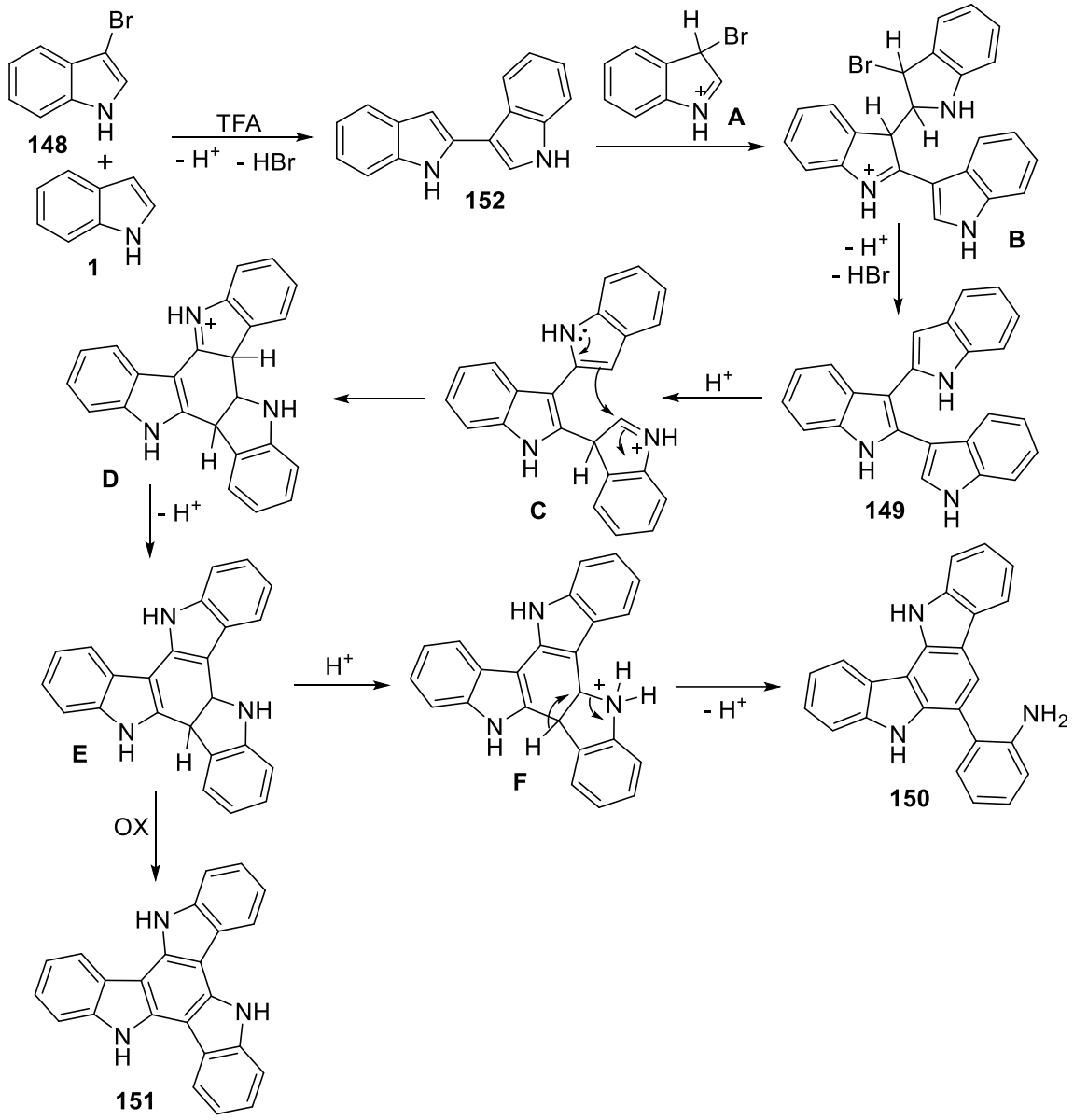


Scheme 1.47: Two-step synthesis of indole trimer **132** and **140** using condensation followed by hydrogenation reaction

In 1986, Bocchireported that the reaction of 3-bromoindole and indole in the presence of excess of trifluoroacetic acid (TFA) in dry dichloromethane (DCM) at room temperature for 1 h gave mixture of indole dimer **133** and trimers **149-151**, **132** and **140** (**Scheme 1.48**).[128]



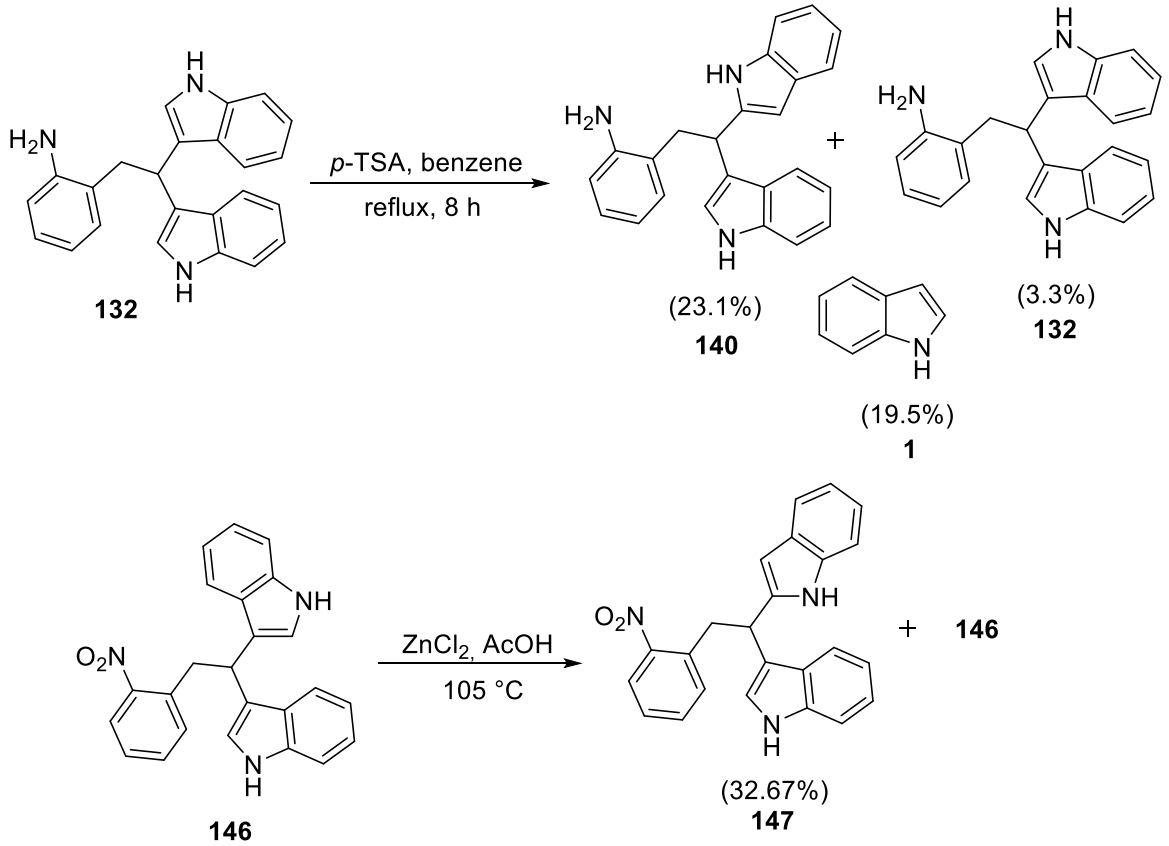
Scheme 1.48a: TFA-catalyzed synthesis of indole dimers and trimers



Scheme 1.48b: Proposed mechanism for the synthesis of **149, 150** and **151**

Th proposed mechanism for the synthesis of **149, 150** and **151** involves the attack of bromoindolinium cation **A** on the indole substrate to give an intermediate which rearomatizes with the loss of a proton and of hydrogen bromide (HBr), as shown in the **Scheme 1.48b**. It is previously reported that the indole dimer **133** and trimers **132, 140** formed from the reaction of protonated indole on indole itself.

Ishii groupextended their work and reported the Plancher rearrangement reaction participation for the conversion of indole 3,3'-trimer **132** to 2,3'-trimer **140**. For this**,** the reaction of 3,3'-trimer **132** under a more strongly acidic condition such as *p*-toluenesulfonic acid in benzene gave 2,3'-trimer **140** and indole (**1**) along with recovered 3,3'-trimer **132** in 23.1%, 19.5% and 3.3% yields, respectively (**Scheme 1.49**).[129] Similarly, the treatment of pure **146** with anhydrous zinc chloride in acetic acid gave 2,3'-diindolylmethane **147** with trace amount of **146**, without formation of indole (**1**) itself. This evidence strongly support the formation of 2,3'-trimer **140** from the 3,3'-trimer **132** *via* Plancher rearrangement (**Scheme 1.49**).



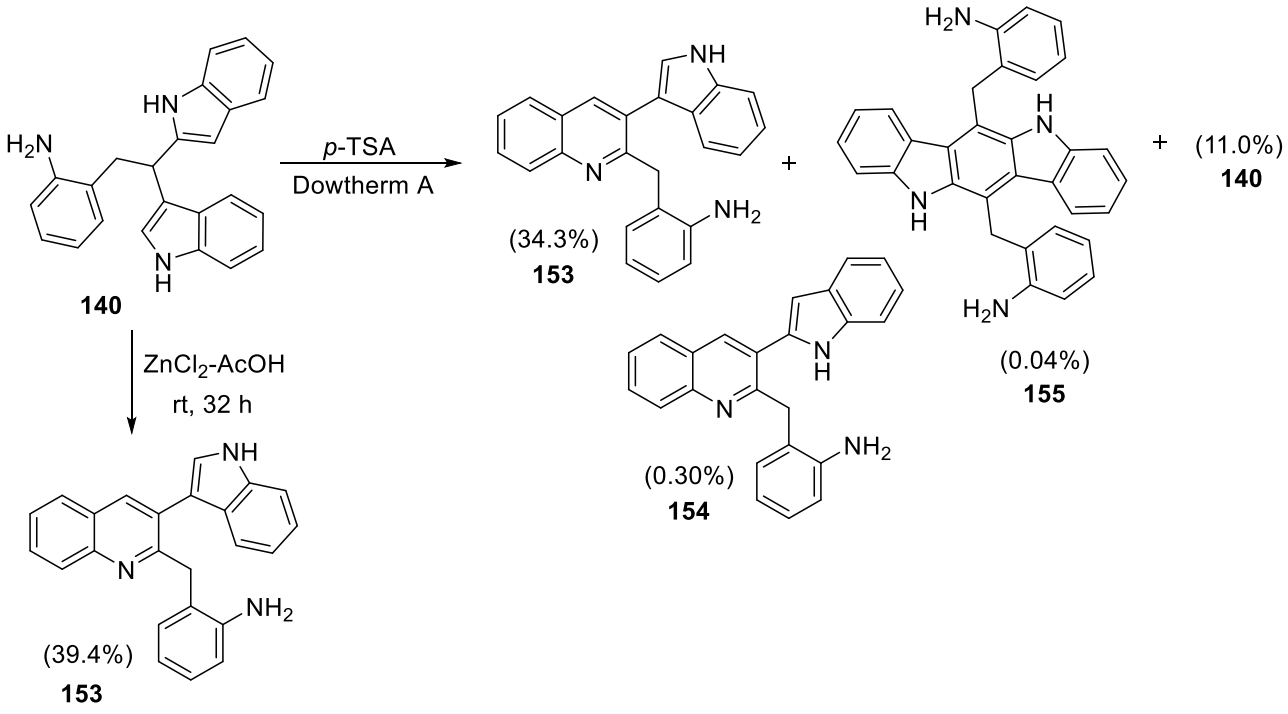
Scheme 1.49: Synthesis of **140** and **147** *via* Plancher rearrangement from **132** and **146** respectively

Several other acidic conditions on the 3,3'-trimer **132** were studied and the results are tabulated in table 1.7. The desired product 2,3'-trimer **140** was not formed in the presence of $ZnCl_2$-AcOH at room temperature, this may be due to poor solubility of **132** in AcOH at room temperature.

Table 1.7: Yields of rearranged products from 3,3'-trimer **132** under various acidic conditions

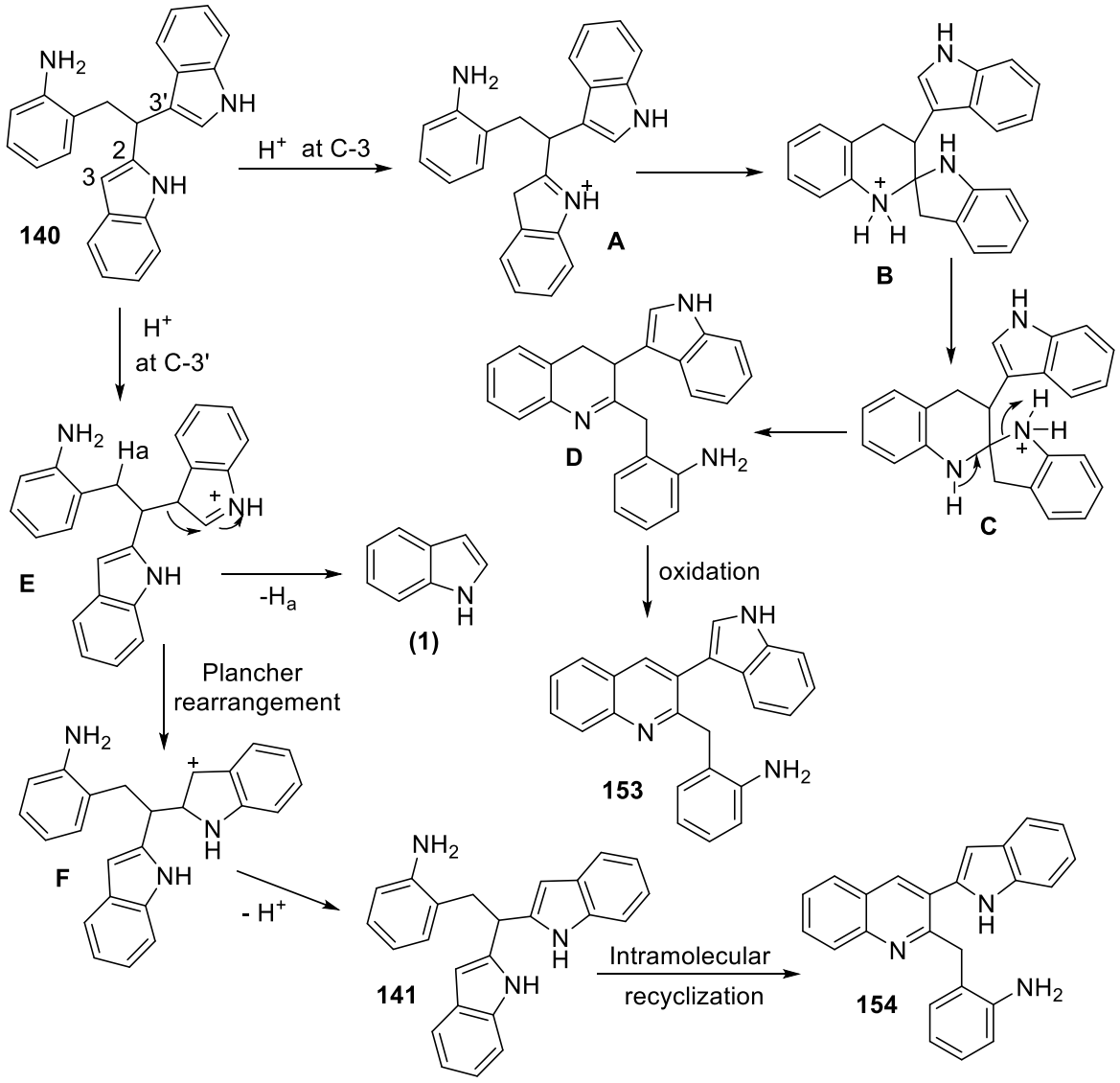
Sr.No.	Conditions	Yield (%)			
		3,3'-trimer **(132)**	Indole **(1)**	Dimer **(133)**	2,3'-trimer **(140)**
1	*p*-TSA, Benzene, reflux, 8 h	3.3	19.5	-	23.1
2	$BF_3.Et_2O$, rt, 5 days	9.6	5.0	26.9	33.9
3	$ZnCl_2$-AcOH, 105 °C, 4 h	15.3	4.6	6.1	30.7
4	$ZnCl_2$-AcOH, rt, 21 h	92.9	-	-	-

Subsequently, Ishii and co-workers executed the treatment of 2,3'-trimer **140** with *p*-TSA in Dowtherm A which gave the indol-3-ylquinoline **153**, indol-2-ylquinoline **154**, tetramer **155** and starting material **140** in 34.3%. 0.30%, 0.04% and 11.0% yields, respectively. On treating 2,3'-trimer **140** with zinc chloride in acetic acid at room temperature for 32 h indol-3-ylquinoline **153** was obtained in 39.4% yield as sole product (**Scheme 1.50a**).[130]



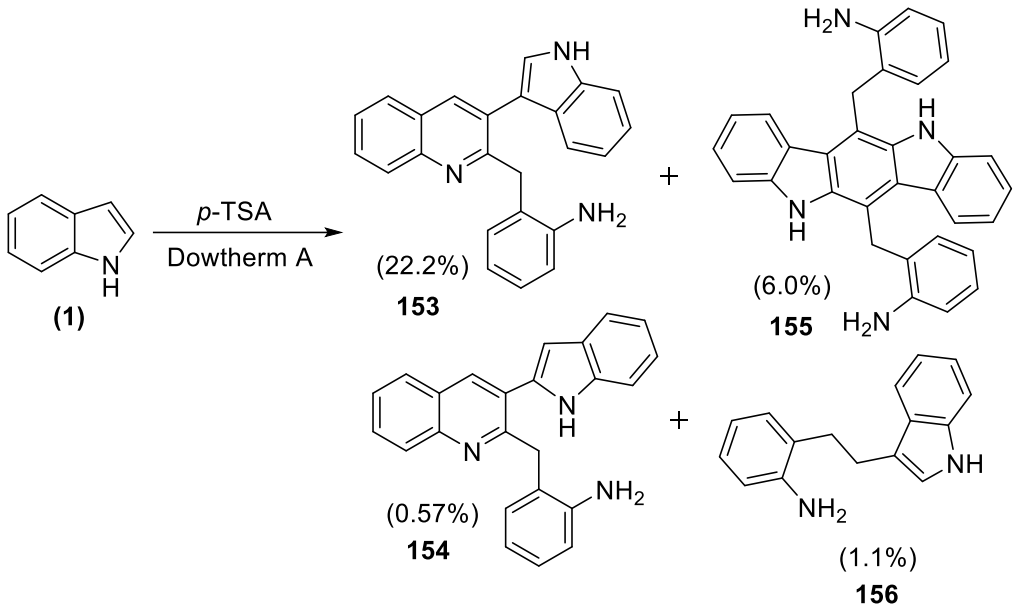
Scheme 1.50a: Intramolecular recyclization of 2,3'-trimer **140** under *p*-TSA, Dowtherm A and $ZnCl_2$-AcOH conditions

Rearrangement of 2,3'-trimer **140** to the products **153** and **154** invovles Plancher rearrangement reaction as shown in **Scheme 1.50b.**

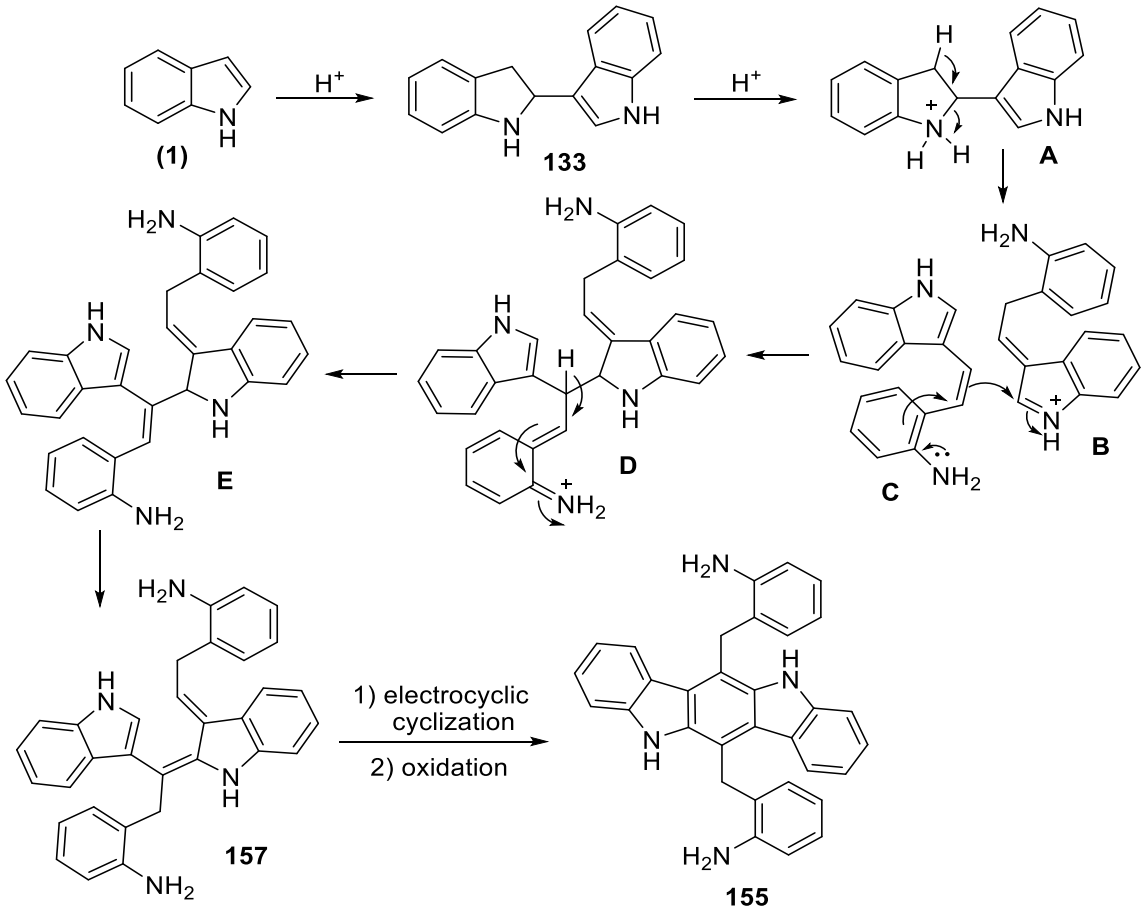


Scheme 1.50b: Mechanism for the synthesis of **153** and **154** from **140**

Indole (**1**) treated with *p*-TSA in Dowtherm A, indol-3-ylquinoline **153**, indol-2-ylquinoline **154**, dihydro-dimer **156** and tetramer **155** were obtained in 22.2%, 0.57%, 1.1% and 6.0% yields, respectively (**Scheme 1.51a**). It is believed that the tetramer **155** is produced by dimerization of dimer **133** *via* electrocyclic cyclization of **157** followed by oxidation as shown in **Scheme 1.51b.** However, when 2,3'-trimer **140** was treated under same reaction conditions it afforded **155** in a very low yield (0.04%) **(Scheme 1.50a)**.



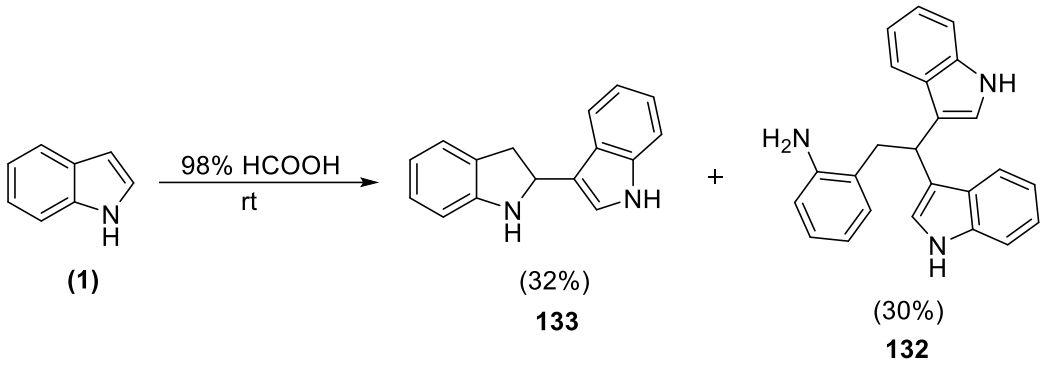
Scheme 1.51a: *p*-TSA catalyzed polymerization of indole (**1**)



Scheme 1.51b: Mechanism for the synthesis of **155**

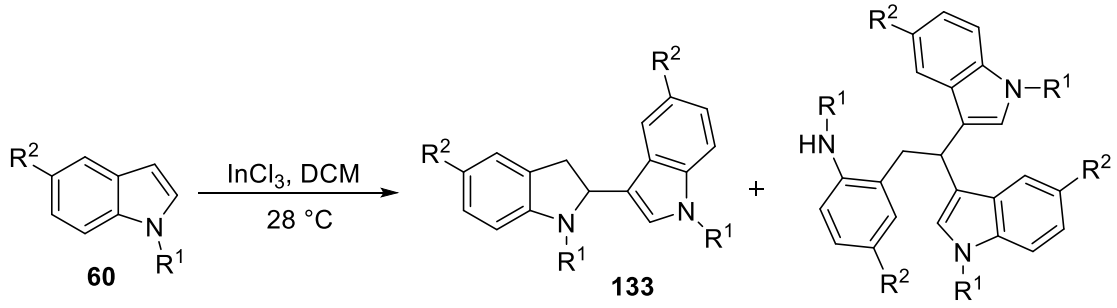
This might be due to the formation of a small amount of indole from the cation **E** under acidic conditions through the pathway shown in **Scheme 1.50b**.

Chakrabarty and co-workers reported 98% formic acid catalyzed formation of indole dimer **133** and trimer **132** in 32% and 30% yields, respectively **(Scheme 1.52)**.[131]



Scheme 1.52: Formic acid-catalyzed synthesis of **132** and **133**

Jaisankar group demonstrated $InCl_3$-catalyzed synthesis of indole dimers **133** and trimers **132** in dichloromethane (**Scheme 1.53**).[132] Here, indole (**1**) undergo self-addition to afford 3,3'-trimer **132** and unexpected 3-acetylindole in 46% and 40% yields, respectively. In case of 5-methoxyindole and *N*-substituted indole derivatives, indole dimers **133** and trimers **132** were formed in fairly good yield as shown in **Scheme 1.53**. The reaction of 3-substituted indole under same reaction conditions did not produce any product and starting material recovered.



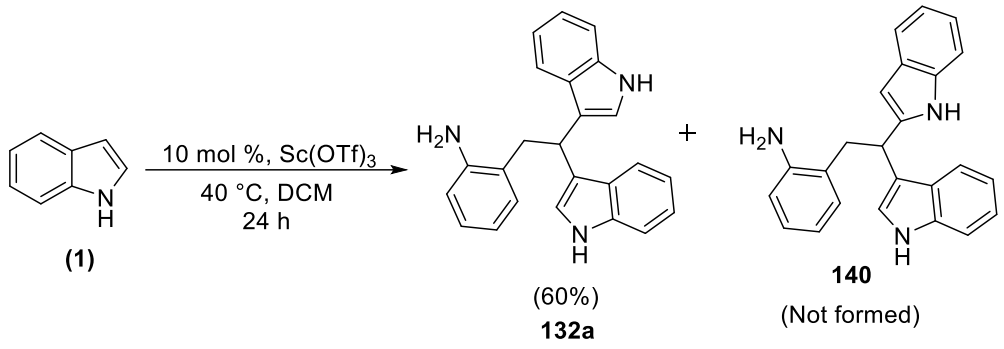
R^1	R^2	133	132
H	Ts	61	0
H	Me	51	34
OMe	H	0	74
OMe	Ts	71	0
OMe	Me	53	0

Scheme 1.53: $InCl_3$ catalyzed synthesis of indole dimer **133** and trimer **132**

Lewis acid catalyzed reactions are of great interest in organic synthesis[133, 134] but most of these conventional Lewis acids promoted reactions require a stoichiometric amount of catalysts and anhydrous conditions.[135] As mentioned in introduction, rare earth metal triflates have been found as the unique green Lewis acid.[136] They have been employed for several carbon-carbon and carbon-heteroatom bond formation reactions[137-140] in excellent yields. They are water tolerant, less toxic, non-corrosive and reusable without much loss in activity. In continuation of our interest in the catalytic application of metal triflates, we have studied the polymerization of indole **(1)** in presence of catalytic amount of scandium triflate $Sc(OTf)_3$.

1.9 Results and discussion

Initially, we started the reaction of 1 mmol of indole with 10 mol % of scandium triflate $Sc(OTf)_3$ in 5 mL of dichloromethane (DCM). Progress of the reaction was monitored by thin layer chromatography, after 24 h a new spot appeared along with starting material which was purified by column chromatography. The NMR analysis of the product was consistent with 3,3′-trimer **132a** (systematic name: 2-(2,2-di(1*H*-indol-3-yl)ethyl)aniline) and not with 2,3′-trimer **140** (systematic name: 2-(2-(1*H*-indol-2-yl)-2-(1*H*-indol-3-yl)ethyl)aniline), as ^{1}H NMR of 3,3′-trimer **132a** showed a triplet at δ 4.85 and a doublet at δ 3.35 for one proton and two protons, respectively having same coupling constant J = 7.5 Hz and singlet at δ 4.67 for two protons of primary aromatic amine ($-NH_2$). In aromatic region, in addition to peaks in the range of δ 6.33-7.52 for 14 protons, broad singlet was observed at δ 10.68 for two protons of - NH of indole, whereas absence of singlet peak at δ 6.22 for C-3 proton of indole and two separate broad singlet peaks at δ 10.84 and δ 10.88 for two unsymmetrical –NH proton of indole of 2,3′-trimer **140** differs the structure from 3,3′-trimer **132a**.[126, 128, 129] Similarly, in the ^{13}C NMR of 3,3′-trimer **132a** two peaks appeared at δ 36.3 and δ 32.9 while other fourteen aromatic carbons appeared in the range of δ 111.7 – 146.7 which is again are consistent with 3,3′-trimer structure. Based on ^{1}H and ^{13}C NMR data it was concluded that the structure of the product is 3,3'-trimer **132a (Figure 1.14)**. The isolated yield of the product was 60% **(Scheme 1.54)**.



Scheme 1.54: $Sc(OTf)_3$ catalyzed synthesis of 3,3′-trimer **132a**

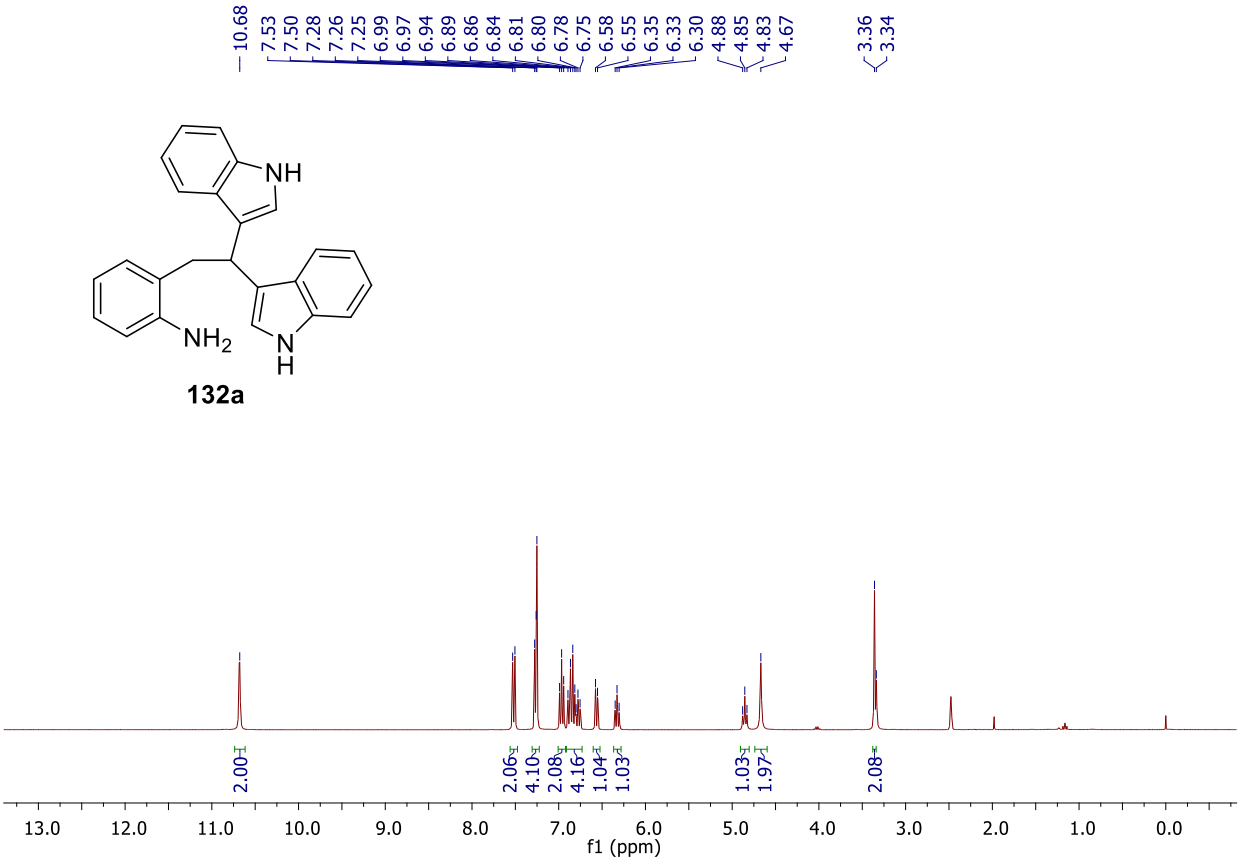


Figure 1.17a: ^{1}H NMR spectra of 2-(2,2-di(1*H*-indol-3-yl)ethyl)aniline) **(132a)** in DMSO-d_6

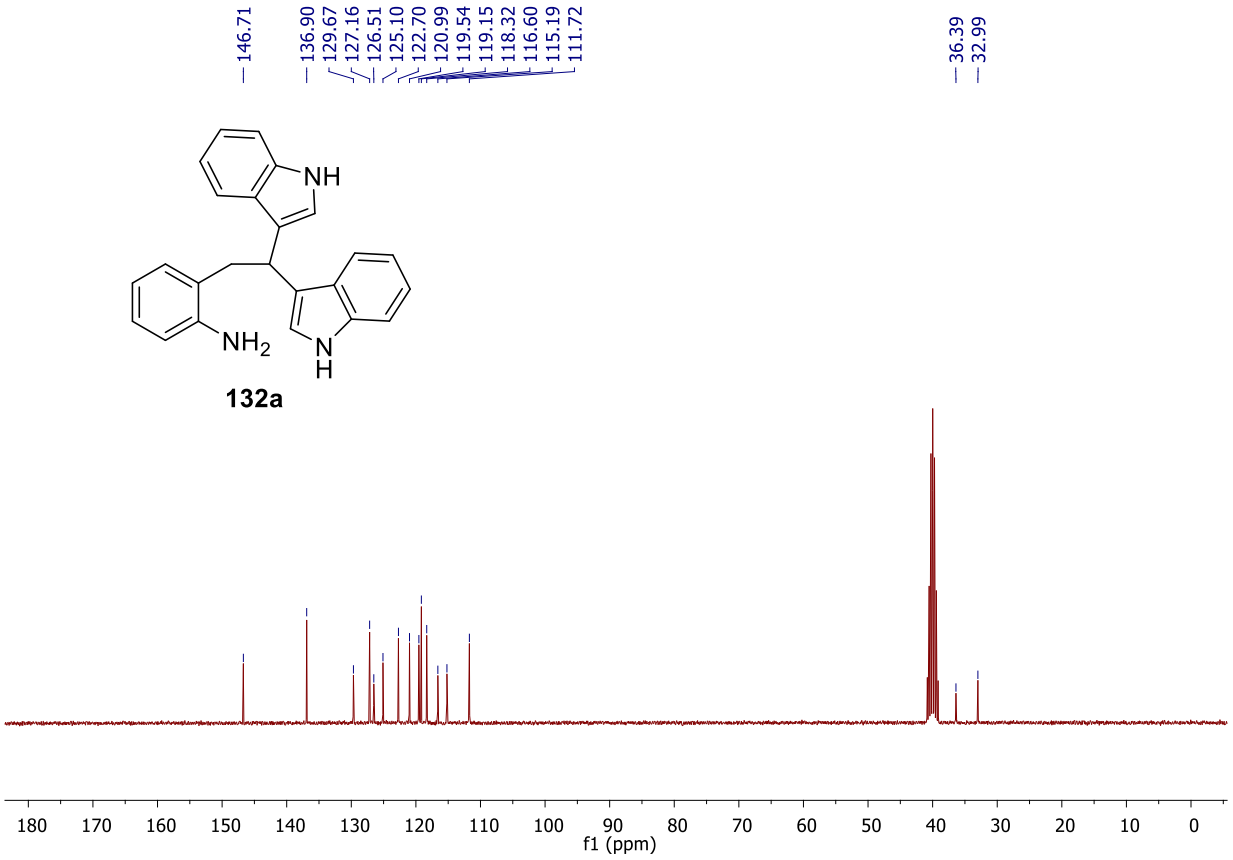
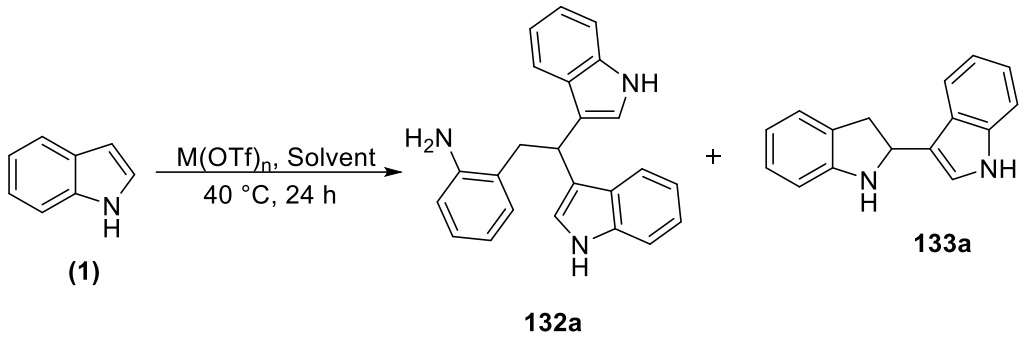


Figure 1.17b: ^{13}C NMR spectra of 2-(2,2-di(1*H*-indol-3-yl)ethyl)aniline) **(132a)** in DMSO-d_6

Bisai *et al.*[141] has also observed formation of 3,3′-trimer **132a** in 55% yield by treating indole with 10 mol % $In(OTf)_3$ during his work on Friedel-Crafts alkylations of 3-hydroxy-3-methyloxindole with indole.

To increase the yield of the product we further screened different solvents as shown in Table 1.8 using $Sc(OTf)_3$ (10 mol %) as catalyst. It was found that best yields were obtained in DCM (60%) and dichloroethane (48%) whereas other solvents such as acetonitrile, 1,4-dioxane and ethanol afforded very low yields. It is worth to mention that in some of these solvents the formation of intermediate product 3-(indolin-2-yl)-1*H*-indole **133a** was obtained in less than 5% yield and the starting material was recovered. Thus, we selected DCM as the solvent of choice for further study. Next, we studied the effect of different metal triflates as catalysts in DCM and results are shown in Table 1.8. Among different triflates screened such as $Sc(OTf)_3$, $Bi(OTf)_3$, AgOTf, $Ce(OTf)_3$, $Yb(OTf)_3$, $Cu(OTf)_2$, $Y(OTf)_3$, $In(OTf)_3$, $Eu(OTf)_3$ and $La(OTf)_3$, $Sc(OTf)_3$ gave the best yield (60%). In absence of catalysts, no conversion was observed.

Table 1.8: Effect of solvents and catalyst $M(OTf)_n$ on synthesis of 3,3′-trimer **132a**



Entry	Catalyst (10 mol %)	Solvent	Yield (%)[b]	
			132a	133a
1	$Sc(OTf)_3$	Dichloromethane	60	0
2	$Sc(OTf)_3$	Dichloroethane	48	0
3	$Sc(OTf)_3$	Chloroform	27	0
4	$Sc(OTf)_3$	Toluene	19	<5[c]
5	$Sc(OTf)_3$	Acetonitrile	10	<5[c]
6	$Sc(OTf)_3$	1,4-Dioxane	<5[c]	0
7	$Sc(OTf)_3$	Ethanol	<5[c]	0
8	$Bi(OTf)_3$	Dichloromethane	32	0
9	AgOTf	Dichloromethane	18	<5[c]
10	$Ce(OTf)_3$	Dichloromethane	12	<5[c]
11	$Yb(OTf)_3$	Dichloromethane	<5[c]	0
12	$Cu(OTf)_2$	Dichloromethane	-[d]	-[d]
13	$Y(OTf)_3$	Dichloromethane	<5[c]	0
14	$In(OTf)_3$	Dichloromethane	55	0
15	$Eu(OTf)_3$	Dichloromethane	16	<5[c]
16	$La(OTf)_3$	Dichloromethane	14	<5[c]

[a]Reaction condition: Indole (1 mmol), $M(OTf)_n$ (10 mol%), Solvent (5 ml) at 40 °C for 24 h; [b]Isolated Yield; [c]Based on TLC, product was not isolated; [d]complex TLC

After performing solvent and catalyst study, we standardized catalyst loading, reaction time and temperature. As shown in Table 1.9, the yield of **132a** increased from 49% to 66% on increasing catalyst loading from 5 mol % to 15 mol % (Entry 1-3, Table 1.9). Further increase in catalyst loading did not improve the yield but resulted in sluggish reaction with a mixture of products **132a** and **133a**. Increasing reaction time from 24 h to 72 h did not result in an increase in yield (Entry 6, Table 1.9). Also increasing reaction temperature from 40 °C to 80 °C resulted in the disappearance of **132a**.

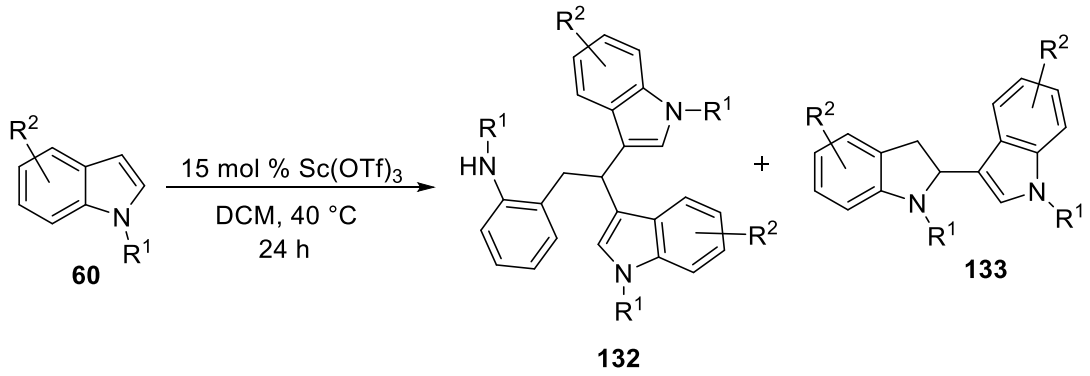
Table 1.9: Effect of catalyst loading and temperature on synthesis of 3,3′-trimer **132a**

Entry	Catalyst loading (mol %)	Temp (°C)	Time (h)	Yield (%)[a]	
				132a	**133a**
1	5	40	24	49	0
2	10	40	24	60	0
3	**15**	**40**	**24**	**66**	**0**
4	20	40	24	65[b]	<5[c]
5	15	25	24	52	0
6	15	40	72	64	<5[c]
7	100	40	24	-[d]	-[d]

[a]Isolated yield; [b]At 80 °C no formation of **132a** was observed; [c]Based on TLC, product was not isolated; [d]complex TLC

Finally, to examine the scope of the protocol we synthesized different 3,3′-trimers **132a-132i** by reacting substituted indoles in the presence of 15 mol % $Sc(OTf)_3$ as catalyst in dichloromethane. The results are shown in Table 1.10. It was observed that C-5 and C-6 substituted indole (R^1 = H) with electron withdrawing group **60b-60f** afforded a lower yield of **132b-132f** as compared to that with electron donating group of **60h-60i** (Table 1.10). Whereas, indole with strong electron withdrawing cyano group of **60g** was unable to produce the corresponding product. In the case of 4-methylindole **(60j),** 3-(indolin-2-yl)indole **133j** was obtained in 50% yield (Table 1.10). The structure of compound **133j** was confirmed by ^1H and ^{13}C NMR data as shown in figure 1.15.

Table 1.10: $Sc(OTf)_3$ catalyzed synthesis of 3,3′-trimer [or 3,3′-(*o*-aminophenethylidene)di-indole] **132** and 3-(indolin-2-yl)indole **133**



Indole 60			yield (%)[a]	
Entry	**R^1**	**R^2**	**132**	**133**
a	H	H	66	0
b	H	5-Cl	54	0
c	H	5-Br	52	0
d	H	5-F	51	0
e	H	6-Cl	52	0
f	H	6-$COOCH_3$	45	0
g	H	5-CN	0	0
h	H	5-OCH_3	76	0
i	H	5-CH_3	74	0
j	H	4-CH_3	0	50
k	CH_3	H	54	0
l	CH_3	5-Br	50	0
m	CH_3	5-CH_3	0	56
n	CH_3	5-OCH_3	0	58

[a]Isolated yield

Next, we turned our attention towards the *N*-methylindole and it's derivatives. We found that **60k** and **60l** on treatment with $Sc(OTf)_3$ under the optimized reaction conditions gave the desired products **132k** and **132l** in 54% and 50% yields, respectively along with starting material (Table 1.10). Surprisingly, 5-methyl-*N*-methylindole **(60m)** and 5-methoxy-*N*-methylindole **(60n)** afforded corresponding dimer **133m** and **133n** instead of the trimer, in 56% and 58% yields, respectively. It was also observed that azaindole and 3-substituted indoles did not undergo this type of reaction.

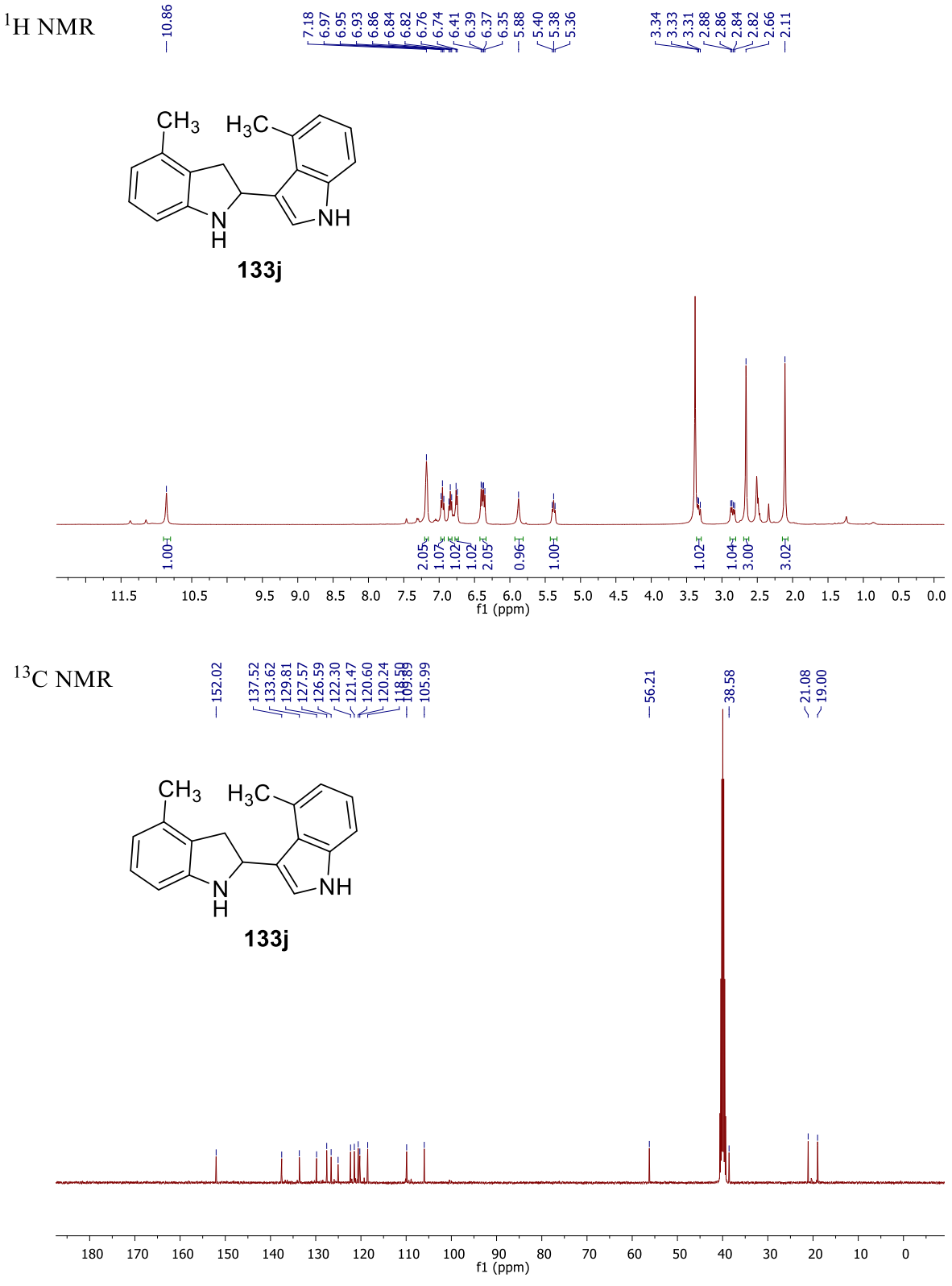
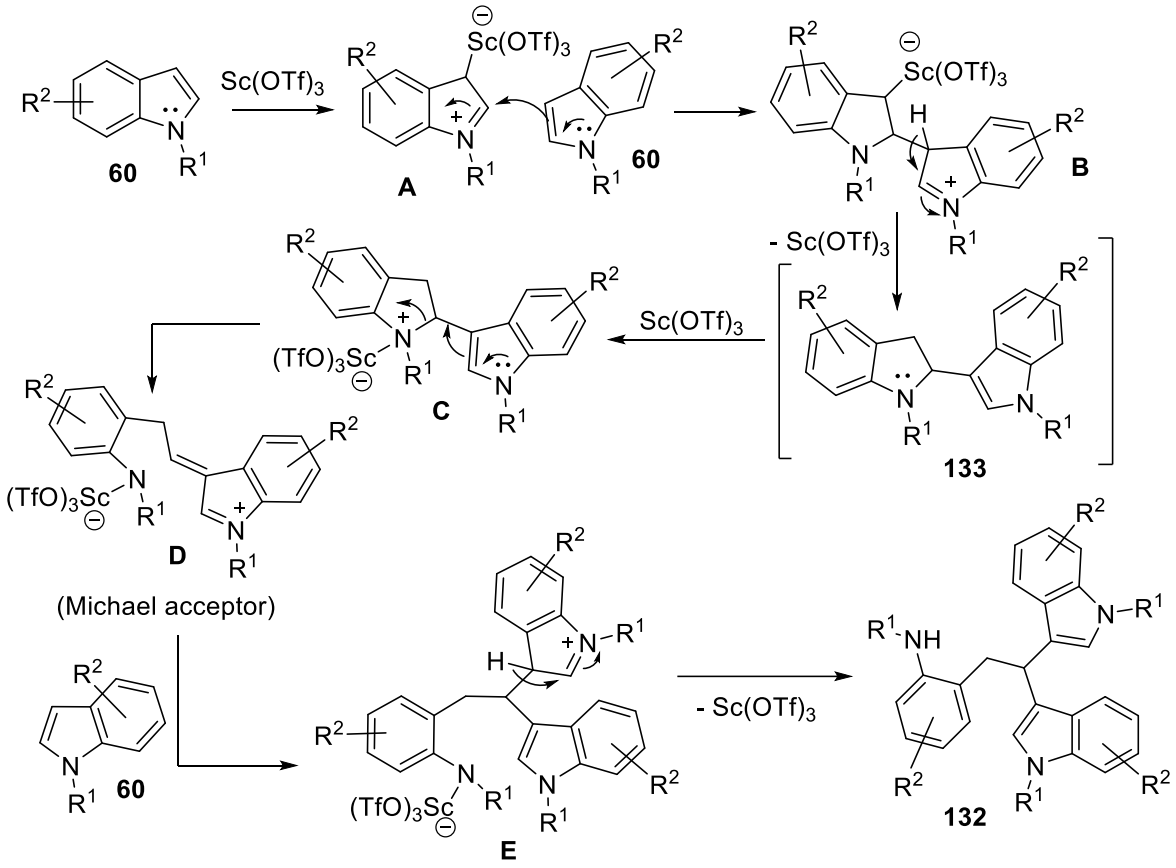


Figure 1.18: ^{1}H and ^{13}C NMR spectra of 4-methyl-3-(4-methylindolin-2-yl)indole **(133j)** in DMSO-d_6

Consistent with the previous reports,[141, 142] we speculated that the actual mechanism for the formation of dimer **133** and trimer **132** in the presence of Lewis acid such as metal triflates, might be electrophilic substitution in nature. The substituent effect of substrate **60** and the product formation is in consistence with the proposed mechanism **(Scheme 1.55)**. When electron withdrawing groups present on the indole ring it reduces the nucleophilicity and results into the lower yields of products compared to electron donating groups. Initially, $Sc(OTf)_3$ co-ordinates to the C-3 carbon of indole **60** to generate indolinium cation **A** this could reacts with second molecule of indole to afford indole dimer **133,** which has been isolated in case of **60j, 60m** and **60n** whereas in other cases it further gets converted into the intermediate **D** that acts as a Michael acceptor to react with third molecule of indole **60** to furnish the final indole-3,3′-trimer product **132.**



Scheme 1.55: Proposed mechanism for the synthesis of dimer **133** and trimer **132**

1.10 Conclusions

In conclusion, we have studied scandium triflate catalyzed polymerization of indole and found that the product formation is dependent on the substituent present on the indole ring. In case of indole with electron withdrawing or donating groups **60(a-i)** afforded the corresponding indole-3,3′-trimer **132(a-i)** in fairly good yield except 4-methylindole which gaves indole dimer **133j** whereas N-methylindole and its 5-bromo derivative with electron withdrawing group afforded indole-3,3-trimer **132k** and **132l** respectively**,** but in case of electron donating groups **60(m-n)** furnished indole dimer **133(m-n).** We have synthesized few new dimer and trimer compounds such as **132b - 132f, 132i , 133j, 132l** and **133m**, while other compounds analytical data are matched with the corresponding synthesized compounds.

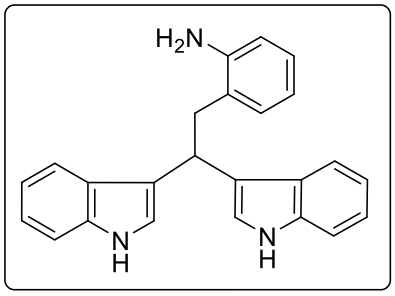
1.11 Experimental

General information

Indole and metal triflates were purchased from Sigma-Aldrich, India melting points were determined by the open capillary tube method using a melting point apparatus (EZ-Melt) and are uncorrected. IR Spectra were recorded on an FT-IR spectrometer and the values are expressed in cm^{-1}. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker (300 MHz & 400 MHz) NMR spectrometer. Thin layer chromatography (TLC) was performed on pre-coated alumina sheets and detected under UV light. Silica gel (100–200 mesh) was used for column chromatography.

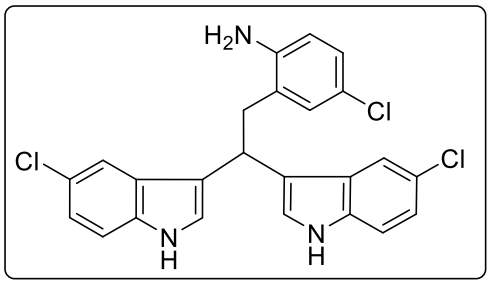
General procedure for the synthesis of substituted 3,3′-(*o*-aminophenethylidene)di-indole 132 and 3-(indolin-2-yl)indole 133 : A mixture of substituted indole **60** (1.0 mmol), dichloromethane (5 mL) and $Sc(OTf)_3$ 15 mol % in a round bottom flask of 10 mL was stirred for 24 h at reflux. The progress of the reaction was monitored using TLC (ethyl acetate-hexane 6 : 4 *v/v*). After completion of the reaction, the reaction mixture was diluted with water (5 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography on silica gel (100–200 mesh) to afford the pure product **132** or **133.**

2-(2,2-Di(1*H*-indol-3-yl)ethyl)aniline (132a)



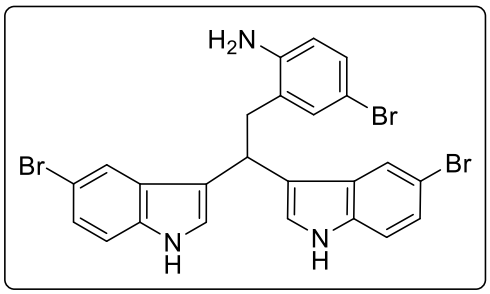
Yield 62%; brown solid; mp 169−170 °C; FT-IR ν_{max} (KBr): 3433, 3333, 3209, 3055, 2932, 1620, 1450, 1250, 802, 748 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.68 (s, 2H), 7.52 (d, J = 7.9 Hz, 2H), 7.30 – 7.22 (m, 4H), 6.97 (t, J = 7.1 Hz, 2H), 6.90 – 6.73 (m, 4H), 6.56 (d, J = 6.9 Hz, 1H), 6.33 (t, J = 6.8 Hz, 1H), 4.85 (t, J = 7.5 Hz, 1H), 4.67 (s, 2H), 3.35 (d, J = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.7, 136.9, 129.6, 127.1, 126.5, 125.1, 122.7, 120.9, 119.5, 119.1, 118.3, 116.6, 115.1, 111.7, 36.3, 32.9.

2-(2,2-Bis(5-chloro-1*H*-indol-3-yl)ethyl)-4-chloroaniline (132b)



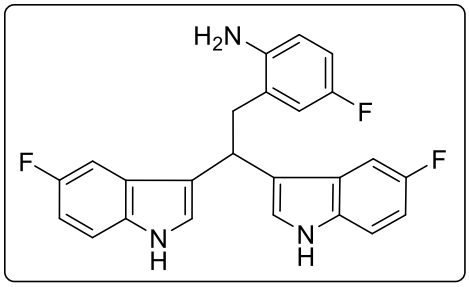
Yield 54%; brown solid; mp 104−106 °C; FT-IR ν_{max} (KBr): 3441, 2932, 1458, 1273, 1095, 802, 741 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 2H), 7.48 (dd, J = 17.9, 1.9 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 6.98 (dd, J = 8.6, 1.9 Hz, 2H), 6.90 (d, J = 2.3 Hz, 1H), 6.82 (dd, J = 8.5, 2.4 Hz, 1H), 6.59 (d, J = 8.5 Hz, 1H), 5.05 (s, 2H), 4.87 (t, J = 7.6 Hz, 1H), 3.31 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.9, 135.3, 129.2, 128.1, 126.5, 126.3, 124.7, 123.1, 121.1, 119.6, 118.7, 118.4, 116.3, 113.3, 35.7, 32.1;

2-(2,2-Bis(5-bromo-1*H*-indol-3-yl)ethyl)-4-bromoaniline (132c)



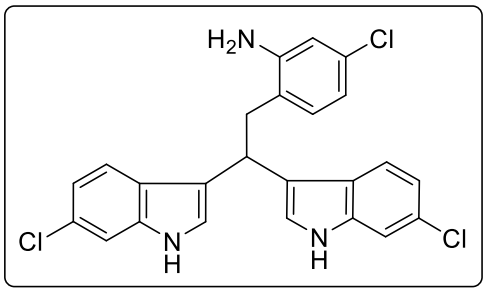
Yield 52%; brown solid; mp 194−196 °C; FT-IR ν_{max} (KBr): 3441, 2924, 1497, 1242, 1080, 795, 733 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 2H), 7.64 (d, J = 1.2 Hz, 2H), 7.44 (d, J = 2.0 Hz, 2H), 7.26 (d, J = 8.6 Hz, 1H), 7.09 (dd, J = 8.6, 1.7 Hz, 1H), 7.02 (d, J = 2.0 Hz, 1H), 6.93 (dd, J = 8.5, 2.1 Hz, 1H), 6.54 (d, J = 8.5 Hz, 1H), 5.07 (s, 1H), 4.86 (t, J = 7.6 Hz, 1H), 3.29 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.3, 135.5, 131.1, 129.1, 128.8, 127.0, 124.6, 123.6, 121.7, 118.3, 116.9, 113.8, 111.2, 107.2, 35.8, 32.1.

2-(2,2-Bis(5-fluoro-1*H*-indol-3-yl)ethyl)-4-fluoroaniline (132d)



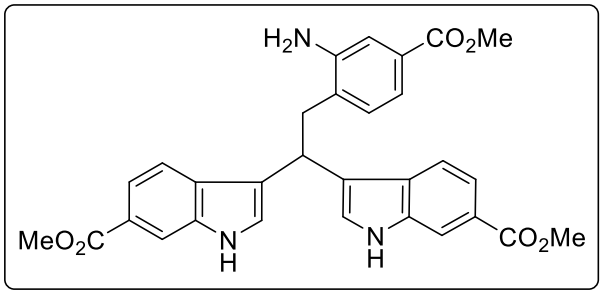
Yield 51%; brown solid; mp 164−166 °C; FT-IR ν_{max} (KBr): 3464, 3256, 2924, 1628, 1489, 1265, 1026, 856, 741 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 2H), 7.45 (d, J = 1.8 Hz, 2H), 7.26 (dd, J = 8.7, 4.5 Hz, 3H), 7.22 (d, J = 2.1 Hz, 1H), 6.82 (td, J = 9.2, 2.3 Hz, 2H), 6.69 (dd, J = 10.3, 2.6 Hz, 1H), 6.62 (td, J = 8.5, 2.8 Hz, 1H), 6.56 (dd, J = 8.5, 5.4 Hz, 1H), 4.81 (t, J = 7.6 Hz, 1H), 4.72 (s, 2H), 3.32 (d, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.7 (d, J = 230.2 Hz), 153.6, 143.2, 133.5, 127.1 (d, J = 9.7 Hz), 126.5 (d, J = 6.5 Hz), 124.9, 118.8 (d, J = 4.6 Hz), 115.9, 115.6 (d, J = 9.1 Hz), 112.8 (s), 112.5 (d, J = 9.8 Hz), 109.1 (d, J = 26.0 Hz), 104.1 (d, J = 23.1 Hz), 35.7, 32.3.

2-(2,2-Bis(6-chloro-1*H*-indol-3-yl)ethyl)-5-chloroaniline (132e)



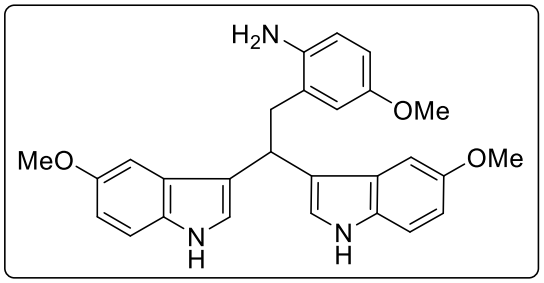
Yield 52%; brown solid; mp 232−234 °C; FT-IR ν_{max} (KBr): 3441, 3387, 3063, 2924, 1620, 1450, 1095, 849, 802 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.32 (s, 4H), 6.85 (d, J = 8.1 Hz, 2H), 6.73 (d, J = 8.0 Hz, 1H), 6.61 (s, 1H), 6.29 (d, J = 7.2 Hz, 1H), 5.14 (s, 2H), 4.80 (t, J = 7.3 Hz, 1H), 3.31 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.5, 137.2, 131.2, 130.9, 125.9, 125.8, 123.9, 123.3, 120.8, 118.9, 118.7, 115.6, 114.0, 111.3, 35.6, 32.4.

Dimethyl 3,3'-(2-(2-amino-4-(methoxycarbonyl)phenyl)ethane-1,1-diyl)bis(1*H*-indole-6-carboxylate) (132f)



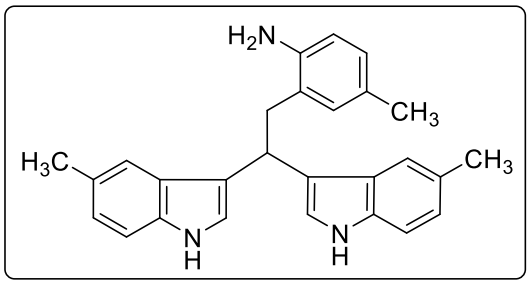
Yield 45%; brown solid; mp 213−214 °C; FT-IR ν_{max} (KBr): 3364, 3286, 2924, 1697, 1620, 1435, 1296, 1250, 825, 771 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.22 (s, 1H), 7.96 (s, 1H), 7.57 (d, J = 7.7 Hz, 2H), 7.47 (d, J = 8.5 Hz, 1H), 7.23 (s, 1H), 6.89 (q, J = 7.8 Hz, 1H), 5.18 (s, 1H), 4.98 (t, J = 7.6 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 2H), 3.43 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.7, 167.1, 147.2, 136.4, 130.5, 130.1, 129.9, 128.1, 127.2, 122.1, 119.3, 119.2, 119.1, 117.1, 115.5, 113.8, 55.4, 52.2, 36.4, 32.1.

2-(2,2-Bis(5-methoxy-1*H*-indol-3-yl)ethyl)-4-methoxyaniline (132h)



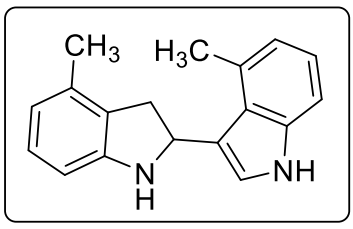
Yield 76%; brown solid; mp 117−119 °C; FT-IR ν_{max} (KBr): 3450, 3418, 3050, 2924, 1620, 1428, 795, 741 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 2H), 7.25 (d, J = 2.3 Hz, 2H), 7.19 (s, 1H), 7.16 (s, 1H), 7.02 (d, J = 2.4 Hz, 2H), 6.66 (d, J = 2.4 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 6.52 (t, J = 5.3 Hz, 2H), 6.42 (dd, J = 8.5, 2.9 Hz, 1H), 4.75 (t, J = 7.5 Hz, 1H), 4.38 (s, 2H), 3.67 (s, 6H), 3.42 (s, 3H), 3.32 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.9, 151.2, 140.4, 132.1, 127.5, 127.0, 123.5, 118.9, 116.1, 115.1, 112.2, 111.9, 110.8, 101.8, 55.7, 55.3, 36.5, 32.9.

2-(2,2-Bis(5-methyl-1*H*-indol-3-yl)ethyl)-4-methylaniline (132i)



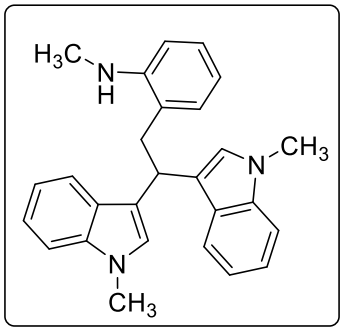
Yield 74%; brown solid; mp 178−179 °C; FT-IR ν_{max} (KBr): 3464, 3418, 3055, 2924, 1628, 1420, 795, 741 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 7.30 (s, 1H), 7.17 (d, J = 7.0 Hz, 2H), 6.82 (d, J = 7.8 Hz, 1H), 6.62 (d, J = 7.5 Hz, 1H), 6.48 (d, J = 7.6 Hz, 1H), 4.78 (t, J = 6.2 Hz, 1H), 4.46 (s, 1H), 3.26 (d, J = 6.7 Hz, 1H), 2.30 (s, 3H), 2.00 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.1, 135.3, 130.2, 127.4, 126.9, 126.5, 125.5, 124.8, 122.8, 122.6, 119.1, 118.7, 115.4, 111.4, 36.5, 33.3, 21.8, 20.8.

4-Methyl-3-(4-methylindolin-2-yl)-1*H*-indole (133j)



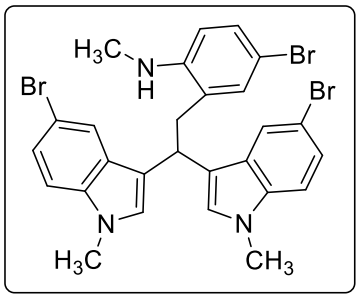
Yield 50%; colorless solid; mp 124−125 °C; FT-IR ν_{max} (KBr): 3402, 3256, 3047, 2924, 1420, 1265, 1026, 741 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 7.18 (s, 2H), 6.95 (t, J = 7.5 Hz, 1H), 6.84 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 6.9 Hz, 1H), 6.38 (dd, J = 13.7, 7.6 Hz, 2H), 5.88 (s, 1H), 5.38 (t, J = 7.8 Hz, 1H), 3.35 – 3.27 (m, 1H), 2.85 (dd, J = 15.4, 6.8 Hz, 1H), 2.66 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.2, 137.5, 133.6, 129.8, 127.6, 126.6, 125.0, 122.3, 121.5, 120.6, 120.2, 118.5, 109.9, 105.1, 56.2, 38.6, 21.1, 19.0.

2-(2,2-Bis(1-methyl-1*H*-indol-3-yl)ethyl)-*N*-methylaniline (132k)



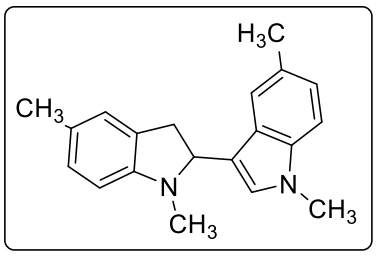
Yield 54%; colorless solid; mp 135−137 °C; FT-IR ν_{max} (KBr): 3433, 3055, 2924, 1605, 1512, 1474, 1065, 820, 741 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.53 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 7.22 (s, 2H), 7.07 (t, J = 7.5 Hz, 2H), 6.92 (dt, J = 17.9, 5.4 Hz, 4H), 6.44 (d, J = 8.0 Hz, 1H), 6.36 (t, J = 7.3 Hz, 1H), 4.95 – 4.89 (m, 1H), 4.87 (d, J = 7.4 Hz, 1H), 3.69 (s, 6H), 3.34 (d, J = 7.4 Hz, 2H), 2.63 (d, J = 4.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.1, 137.2, 128.9, 127.4, 127.09, 126.1, 125.1, 121.2, 119.6, 118.5, 118.5, 115.9, 109.9, 109.3, 36.4, 32.7, 32.2, 30.8.

2-(2,2-Bis(5-bromo-1-methyl-1*H*-indol-3-yl)ethyl)-4-bromo-*N*-methylaniline (132l)



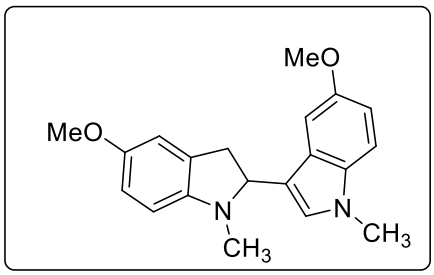
Yield 50%; white solid; mp 220−221 °C; FT-IR ν_{max} (KBr): 3441, 2924, 1504, 1474, 1288, 1049, 795, 733 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.63 (d, J = 1.8 Hz, 2H), 7.34 (s, 1H), 7.32 (s, 1H), 7.29 (s, 2H), 7.19 (d, J = 1.9 Hz, 1H), 7.17 (d, J = 1.9 Hz, 1H), 7.06 (dd, J = 8.6, 2.4 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.36 (d, J = 8.7 Hz, 1H), 5.25 (d, J = 4.9 Hz, 1H), 4.87 (t, J = 7.6 Hz, 1H), 3.71 (s, 6H), 3.23 (d, J = 7.6 Hz, 2H), 2.64 (d, J = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.2, 135.9, 131.5, 129.5, 129.0, 128.8, 127.2, 123.8, 121.8, 117.8, 112.1, 111.5, 111.2, 106.9, 36.3, 33.0, 31.2, 30.7.

3-(1,5-Dimethylindolin-2-yl)-1,5-dimethyl-1*H*-indole (133m)



Yield 56%; white solid; mp 142−144 °C; FT-IR ν_{max} (KBr): 3047, 2908, 2854, 1612, 1489, 1327, 1265, 795 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.31 (d, J = 12.6 Hz, 3H), 6.98 (d, J = 8.1 Hz, 1H), 6.88 (d, J = 9.5 Hz, 2H), 6.46 (d, J = 7.6 Hz, 1H), 4.48 – 4.37 (m, 1H), 3.74 (s, 3H), 3.36 (s, 3H), 3.18 (dd, J = 15.3, 8.6 Hz, 1H), 3.10 – 2.93 (m, 1H), 2.33 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.6, 136.2, 129.5, 128.7, 127.8, 127.4, 126.1, 126.6, 125.2, 123.3, 119.6, 113.5, 110.1, 107.6, 65.2, 37.4, 34.9, 32.8, 21.7, 21.0.

5-Methoxy-3-(5-methoxy-1-methylindolin-2-yl)-1-methyl-1*H*-indole (133n)



Yield 58%; white solid; mp 104−105 °C; FT-IR ν_{max} (KBr): 2947, 2831, 1620, 1490, 1242, 1026, 802 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (d, J = 9.9 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 6.83 – 6.74 (m, 1H), 6.66 (dd, J = 8.3, 2.0 Hz, 1H), 6.48 (d, J = 8.4 Hz, 1H), 4.48 – 4.38 (m, 1H), 3.73 (s, 1H), 3.68 (s, 1H), 3.67 (s, 1H), 3.37 (s, 1H), 3.23 (dd, J = 15.5, 8.4 Hz, 1H), 2.98 (dd, J = 15.1, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.5, 152.9, 148.0, 132.9, 130.8, 129.0, 127.2, 113.8, 112.2, 111.7, 111.5, 111.0, 107.1, 102.0, 65.3, 55.9, 55.8, 37.5, 35.3, 32.9.

1.12 References

[1] Baeyer, A. *Berichte der deutschen chemischen Gesellschaft* **1880,** *13*, 2254.

[2] Based on a survey of SciFinder Scholar **2007** (ACS), crplus and medline databases.

[3] Sundberg, R. J., *The Chemistry of Indoles*. Academic Press, New York: **1970**.

[4] J., Q. L. D. T., *In Fundamentals of Heterocyclic Chemistry: Importance in Nature and in the Synthesis of Pharmaceuticals*. John Wiley & Sons, Inc.,: **2010**.

[5] Schlittler, E., *The Alkaloids: Chemistry and Physiology*. Academic Press: **1965**; Vol. 8, p 287.

[6] Chen, F.-E.; Huang, J. *Chemical Reviews* **2005,** *105*, 4671.

[7] Khan, T. M.; Benaich, N.; Malone, C. F.; Bernardos, R. L.; Russell, A. R.; Downes, G. B.; Barresi, M. J.; Hutson, L. D. *Journal of the Peripheral Nervous System* **2012,** *17*, 76.

[8] Schneider, C. *Angewandte Chemie International Edition* **2002,** *41*, 4217.

[9] Kaushik, N.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C.; Verma, A.; Choi, E. *Molecules* **2013,** *18*, 6620.

[10] S. M. Bronner, G. Y. J. I., N. K. Garg, *Heterocycles in Natural Product Synthesis*. Wiley-VCH Verlag GmbH & Co. KGaA: , **2011**.

[11] Bandini, M.; Eichholzer, A. *Angewandte Chemie International Edition* **2009,** *48*, 9608.

[12] Erdmann, O. L. *Journal für Praktische Chemie* **1841,** *24*, 1.

[13] Baeyer, A.; Knop, C. A. *Justus Liebigs Annalen der Chemie* **1866,** *140*, 1.

[14] Baeyer, A. *Justus Liebigs Annalen der Chemie* **1866,** *140*, 295.

[15] Robinson, B. *Chemical Reviews* **1969,** *69*, 227.

[16] Möhlau, R. *Berichte der deutschen chemischen Gesellschaft* **1881,** *14*, 171.

[17] Madelung, W. *Berichte der deutschen chemischen Gesellschaft* **1912,** *45*, 1128.

[18] Gassman, P. G.; Van Bergen, T. J.; Gilbert, D. P.; Cue, B. W. *Journal of the American Chemical Society* **1974,** *96*, 5495.

[19] Gassman, P. G.; Van Bergen, T. J.; Gruetzmacher, G. *Journal of the American Chemical Society* **1973,** *95*, 6508.

[20] Gupta, R. K.; Haslam, E. *Journal of the Chemical Society, Perkin Transactions 1* **1978**, 892.

[21] Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Letters* **1989,** *30*, 2129.

[22] Reissert, A.; Heller, H. *Berichte der deutschen chemischen Gesellschaft* **1904,** *37*, 4364.

[23] Reissert, A. *Berichte der deutschen chemischen Gesellschaft* **1905,** *38*, 1603.

[24] Velezheva, V. S.; Kornienko, A. G.; Topilin, S. V.; Turashev, A. D.; Peregudov, A. S.; Brennan, P. J. *Journal of Heterocyclic Chemistry* **2006,** *43*, 873.

[25] Gribble, G. W. *Journal of the Chemical Society, Perkin Transactions 1* **2000**, 1045.

[26] Castro, C. E.; Havlin, R.; Honwad, V. K.; Malte, A. M.; Moje, S. W. *Journal of the American Chemical Society* **1969,** *91*, 6464.

[27] Hegedus, L. S.; Allen, G. F.; Waterman, E. L. *Journal of the American Chemical Society* **1976,** *98*, 2674.

[28] Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *Journal of the American Chemical Society* **1978,** *100*, 5800.

[29] Fürstner, A.; Jumbam, D. N. *Tetrahedron* **1992,** *48*, 5991.

[30] Fürstner, A.; Bogdanović, B. *Angewandte Chemie International Edition in English* **1996,** *35*, 2442.

[31] Wang, Z., Fürstner Indole Synthesis. In *Comprehensive Organic Name Reactions and Reagents*, John Wiley & Sons, Inc.: 2010.

[32] Larock, R. C.; Yum, E. K. *Journal of the American Chemical Society* **1991,** *113*, 6689.

[33] Larock, R. C.; Yum, E. K.; Refvik, M. D. *The Journal of Organic Chemistry* **1998,** *63*, 7652.

[34] Kaspar, L. T.; Ackermann, L. *Tetrahedron* **2005,** *61*, 11311.

[35] Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angewandte Chemie International Edition* **2005,** *44*, 403.

[36] Smith, G. F. *Chemistry and Industry* **1957**, 3544.

[37] Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A. R.; Mayr, H. *The Journal of Organic Chemistry* **2006,** *71*, 9088.

[38] Katritzky, A. R.; Akutagawa, K. *Tetrahedron Letters* **1985,** *26*, 5935.

[39] Smith, G. F. *Chemistry and Industry* **1954,** *20*, 1451.

[40] G. M. Barrett, A.; Christopher Braddock, D. *Chemical Communications* **1997**, 351.

[41] Kobayashi, S.; Manabe, K., Green Lewis acid catalysis in organic synthesis. In *Pure and Applied Chemistry*, **2000**; Vol. 72, p 1373.

[42] Forsberg, J. H.; Spaziano, V. T.; Balasubramanian, T. M.; Liu, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *The Journal of Organic Chemistry* **1987,** *52*, 1017.

[43] Collins, S.; Hong, Y. *Tetrahedron Letters* **1987,** *28*, 4391.

[44] Harrowfield, J.; Kepert, D.; Patrick, J.; White, A. *Australian Journal of Chemistry* **1983,** *36*, 483.

[45] Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W. L. *Chemical Reviews* **2002,** *102*, 2227.

[46] Kumar, M. P.; Liu, R.-S. *The Journal of Organic Chemistry* **2006,** *71*, 4951.

[47] Kurisaki, T.; Naniwa, T.; Yamamoto, H.; Imagawa, H.; Nishizawa, M. *Tetrahedron Letters* **2007,** *48*, 1871.

[48] Banerji J., C. A., Manna S., Pascard C., Prange T., Shoolery J. N. *Heterocycles* **1981,** *15*, 325.

[49] Zhou, L.; Doyle, M. P. *The Journal of Organic Chemistry* **2009,** *74*, 9222.

[50] Oh, C. H.; Karmakar, S.; Park, H.; Ahn, Y.; Kim, J. W. *Journal of the American Chemical Society* **2010,** *132*, 1792.

[51] Bonnamour, J.; Bolm, C. *Organic Letters* **2011,** *13*, 2012.

[52] Yang, F.; Ji, K.-G.; Ali, S.; Liang, Y.-M. *The Journal of Organic Chemistry* **2011,** *76*, 8329.

[53] Flanagan, J. C. A.; Dornan, L. M.; McLaughlin, M. G.; McCreanor, N. G.; Cook, M. J.; Muldoon, M. J. *Green Chemistry* **2012,** *14*, 1281.

[54] Reddy, B. V. S.; Reddy, M. R.; Rao, Y. G.; Yadav, J. S.; Sridhar, B. *Organic Letters* **2013,** *15*, 464.

[55] Nagarajan, R.; Perumal, P. T. *Tetrahedron* **2002,** *58*, 1229.

[56] Tran, P.; Tran, H.; Hansen, P.; Do, M.; Le, T. *Molecules* **2015,** *20*, 19605.

[57] Yadav, J. S.; Reddy, B. V. S.; Rao, K. V. R.; Kumar, G. G. K. S. N. *Tetrahedron Letters* **2007,** *48*, 5573.

[58] Gohain, M.; Marais, C.; Bezuidenhoudt, B. C. B. *Tetrahedron Letters* **2012,** *53*, 4704.

[59] Hao, L.; Pan, Y.; Wang, T.; Lin, M.; Chen, L.; Zhan, Z.-p. *Advanced Synthesis & Catalysis* **2010,** *352*, 3215.

[60] Wang, S.; Chai, Z.; Wei, Y.; Zhu, X.; Zhou, S.; Wang, S. *Organic Letters* **2014,** *16*, 3592.

[61] Reddy, A. V.; Ravinder, K.; Goud, T. V.; Krishnaiah, P.; Raju, T. V.; Venkateswarlu, Y. *Tetrahedron Letters* **2003,** *44*, 6257.

[62] Yadav, J. S.; Reddy, B. V. S.; Baishya, G.; Reddy, K. V.; Narsaiah, A. V. *Tetrahedron* **2005,** *61*, 9541.

[63] Gohain, M.; Jacobs, J.; Marais, C.; Bezuidenhoudt, B. C. B. *Australian Journal of Chemistry* **2013,** *66*, 1594.

[64] Oelerich, J.; Roelfes, G. *Organic & Biomolecular Chemistry* **2015,** *13*, 2793.

[65] Ma, S.; Yu, S.; Peng, Z. *Organic & Biomolecular Chemistry* **2005,** *3*, 1933.

[66] Gohain, M.; Lin, S.; Bezuidenhoudt, B. C. B. *Tetrahedron Letters* **2015,** *56*, 2579.

[67] Shi, M.; Cui, S.-C.; Li, Q.-J. *Tetrahedron* **2004,** *60*, 6679.

[68] Xie, M.-H.; Xie, F.-D.; Lin, G.-F.; Zhang, J.-H. *Tetrahedron Letters* **2010,** *51*, 1213.

[69] Kutubi, M. S.; Kitamura, T. *Tetrahedron* **2011,** *67*, 8140.

[70] Ma, S.; Yu, S. *Organic Letters* **2005,** *7*, 5063.

[71] Yadav, J. S.; SubbaReddy, B. V.; Gayathri, K. U.; Meraj, S.; Prasad, A. R. *Synthesis* **2006,** 4121.

[72] Dasbasi, T.; Polat-Cakir, S.; Abdullah, M.; Demir, A. S. *Tetrahedron* **2011,** *67*, 3355.

[73] Chen, D.; Yu, L.; Wang, P. G. *Tetrahedron Letters* **1996,** *37*, 4467.

[74] Ji, S.-J.; Zhou, M.-F.; Gu, D.-G.; Wang, S.-Y.; Loh, T.-P. *Synlett* **2003,** 2077.

[75] Mohammadpoor-Baltork I., H. R. M., Ahmad R. K., Nikoofar K. *Letters in Organic Chemistry* **2006,** *3*, 768.

[76] Beltrá, J.; Gimeno, M. C.; Herrera, R. P. *Beilstein Journal of Organic Chemistry* **2014,** *10*, 2206.

[77] Chakrabarty, M.; Ghosh, N.; Basak, R.; Harigaya, Y. *Tetrahedron Letters* **2002,** *43*, 4075.

[78] Magesh, C. J.; Nagarajan, R.; Karthik, M.; Perumal, P. T. *Applied Catalysis A: General* **2004,** *266*, 1.

[79] Khalafi-Nezhad, A.; Parhami, A.; Zare, A.; Zare, A. R. M.; Hasaninejad, A.; Panahi, F. *Synthesis* **2008**, 617.

[80] Pradhan, P. K.; Dey, S.; Giri, V. S.; Jaisankar, P. *Synthesis* **2005,** 1779.

[81] Mi, X.; Luo, S.; He, J.; Cheng, J.-P. *Tetrahedron Letters* **2004,** *45*, 4567.

[82] Reddy, B. M.; Sreekanth, P. M.; Lakshmanan, P. *Journal of Molecular Catalysis A: Chemical* **2005,** *237*, 93.

[83] Hosseini-Sarvari, M. *Synthetic Communications* **2008,** *38*, 832.

[84] Li, J.-T.; Dai, H.-G.; Xu, W.-Z.; Li, T.-S. *Ultrasonics Sonochemistry* **2006,** *13*, 24.

[85] Firestone, G. L.; Sundar, S. N. *Molecular Endocrinology* **2009,** *23*, 1940.

[86] Safe, S.; Papineni, S.; Chintharlapalli, S. *Cancer Letters* **2008,** *269*, 326.

[87] Su, Y.; Vanderlaag, K.; Ireland, C.; Ortiz, J.; Grage, H.; Safe, S.; Frankel, A. E. *Breast Cancer Research* **2007,** *9*, 1.

[88] York, M.; Abdelrahim, M.; Chintharlapalli, S.; Lucero, S. D.; Safe, S. *Clinical Cancer Research* **2007,** *13*, 6743.

[89] McDougal, A.; Gupta, M. S.; Morrow, D.; Ramamoorthy, K.; Lee, J. E.; Safe, S. H. *Breast Cancer Research and Treatment* **2001,** *66*, 147.

[90] Hagiwara, H.; Sekifuji, M.; Hoshi, T.; Qiao, K.; Yokoyama, C. *Synlett* **2007**, 1320.

[91] Sharma, G. V. M.; Janardhan Reddy, J.; Sree Lakshmi, P.; Radha Krishna, P. *Tetrahedron Letters* **2004,** *45*, 7729.

[92] Kong, Y.-C.; Cheng, K.-F.; Cambie, R. C.; Waterman, P. G. *Journal of the Chemical Society, Chemical Communications* **1985**, 47.

[93] Bergman, J.; Norrby, P.-O.; Tilstam, U.; Venemalm, L. *Tetrahedron* **1989,** *45*, 5549.

[94] Bergman, J.; Venemalm, L. *Tetrahedron* **1992,** *48*, 759.

[95] Black, D. S. C.; Craig, D. C.; Kumar, N. *Tetrahedron Letters* **1991,** *32*, 1587.

[96] Chatterjee, A.; Manna, S.; Banerji, J.; Pascard, C.; Prange, T.; Shoolery, J. N. *Journal of the Chemical Society, Perkin Transactions 1* **1980**, 553.

[97] James, D. M.; Kunze, H. B.; Faulkner, D. J. *Journal of Natural Products* **1991,** *54*, 1137.

[98] Kobayashi, J. i.; Tsuda, M.; Agemi, K.; Shigemori, H.; Ishibashi, M.; Sasaki, T.; Mikami, Y. *Tetrahedron* **1991,** *47*, 6617.

[99] Kornet, M. J.; Thio, A. P. *Journal of Medicinal Chemistry* **1976,** *19*, 892.

[100] Joshi K. C., J. R., Chand P. *Heterocycles* **1985,** *23*, 957.

[101] Popp, F. D. *Journal of Heterocyclic Chemistry* **1972,** *9*, 1399.

[102] Sannigrahi, M. *Tetrahedron* **1999,** *55*, 9007.

[103] Nayak A., C. A., Banerji J., Saha M., Manna S., Kanrar S., Hirose T. *Letters in Organic Chemistry* **2008,** *5*, 403.

[104] Scholtz, M. *Berichte der deutschen chemischen Gesellschaft* **1913,** *46*, 1082.

[105] Noland, W. E.; Richards, C. G.; Desai, H. S.; Venkiteswaran, M. R. *The Journal of Organic Chemistry* **1961,** *26*, 4254.

[106] Noland, W. E.; Venkiteswaran, M. R. *The Journal of Organic Chemistry* **1961,** *26*, 4263.

[107] Röder, E. *Archiv der Pharmazie* **1972,** *305*, 96.

[108] Röder, E. *Archiv der Pharmazie* **1972,** *305*, 117.

[109] Noland, W. E.; Konkel, M. J.; Konkel, L. M. C.; Pearce, B. C.; Barnes, C. L.; Schlemper, E. O. *The Journal of Organic Chemistry* **1996,** *61*, 451.

[110] Noland, W. E.; Konkel, M. J.; Fanburg, S. J.; Venkatraman, S.; Britton, D. *Journal of Chemical Crystallography* **1999,** *29*, 9.

[111] Nadkarni, S. V.; Nagarkar, J. M. *Green Chemistry Letters and Reviews* **2011,** *4*, 121.

[112] Alcaide, B.; Almendros, P.; Alonso, J. M.; Fernández, I. *The Journal of Organic Chemistry* **2013,** *78*, 6688.

[113] D. Zhu; J. Chen; M. Liu; J. Ding; H. Wu *J. Braz. Chem. Soc.* **2009,** *20*, 482.

[114] Sundberg *R.J. Indoles; Acadamic press: New York,* **1996**, 7.

[115] Faulkner, D. J. *Nat. Prod. Rep.* **2001,** *18*, 1.

[116] Joule, J. A. M. K. *Heterocyclic Chemistry, 4th ed.; Blackwell Science: Oxford,* **2000**.

[117] M. Ishikura, K. Y. *Nat. Prod. Rep.* **2009,** *26*, 803.

[118] Bifulco, G.; Bruno, I.; Riccio, R.; Lavayre, J.; Bourdy, G. *Journal of Natural Products* **1995,** *58*, 1254.

[119] Chintharlapalli, S.; Papineni, S.; Safe, S. *Molecular Cancer Therapeutics* **2006,** *5*, 1362.

[120] Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Chemical Reviews* **2010,** *110*, 2250.

[121] Soylu, O.; Uzun, S.; Can, M. *Colloid and Polymer Science* **2011,** *289*, 903.

[122] Keller, K. *Berichte der deutschen chemischen Gesellschaft* **1913,** *46*, 726.

[123] Schmitz-Dumont, O.; Horst, J. T. *Justus Liebigs Annalen der Chemie* **1939,** *538*, 261.

[124] Thesing, J.; Mayer, H. *Chemische Berichte* **1954,** *87*, 1084.

[125] Schmitz-Dumont, O.; Hamann, K.; Geller, K. H. *Justus Liebigs Annalen der Chemie* **1933,** *504*, 1.

[126] Ishii, H.; Murakami, K.; Murakami, Y.; Hosoya, K. *Chemical and Pharmaceutical Bulletin* **1977,** *25*, 3122.

[127] Noland, W.; Kuryla, W. *The Journal of Organic Chemistry* **1960,** *25*, 486.

[128] Bocchi, V.; Palla, G. *Tetrahedron* **1986,** *42*, 5019.

[129] Ishii, H.; Murakami, K.; Sakurada, E.; Hosoya, K.; Murakami, Y. *Journal of the Chemical Society, Perkin Transactions 1* **1988**, 2377.

[130] Ishii, H.; Sakurada, E.; Murakami, K.; Takase, S.; Tanaka, H. *Journal of the Chemical Society, Perkin Transactions 1* **1988**, 2387.

[131] Chakrabarty, M.; Khasnobis, S.; Harigaya, Y.; Konda, Y. *Synthetic Communications* **2000,** *30*, 187.

[132] Pal, B.; Sesha Giri, V.; Jaisankar, P. *Catalysis Communications* **2005,** *6*, 711.

[133] Yamamoto, H. *Ed., Lewis Acids in organic Synthesis; Wiley-VCH: Weinheim,* **2000;,** *1 and 2*.

[134] Pons, J.-M., Santelli, M., Eds. *Lewis Acids and Selectivity in Organic Synthesis; CRC: Boca Raton,* **1995**.

[135] Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. *Tetrahedron Letters* **1989,** *30*, 3581.

[136] Kobayashi, S.; Manabe, K. *ChemInform* **2001,** *32*, no.

[137] Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Letters* **2001,** *42*, 3193.

[138] Yadav, J. S.; Reddy, B. V. S.; Pandey, S. K.; Srihari, P.; Prathap, I. *Tetrahedron Letters* **2001,** *42*, 9089.

[139] Yadav, J. S.; Reddy, B. V. S.; Parisse, C.; Carvalho, P.; Rao, T. P. *Tetrahedron Letters* **2002,** *43*, 2999.

[140] Curini, M.; Epifano, F.; Marcotullio, Maria C.; Rosati, O. *European Journal of Organic Chemistry* **2002,** *2002*, 1562.

[141] Kinthada, L. K.; Ghosh, S.; De, S.; Bhunia, S.; Dey, D.; Bisai, A. *Organic & Biomolecular Chemistry* **2013,** *11*, 6984.

[142] Fujino, K.; Yanase, E.; Shinoda, Y.; Nakatsuka, S.-i. *Bioscience, Biotechnology, and Biochemistry* **2004,** *68*, 764.

Chapter II

Catalyst-Free One-Pot Tandem Reduction of Oxo-and Ene/Yne Functionalities by Hydrazine: Synthesis of Substituted Oxindoles from Isatins

2.1 Introduction

Oxindole (indolin-2-one) occupy a vital position in the indole series between indole (**1**) and isatin (**3**) due to their biological properties.[1] The oxindole ring is a core structural motif found in plentiful natural products and pharmaceutically active compounds.[2-10] Substituted and unsubstituted oxindoles also serve as crucial synthetic precursors for the synthesis of highly desirable indole-based heterocycles and alkaloids.[11-15] Moreover, 5-chloro-oxindole is an pharmaceutical intermediate in the synthesis of Tenidap (Systematic name: 1-carbamoyl-5-chloro-3-[hydroxy(2-thienyl)methylene]indol-2-(3*H*)-one) an anti-inflammatory drug. Structure of some selected natural and pharmaceutical compounds containing oxindole core is shown in **Figure 2.1**

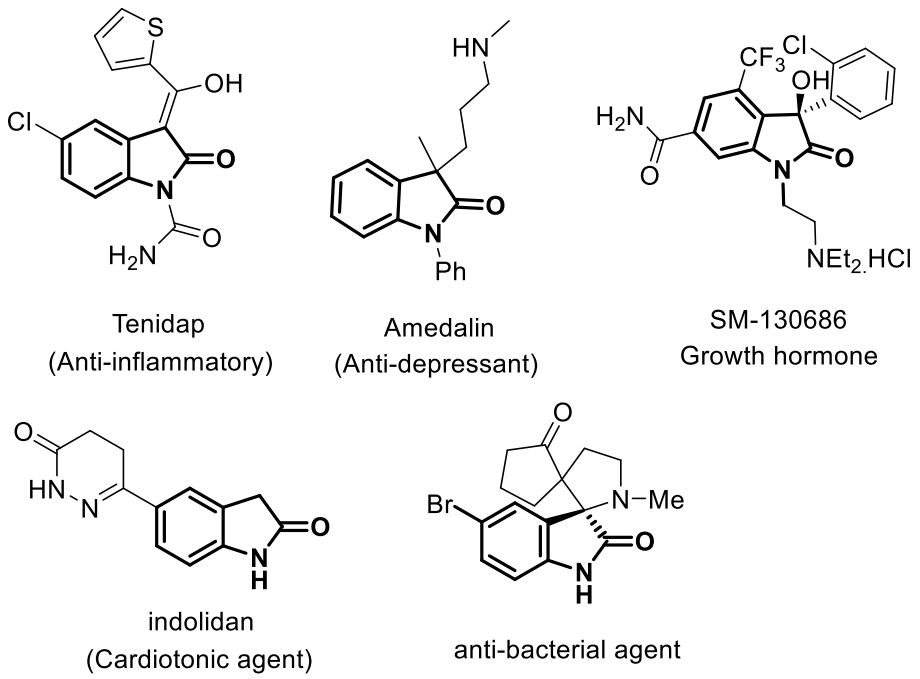
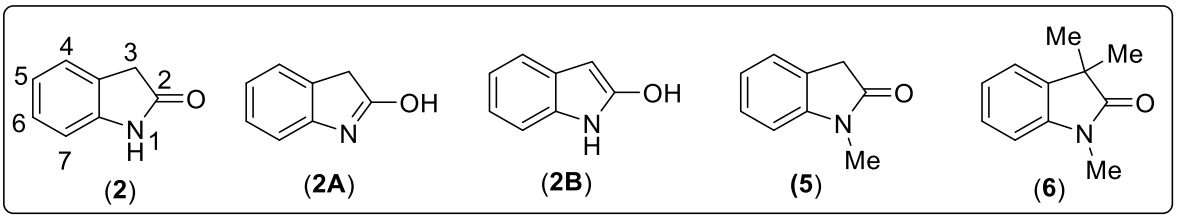


Figure 2.1: Selected examples of natural and pharmaceutically active compounds possessing oxindole core

Oxindole is crystallized from water as colorless needles of melting point 126-127 °C. It is soluble in hot water, alcohol, benzene, ether and acetic acid and it is more soluble in alkaline solutions than in water. Albeit the structure of the oxindole is usually regarded as the lactam of 2-aminophenylacetic acid, the two enol tautomers (**2A** and **2B**) also represent possible structures.It is found that the absorption spectra of oxindole is quite similar to those of *N*-methyloxindole (**5**) and 1,3,3-trimethyloxindole (**6**), indicating that the lactum structure is probably the correct structure for oxindole (**2**).

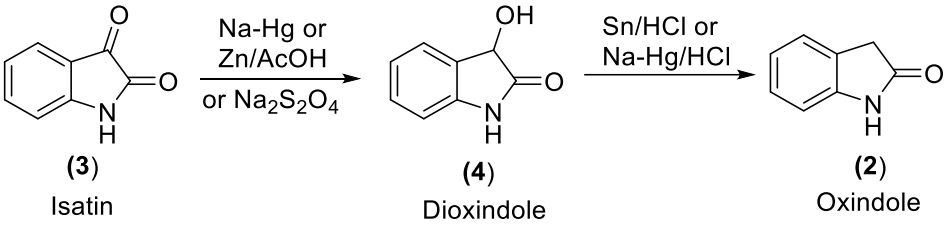


2.2 Synthesis of Oxindole

Over the last few decades, a plethora of synthetic methods including classical and advanced methods have been developed for the preparation of oxindole ring system.[16] The synthetic methods for the synthesis of oxindole can be broadly divided into five categories based on the substrate and the type of bond formation. A brief overview of these methods is given below.

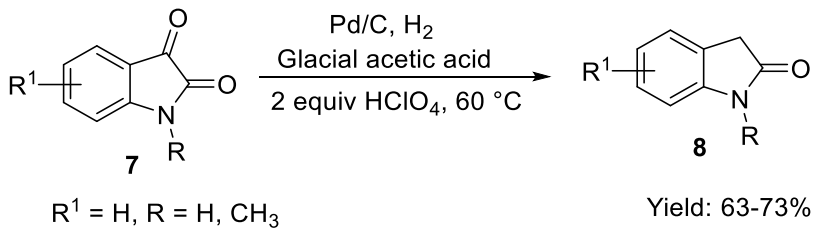
2.2.1 Synthesis from isatins

First synthesis of oxindole was reported by Baeyer in 1866 *via* the reduction of isatin (**3**). Isatin (**3**) was reduced to dioxindole (3-hydroxyoxindole) (**4**) using sodium amalgam in alkaline medium[17, 18] or zinc and acetic acid[19] or sodium hydrosulfite.[20-22] Subsequent reduction of isolable dioxindole (**4**) with tin and hydrochloric acid or sodium amalgam in acid solution gave oxindole (**2**) (**Scheme 2.1**). *N*-Alkylisatins also behaved similar to unsubstituted isatins in these reduction reactions.[23]



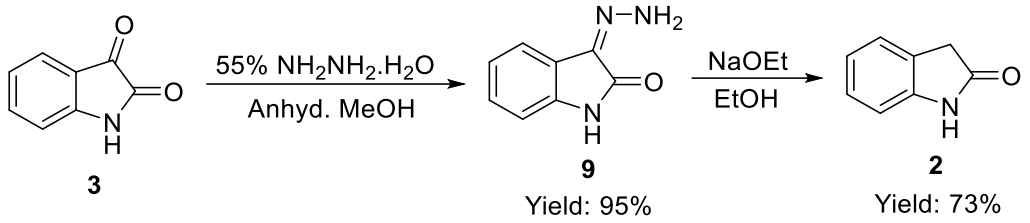
Scheme 2.1: synthesis of oxindole (**2**) *via* reduction of isatin (**3**)

Muchowski reported one step synthesis of oxindole by the palladium-catalyzed hydrogenation of isatin drivatives (**7**) in glacial acetic acid with perchloric acid at 60 °C in 16 h (**Scheme 2.2**).[24]



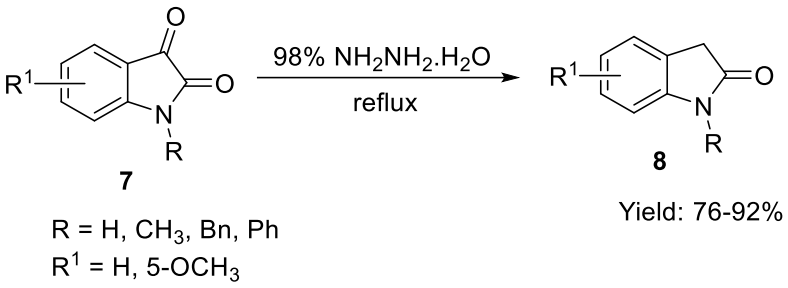
Scheme 2.2: One-pot synthesis of oxindole (**8**)

Soriano established Wolff-Kishner reduction procedure for the synthesis of oxindole by using hydrazine hydrate in the presence of strong base (NaOEt) at reflux condition 3-4 h (**Scheme 2.3**).[25]



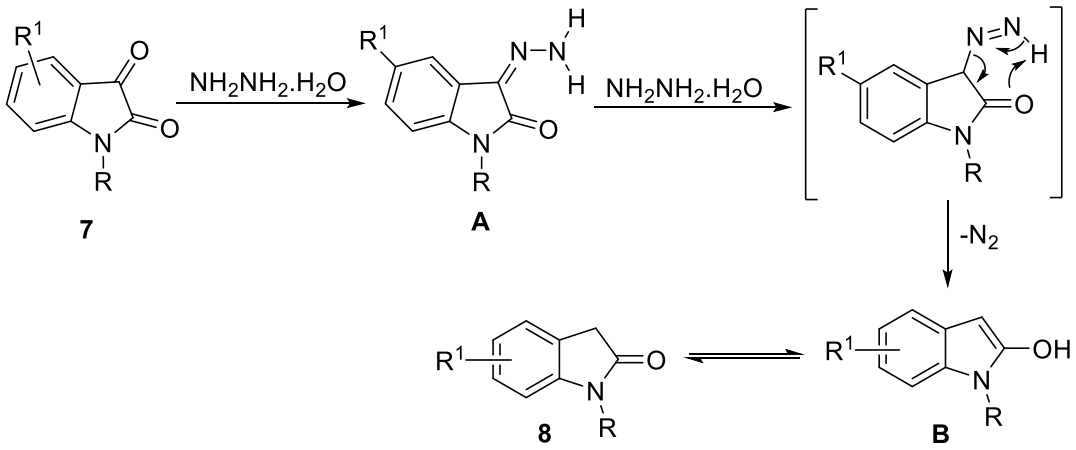
Scheme 2.3: Wolff-Kishner reduction of isatin (**3**)

Crestini group developed direct one-pot reduction of substituted isatins **7** to corresponding oxindoles **8** in the presence of 98% hydrazine hydrate only (without base) in good yield at reflux condition (**Scheme 2.4a** and **2.4b**).[26]



Scheme 2.4a: Wolff-Kishner type reduction of isatin (**7**) in the absence of a base.

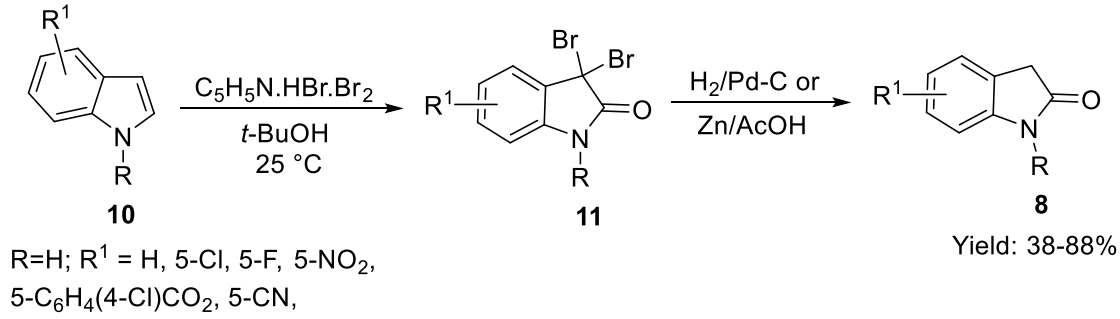
It is proposed that the reation proceeds through formation of hydrazone **A** followed by intramolecular reaction to give **B** which on tautomerizing gives oxindole (**Scheme 2.4b**)



Scheme 2.4b: Proposed mechanism for the reduction of isatin (**7**) without base.

2.2.2 Synthesis from indoles

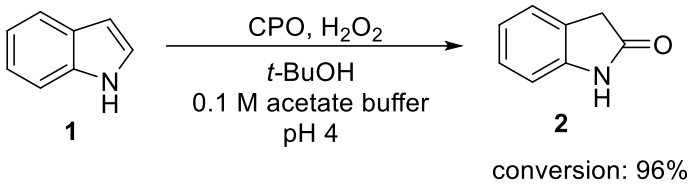
Marfat*et al.* described the oxidation of substitutedindoles to the corresponding 3,3-dibromo-oxindoles *via* pyridinium bromide perbromide (PBPB) as the oxidant followed by hydrogenation over 10% Pd/C in ethanol or zinc in acetic acid to afford corresponding oxindoles in quantitative yields (**Scheme 2.5**).[27] It was found that the reaction works well with indole having an electron withdrawing group at the C-5 position, compared to electron donating group.



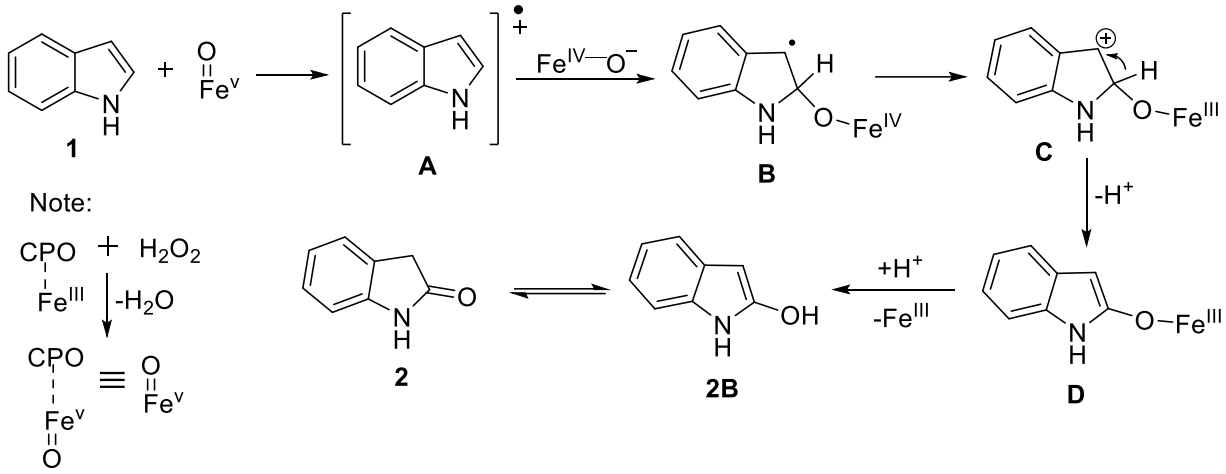
Scheme 2.5: Synthesis of oxindole **8** from indole **10** *via* PBPB followed by hydrogenation

Sheldon and co-workers reported heme enzyme chloroperoxidase (CPO) catalyzed thesynthesis of oxindole *via* oxidation of indole in the presence of hydrogen peroxide (H_2O_2) (**Scheme 2.6a**).[28] All oxygen (>97%) in oxindole is derived from H_2O_2 which was confirmed by the reaction with labeled $H_2{}^{18}O_2$. This indicates that the reaction is two electron oxygen transfer reaction proceeding *via* a concerted mechanism or *via* two fast consecutive one-electron transfer reactions (**Scheme 2.6b**).

Later, Zhai group improved the catalytic activities of enzyme CPO by the additive thioglycolic acid which showed a positive effect on oxidation activity increased 24% at a concentration of 0.5 μM.[29]

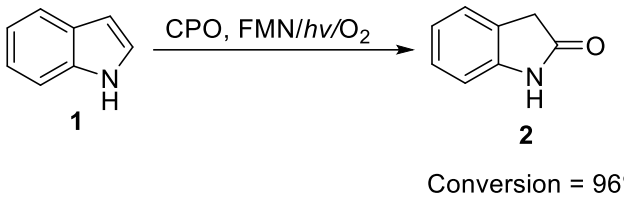


Scheme 2.6: (**a**) Chloroperoxidase (CPO) catalyzed oxidation of indole (**1**)



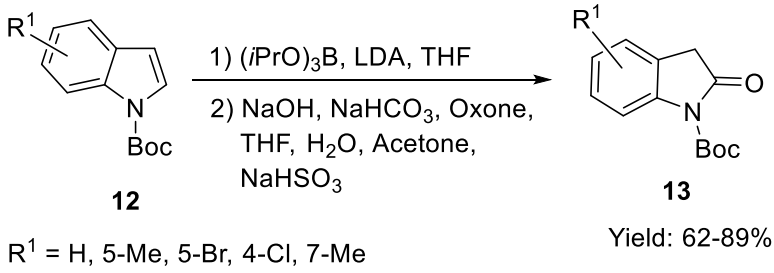
Scheme 2.6: (**b**) Putative mechanism for synthesis of oxindole (**2**) from indole (**1**)

Hollmann *et al*. reported that visible-light driven *in situ* generated H_2O_2 is superior oxidant over the stoichiometric addition of H_2O_2 to promote CPO-catalyzed oxidation of indole to oxindole.[30] The H_2O_2 generation rate can be easily controlled *via* the photocatalyst flavin mononucleotide (FMN) concentration (**Scheme 2.7**).



Scheme 2.7: Light-driven CPO-catalyzed oxidation of indole (**1**) to oxindole (**2**)

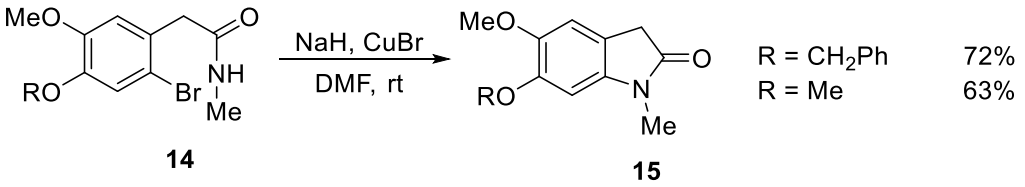
Vazquez and Payack disclosed synthesis of *N*-Boc protected oxindoles **13** from corresponding *N*-protected indoles **12** through 2-(indolyl)borate intermediate which further gets oxidized to the desired product **13**(**Scheme 2.8**).[31]



Scheme 2.8: Synthesis of 1-Boc-oxindoles **13**

2.2.3 Synthesis of C-N bond formation

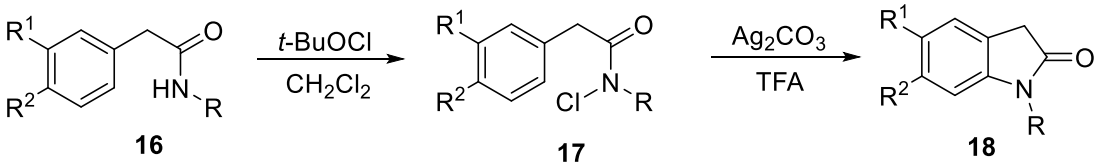
Kametani group prepared substituted *N*-methyl oxindoles **15** by the reaction of *N*-methyl-4-alkoxy-2-bromo-5-methoxy-phenylacetamides **14** with sodium hydride (NaH) and cuprous bromide (CuBr) in dimethylformamide (**Scheme 2.9**).[32]



14 **15**

Scheme 2.9: Synthesis of substituted *N*-methyl oxindoles **15** in presence of CuBr

In 1989, Kikugawa demonstrated the two-step synthesis of *N*-methoxy-2-oxindoles **18** through bond construction between the nitrogen (N) and aryl carbon atom of *N*-methoxy-2-phenylacetamides **16.** In the first step, *N*-chloro-*N*-methoxy-2-phenylacetamides **17** were synthesized by chlorination of *N*-methoxy-2-phenylacetamides **16** with *tert*-butyl hypochlorite in CH_2Cl_2 and further intramolecular cyclization of **17** with silver salt (Ag_2CO_3) in the presence of trifluoroacetic acid (TFA) furnished *N*-methoxy-2-oxindoles **18** in good yield *via N*-methoxy-*N*-acylnitrenium ions intermediate (**Scheme 2.10**).[33]

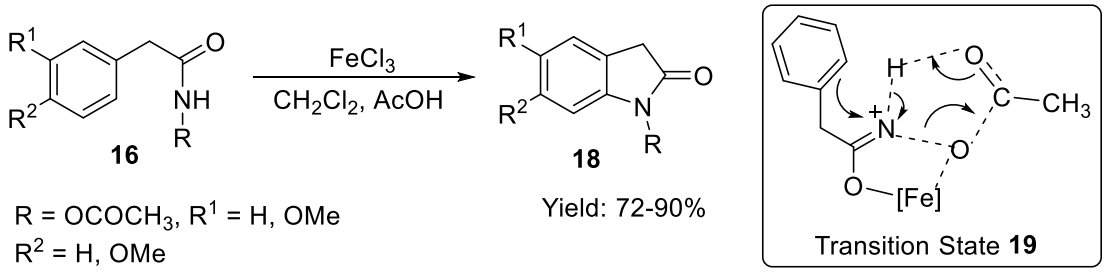


R = OMe, R^1 = H, OMe
R^2 = OMe, Me, Cl, Br, NO_2
NHCOMe

Yield: 64-89%

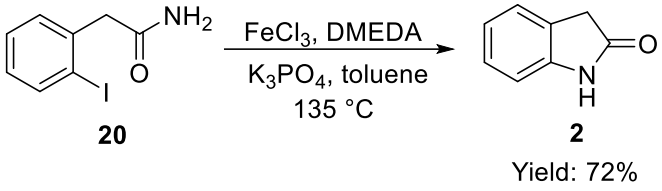
Scheme 2.10: Synthesis of substituted *N*-methoxy-2-oxindoles **18** from the analogous of *N*-methoxyphenylacetamides**16**

Cherest and Lusinchi reported 2 equiv of $FeCl_3$ and 1 equiv of AcOH catalyzed synthesis of oxindoles **18** from *N*-acetyloxyamides **16** in dichloromethane in good yield (**Scheme 2.11**). The enol form of an amidic group of **16** makes iron complexation, which imparts an amidic proton to protonate acetyloxy group to make it good leaving group. Therefore, this methodology does not require prior halogenation as shown in **Scheme 2.11**, but the presence of a hydrogen on the amide nitrogen is essential.[34]



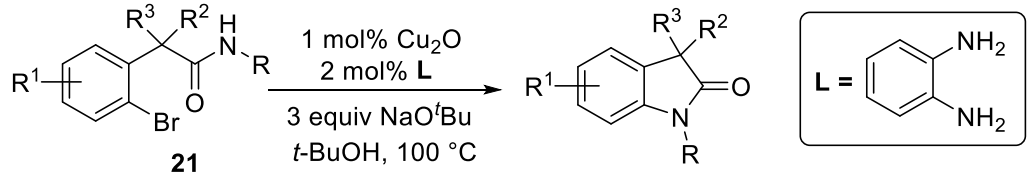
Scheme 2.11: $FeCl_3$-catalyzed synthesis of **18**

In 2008 Bolm and co-workers disclosed the synthesis of oxindole (**2**) *via* 10 mol % $FeCl_3$ catalyzed intramolecular *N*-arylation of primary amide namely 2-(2-iodophenyl)acetamide **20** in presence of 20 mol % of *N*,*N*′-dimethylethylenediamine (DMEDA) as ligand and 2.0 equiv of K_3PO_4 as base in toluene at 135 °C (**Scheme 2.12**).[35] In the case of 2-(2-bromophenyl)-acetamide corresponding cyclization product was not observed.



Scheme 2.12: Synthesis of oxindole (**2**) *via* $FeCl_3$ catalyzed *N*-arylation of primary amide **20**

Recently, Hsieh group developed Cu_2O catalyzed synthesis of oxindoles **22** in good to excellent yields *via* intramolecular *N*-arylation of primary or secondary amides (**Scheme 2.13**). *N*-acetyl-2-(2-bromophenyl)-acetamide **21** (R = $COCH_3$) was treated under same reaction conditions the cyclization accompanied unexpected deprotection of acetyl group, which furnished unprotected oxindole in good yield.[36]



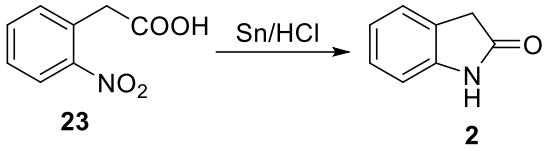
R = H, Me, Bn, Ts, $COCH_3$
R^1 = 2-Cl, 3-Cl, 3-OMe,
R^2 = H, Me, Et, $OCH(CH_3)_2$
R^3 = H, Me, Et, $OCH(CH_3)_2$

Yield: 70-99%

Scheme 2.13: Synthesis of oxindole (**22**) *via* copper catalyzed *N*-arylation of **21**

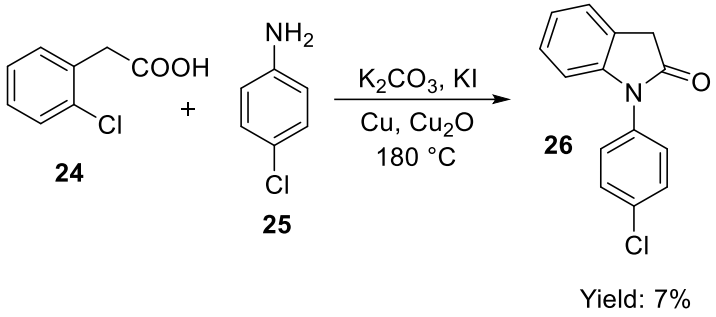
2.2.4 Synthesis *via N*-C-2 bond formation

Baeyer revealed the first synthesis of oxindole (**2**) from an acyclic precursor 2-nitrophenyl acetic acid (**23**) which was reduced to 2-aminophenyl acetic acid and cyclized by tin in hydrochloric acid (**Scheme 2.14**).[37]



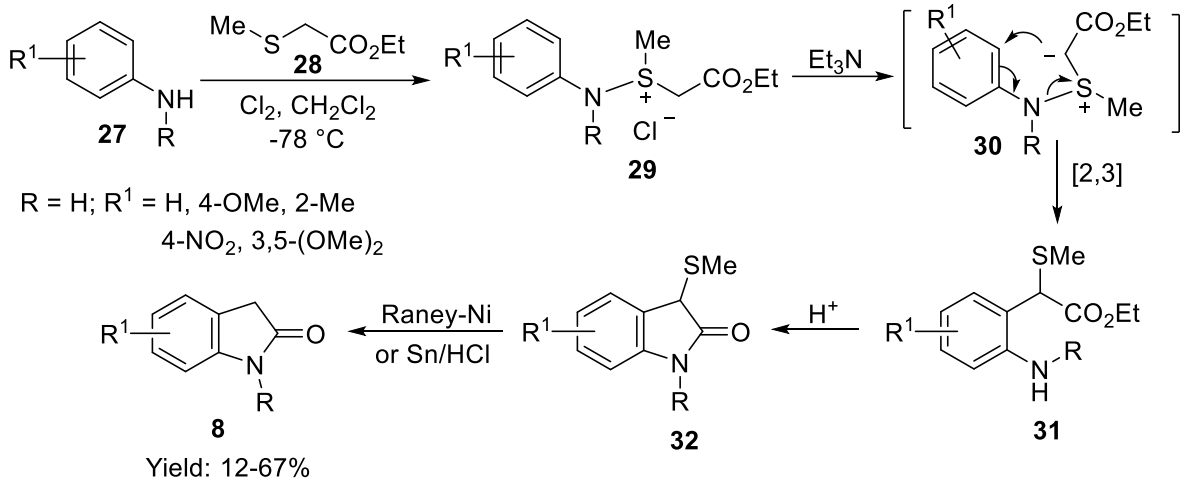
Scheme 2.14: Synthesis of oxindole **2** *via* reductive cyclization of **23**

Ting group reported the synthesis of *N*-phenyloxindole **26** by the reaction of *o*-chlorophenyl acetic acid **24** with 4-chloroaniline **25** *via* copper assisted nucleophilic substitution followed by intramolecular amidation in the presence K_2CO_3 at 180 °C(**Scheme 2.15**).[38]



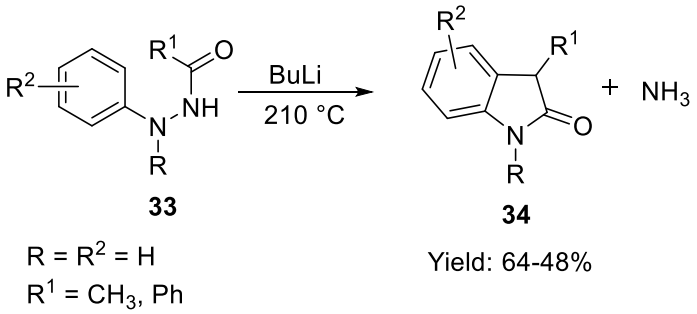
Scheme 2.15: Copper-catalyzed synthesis of *N*-phenyloxindole **26**

In 1973, Gassman and co-workers presented a new method for the synthesis of oxindoles **8**, which includes the conversion of aniline **27** into an aza-sulfonium salt **29** in the presence of ethyl methylthioacetate **28** and elemental chlorine at low temperature followed by base-induced ylide formation to give **30**. The ylide **30** underwent a Sommelet-Hauser type rearrangement to an 2-aminophenyl acetic ester **31**, which on cyclization afforded 3-(methylthio)indolin-2-one **32**. The 3-methylthio group was removed by reductive desulfurization using Raney-nickel or tin in hydrochloric acid (Sn/HCl) (**Scheme 2.16**).[39-43]



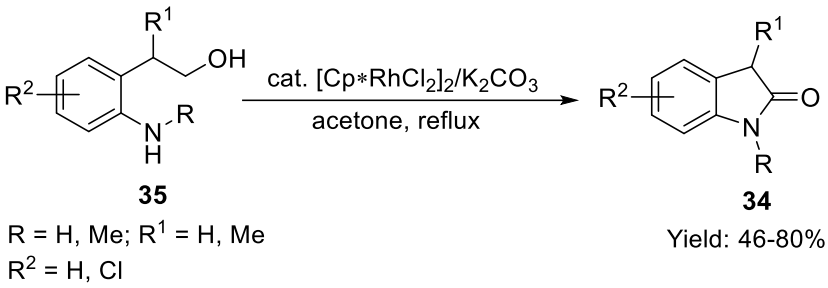
Scheme 2.16: Synthesis of oxindoles **8** from anilines **27** *via* Sommelet-Hauser type rearrangements

Brunner reported the synthesis of oxindole derivatives **34** from *N*-acylphenylhydrazines **33** in the presence of calcium hydride (CaH_2) at 230 °C. This method afforded the oxindole derivatives **34** in moderate yield (41-44%). Like Gassman's oxindole synthesis, the Brunner reaction also involves a rearrangement and cyclization route. Later in 1996, Wolff improved thus method by using butyl lithium (BuLi) in place of CaH_2(**Scheme 2.17**).[44] This modified Brunner reaction has been utilized in the synthesis of natural products, norbornenyl, camphor-containing oxindole moieties etc.[45-47]



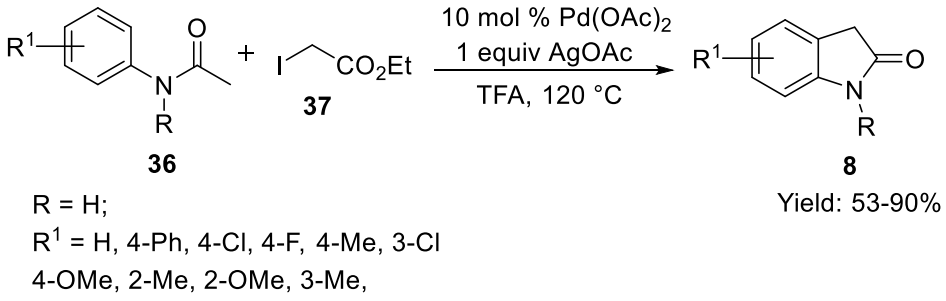
Scheme 2.17: Synthesis of oxindoles **34** *via* modified Brunner reaction

Fujita and co-workers reported preparation of oxindoles **42** in moderate to high yields *via* Cp*Rh complex catalyzed oxidative cyclization of substituted 2-aminophenethyl alcohols **41** in the presence of base K_2CO_3 in acetone under reflux conditions (**Scheme 2.18a**).[48]



Scheme 2.18: Cp*Rh complex catalyzed synthesis of oxindole (**34**) *via* oxidative cyclization of amino alcohols **35**

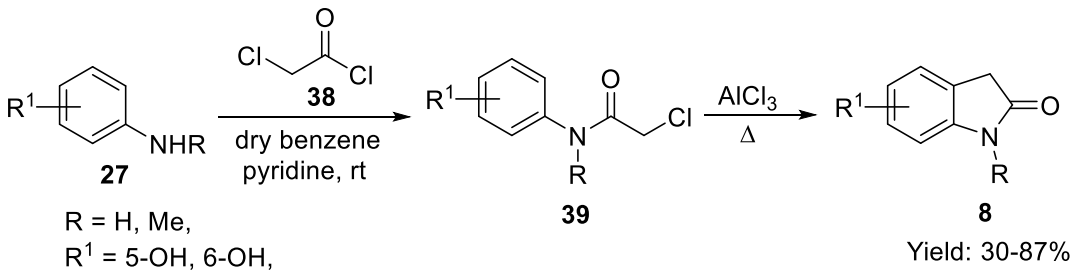
Gandeepan and co-workers demonstrated the synthesis of oxindoles **8** by 10 mol % $Pd(OAc)_2$ catalyzed *ortho*-C-H functionalization of anilides **36** with ethyl-2-iodoacetate **37** using 1 equiv of AgOAc as an additive and TFA as a solvent (**Scheme 2.19a**).[49] This reaction tolerated both the electron-donating group (EDG) and electron withdrawing group (EWG) substituted anilides and furnish the oxindoles **8** in good yields.



Scheme 2.19: Synthesis of oxindole (**8**) *via* Pd-catalyzed *ortho*-C-H functionalization and cyclization of **36**

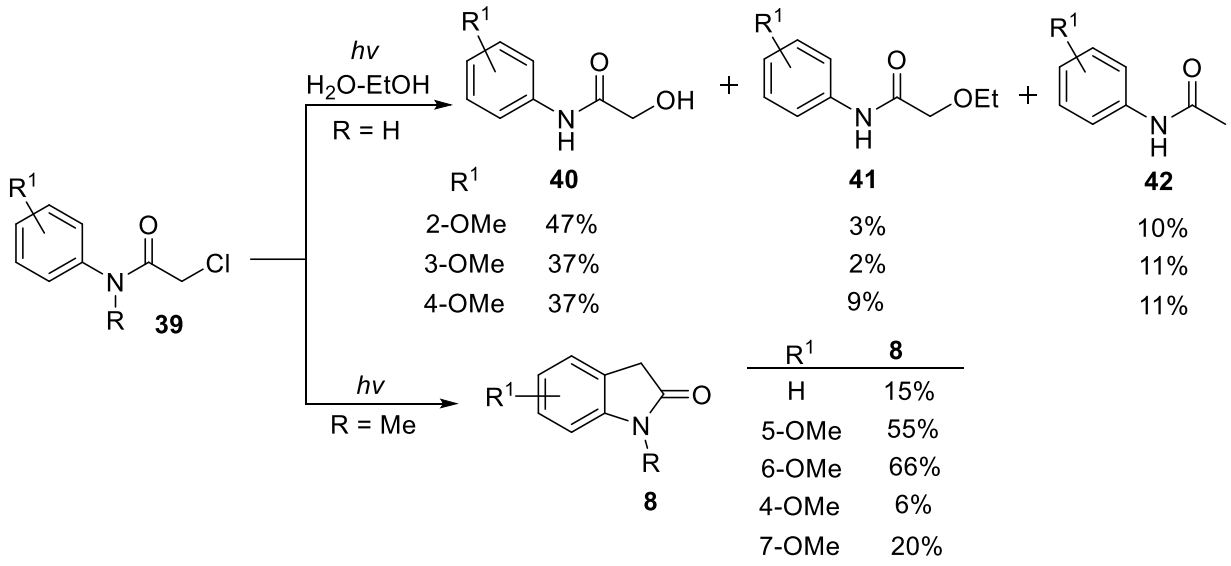
2.2.5 Synthesis *via* (C-3)-(Aryl) bond formation

Daisley and co-workers[50, 51] disclosed the synthesis of substituted oxindoles **8** from anilines **27***via* Friedel-Crafts (F-C) alkylation of substituted 2-chloro-*N*-phenylacetamides **39**, which was synthesized by the reaction of anilines **27** and 2-chloroacetyl chloride **38** (**Scheme 2.20**).



Scheme 2.20: Synthesis of oxindoles **8** from anilines **27** *via* F-C alkylation of **38**

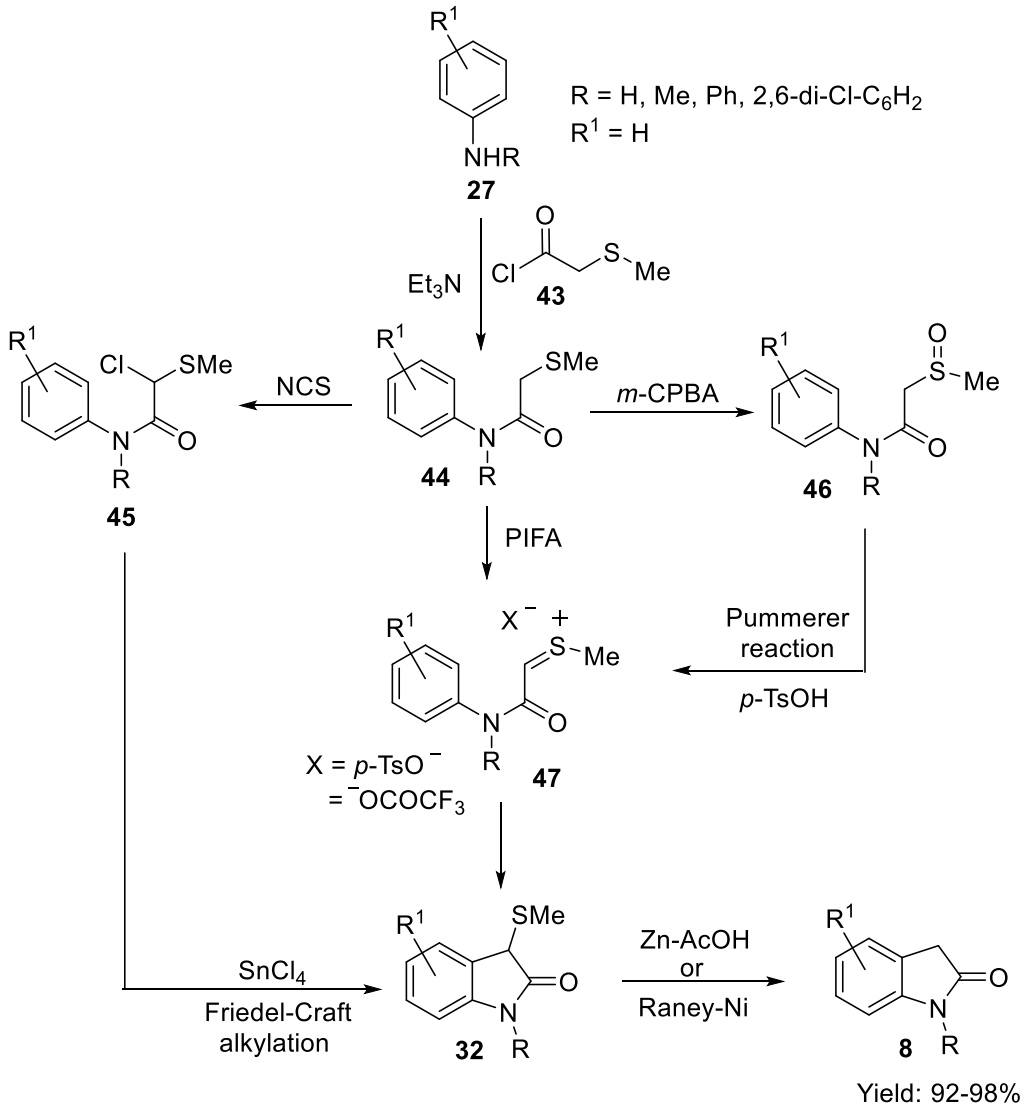
Yonemitsu developed a photochemical synthesis of oxindoles **8** from 2-chloro-*N*-methyl-acetanilide derivatives **39** (R = Me) however, in the case of 2-chloro-acetanilide derivatives **39** (R = H) no photocyclization was observed, instead of that only side-chain substitution products **40**, **41** and **42** were formed. This observation was rationalized by the fact that *N*-unsubstituted acetanilides exist in the *trans* form while *N*-substituted acetanilides exist predominantly in the *cis* form, which reacts intramolecularly to give oxindoles (**Scheme 2.21**).[52]



Scheme 2.21: Synthesis of oxindole (**8**) *via* photochemical reaction.

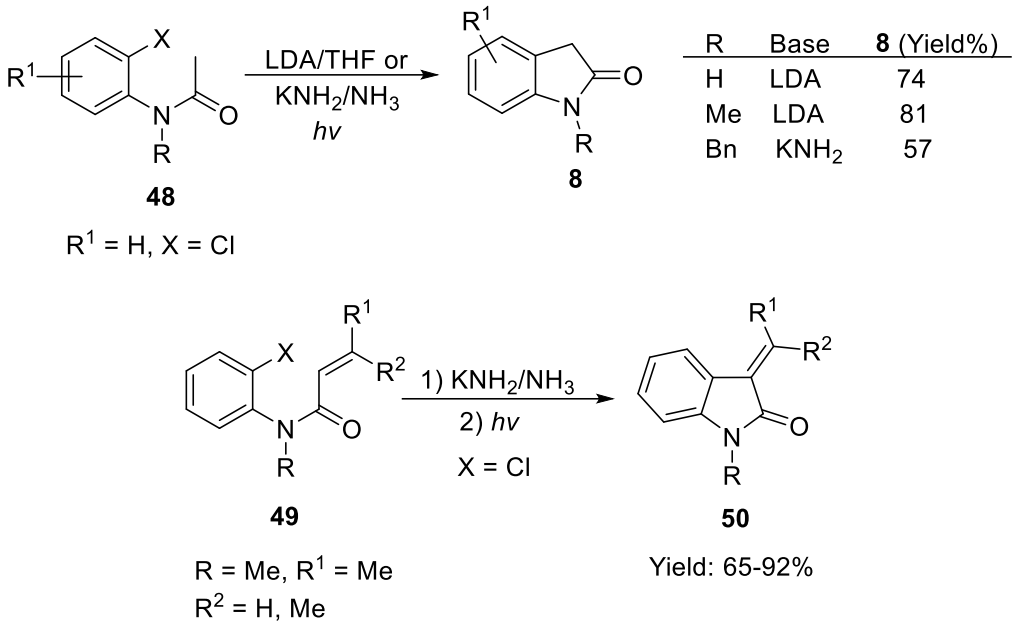
Tamura *et al*. reported a convenient synthesis of oxindoles **8** *via* two synthetic routes, Plummerer and Friedel-Crafts alkylation reactions using the common substrate α-(methylthio)acetanilides **44** which were synthesized by the reaction of anilines **27** with 2-(methylthio)acetyl chloride (**43**) in the presence of triethylamine. Plummerer reaction involved oxidation of α-(methylthio)acetanilides **44** in the presence of *m*-CPBA to give sulfoxide **46**, which was converted to the intermediate **47** upon treatment with *p*-TsOH and subsequent electrophilic attack on the aromatic ring gave the 3-(methylthio)indolin-2-one **32**. Reductive desulfurization of **32** afforded oxindoles **8** (**Scheme 2.22**). Other route involved $SnCl_4$ catalyzed Friedel-Crafts cyclization of 2-chloro-2-(methylthio)acetanilides **45**, obtained by the chlorination of α-(methylthio)-acetanilides **44** in the presence of *N*-chlorosuccinimide (NCS) furnished the 3-(methylthio)indolin-2-one **32** which on successive reduction with Raney-Ni or Zn-AcOH gave oxindoles **8** (**Scheme 2.22**). Later, in 1986 Tamura group[53] introduced the Plummerer type reaction for the synthesis of 3-

(methylthio)indolin-2-one **32**, obtained directly from sulfide **44** by treatment with phenyl iodosyl*bis*(trifluoroacetate) (PIFA) which generated **47** *in situ* and further reductive desulfurization gave oxindoles **8** (**Scheme 2.22**).[54, 55]



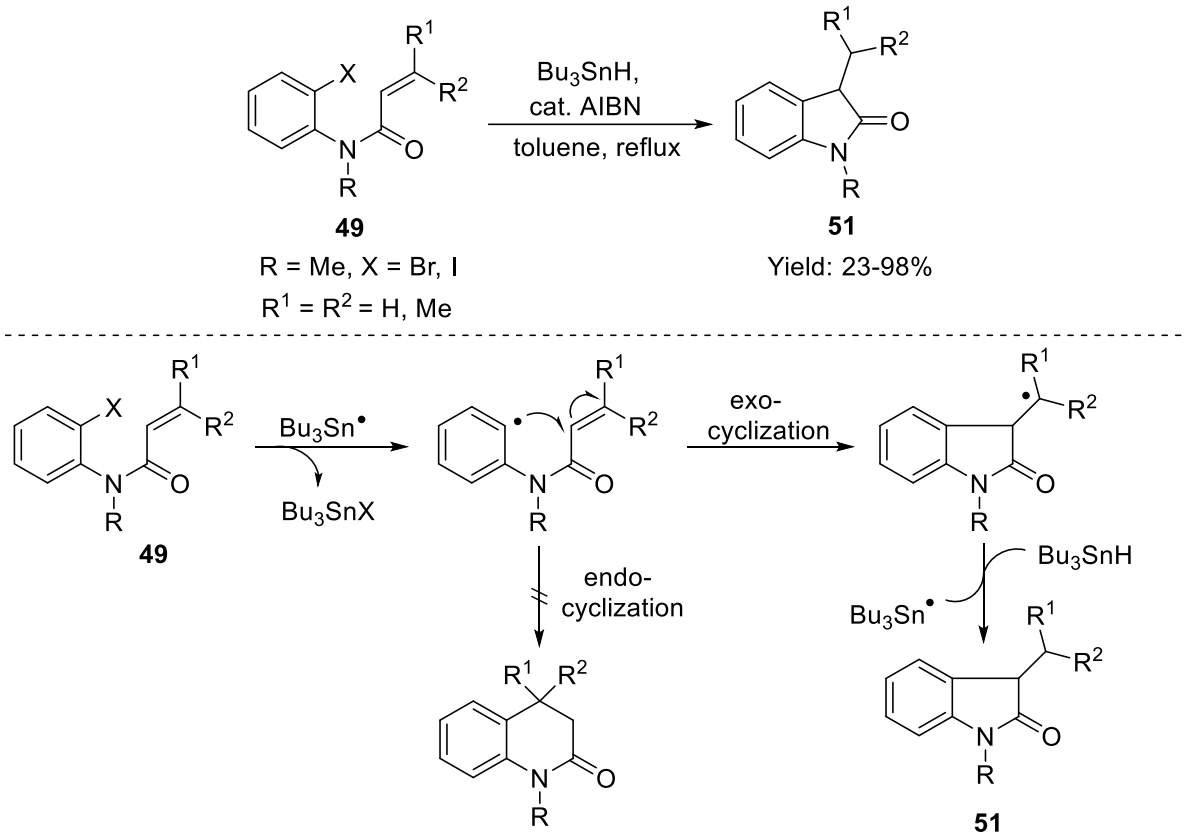
Scheme 2.22: Synthesis of oxindoles **8** from *N*-alkylanilines

In 1985, Wolfe and co-workers developed a new method for the preparation of oxindoles **8**. Upon treatment of 2′-chloroacetanilides **48** with 3 equiv of the base (depending on substituent R either LDA in THF or KNH_2 in NH_3) followed by irradiation with near-UV light, resulting anions reacted to give substituted oxindoles **8** in good yields. Likewise, photoinduced cyclization of α,β-unsaturated acetanilides **49** also furnished 3-alkylideneoxindoles **50** in good to excellent yields (**Scheme 2.23**).[2, 56]

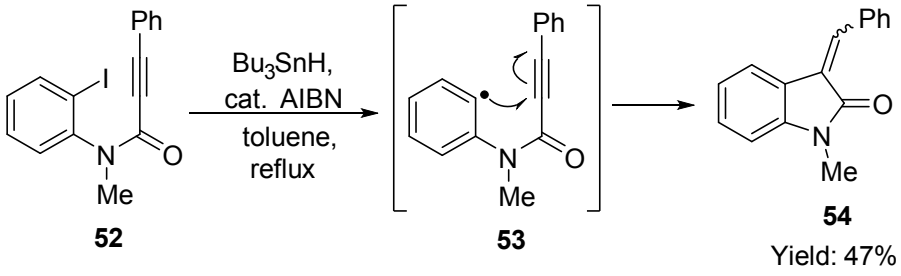


Scheme 2.23: Synthesis of oxindoles (**8**) and 3-alkylidene oxindoles (**50**) *via* base assisted photoinduced cyclization

Jones and co-workers demonstrated the synthesis of 3-substituted *N*-methyl-2-oxindoles **51** in high yields by the treatment of *N*-methyl-2-bromoacryloylanilides **49** (X = Br) with tri-*n*-butylstannane (Bu_3SnH) and a catalytic amount of azobisisobutyronitrile (AIBN) in toluene under reflux condition (**Scheme 2.24a**).[57-59] In the case of *N*-unsubstituted-2-bromoacryloylanilide, no cyclization product was obtained. Afterwards in 1988, Jordon[60] treated *N*-methyl-2-iodoacryloylanilides **49** (X = I) under similar reaction conditions and obtained 3-substituted *N*-methyl-2-oxindoles **51** along with uncyclized product in case of *N*-unsubstituted-2-iodoacryloylanilide. The 2-iodopropynamide **52** gave exclusive *exo*-cyclic product **54** *via* intermediate aryl radical **53** which attacks onto the α-position of the unsaturated system giving a mixture of E- and Z-isomers of **54** in 47% yield (Z-isomer: 32% and E-isomer: 5%) (**Scheme 2.24b**).

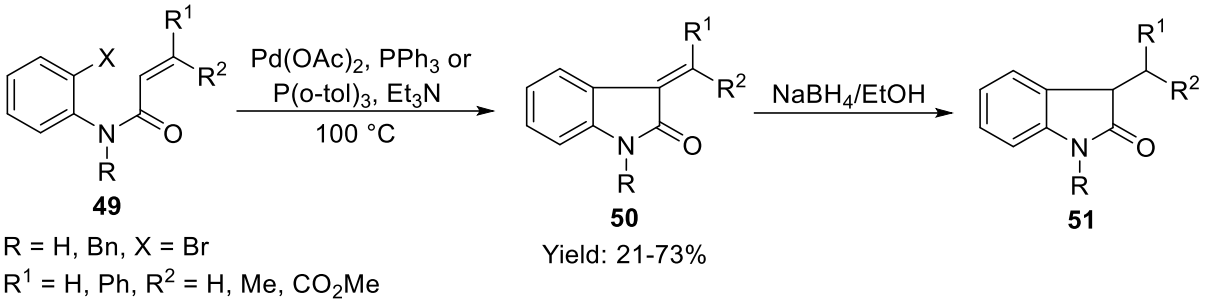


Scheme 2.24a: Synthesis of oxindoles (**51**) *via* intramolecular radical cyclization of **49** by Bu_3SnH and AIBN



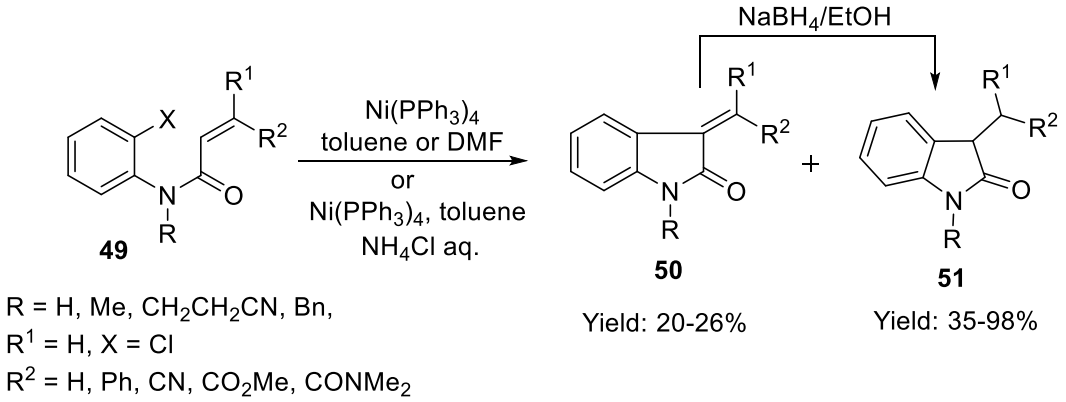
Scheme 2.24b: Intramolecular exo-radical cyclization of **52**

Ban[61] and Heck[62] independently reported organopalladium complex catalyzed synthesis of 3-alkylidene-oxindoles **50** through intramolecular *exo*-trig cyclization of *N*-acryloyl-2′-bromo anilines **49**, which can be further converted into 3-substituted-2-oxindoles **51** in the presence of $NaBH_4$ in EtOH (**Scheme 2.25**).



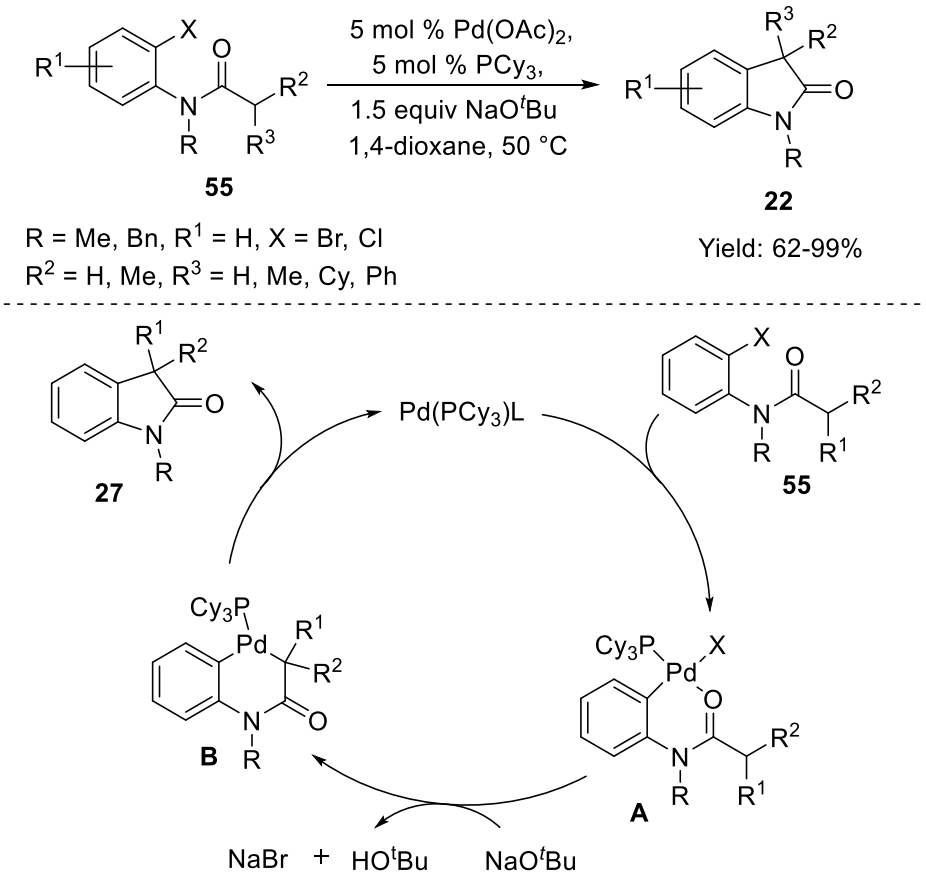
Scheme 2.25: Synthesis of oxindoles **51** *via* Palladium-catalyzed intramolecular cyclization of **49** followed by $NaBH_4$ reduction

Ban group later described the synthesis of oxindole derivatives **50** and **51** *via* organonickel complex catalyzed intramolecular *exo*-trig cyclization of *N*-alkenyl-2′-chloroanilides **49** in toluene or *N*,*N*-Dimethylformamide (DMF) depending on the substituent R^1 of **49** (**Scheme 2.27**).[63, 64] Rodriguez group also explored the synthesis of oxindole derivatives **50** and **51** in high yields from substrates having electron withdrawing groups on the alkene using organo-nickel complex followed by the hydrolysis.[65]



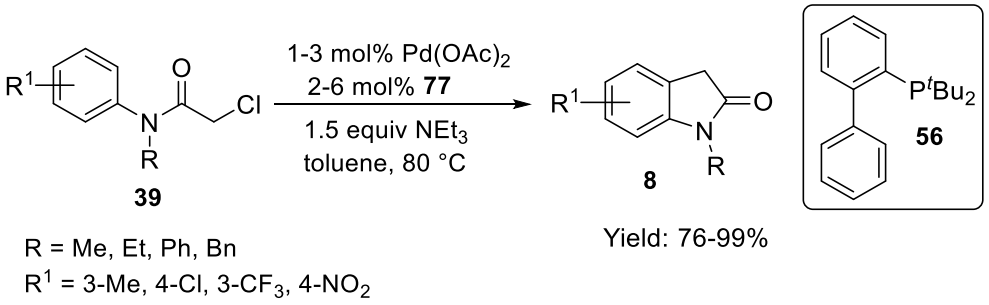
Scheme 2.26: Organonickel complex catalyzed synthesis of oxindole derivatives

Hartwig and co-workers disclosed the synthesis of oxindoles **22** in high yield with complete regioselectivity *via* 5 mol % $Pd(OAc)_2$ catalyzed α-arylation of *N*-(2-halophenyl)amides **55** (**Scheme 2.27**).[66, 67] It was observed that the rate of oxidative addition of *N*-(2-bromophenyl)amide to Pd(0) is faster than that of *N*-(2-chlorophenyl)amide.



Scheme 2.27: Synthesis of oxindoles **22** *via* Palladium-catalyzed α-arylation of *N*-(2-halophenyl)amides **55** with proposed mechanism

Buchwald group developed a regioselective synthesis of substituted oxindoles **8** from α-chloroacetanilides **39** through $Pd(OAc)_2$ catalyzed C-H functionalization in the presence of 2-(di-tert-butylphosphino)biphenyl **56** as a ligand and triethylamine (Et_3N) as a base in toluene (**Scheme 2.28**).[68] Substituted oxindoles **8** were obtained in high yields with high level of functional group tolerance without pre-functionalization of substrate **39**.



Scheme 2.28: Synthesis of oxindoles **8** *via* palladium-catalyzed C-H functionalization of α-chloroacetanilide **39**

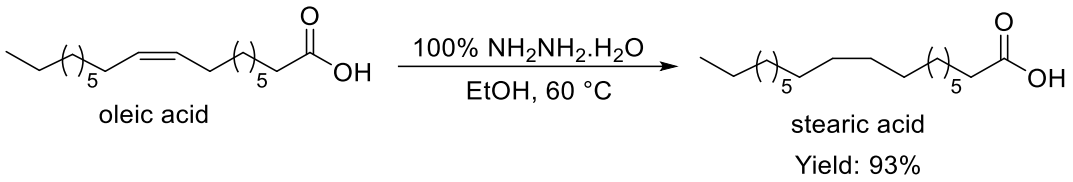
The classical approach to access substituted oxindoles is based on the one-step derivatization of isatins under Wolff–Kishner reduction[25, 26, 69] conditions involving hydrazine hydrate **(Scheme 2.3 and 2.4)**. This strategy is still widely used and is quite appealing to synthetic chemists because several substituted isatins are commercially available and are relatively inexpensive. Moreover, the reductive transformation of isatins to oxindoles is generally a high-yielding process.

2.3 Hydrazine hydrate ($NH_2NH_2.H_2O$) as reducing reagent

Hydrazine hydrate is commercially available. It is a colorless fuming liquid (mp -52 °C, bp 120-121 °C, d = 1.027 g/mL) with a faint ammonia-like odor and is soluble in water and alcohol. The synthetic utilities of hydrazine hydrate ($NH_2NH_2.H_2O$) have been comprehensively investigated.[70] Among various reducing agents, hydrazine hydrate stands out a very powerful reducing agent which reduces many functional groups such as carbonyl compounds, alkenes, alkynes and nitro groups under mild reaction conditions.

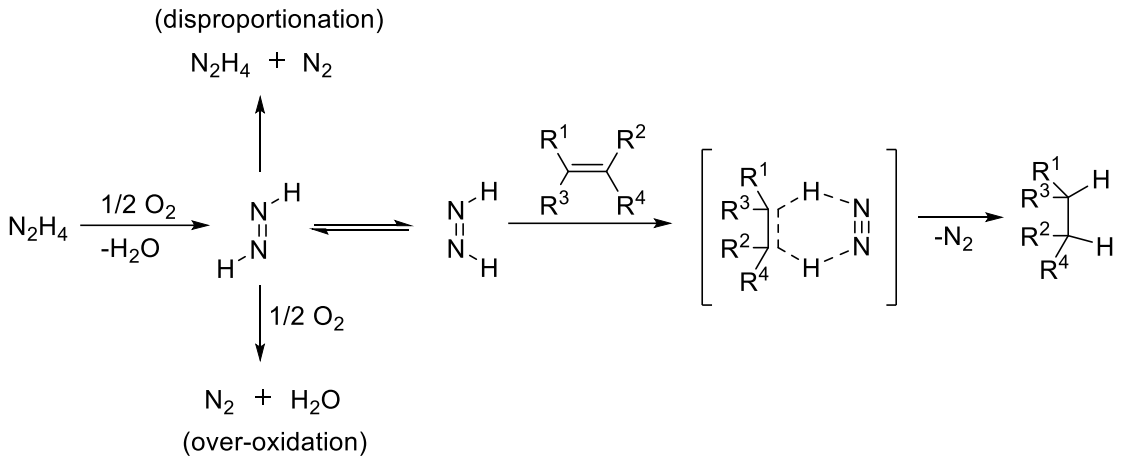
2.3.1 Reduction of unsaturated compounds

Rao *et al.* has shown that hydrazine hydrate can be effectively used as a reducing agent for the reduction of carbon-carbon double bond. They have obtained stearic acid from oleic acid in excellent yield (93%) using hydrazine hydrate in ethanol (**Scheme 2.29**).[71]



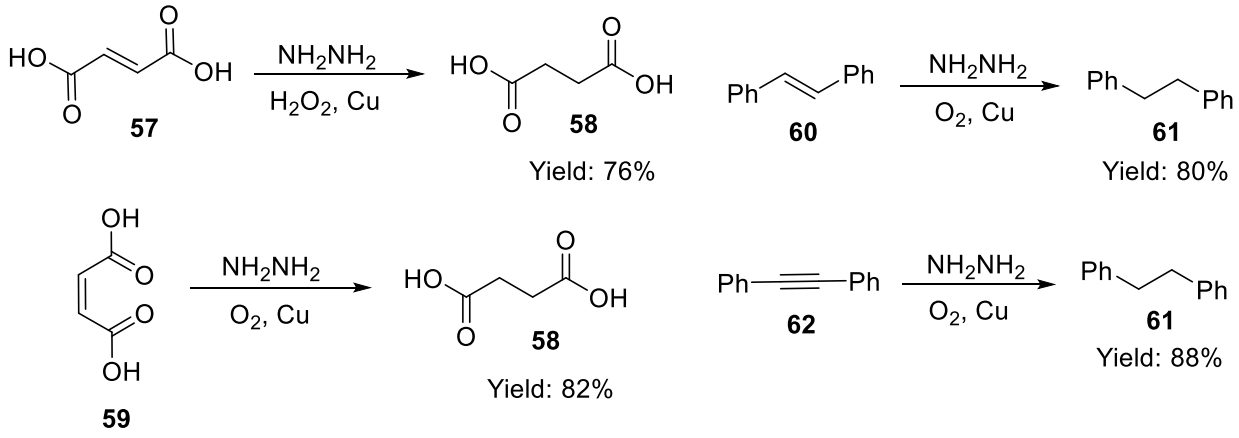
Scheme 2.29: Reduction of oleic acid into stearic acid by hydrazine hydrate

It is believed that hydrazine (N_2H_4) undergoes oxidation (dehydrogenation) to produce diimide (N_2H_2) *in situ* which acts as a transfer-hydrogenation agent in the reduction process (**Scheme 2.30**).[72]



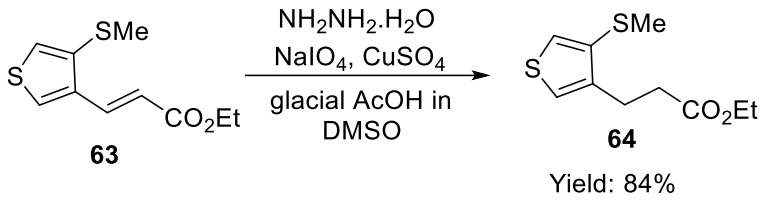
Scheme 2.30: Proposed mechansim for the reduction of olefin by $N_2H_4.H_2O$ and O_2

Following are the examples where oxidants such as H_2O_2, $NaIO_4$, $K_3[(FeCN)_6]$, Se, benzene seleninic acid, hypervalent iodine and even molecular oxygen (O_2) have been used to catalyzed the selective reduction of unsaturated carbon–carbon bonds by using hydrazine. The oxidation of hydrazine to diimide by using molecular oxygen typically requires a catalyst (e.g., copper, iron and guanidine salts and various flavin derivatives) to promote the reaction. E. J. Corey group demonstrated the reduction of unsaturated compounds such as fumaric acid (**57**), maleic acid (**59**) into succinic acid (**58**) and *trans*-stilbene (**60**) and diphenylacetylene (**62**) into 1,2-diphenylethane using hydrazine in presence oxidising agent H_2O_2 and trace amount of copper ion (**Scheme 2.31**).[73]



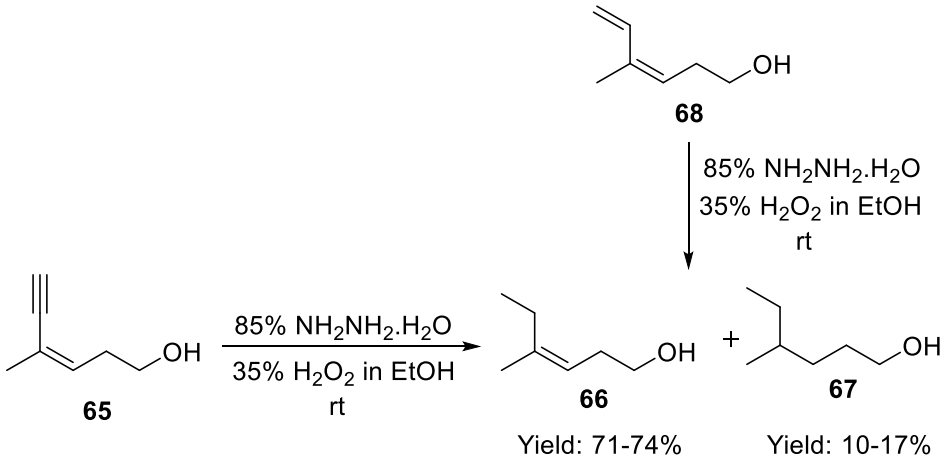
Scheme 2.31: Reduction of unsaturated compounds using NH_2NH_2, H_2O_2/O_2 and copper ion

Schlessinger *et al.* revealed the reduction of unsaturated double bond of thiophene derivatives **63** into its dihydro-analogue **64** without concomitant formation of either sulphone or sulphoxide by diimide in *situ* generated by the oxidation of hydrazine hydrate in the presence of sodium metaperiodate ($NaIO_4$) and copper sulfate (**Scheme 2.32**).[74]



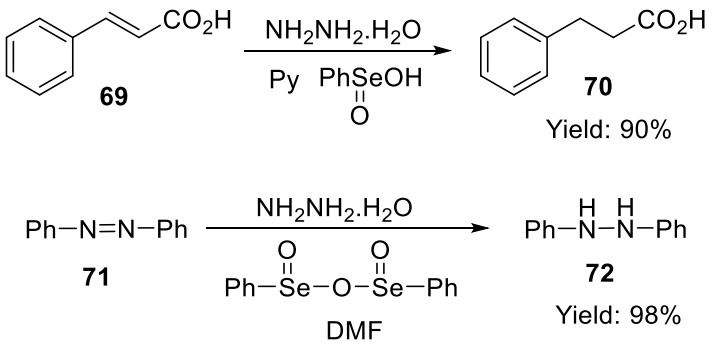
Scheme 2.32: Reduction of conjugated double bond using NH_2NH_2 in presence of $NaIO_4/CuSO_4$

Mori group disclosed the reduction of conjugated alkene and alkyne bond using large excess of hydrazine in presence of H_2O_2 as oxidising agent. They obtained **66** in 71 and 74% from **65** and **68**, respectively. A small amount of completely reduced alcohol **67** (10-17%) was also obtained under these conditions (**Scheme 2.33**).[75]



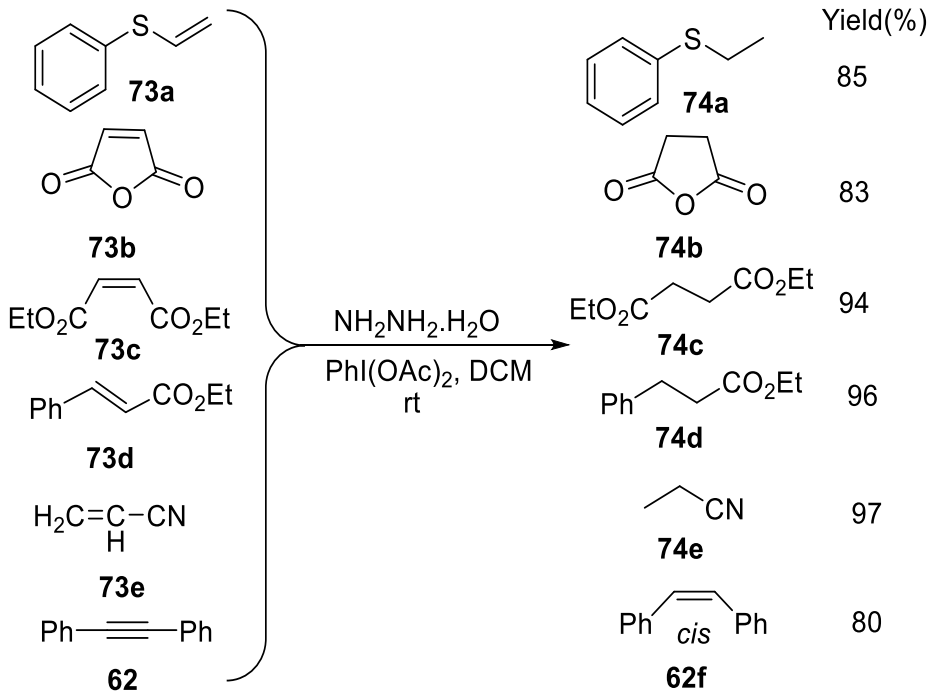
Scheme 2.33: Reduction of conjugated alkene and alkynes using $NH_2NH_2.H_2O$and H_2O_2 in EtOH as reducing agent

Back *et al.* introduced benzeneseleninic acid and its anhydride as an oxidizing agent for the oxidation of hydrazine hydrate to produce diimide *in situ* which converts cinnamic acid (**69**) into hydro-cinnamic acid (**70**) in pyridine and azobenzene (**71**) to *N,N'*-diphenylhydrazine (**72**) in DMF (**Scheme 2.34**). [76]



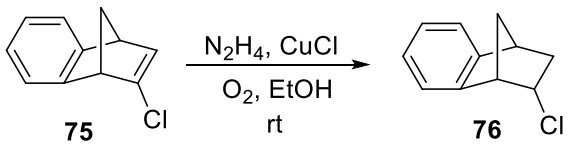
Scheme 2.34: Reduction of cinnamic acid (**69**) and azobenzene (**71**) *via* benzeneseleninic acid and its anhydride oxidation of hydrazine hydrate respectively

Moriarty group reported reduction of unsaturated compounds **73** (**a-e**) and **62** into **74** (**a-e**) and **62f** in good yields through the iodobenzene diacetate $PhI(OAc)_2$ oxidation of hydrazine hydrate in dichloromethane at room temperature (**Scheme 2.35**).[77] It revealed that sulfur of **73a** was not oxidized into sulfone or sulfoxide in the reaction, whereas diphenylacetylene **62** was reduced stereospecifically to the *cis*-1,2-diphenylethene **62f** rather than over-reduction product 1,2-diphenylethane.



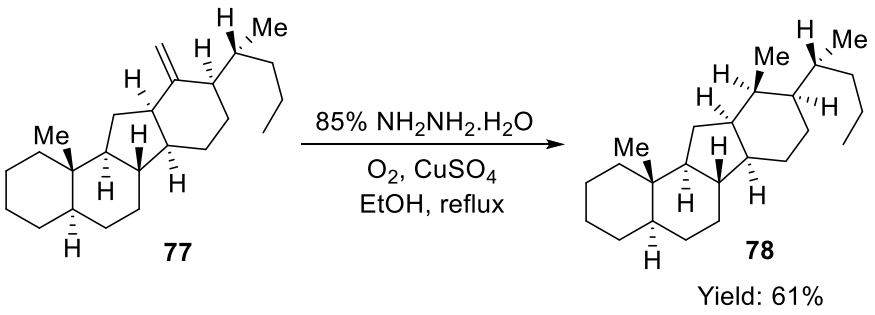
Scheme 2.35: Reduction of conjugated alkenes by $PhI(OAc)_2$ oxidation of hydrazine hydrate

Wilt and co-workers reported the reduction of 2-chlorobenzonorbornadiene **75** into 2-chloro-benzonorbornene **76** in 22% yield by the use of diimide, generated from hydrazine in the presence of oxygen (air) and cuprous chloride (CuCl) at room temperature (**Scheme 2.36**).[78]



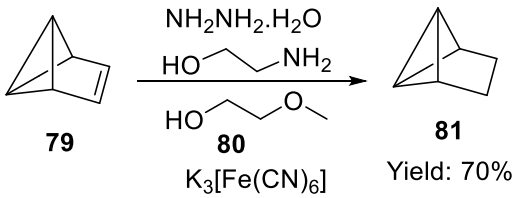
Scheme 2.36: Reduction of 2-chlorobenzonorbornadiene **75** into 2-chlorobenzonorbornene **76** by hydrazine-oxygen in CuCl

Chang and co-workers reported the reduction of the olefinic double bond of **77** by hydrazine hydrate-oxygen-copper ion system under reflux condition to get 5β,12α-cholajervane **78** in 61% yield (**Scheme 2.37**).[79]



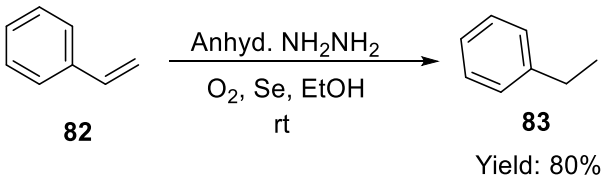
Scheme 2.37: Reduction of alkene using hydrazine hydrate-oxygen-copper ion system

Christl described the reduction of benzvalene (**79**) using diimide generated in *situ* from potassium ferricyanide $K_3[Fe(CN)_6]$ oxidation of hydrazine hydrate in the presence of ethanolamine and 2-methoxyethanol (**80**) to give furnish tricyclo[3.1.0.$0^{2,6}$]hexane (**81**) in 70% yield (**Scheme 2.38**).[80]



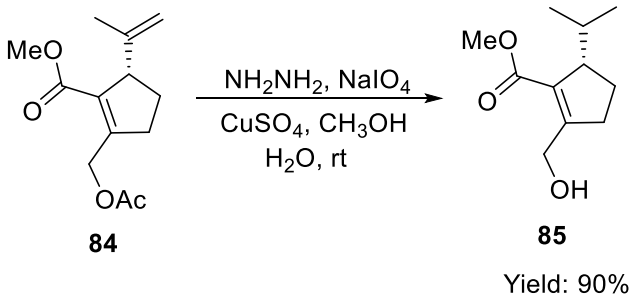
Scheme 2.38: Reduction of benzvalene (**79**) by hydrazine hydrate with oxidizing agent $K_3[Fe(CN)_6]$

Sonoda and co-workers reported the synthesis of ethylbenzene (**83**) *via* reduction of styrene (**82**) using selenium catalyzed generation of diimide from hydrazine and oxygen in EtOH at room temperature (**Scheme 2.39**).[81]



Scheme 2.39: Selenium catalyzed hydrogenation of styrene (**82**)with hydrazine

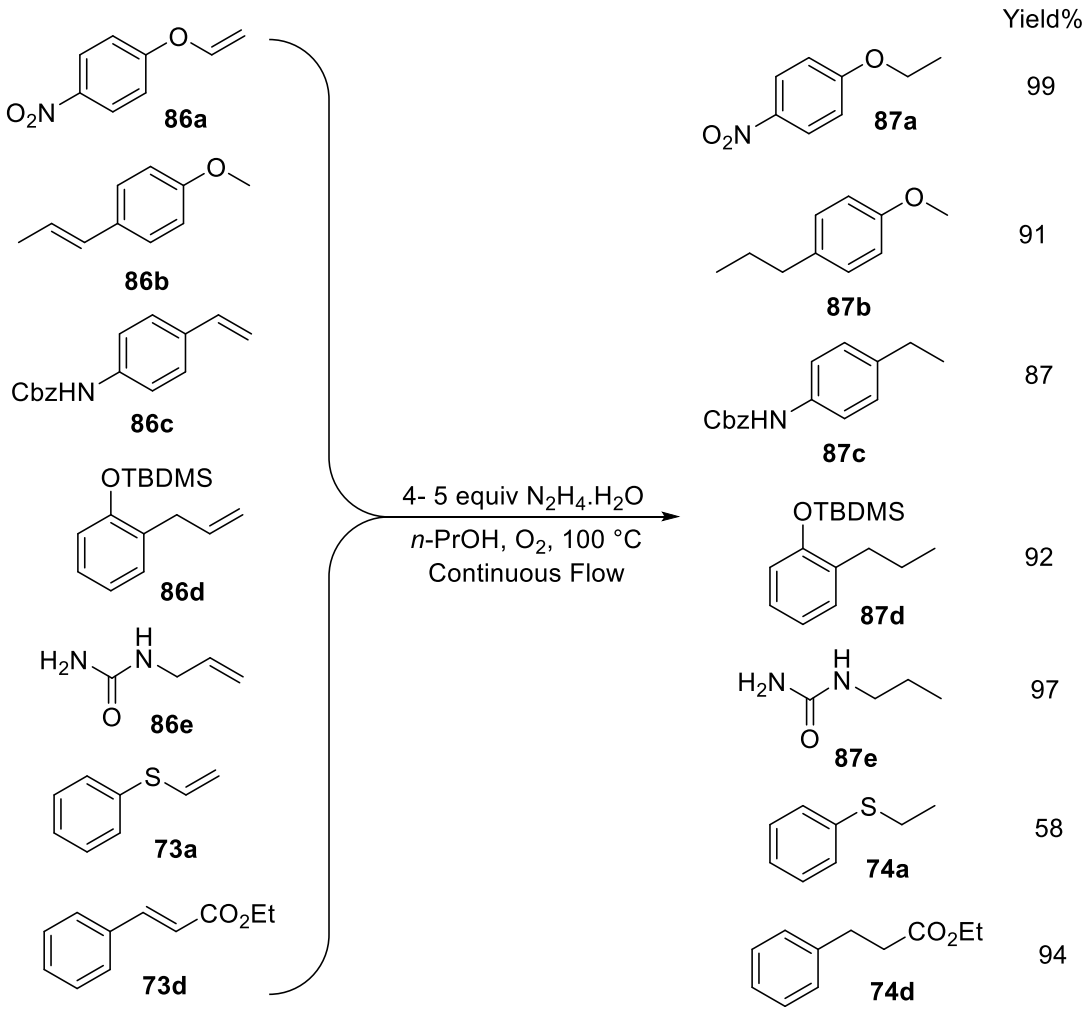
Paquette group demonstrated the reduction of isoprenyl side chain and deprotection of acyl group of **84** *via* copper-catalyzed sodium metaperiodate oxidation of hydrazine in absence of oxygen at room temperature (**Scheme 2.40**).[82]



Scheme 2.40: Reduction of isoprenyl side chain and deprotection of acyl group of **84** by Cu-catalyzed sodium periodate oxidation of hydrazine

Catalyst-free oxidation of hydrazine with molecular oxygen is rather inefficient as it requires an excess amount of hydrazine and proceeds at a sluggish rate. The reactive diimide intermediate is also prone to disproportionation (reformation to hydrazine) and over oxidation under these conditions. In recent times, specialized reactors have been developed to perform the catalyst-free selective reduction of terminal olefins by using hydrazine hydrate and molecular oxygen at high temperature and pressure in continuous-flow mode.[83]

Kappe and co-workers demonstrated the catalyst-free method for *in situ* generation of diimide from hydrazine hydrate-molecular oxygen system in continuous-flow mode, which was applied to the selective reduction of various olefins to the corresponding alkanes in excellent yields (58-99%) and high selectivity (**Scheme 2.41**).[83] Interestingly, several functional groups were well tolerated and the reaction times were very less.

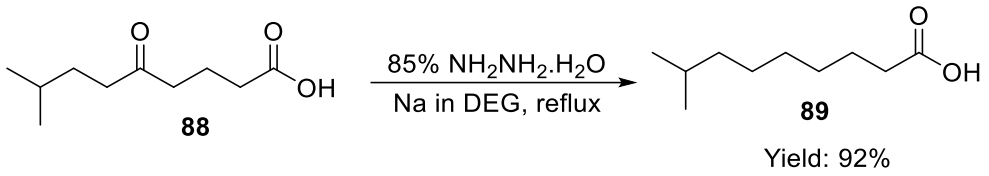


Scheme 2.41: Reduction of olefin by $N_2H_4.H_2O$ and O_2 using continuous flow method

2.3.2 Reduction of oxygen functional groups

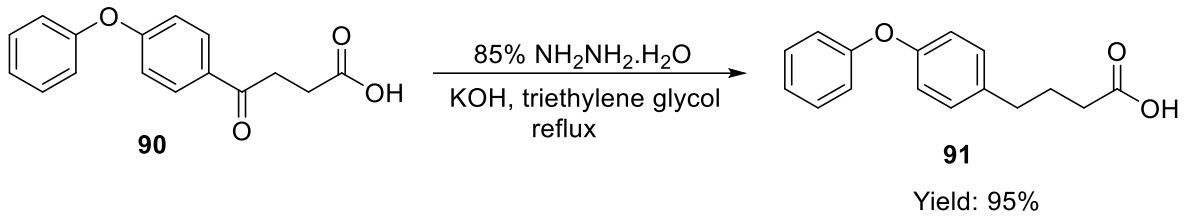
The deoxygenation of aldehydes and ketones to methyl or methylene derivatives respectively *via*heating the corresponding hydrazone (or semicarbazone) derivative in the presence of analkaline catalyst in a sealed tube at 160-200 °C. The reaction is known as Wolff-Kishner reduction.[84] Huang-Minlon[85, 86] used high boiling solvent like ethylene glycol or diethylene glycol (DEG) to avoid sealed tube techniques and made this a practical reaction at atmospheric pressure. Numerous modified procedures of Wolff-Kishner reduction have been reported. The improvement has focused on driving hydrazone formation to completion by removal of water and by the use of high concentrations of hydrazine.

Fieser reported the reduction of 5-keto-8-methylnonanoic acid **88** into isodecanoic acid **89** by using 85% hydrazine hydrate along with metallic sodium in diethylene glycol (DEG) under reflux conditions for 48h (**Scheme 2.42**).



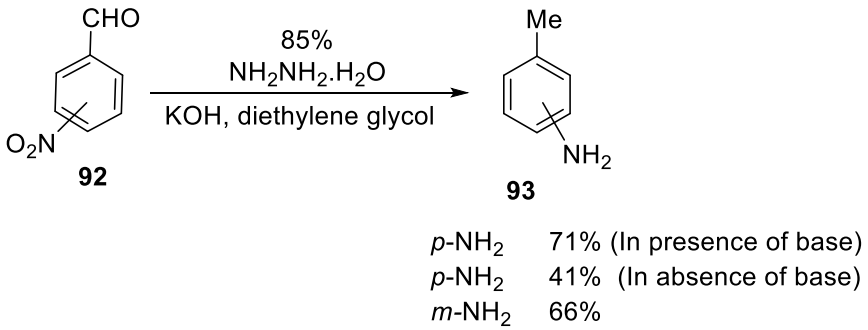
Scheme 2.42: Reduction of **112** into **113** using hydrazine hydrate in the presence of sodium in DEG

Huang-Minlon introduced sodium or potassium hydroxide in place of metallic sodium for the reduction of β-(*p*-Phenoxybenzoyl)-propionic acid (**90**) into 4-(*p*-phenoxyphenyl)butanoic acid (**91**) *via* 85% hydrazine hydrate in triethylene glycol at reflux condition (**Scheme 2.43**).[85] This methodology reduces the time and is applicable for the large-scale production with excellent yields.



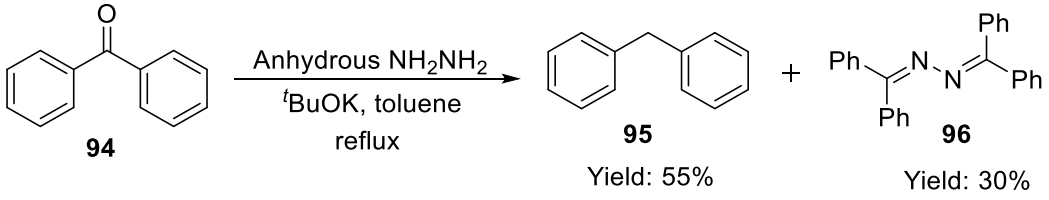
Scheme 2.43: Base-catalysed reduction of **90** into **91** using hydrazine hydrate at reflux

Huang-Minlongroup observed that nitro group also gets reduced during the reduction of a carbonyl group using 85% hydrazine hydrate in the presence of KOH in ethylene glycol. The *meta* and *para*-nitrobenzaldehyde **(92)** were reduced to the corresponding *meta* and *para*-toluidine **(93)** in 66% and 71% yield, respectively. In the case of *para*-nitrobenzaldehyde, *para*-toluidine was obtained in 41% yield in the absence of KOH base (**Scheme 2.44**). [87]



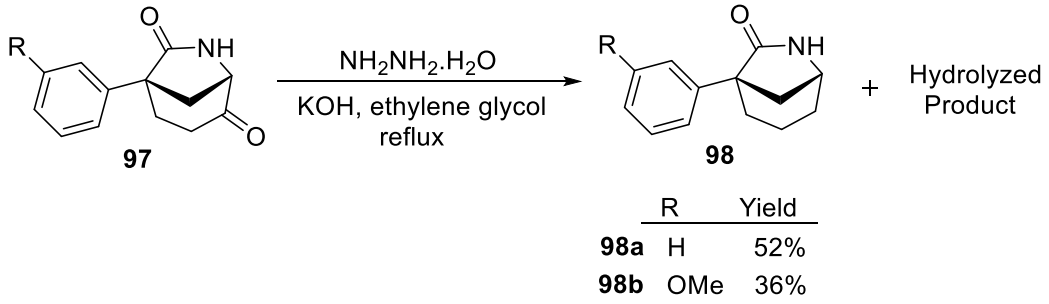
Scheme 2.44: Reduction of *meta* and *para*-nitrobenzaldehyde using 85% $NH_2NH_2.H_2O$ with and without KOH

Grundon *et al.* demonstrated the reduction of benzophenone (**94**) to diphenylmethane (**95)** along with benzophenone azine (**96**) in 50% and 30% yield respectively *via* anhydrous hydrazine in presence of potassium *t*-butoxide in toluene at reflux condition for 12 h (**Scheme 2.45**).[88] In the case of benzophenone hydrazone, the product **95** was obtained in 85% yield in 4 h under same reaction conditions. Use of DMSO as solvent furnished diphenylmethane (**95**) in lower yield after a longer reaction time.



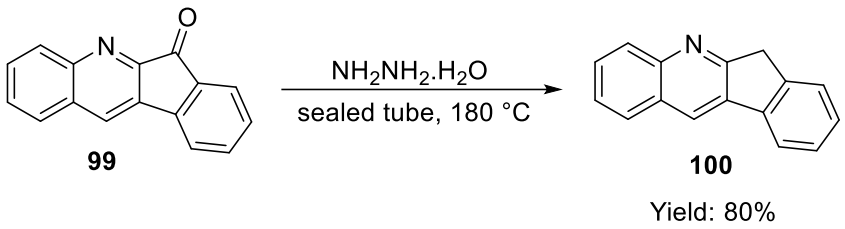
Scheme 2.45: Reduction of benzophenone (**94**) through anhydrous hydrazine

The highly basic condition of Wolff-Kishner reduction reaction is unsuitable for base-sensitive substrates such as esters and lactones which are normally hydrolyzed to the corresponding acids and alcohols and requires reesterification. Similarly, amides and lactam moieties are susceptible to attack. For instance, in 1976 Takeda group disclosed the Wolff-Kishner reduction of **97**(**a-b**) with hydrazine hydrate and potassium hydroxide in ethylene glycol to give **98**(**a-b**) in low yields due to the concomitant hydrolysis of the lactam (**Scheme 2.46**).[89]



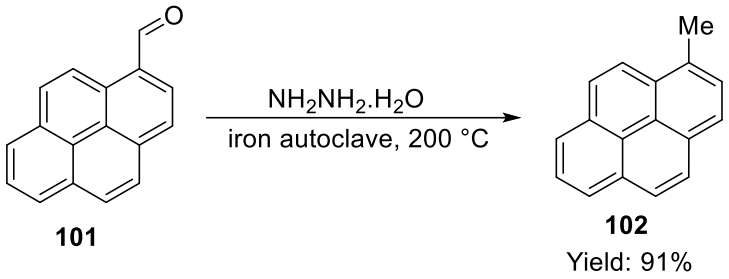
Scheme 2.46: Wolff-Kishner reduction of base-sensitive substrate **97**

There are certain instances in which carbonyl groups have been reduced to the hydrocarbons by excess hydrazine hydrate without the use of strong bases such as alkoxide or hydroxide.
In 1937, Borsche and co-workers demonstrated the reduction of 2,3-benzo-1-azafluorenone (**99**) into 2,3-benzo-1-azafluorene (**100**) by heating hydrazine hydrate in a sealed tube at 180 °C for 16 h (**Scheme 2.47**).[90]



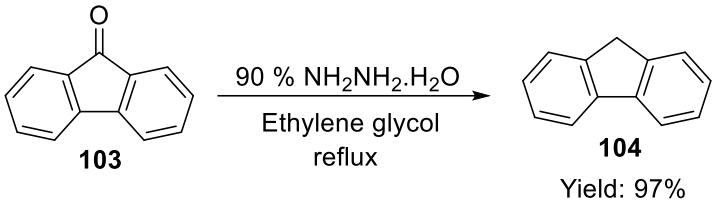
Scheme 2.47: Reduction of 2,3-benzo-1-azafluorenone (**99**) by hydrazine hydrate

In the same year, Vollmann *et al.* reported the reduction of pyrene-3-aldehyde **(101)** into 3-methylpyrene **(102)** in 91% yield by heating hydrazine hydrate at 200 °C in an iron autoclave for 8 h **(Scheme 2.48)**.[91]



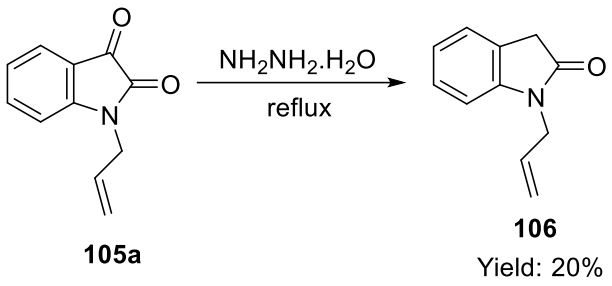
Scheme 2.48 : Reduction of pyrene-3-aldehyde **(101)** by hydrazine hydrate in an iron autoclave

Later, in 1955 Harris group described the reduction of fluorenone **(103)** by the Wolff-Kishner method without an alkaline catalyst in ethylene glycol in sealed tube and obtained fluorene (**104**) in 97% yield at reflux (**Scheme 2.49**).[92]



Scheme 2.49: Reduction of fluorenone (**103**) into fluorene (**104**) using hydrazine hydrate

To the best of our knowledge, since the first application of the Wolff–Kishner reaction in the synthesis of oxindoles from isatins, there is only one report of a Wolff–Kishner reduction on an *N*-ene-/yne-substituted isatin. Recently while describing the synthesis of the hodgkinsine and hodgkinsine B alkaloids, Willis *et al.* reported the synthesis of *N*-allyloxindole (**106**) from *N*-allylisatin (**105a**) in only 20% yield by using hydrazine hydrate (**Scheme 2.50**).[93]

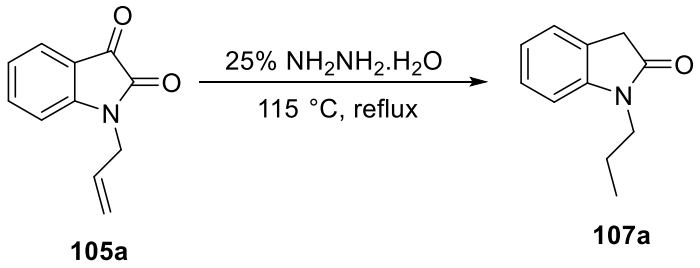


Scheme 2.50: Synthesis of *N*-allyl oxindole (**106**) by hydrazine hydrate

The reasons behind such a poor yield were not discussed in the paper. On the basis of our results, we suspect the loss in yield could be caused by the reduction of the allyl group under these conditions. It is quite possible that other researchers may have faced a similar challenge while attempting to prepare *N*-alkenyl/alkynyloxindoles from the corresponding isatins and the undesired results were never reported. In this chapter, we report the tandem reduction of oxo- and *N* ene-/yne-substituted isatins to oxindole derivatives, which offers novel insight into the scope of the Wolff–Kishner procedure. The reaction is performed under catalyst-free refluxing conditions in the presence of hydrazine hydrate (25% in H_2O). We believe these counter-intuitive results will be of significant importance to the synthetic and medicinal chemistry community.

2.4 Results and discussion

Inspired by previous reports of the Wolff–Kishner procedure for the preparation of oxindoles from isatins, we initially subjected *N*-allylisatin (**105a**) to an excess amount of hydrazine hydrate at reflux temperature (115 °C). Clean conversion of the reactant to the product was evidenced by TLC analysis. The NMR spectroscopic data of the isolated product revealed that along with the C3-oxo group of isatin the allyl group was also reduced efficiently to deliver 1-propyl-2-oxindole (**107a**) (**Scheme 2.51**).[26]



Scheme 2.51: Synthesis of 1-propyl-2-oxindole (**107a**) using 25% $NH_2NH_2.H_2O$

If the temperature of the reaction was lowered to 80 °C, the reaction did not go to completion. A significant amount of the starting material remained unreacted in the reaction mixture even after 48 h of heating. Subsequently, we settled with the reflux temperature and decided to investigate in detail the reduction of *N*-(2-alkenyl)/propargylisatins possessing differently substituted unsaturated carbon–carbon bonds by using hydrazine hydrate. Several substituted isatins were obtained from commercial sources and were converted into *N*-(2-alkenyl)/propargyl derivatives **105(a–n)** in quantitative yields by using reagents such as allyl bromide, prenyl bromide, cinnamyl bromide and propargyl bromide following a published procedure.[94] These substitutions are important as such and are also aptly suited for further chemical manipulations. The tandem reduction of the C-3 ketone and the olefinic group proceeded quite smoothly for isatins bearing monosubstituted and disubstituted unsaturations. The yields of the isolated products in all cases were found to be high except for nitro-substituted isatin **105j (**Table 2.1). Interestingly, the nitro group along with the oxo and olefin functionalities also underwent reduction to afford 5-amino-1-(3-phenylpropyl)indolin-2-one (**107j**) in 57% yield. Although the reduction of nitroarenes by using hydrazine hydrate has been previously reported, the use of an iron source appears to be a necessary condition to catalyze the reduction process.[95, 96] Furthermore and quite surprisingly, selective reduction of the C-3 oxo group was observed for *N*-prenyl-isatin (**105k**, a trisubstituted carbon–carbon unsaturation; Table 2.1, entry 11) to produce 1-prenyl-2-oxindole (**107k**). Even after 24 h of refluxing, the olefin group of **105k** was not reduced under these reaction conditions.

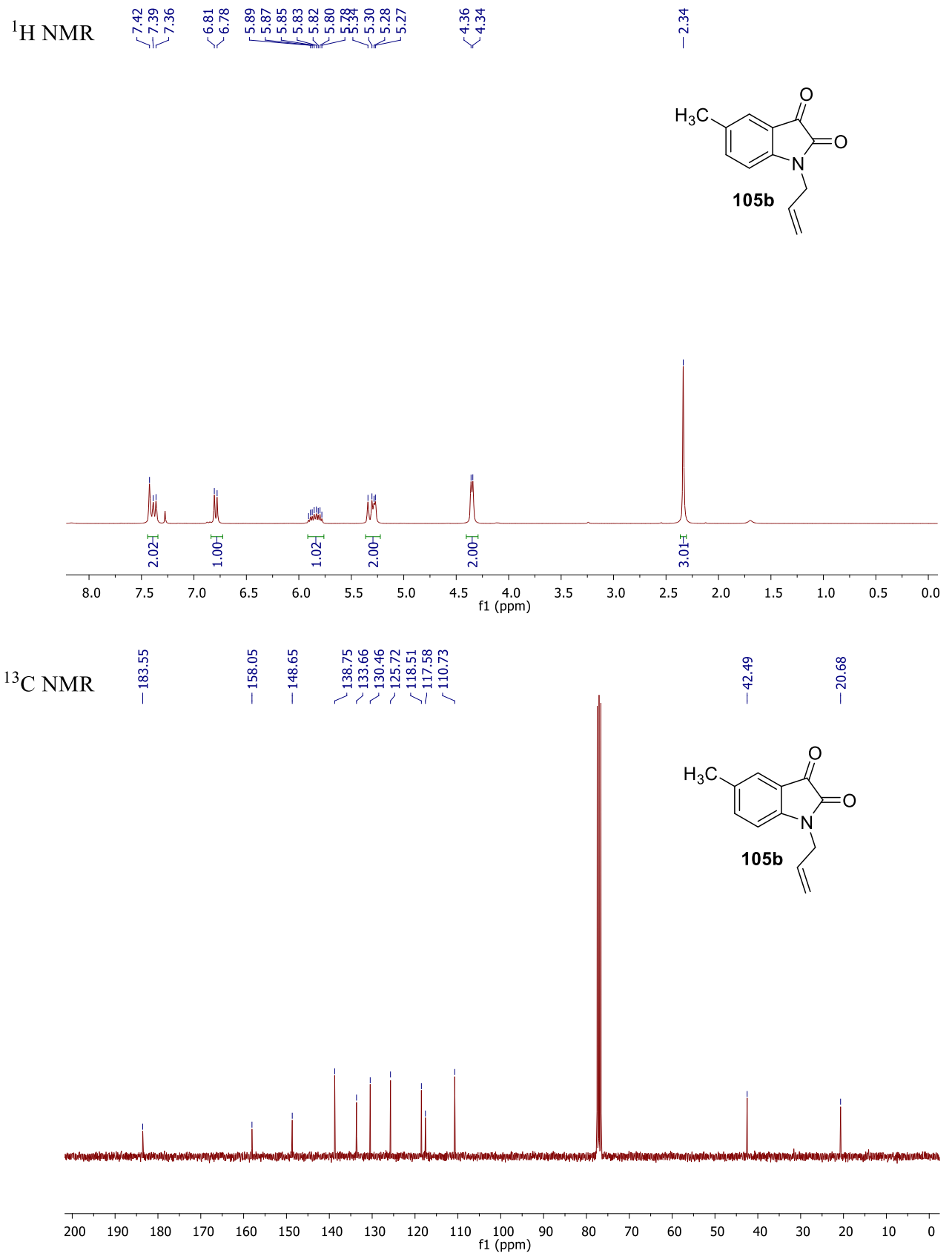


Figure 2.2: ^{1}H and ^{13}C NMR spectra of 1-allyl-5-methylindoline-2,3-dione **(105b)** in $CDCl_3$

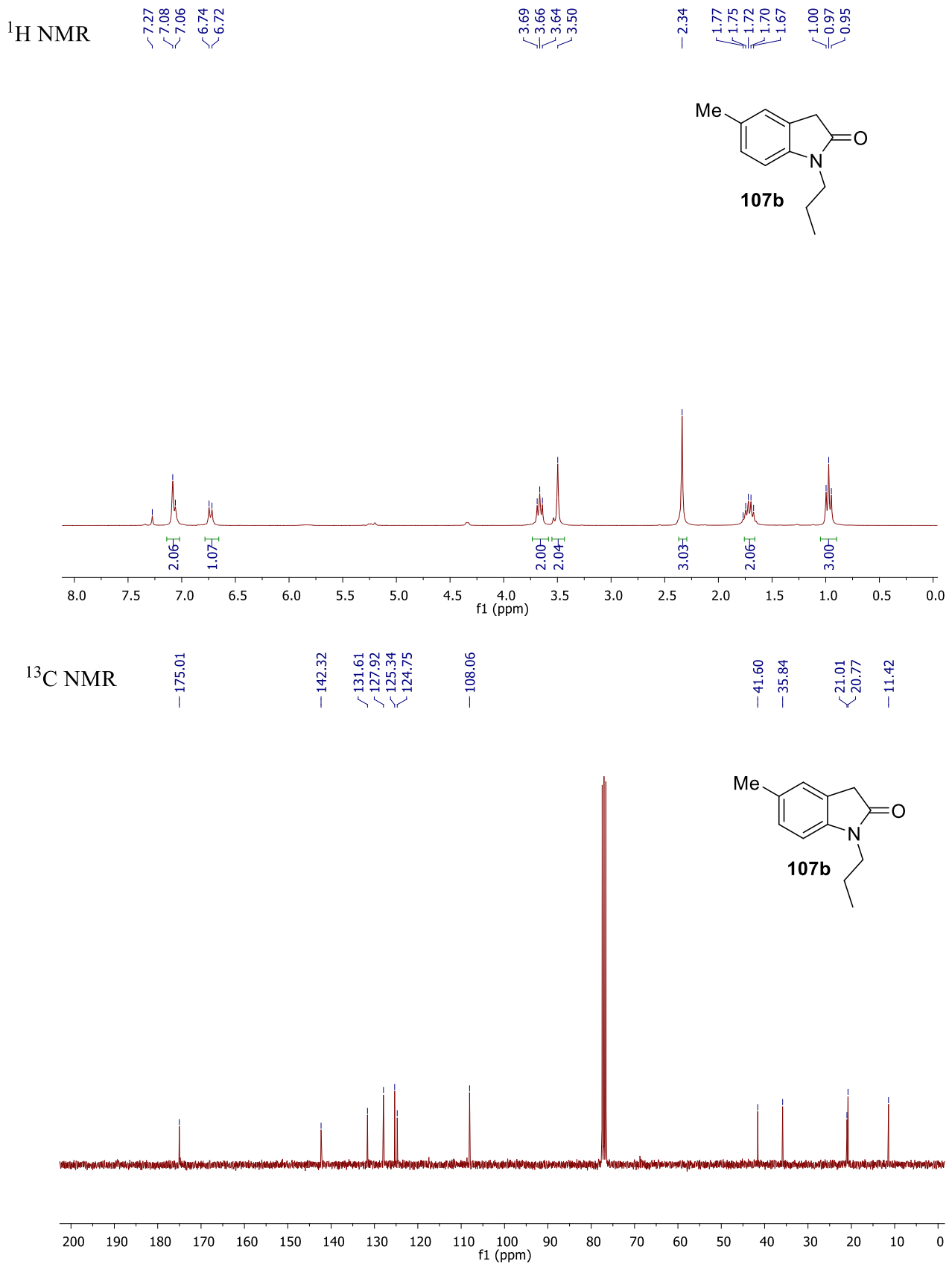
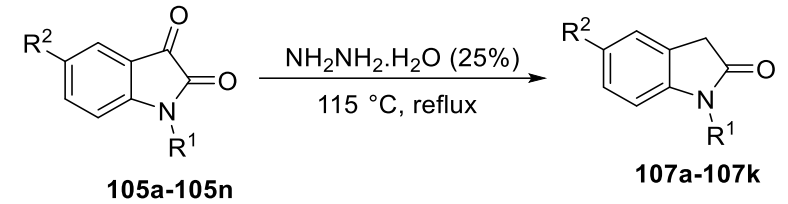


Figure 2.3: ^{1}H and ^{13}C NMR spectra of 5-methyl-1-propylindolin-2-one **(107b)** in $CDCl_3$

The yield (20%) for the synthesis of related compound *N*-allyloxindole by Willis *et al.* was reported to be in two steps starting from isatin (*N*-allylation followed by hydrazine-mediated reduction of the C-3 oxo group). Among the two steps, the *N*-allylation of isatin presumably proceeds in near-quantitative yield and we suspect the bulk of the loss in the yield might occur in the reduction step, as our results show that the allyl group is prone to reduction under these conditions (Table 2.1, entry 1).

Table 2.1. Tandem reduction of oxo- and ene-/yne-substituted isatins by using hydrazine hydrate.[a]



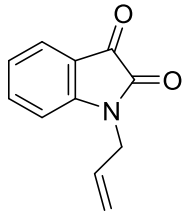
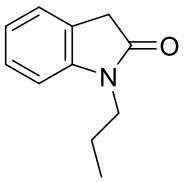
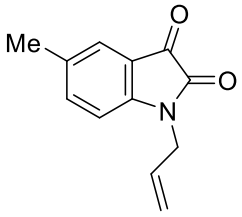
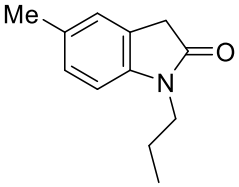
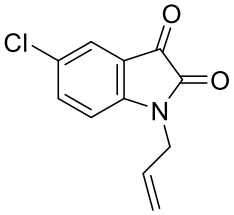
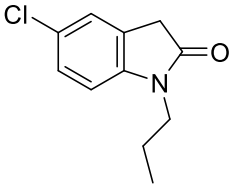
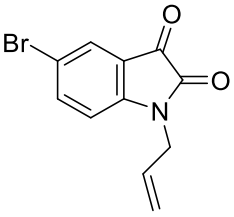
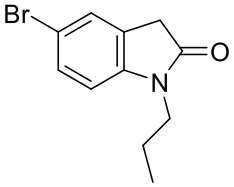
105a-105n

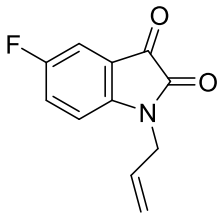
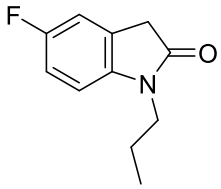
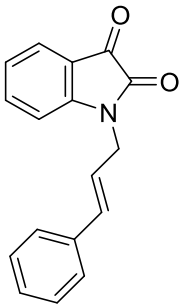
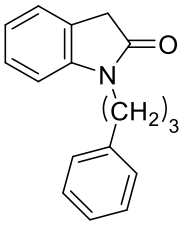
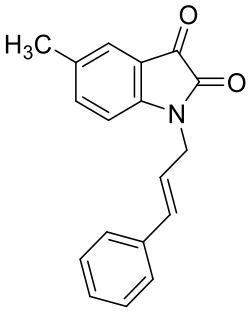
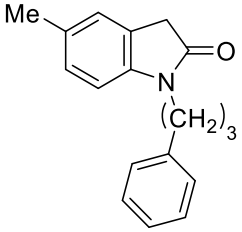
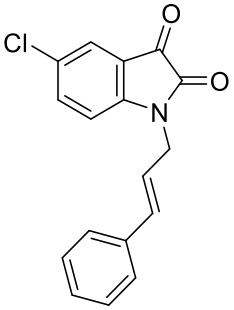
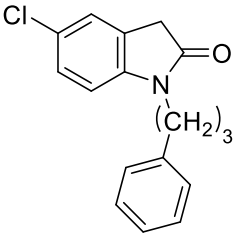
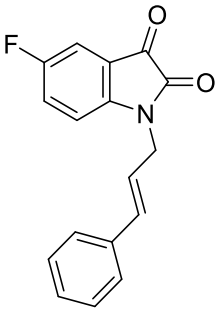
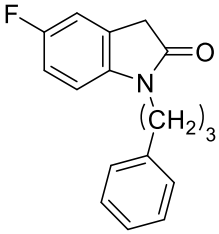
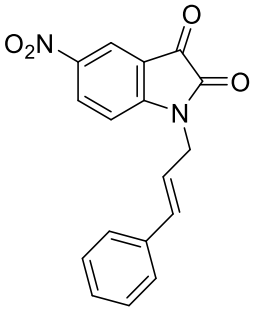
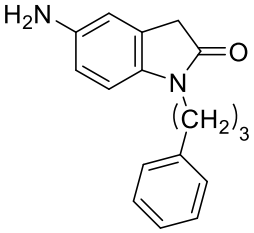
107a-107k

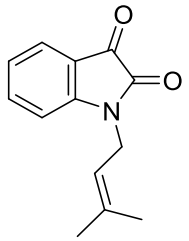
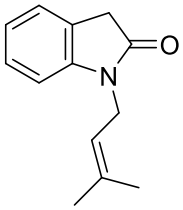
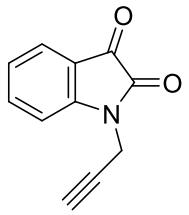
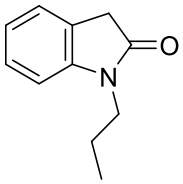
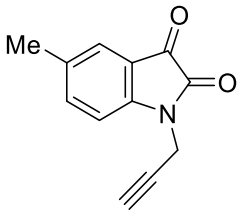
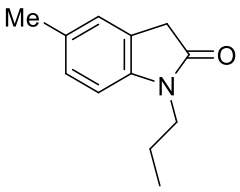
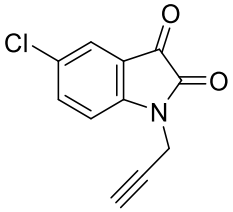
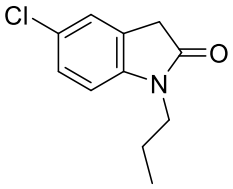
R^1 = allyl, cinnamyl, prenyl, propargyl

R^2 = H, CH_3, Cl, Br, F, NO_2

Yield: 52-89%

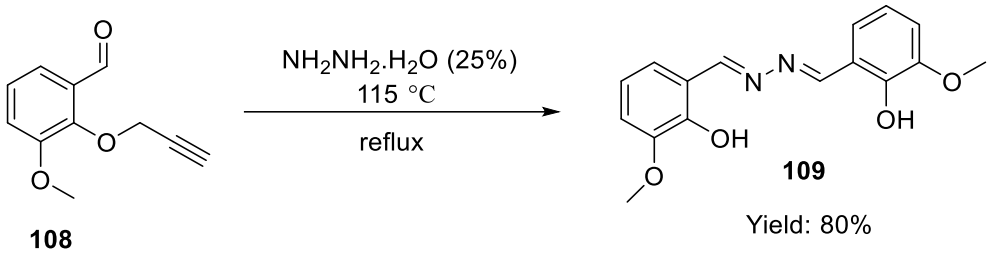
S. No.	Substrate		Product		Time (h)	Yield[b](%)
1		**105a**		**107a**	4	83
2		**105b**		**107b**	4	81
3		**105c**		**107c**	4	80
4		**105d**		**107d**	5	78

5		**105e**		**107e**	4	80
6		**105f**		**107f**	14	75
7		**105g**		**107g**	14	73
8		**105h**		**107h**	14	71
9		**105i**		**107i**	14	71
10		**105j**		**107j**	4	52

11		**105k**		**107k**	24	89
12		**105l**		**107a**	4	71
13		**105m**		**107b**	4	70
14		**105n**		**107c**	4	68

[a] Reaction conditions: Isatin (30 mg), $NH_2NH_2 \cdot H_2O$ (25%, 2 mL), reflux. [b] Yield if isolated product.

Next, isatins **105(l–n)** possessing an alkyne group were exposed to similar conditions. Remarkably, these propargyl substituted isatins also underwent a tandem reduction to produce 1-propyl-2-oxindoles **107(a-c)** quite efficiently (Table 2.1, entries 12–14). Encouraged by these results, we subsequently attempted to scale up the reaction from milligram scale to gram quantities. We were quite happy to find that the reaction could be scaled up without any difficulty. When 1g of *N*-allylisatin (**105a**) was heated at reflux in 30 mL of hydrazine hydrate (25%) for 4 h, 0.81 g of 1-propyl-2-oxindole (**107a**, 87%) was obtained. We further proceeded to investigate the reduction of compounds having a substitution make up of oxo– and carbon–carbon unsaturations, analogous to the isatins described below by using hydrazine hydrate (**Scheme 2.52**). Interestingly, such compounds that is 2-methoxy-6-(prop-2-ynyloxy)benzaldehyde **(108)**, underwent condensation with hydrazine to produce aldazine **109** under the reaction conditions. Notably, the alkyne functionality of the propargyl group of **108** was not reduced under these conditions, but the entire group was lost during the process **(Scheme 2.52)**. The spectroscopic data of **109** was found to be in agreement with the literature report **(Figure 2.4).**



Scheme 2.52. The reaction of hydrazine hydrate with 2-methoxy-6-(prop-2-ynyloxy)benzaldehyde (**108**)

It appears from our results that the tandem reduction of the oxo and ene/yne functionalities by using hydrazine is unique to *N*-(2-alkenyl)/propargylisatins, for which the reduction of the C-3 oxo group involves the well-known Wolff–Kishner mechanism and the reduction of the olefinic group is facilitated by the *in situ* formation of a diimide (created by the aerobic oxidation of hydrazine hydrate), which is consistent with the previously reported mechanism. Currently, we are actively evaluating the full scope of this mechanism.

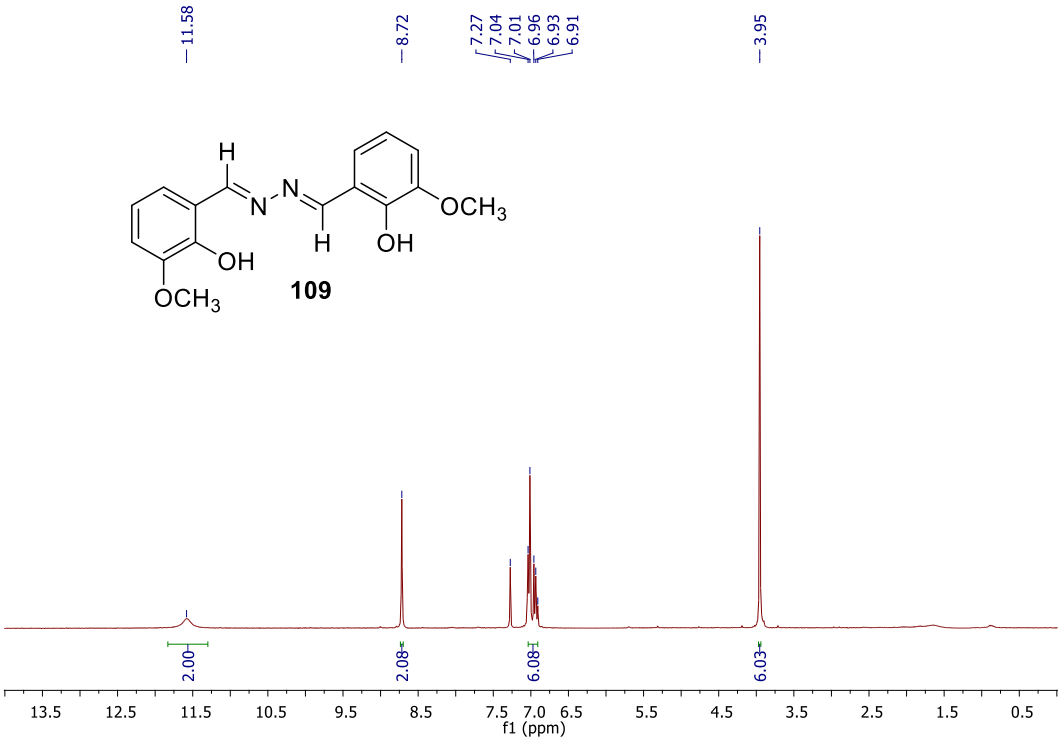


Figure 2.4a: ^{1}H NMR spectra of 6,6'-((1E,1'E)-hydrazine-1,2-diylidene-bis(methanylylidene))-bis(2-methoxyphenol) **(109)** in $CDCl_3$

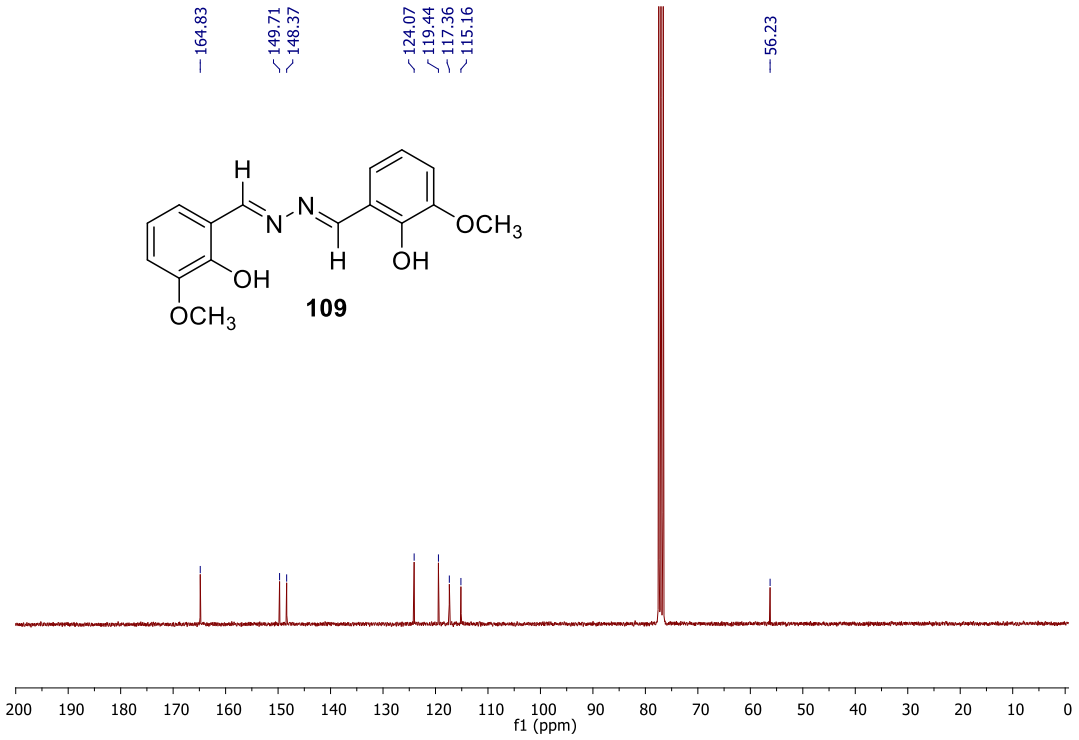


Figure 2.4b: ^{13}C NMR spectra of 6,6'-((1E,1'E)-hydrazine-1,2-diylidene-bis(methanylylidene))-bis(2-methoxyphenol) **(109)** in $CDCl_3$

2.5 Conclusions

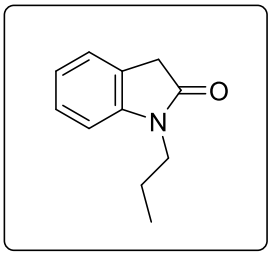
In conclusion, the reduction of *N*-(2-alkenyl)/propargylisatins by using hydrazine hydrate (25% in H_2O) led to *N*-alkyloxindoles. This is an unprecedented example of a tandem reduction of two functionalities (i.e., anoxo group and alkene/alkyne) present in isatin under catalyst-free conditionsat ambient pressure. The reaction offers clean conversion of the reactants into products in excellent yields, which can be easily scaled up to gram quantities. As an added advantage, the *N*-(2-alkenyl)/propargylisatins can potentially be further chemically manipulated (e.g., chain elongation by using the alkyne functionality) to prepare diversely substituted oxindoles. The observed counterintuitive double reduction provides further insight into the full scope of the Wolff–Kishner procedure to prepare substituted 2-oxindoles.

2.6 Experimental

All reagents and solvents were used as supplied by commercial sources without further purification. Commercially available hydrazine hydrate (reagent grade, 50-60%) was diluted to half its concentration using distilled water. Melting points were measured using an MEL-TEMP II apparatus and are uncorrected. Precoated fluorescent silica gel TLC plates were used to monitor the progress of the reactions. The ^{1}H and ^{13}C NMR spectra were obtained by a 300 MHz FT-NMR spectrometer. Chemical shifts of the ^{1}H NMR spectra are reported in parts per million (ppm) downfield from tetramethylsilane. IR spectra were recorded FT-IR Spectrometer and values are expressed in cm^{-1}. The ESI-MS spectra were obtained at the Department of Chemistry, Dalhousie University, by Mr. Xiao Feng.

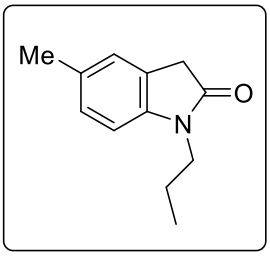
General procedure for the synthesis of substituted oxindoles by using hydrazine hydrate: *N*-(2-Alkenyl)/propargylisatin **105** (0.03 g) was mixed with hydrazine hydrate (25%, 2 mL) and heated at 115 °C (see Table 2.1 for the reaction time). Upon completion of thereaction (as evidenced by TLC), the excess amount of hydrazine hydrate was evaporated under reduced pressure and the residue was subjected to flash column chromatography (silica gel; hexanes/ethyl acetate, 96:04) to give 1-alkyl-2-oxindole **107**.

1-Propylindolin-2-one (107a).



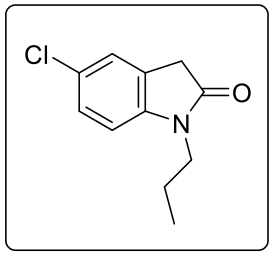
Yellow solid; mp 64-66 °C; FT-IR ν_{max} (neat): 2968, 2926, 2878, 2865, 1689, 1612, 1462, 1353, 743 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.20 (m, 2H), 7.03 (t, J= 7.5 Hz, 1H), 6.84 (d, J= 7.7 Hz, 1H), 3.69 (t, J= 7.4 Hz, 2H), 3.53 (s, 2H), 1.80–1.64 (m, 2H), 0.98 (t, J= 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 144.7, 127.8, 124.7, 124.4, 122.1, 108.4, 41.6, 35.8, 20.8, 11.4.

5-Methyl-1-propylindolin-2-one (**107b**)



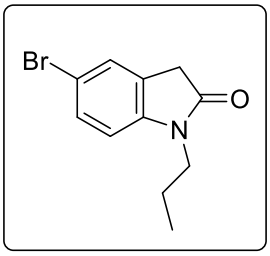
White solid; mp 102-104 °C; FT-IR ν_{max} (neat): 2960, 2920, 2869, 1704, 1494, 1343, 1202, 821, 743, 675 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13–7.00 (m, 2H), 6.73 (d, J = 8.0 Hz, 1H), 3.66 (t, J = 7.3 Hz, 2H), 3.50 (s, 2H), 2.34 (s, 3H), 1.78–1.62 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 142.3, 131.6, 127.9, 125.34, 124.7, 108.1, 41.6, 35.8, 21.0, 20.8, 11.4;ESI-MS m/z calcd for $C_{11}H_{12}NNaO$ $[M+Na]^+$: 212.1051; found $[M+Na]^+$: 212.1046.

5-Chloro-1-propylindolin-2-one (107c)



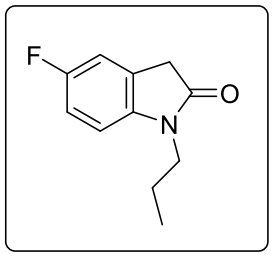
White solid; mp 115-116 °C; FT-IR νmax (neat): 2966, 2925, 2878, 1695, 1609, 1486, 1342, 820, 744, 648 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.18 (m, 2H), 6.75 (d, J = 8.6 Hz, 1H), 3.66 (t, J = 7.2 Hz, 2H), 3.52 (s, 2H), 1.75–1.63 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 143.3, 127.7, 127.4, 126.3, 124.9, 109.1, 41.7, 35.6, 20.7, 11.4.

5-Bromo-1-propylindolin-2-one (107d)



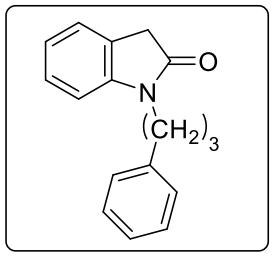
Yellow solid; mp 96-98 °C; FT-IR ν_{max} (neat): 2964, 2932, 2875, 1693, 1604, 1483, 1340, 820, 746, 667 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.33 (m, 2H), 6.71 (d, J = 8.1 Hz, 1H), 3.66 (t, J = 7.3 Hz, 2H), 3.53 (s, 2H), 1.78–1.63 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 143.8, 130.6, 127.6, 126.7, 114.7, 109.7, 41.7, 35.6, 20.7, 11.7.

5-Fluoro-1-propylindolin-2-one (107e).



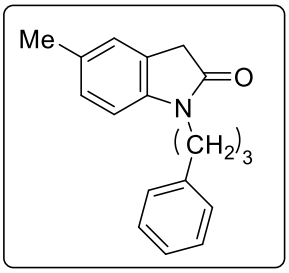
White solid; mp 110-112 °C; FT-IR ν_{max} (neat): 2970, 2946, 2927, 2880, 1691, 1605, 1490, 1452, 1345, 855, 811, 767, 748, 674 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06–6.90 (m, 2H), 6.74 (dd, J = 8.3, 4.1 Hz, 1H), 3.67 (t, J = 7.3 Hz, 2H), 3.53 (s, 2H), 1.78–1.61 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 159.0 (d, $^1J_{C\text{-}F}$ = 240 Hz) 140.6, 140.5, 126.2 (d, $^3J_{C\text{-}F}$ = 9 Hz), 114.0 (d, $^2J_{C\text{-}F}$ = 24 Hz), 112.6 (d, $^2J_{C\text{-}F}$ = 25 Hz), 108.6 (d, $^3J_{C\text{-}F}$ = 8 Hz), 41.7, 36.0, 20.7, 11.4;ESI-MS m/z calcd for $C_{11}H_{12}FNNaO$ $[M+Na]^+$: 216.0801; found $[M+Na]^+$: 216.0795.

1-(3-Phenylpropyl)indolin-2-one (107f).



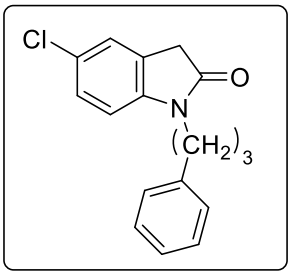
Brown liquid; FT-IR ν_{max} (neat): 2925, 2859, 1704, 1612, 1488, 1465, 1352, 1152, 745, 697 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.16 (m, 7H), 7.03 (t, J = 7.4 Hz, 1H), 6.74 (d, J = 7.9 Hz, 1H), 3.76 (t, J = 7.3 Hz, 2H), 3.52 (s, 2H), 2.72 (t, J = 7.7 Hz, 2H), 2.12–1.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 144.5, 141.1, 128.4, 128.3, 127.8, 126.1, 124.7, 124.5, 122.2, 108.3, 39.6, 35.8, 33.2, 28.8;ESI-MS m/z calcd for$C_{17}H_{17}NNaO$ $[M+Na]^+$: 274.1208; found $[M+Na]^+$: 274.1202.

5-Methyl-1-(3-phenylpropyl)indolin-2-one (**107g**).



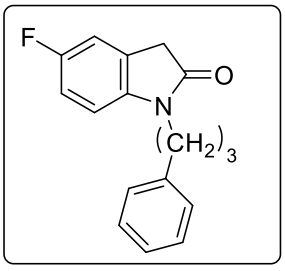
Yellow oil; FT-IR ν_{max} (neat): 2920, 2860, 1701, 1598, 1492, 1452, 1349,1171, 803, 745, 698 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.17 (m, 5H), 7.06 (d, J = 11.0 Hz, 2H), 6.63 (d, J = 7.8 Hz, 1H), 3.75 (t, J = 7.2 Hz,2H), 3.49 (s, 2H), 2.72 (t, J = 7.7 Hz, 2H), 2.34 (s, 3H), 2.10–1.93 (m, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 175.1, 142.1, 141.1, 131.7, 128.4, 128.3, 127.9, 126.1, 125.4, 124.7, 108.0,39.6, 35.8, 33.2, 28.8, 21.1;ESI-MS m/z calcd for$C_{18}H_{19}NNaO$ $[M+Na]^+$: 288.1364; found$[M+Na]^+$: 288.1359.

5-Chloro-1-(3-phenylpropyl)indolin-2-one (**107h**).



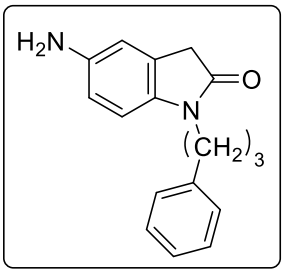
Yellow oil; FT-IR ν_{max} (neat): 2925, 2858,1703, 1611, 1551, 1482, 1346, 1156, 804, 746, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.17 (m, 7H), 6.62 (d, J = 8.8 Hz, 1H), 3.74 (t, 2H), 3.50 (s, 2H), 2.71 (t, J = 7.6 Hz,2H), 2.09–1.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 143.0, 140.9, 128.5, 128.3,127.7, 127.5, 126.3, 126.1, 124.9, 109.1, 39.7, 35.6, 33.1, 28.6;ESI-MS m/z calcd for$C_{17}H_{16}ClNNaO$ $[M+Na]^+$: 308.0818; found $[M+Na]^+$: 308.0813.

5-Fluoro-1-(3-phenylpropyl)indolin-2-one (**107i**).



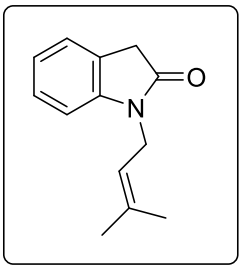
Yellow oil; FT-IR ν_{max} (neat): 2927, 2860, 1703, 1608, 1487, 1452, 1347, 1159, 805, 747, 698, 676 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.15 (m, 5H), 7.05–6.88 (m, 2H), 6.67–6.57 (m, 1H), 3.74 (t, J = 7.3 Hz, 2H), 3.51 (s, 2H), 2.72 (t, J = 7.6 Hz, 2H), 2.10–1.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 159.0 (d, $^1J_{C\text{-}F}$ = 240 Hz) 140.9, 140.5, 128.5, 128.3, 126.2 (d, $^3J_{C\text{-}F}$ = 8 Hz), 126.1, 113.9 (d, $^2J_{C\text{-}F}$ = 24 Hz), 112.6 (d, $^2J_{C\text{-}F}$= 24 Hz), 108.6 (d, $^3J_{C\text{-}F}$ = 8 Hz), 39.7, 36.0, 33.1, 28.6;ESI-MS m/z calcd for $C_{17}H_{16}FNNaO$ $[M+Na]^+$: 292.1114; found $[M+Na]^+$: 292.1108.

5-Amino-1-(3-phenylpropyl)indolin-2-one (**107j**).



Brown liquid; FT-IR ν_{max} (neat): 3344, 3225, 2924, 2857, 1677, 1595, 1491, 1357, 1200,806, 746, 698 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.14 (m, 5H), 6.76 (s, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 8.2 Hz, 1H), 3.71 (t, J = 7.0 Hz, 2H), 3.46 (s, 2H), 2.70 (t, J = 7.6 Hz, 2H), 2.10–1.90 (m, 2H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 174.5, 141.1, 139.8, 137.6, 128.4, 128.3, 126.1, 126.1, 114.8, 113.6, 108.8, 39.7,36.1, 33.2, 28.8;ESI-MS m/z calcd for $C_{17}H_{18}N_2NaO$ $[M+Na]^+$: 289.1303; found$[M+Na]^+$: 289.1311.

1-(3-Methylbut-2-enyl)indolin-2-one (**107k**).



Brown liquid; FTIRν_{max} (neat): 3055, 2915, 1703, 1612, 1465, 1350, 746 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.20 (m, 2H), 7.03 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 5.19 (t, J = 6.2 Hz, 1H),4.33 (d, J = 6.5 Hz, 2H), 3.54 (s, 2H), 1.84 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 144.6, 136.6, 127.7, 124.6, 124.3, 122.1, 118.4, 108.7, 38.0, 35.9, 25.6, 18.7;ESI-MS m/z calcd for$C_{13}H_{15}NNaO$ $[M+Na]^+$: 224.1051; found $[M+Na]^+$: 224.1046.

2.7 References

[1] Wiseman, E. H.; Chiaini, J.; McManus, J. M. *Journal of Medicinal Chemistry* **1973,** *16*, 131.

[2] Goehring, R. R.; Sachdeva, Y. P.; Pisipati, J. S.; Sleevi, M. C.; Wolfe, J. F. *Journal of the American Chemical Society* **1985,** *107*, 435.

[3] Kauffman, R. F.; Robertson, D. W.; Franklin, R. B.; Sandusky, G. E.; Dies, F.; McNay, J. L.; Hayes, J. S. *Cardiovascular Drug Reviews* **1990,** *8*, 303.

[4] Canas-Rodriguez, A.; Leeming, P. R. *Journal of Medicinal Chemistry* **1972,** *15*, 762.

[5] Ready, J. M.; Reisman, S. E.; Hirata, M.; Weiss, M. M.; Tamaki, K.; Ovaska, T. V.; Wood, J. L. *Angewandte Chemie International Edition* **2004,** *43*, 1270.

[6] Galliford, C. V.; Scheidt, K. A. *Angewandte Chemie International Edition* **2007,** *46*, 8748.

[7] Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Tuntland, T.; Zhang, K.; Karanewsky, D.; He, Y. *Bioorganic & Medicinal Chemistry Letters* **2006,** *16*, 2109.

[8] Natarajan, A.; Guo, Y.; Harbinski, F.; Fan, Y.-H.; Chen, H.; Luus, L.; Diercks, J.; Aktas, H.; Chorev, M.; Halperin, J. A. *Journal of Medicinal Chemistry* **2004,** *47*, 4979.

[9] Silva, B. V.; Ribeiro, N. M.; Pinto, A. C.; Vargas, M. D.; Dias, L. C. *Journal of the Brazilian Chemical Society* **2008,** *19*, 1244.

[10] Cerchiaro, G.; Ferreira, A. M. d. C. *Journal of the Brazilian Chemical Society* **2006,** *17*, 1473.

[11] Robinson, B., Chapter 5 Alkaloids of the Calabar Bean. In *The Alkaloids: Chemistry and Physiology*, Manske, R. H. F., Ed. Academic Press: **1968**; Vol. 10, p 383.

[12] Coxworth, E., Chapter 2 Alkaloids of the Calabar Bean. In *The Alkaloids: Chemistry and Physiology*, Manske, R. H. F., Ed. Academic Press: **1965**; Vol. 8, p 27.

[13] Fensome, A.; Adams, W. R.; Adams, A. L.; Berrodin, T. J.; Cohen, J.; Huselton, C.; Illenberger, A.; Kern, J. C.; Hudak, V. A.; Marella, M. A.; Melenski, E. G.; McComas, C. C.; Mugford, C. A.; Slayden, O. D.; Yudt, M.; Zhang, Z.; Zhang, P.; Zhu, Y.; Winneker, R. C.; Wrobel, J. E. *Journal of Medicinal Chemistry* **2008,** *51*, 1861.

[14] Li, P.; Buchwald, S. L. *Angewandte Chemie International Edition* **2011,** *50*, 6396.

[15] Li, P.; Buchwald, S. L. *Angewandte Chemie* **2011,** *123*, 6520.

[16] Karp, G. M. *Organic Preparations and Procedures International* **1993,** *25*, 481.

[17] Baeyer, A. *Berichte der deutschen chemischen Gesellschaft* **1868,** *1*, 17.

[18] Baeyer, A.; Knop, C. A. *Justus Liebigs Annalen der Chemie* **1866,** *140*, 1.

[19] Heller, G. *Berichte der deutschen chemischen Gesellschaft* **1904,** *37*, 938.

[20] Marschalk, C. *Berichte der deutschen chemischen Gesellschaft* **1912,** *45*, 582.

[21] Marschalk, C. *Journal für Praktische Chemie* **1913,** *88*, 227.

[22] Klab, L. *Berichte der deutschen chemischen Gesellschaft* **1911,** *44*, 1455.

[23] Colman, H. G. *Justus Liebigs Annalen der Chemie* **1888,** *248*, 114.

[24] Muchowski, J. M. *Canadian Journal of Chemistry* **1969,** *47*, 857.

[25] Soriano, D. S. *Journal of Chemical Education* **1993,** *70*, 332.

[26] Crestini, C.; Saladino, R. *Synthetic Communications* **1994,** *24*, 2835.

[27] Marfat, A.; Carta, M. P. *Tetrahedron Letters* **1987,** *28*, 4027.

[28] van Deurzen, M. P. J.; van Rantwijk, F.; Sheldon, R. A. *Journal of Molecular Catalysis B: Enzymatic* **1996,** *2*, 33.

[29] Bai, C.; Jiang, Y.; Hu, M.; Li, S.; Zhai, Q. *Catalysis Letters* **2009,** *129*, 457.

[30] Perez, D. I.; Grau, M. M.; Arends, I. W. C. E.; Hollmann, F. *Chemical Communications* **2009**, 6848.

[31] Vazquez, E.; Payack, J. F. *Tetrahedron Letters* **2004,** *45*, 6549.

[32] Kametani, T.; Ohsawa, T.; Ihara, M. *Journal of the Chemical Society, Perkin Transactions 1* **1981**, 290.

[33] Kawase, M.; Kitamura, T.; Kikugawa, Y. *The Journal of Organic Chemistry* **1989,** *54*, 3394.

[34] Cherest, M.; Lusinchi, X. *Tetrahedron Letters* **1989,** *30*, 715.

[35] Correa, A.; Elmore, S.; Bolm, C. *Chemistry – A European Journal* **2008,** *14*, 3527.

[36] Jhan, Y.-H.; Kang, T.-W.; Hsieh, J.-C. *Tetrahedron Letters* **2013,** *54*, 1155.

[37] Baeyer, A. *Berichte der deutschen chemischen Gesellschaft* **1878,** *11*, 582.

[38] Ting, P. C.; Kaminski, J. J.; Sherlock, M. H.; Tom, W. C.; Lee, J. F.; Bryant, R. W.; Watnick, A. S.; McPhail, A. T. *Journal of Medicinal Chemistry* **1990,** *33*, 2697.

[39] Gassman, P. G.; Van Bergen, T. J. *Journal of the American Chemical Society* **1973,** *95*, 2718.

[40] Gassman, P. G.; Van Bergen, T. J.; Gruetzmacher, G. *Journal of the American Chemical Society* **1973,** *95*, 6508.

[41] Gassman, P. G.; Van Bergen, T. J. *Journal of the American Chemical Society* **1974,** *96*, 5508.

[42] Gassman, P. G.; Gruetzmacher, G.; Van Bergen, T. J. *Journal of the American Chemical Society* **1974,** *96*, 5512.

[43] Wright, S. W.; McClure, L. D.; Hageman, D. L. *Tetrahedron Letters* **1996,** *37*, 4631.

[44] Wolff, J.; Taddei, M. *Tetrahedron* **1986,** *42*, 4267.

[45] Brunner, K. *Monatshefte für Chemie und verwandte Teile anderer Wissenschaften* **1896,** *17*, 479.

[46] Brunner, K. *Monatshefte für Chemie und verwandte Teile anderer Wissenschaften* **1897,** *18*, 95.

[47] Robertson, D. W.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. *Journal of Medicinal Chemistry* **1987,** *30*, 824.

[48] Fujita, K.-i.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Organic Letters* **2004,** *6*, 2785.

[49] Gandeepan, P.; Rajamalli, P.; Cheng, C.-H. *Synthesis* **2016,** *48*, 1872.

[50] Beckett, A. H.; Daisley, R. W.; Walker, J. *Tetrahedron* **1968,** *24*, 6093.

[51] Walker, J.; Daisley, R. W.; Beckett, A. H. *Journal of Medicinal Chemistry* **1970,** *13*, 983.

[52] Hamada, T.; Okuno, Y.; Ohmori, M.; Nishi, T.; Yonemitsu, O. *Chemical and Pharmaceutical Bulletin* **1981,** *29*, 128.

[53] Tamura, Y.; Yakura, T.; Shirouchi, Y.; Haruta, J.-I. *Chemical and Pharmaceutical Bulletin* **1986,** *34*, 1061.

[54] Tamura, Y.; Uenishi, J.-i.; Maeda, H.; Choi, H.-d.; Ishibashi, H. *Synthesis* **1981,** 534.

[55] Tamura, Y.; Uenishi, J.; Choi, H.; Haruta, J.; Ishibashi, H. *Chemical and Pharmaceutical Bulletin* **1984,** *32*, 1995.

[56] Wolfe, J. F.; Sleevi, M. C.; Goehring, R. R. *Journal of the American Chemical Society* **1980,** *102*, 3646.

[57] Jones, K.; Thompson, M.; Wright, C. *Journal of the Chemical Society, Chemical Communications* **1986**, 115.

[58] Wright, C.; Shulkind, M.; Jones, K.; Thompson, M. *Tetrahedron Letters* **1987,** *28*, 6389.

[59] Jones, K.; Wilkinson, J.; Ewin, R. *Tetrahedron Letters* **1994,** *35*, 7673.

[60] Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron Letters* **1988,** *29*, 6657.

[61] Mori, M.; Ban, Y. *Tetrahedron Letters* **1979,** *20*, 1133.

[62] Terpko, M. O.; Heck, R. F. *Journal of the American Chemical Society* **1979,** *101*, 5281.

[63] Mori, M.; Ban, Y. *Tetrahedron Letters* **1976,** *17*, 1807.

[64] Mori, M.; Hashimoto, Y.; Ban, Y. *Tetrahedron Letters* **1980,** *21*, 631.

[65] Canoira, L.; Rodriguez, J. G. *Journal of Heterocyclic Chemistry* **1985,** *22*, 1511.

[66] Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *The Journal of Organic Chemistry* **1998,** *63*, 6546.

[67] Lee, S.; Hartwig, J. F. *The Journal of Organic Chemistry* **2001,** *66*, 3402.

[68] Hennessy, E. J.; Buchwald, S. L. *Journal of the American Chemical Society* **2003,** *125*, 12084.

[69] Jha, M.; Chou, T.-Y.; Blunt, B. *Tetrahedron* **2011,** *67*, 982.

[70] Furst, A.; Berlo, R. C.; Hooton, S. *Chemical Reviews* **1965,** *65*, 51.

[71] Aylward, F.; Rao, C. V. N. *Journal of Applied Chemistry* **1956,** *6*, 248.

[72] Hünig, S.; Müller, H. R.; Thier, W. *Angewandte Chemie International Edition in English* **1965,** *4*, 271.

[73] Corey, E. J.; Mock, W. L.; Pasto, D. J. *Tetrahedron Letters* **1961,** *2*, 347.

[74] Hoffman, J. M.; Schlessinger, R. H. *Journal of the Chemical Society D: Chemical Communications* **1971**, 1245.

[75] Mori, K.; Ohki, M.; Sato, A.; Matsui, M. *Tetrahedron* **1972,** *28*, 3739.

[76] Back, T. G.; Collins, S.; Kerr, R. G. *The Journal of Organic Chemistry* **1981,** *46*, 1564.

[77] Moriarty, R. M.; Vaid, R. K.; Duncan, M. P. *Synthetic Communications* **1987,** *17*, 703.

[78] Wilt, J. W.; Gutman, G.; Ranus, W. J.; Zigman, A. R. *The Journal of Organic Chemistry* **1967,** *32*, 893.

[79] Ebersole, R. C.; Chang, F. C. *The Journal of Organic Chemistry* **1973,** *38*, 2579.

[80] Christl, M.; Brüntrup, G. *Chemische Berichte* **1974,** *107*, 3908.

[81] Kondo, K.; Murai, S.; Sonoda, N. *Tetrahedron Letters* **1977,** *18*, 3727.

[82] Roberts, R. A.; Schuell, V.; Paquette, L. A. *The Journal of Organic Chemistry* **1983,** *48*, 2076.

[83] Pieber, B.; Martinez, S. T.; Cantillo, D.; Kappe, C. O. *Angewandte Chemie International Edition* **2013,** *52*, 10241.

[84] Todd, D., The Wolff-Kishner Reduction. In *Organic Reactions*, John Wiley & Sons, Inc.: **2004**.

[85] Huang, M. *Journal of the American Chemical Society* **1946,** *68*, 2487.

[86] Huang, M. *Journal of the American Chemical Society* **1949,** *71*, 3301.

[87] Huang, M. *Journal of the American Chemical Society* **1948,** *70*, 2802.

[88] Grundon, M. F.; Henbest, H. B.; Scott, M. D. *Journal of the Chemical Society (Resumed)* **1963**, 1855.

[89] Takeda, M.; Inoue, H.; Noguchi, K.; Honma, Y.; Kawamori, M.; Tsukamoto, G.; Saito, S. *Chemical and Pharmaceutical Bulletin* **1976,** *24*, 1002.

[90] Borsche, W. *Justus Liebigs Annalen der Chemie* **1937,** *532*, 127.

[91] Vollmann, H.; Becker, H.; Corell, M.; Streeck, H. *Justus Liebigs Annalen der Chemie* **1937,** *531*, 1.

[92] Harris, A. S.; White, E. N.; McNeil, D. *Journal of the Chemical Society (Resumed)* **1955**, 4216.

[93] Snell, R. H.; Durbin, M. J.; Woodward, R. L.; Willis, M. C. *Chemistry – A European Journal* **2012,** *18*, 16754.

[94] Rambabu, D.; Kiran Kumar, S.; Yogi Sreenivas, B.; Sandra, S.; Kandale, A.; Misra, P.; Basaveswara Rao, M. V.; Pal, M. *Tetrahedron Letters* **2013,** *54*, 495.

[95] Cantillo, D.; Moghaddam, M. M.; Kappe, C. O. *The Journal of Organic Chemistry* **2013,** *78*, 4530.

[96] Lauwiner, M.; Rys, P.; Wissmann, J. *Applied Catalysis A: General* **1998,** *172*, 141.

Chapter III

Transition Metal Catalyzed Synthesis of Indole-fused Sulfur Containing Heterocyclic Compounds

3.1 INTRODUCTION

The reactions catalyzed by transition metals constitute a large part of the tools used in organic synthesis. The presence of empty energetically accessible d-orbitals make complexes of transition metals favorite aides in the never-ending quest for ways to build new molecules. Transition metals have unique ability to activate various organic compounds and through this activation they can catalyze various cross-coupling reactions such as Kumada,[1] Negishi,[2, 3] Buchwald-Hartwig,[4-6] Heck,[7] Suzuki–Miyaura,[8, 9] Stille,[10-12] Ullmann coupling and condensation,[13] Hiyama,[14] Sonogashira,[15] etc. which are very powerful methods for the creation of carbon-carbon (C-C) and carbon-hetero (C-Y) bonds, where Y = N, O, S, P, Si, B (**Figure 3.1**). These reactions have been successfully applied in the pharmaceutical, agrochemical and fine chemical industries.[16]

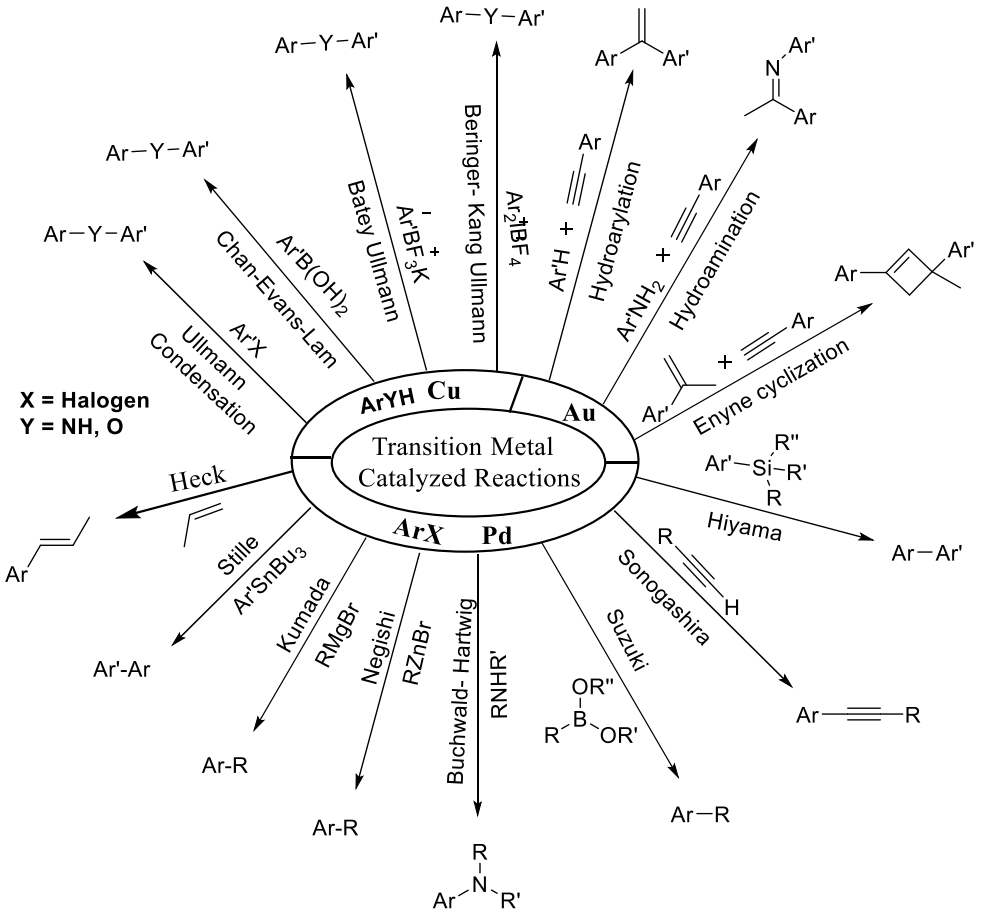


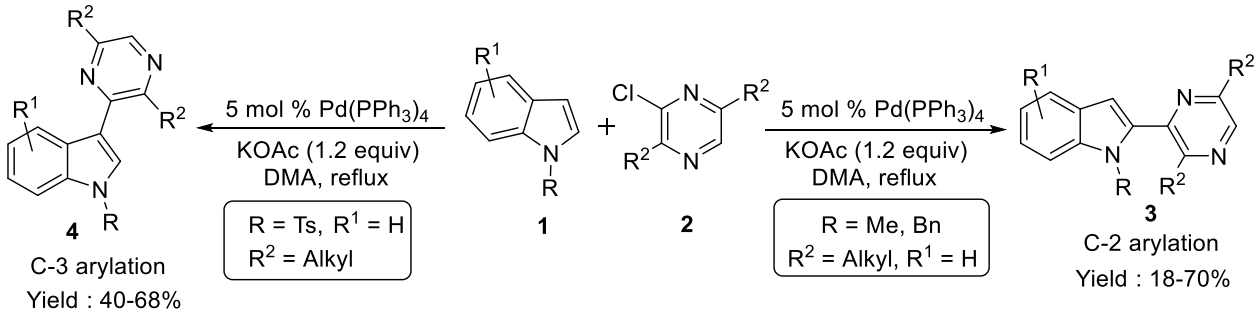
Figure 3.1: Transition metal catalyzed reactions for the construction of C-C and C-Y bond

Chapter III of the thesis is focused on the synthesis of novel indole-annulated heterocyclic compounds using transition metals (Pd, Cu and Au) catalyzed reactions. A brief overview of recent development in the transition metal catalyzed synthesis and C-H and N-H functionalization of indole based heterocycles.

3.1.1 Palladium-catalyzed coupling reactions of indole derivatives

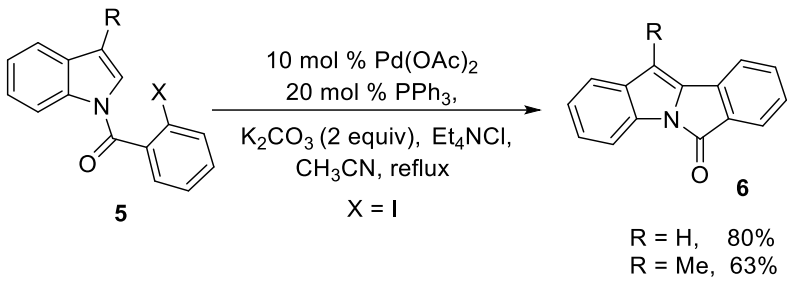
Palladium catalyzed arylation of heteroaromatics with aryl halides, is the most developed type of C–H functionalization of heterocyclic compounds. This chemistry has been rapidly growing and new types of direct intra- and inter-molecular reactions as well as cascade transformations of heterocycles, such as C-H arylation, heteroarylation have been developed. Palladium complexes are among the most frequently used catalysts for the functionalization of heteroaromatic compounds.

Ohta and co-workers reported first direct C-2 and C-3 arylation of *N*-alkylated indoles **1** with 2-chloro-3,6-dialkylpyrazines (**2**) in the presence of 5 mol % $Pd(PPh_3)_4$ and 1.2 equiv of potassium acetate (KOAc) in *N,N*-dimethylacetamide (DMA) under reflux condition (**Scheme 3.1**).[17] They found that 1-tosylindole furnished C-3 arylated products **4** in moderate to good yields. Whereas 1-alkyl and benzylindoles under the same conditions afforded C-2 arylated products **3**.



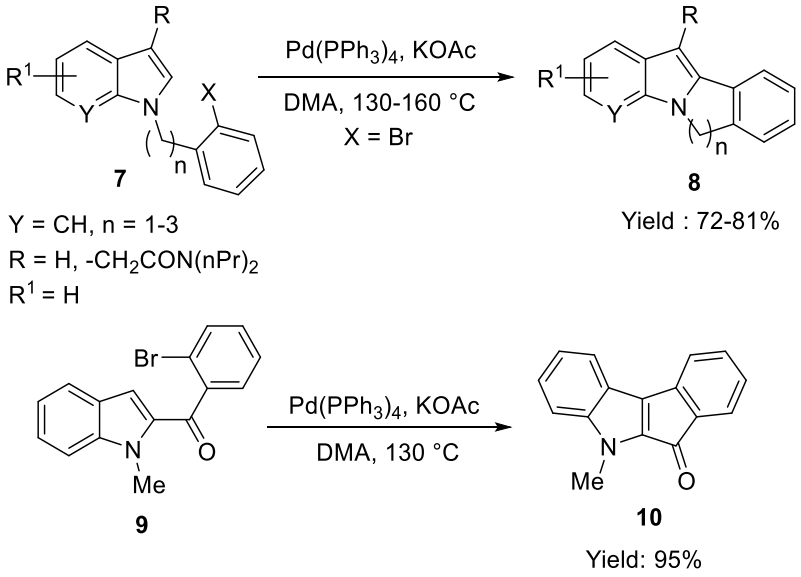
Scheme 3.1: Selective C-2 and C-3 arylation of indoles **1** with chloropyrazines **2**

Ronald Grigg reported an intramolecular arylation of iodo-1-aroylindoles **5** in the presence of 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, 2 equiv K_2CO_3 and tetraethylammonium chloride affording good yields of tetracyclic products **6** (**Scheme 3.2**).[18-20] Lower yield was obtained when indole **5** was substituted at C-3 position as compared to unsubstituted derivative.



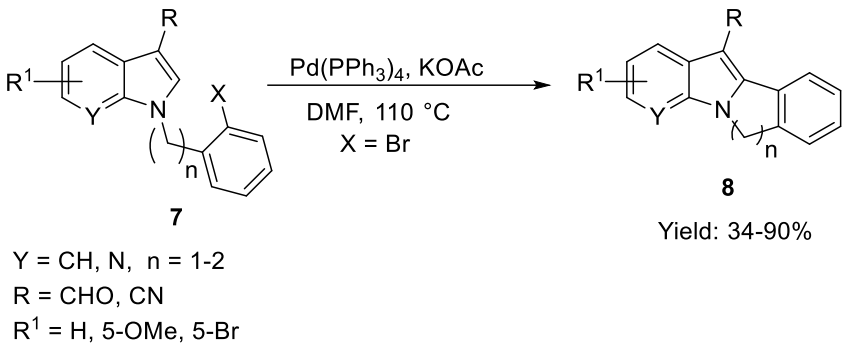
Scheme 3.2: Pd-catalyzed intramolecular arylation of iodo-1-aroylindoles **5**

Kozikowski described a methodology towards the synthesis of polycyclic indoles **8** and **10** featuring intramolecular cyclization of indoles **7** and **9** respectively (**Scheme 3.3**).[21] It was demonstrated that intramolecular C–H arylation proceeded readily in the presence of $Pd(PPh_3)_4$ and KOAc in dimethylacetamide (DMA) affording polycyclic products **8** and **10** in very good yields.



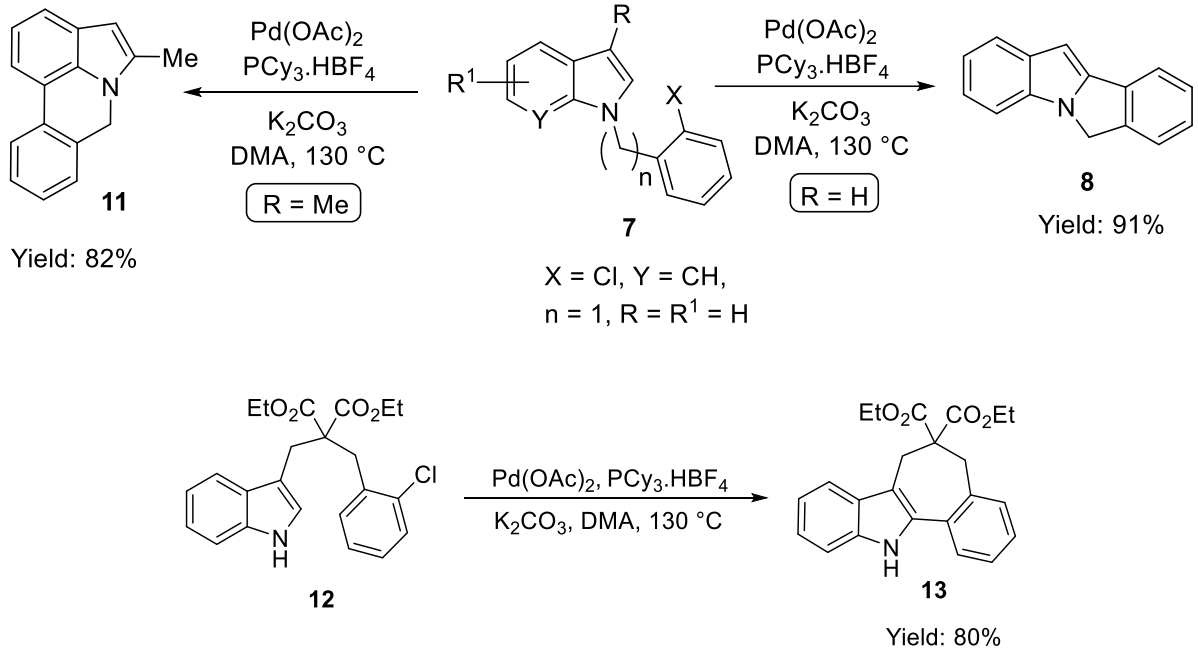
Scheme 3.3: Synthesis of polycyclic indoles **8** and **10**

Later, Merour developed a palladium catalyzed method for the intramolecular annulation of **7**, leading to polycyclic indole- and pyrrolo[2,3-*b*]pyridine containing structures **8** (**Scheme 3.4**).[22] Annulated products **8** were obtained in moderate to high yields and sensitive functional groups such as aldehyde, cyano and halogens were very well tolerated under these conditions.



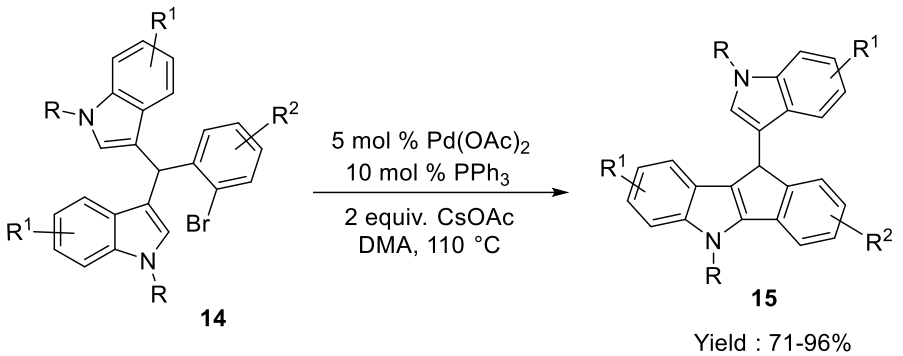
Scheme 3.4: Intramolecular cyclization of **7** with sensitive functional group

Fagnou group reported an intramolecular arylation of heteroarenes indole **7** and **12** using catalytic system $Pd(OAc)_2$ (1 mol %), $PCy_3.HBF_4$ (2 mol %) and 2 equiv. of K_2CO_3 in DMA affording indole-fused polycyclic ring systems **8**, **11** and **13** in good to high yields (**Scheme 3.5**).[23, 24]



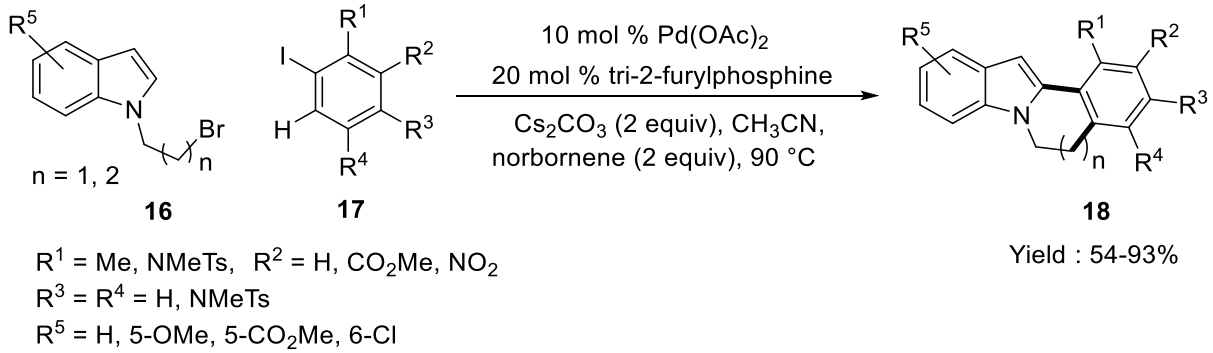
Scheme 3.5: Pd-catalyzed intramolecular direct arylation of indoles **7** and **12**

Shun Ji group demonstrated the synthesis of fused tetracyclic *bis*indole alkaloid analogs **15** *via* palladium catalyzed intramolecular direct C-H arylation of symmetrical and unsymmetrical 3,3'-*bis*(1*H*-indol-3-yl)methanes derivatives **14** (**Scheme 3.6**).[25] *Bis*(indolyl)methanes having different functional groups gave corresponding tetracyclic compounds in good to excellent yield.

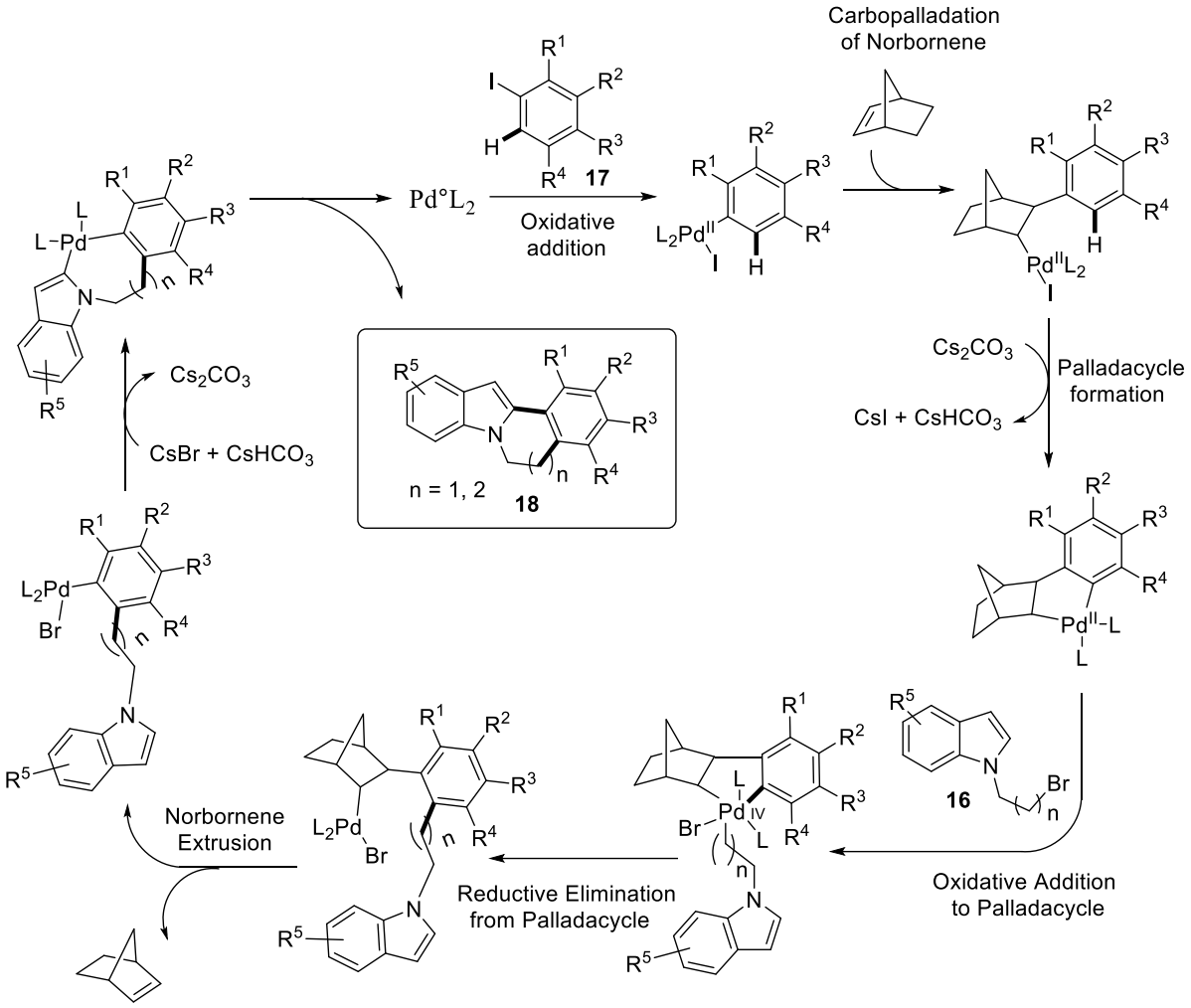


Scheme 3.6: Pd-catalyzed intramolecular indole C-2 arylation of *bis*indole derivatives **14**.

Lautens and co-workers reported the annulation of *N*-bromoalkylindoles **16** and aryl iodides **17** in the presence of catalytic amounts of $Pd(OAc)_2$, tri-2-furylphosphine, Cs_2CO_3 and a stoichiometric amount of norbornene to generate six- and seven-membered ring annulated indoles **18** (**Scheme 3.7**). This method involved Catellani norbornene-mediated Pd-catalyzed tandem *ortho*-alkylation/C–H functionalization between an aryl iodide and *N*-bromoalkylindoles.[26] Optimized conditions were applied to a number of substituted indoles and aryl iodides with electron-donating and electron-withdrawing groups, where both were shown to be well tolerated and produced consistently good to excellent yields of corresponding annulated indoles.



Scheme 3.7a: Synthesis of annulated indoles **18** *via* Pd-catalyzed tandem alkylation/direct arylation reaction

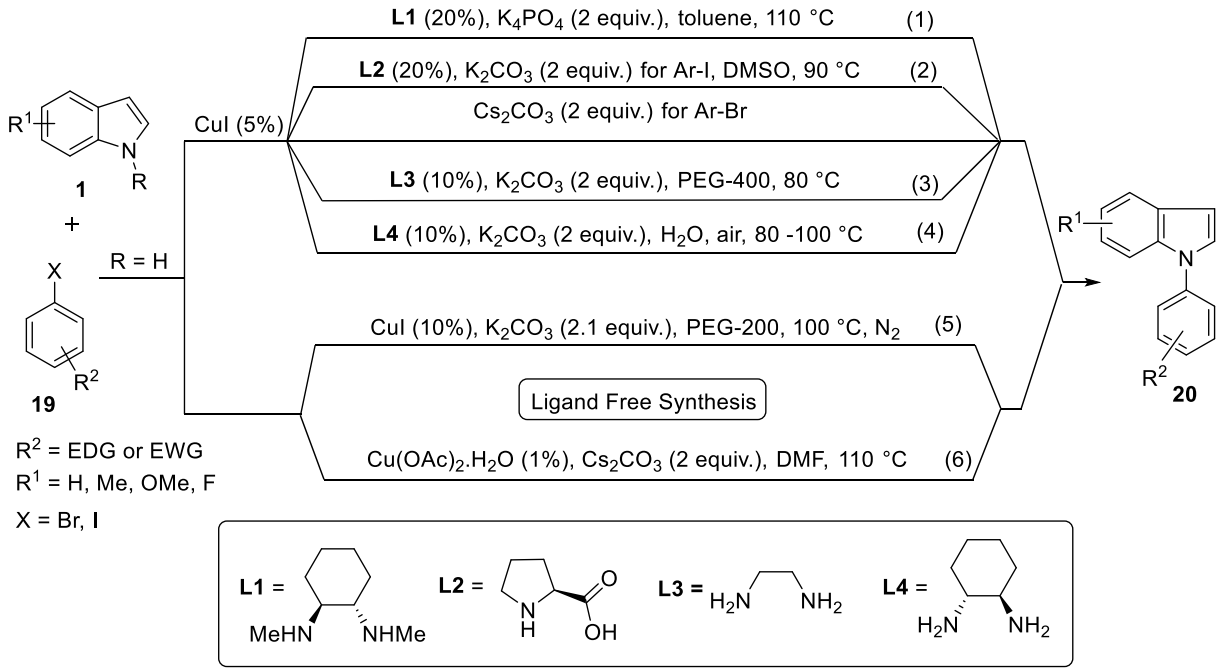


Scheme 3.7b: Proposed reaction mechanism for the synthesis of annulated indoles **18**

3.1.2 Copper-catalyzed coupling reactions of indole derivatives

Despite wide applicability and high efficiency of Pd-based catalytic systems, the high cost of the catalyst stimulates the development of cheaper alternatives. The resurgence of interest in Ullmann-type reactions and application of copper catalysts for carbon–carbon and carbon–heteroatom bond formation as well as other reactions are clearly observed in recent years. Many research groups have been involved in the development of more efficient copper/ligand combinations to widen the scope of such reactions in terms of substrate tolerance, copper loading, milder reaction conditions, enhanced chemoselectivity and enantioselectivity.[27] The progress has been so spectacular that, in numerous cases, the use of copper systems is now a serious rival for the alternative palladium-catalyzed procedures. The range of nucleophiles

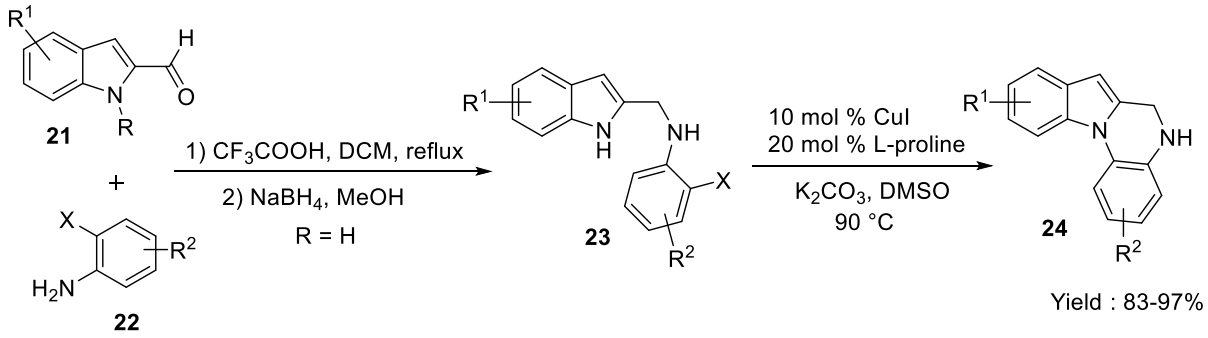
suitable for Ullmann-type arylations has become wider with time and nowadays N-, O-, S-, P- and C-aryl bonds formation are easily accessible through these processes. Such bonds can be found in many bioactive organic compounds[28, 29] as well as in materials chemistry.[30, 31] The following are the examples of Ullmann-type reactions namely those Cu-catalysed *N*-arylations of indole derivatives in which aryl halides are involved. Buchwald and co-workers demonstrated the known copper chelating high efficiency of 1,2-diamine ligand **L1** for the coupling of substituted aryl bromides and iodides **19** with a variety of indoles **1**. The desired *N*-arylindoles **20** were obtained in yields up to 99% under the usual conditions (**Scheme 3.8,** Eq. (**1**)).[32] Ma and co-workers showed that amino acid L-proline bidentate ligand **L2** was particularly effective and led to the successful coupling of numerous aryl bromides and iodides **19** with various indoles **1**, often at a mild temperature (**Scheme 3.8,** Eq. (**2**)).[33] Chandrasekhar achieved efficiently Buchwald *N*-arylation of indole in PEG-400 as solvent medium in the presence of CuI/ligand **L3** system under mild reaction conditions (**Scheme 3.8,** Eq. (**3**)).[34] Nageswar and co-workers discovered the Cu-catalysed C-N cross coupling of aryl bromides or iodides **19** with substituted indoles **1** by using 1,2-diaminocyclohexane **L4** as ligand and water as an environmentally benign, safe, and nontoxic reaction medium (**Scheme 3.8**, Eq. (**4**)).[35]



Scheme 3.8: Selected examples of the copper-catalyzed C-N bond formation between substituted indole **1** and various aryl bromide or iodides **19**.

Lately, several "ligand-free" systems have emerged for the *N*-arylation of indole catalyzed by copper compounds. Jun Luo group reported the synthesis of *N*-arylindole **20** in good to excellent yield using coupling of aryl bromides or iodides **19** and substituted indole **1** under "ligand-free" conditions with 10 mol % of CuI in the presence of K_2CO_3 as a base in PEG-200 media (**Scheme 3.8**, Eq. (**5**)).[36] A similar ligand-free system was reported by Lang and co-workers but relatively low catalyst amount of $Cu(OAc)_2.H_2O$ (1 mol %) was used to catalyze *N*-arylation of indole with aryl iodides in the presence of 2 equiv. Cs_2CO_3 as a base in DMF (**Scheme 3.8**, Eq. (**6**)).[37]

Liu and co-workers developed an efficient synthesis of tetracyclic products, 5,6-dihydroindolo[1,2-*a*]quinoxalines **24** *via* copper catalyzed intramolecular C-N coupling reaction under microwave irradiation (**Scheme 3.9**).[38] Good to excellent yields of **24** were obtained using a catalytic system of CuI/L-proline/K_2CO_3 in DMSO under microwave irradiation in 45 minutes. The required cyclization precursors, aryl substituted (1*H*-indol-2-yl)methanamines **23** were easily prepared by reductive amination of 1*H*-indole-2-carbaldehydes **21** with 2-haloanilines **22** in good yields.



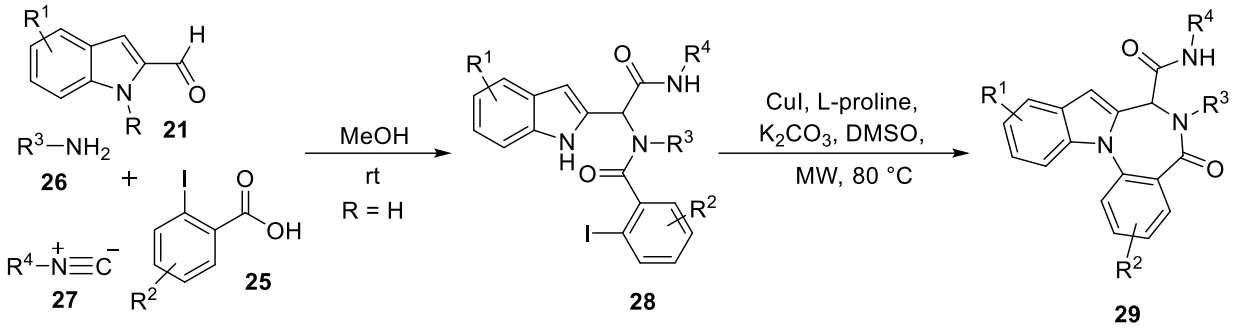
R^1 = H, 5-F, 5-Br, 5-NO_2, 5-Me, 5-OMe
R^2 = H, 5-Cl, 5-F, 4-Cl, 4-Me, 4-CF_3
X = I, Br

Scheme 3.9: Synthesis of 5, 6-dihydroindolo[1,2-*a*]quinoxalines **24** by CuI catalyzed intramolecular *N*-arylation

Liu group constructed a library of indole based heterocyclic compounds by a sequence of Ugi four-component reactions incorporating the indole motif and copper catalyzed C-N coupling (**Scheme 3.10a**).[39] The Ugi products **28** were synthesized by condensation of 1*H*-indole-2-carbaldehydes **21**, 2-iodobenzoic acids **25**, amines **26** and isocyanides **27**. The linear precursors **28** contain five potential nucleophilic sites, i.e. indole C-3, indole N-1, the α-C of the secondary

amide, the oxygen and NH of the secondary amide. When substrates **28** were subjected to copper catalysis**,** N-1 arylation products **29** were preferentially formed.

a)



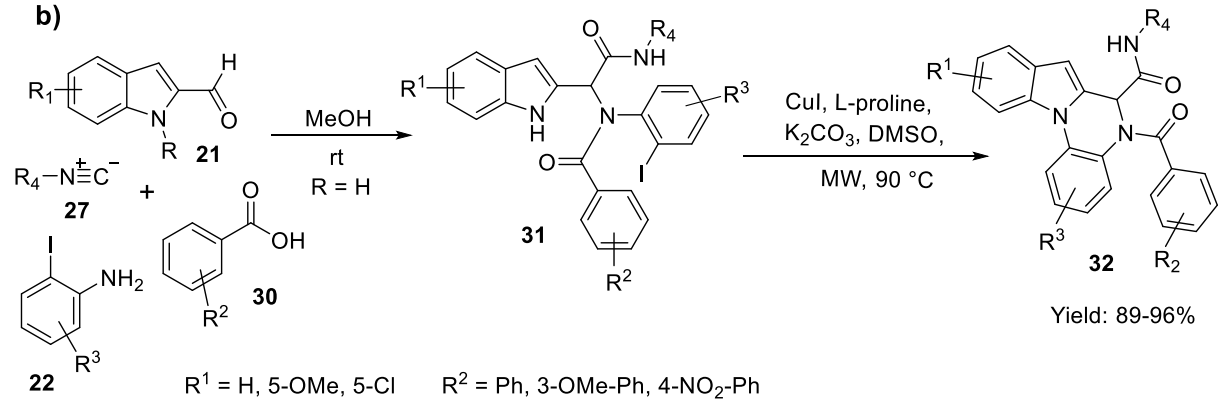
R^1 = H, 5-OMe, 5-Cl R^2 = H, 5-Cl, 5-Me
R^3 = Ph, *n*-propyl R^4 = cyclohexyl, *n*-butyl

Yield: 87-95%

Scheme 3.10a: Post functionalization of Ugi four-component product *via* C-N coupling for the synthesis of indole-fused compounds **29**

Further, the diversity was expanded by incorporating the directing iodide group to the amine input of the Ugi reaction (**Scheme 3.10b**). The acyclic, peptide-like α-acylaminoamides **31** were obtained by Ugi condensations of 1*H*-indole-2-carbaldehydes **21**, carboxylic acids **30**, 2-iodoanilines **22** and isocyanides **27** which were then converted to indole fused compounds **32** *via* copper catalyzed C-N coupling reaction.

b)

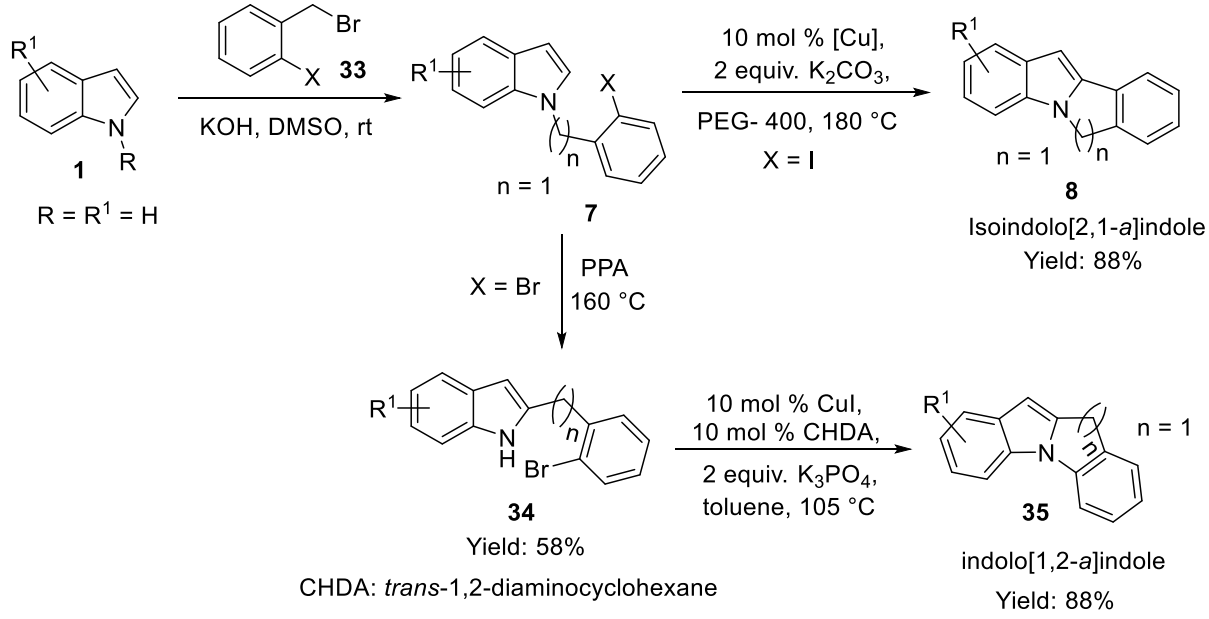


R^1 = H, 5-OMe, 5-Cl R^2 = Ph, 3-OMe-Ph, 4-NO_2-Ph
R^3 = H, 5-Cl R^4 = cyclohexyl, *n*-butyl,

Yield: 89-96%

Scheme 3.10b: Construction of indole-fused compounds **32** *via* Ugi four-component reactions followed by Cu catalyzed C-N coupling

Sanmartin *et al.* disclosed a direct approach for the synthesis of isoindolo[2,1-*a*]indole **8** and indolo[1,2-*a*]indole **35** *via* copper-catalyzed intramolecular direct C- and N-arylations (**Scheme 3.11**).[40] The required precursors **7** was easily prepared by alkylation of indole (**1**) with 2-halobenzylbromide (**33**) in presence of KOH in DMSO while **34** was obtained by migration of the 2-bromobenzyl group from the nitrogen to the C2 position of the indole upon heating of **7** in the presence of polyphosphoric acid (PPA).



Scheme 3.11: Synthesis of isoindolo[2,1-*a*]indole **8** and indolo[1,2-*a*]indole **35** *via* copper catalyzed C-N coupling

3.1.3 Gold-catalyzed reactions for the synthesis of indole derivatives

Gold catalysis is considered as one of the most important breakthroughs in organic synthesis for the synthesis of common core structures of various natural products, synthetic intermediates and pharmaceuticals during the last decade.[41-44] Hashmi and coworkers developed first gold-catalyzed methodology for C-C bond formation using gold catalyst.[45] Generally, Au(I) and Au(III) act as soft Lewis acids and they preferentially coordinate with soft Lewis bases, such a property allows it to activate unsaturated functionalities such as alkynes, alkenes and allenes to become susceptible to be attacked by various nucleophiles, such as alcohols/water,[46-50] nitrogen,[51, 52] carbon nucleophiles,[53-58] carboxylic acids,[59] ketones[45, 60-62] and thiols[63] to create C-C and C-X bonds under extremely mild conditions.

In addition, gold catalysts are exceptionally alkynophilic and not oxophilic as most Lewis acids. Thus, oxygen, water and alcohols are often well-tolerated, in sharp contrast to most air- and moisture-sensitive Lewis acid or transition metal-catalyzed transformations in gold catalyzed reactions. Gold (I)-catalyzed nucleophilic addition reactions proceed through outer-sphere and inner-sphere mechanisms as illustrated in **Figure 3.2**.[64] Mechanistically, gold catalysis is generally expressed through the π-activation of the electrophilic partner with a consequent *anti*-attack of the aromatic compounds (*outer-sphere type pathway*). However, the possibility of forming discrete aryl gold intermediates (usually referred as auration reaction of arenes) makes the *syn* addition process (*inner-sphere type pathway*) a feasible alternative (**Figure 3.2**). In the realm of the gold co-ordination to unsaturated hydrocarbons, gold arene interactions are weaker than those of Au-[Alkyne/alkene/allene].

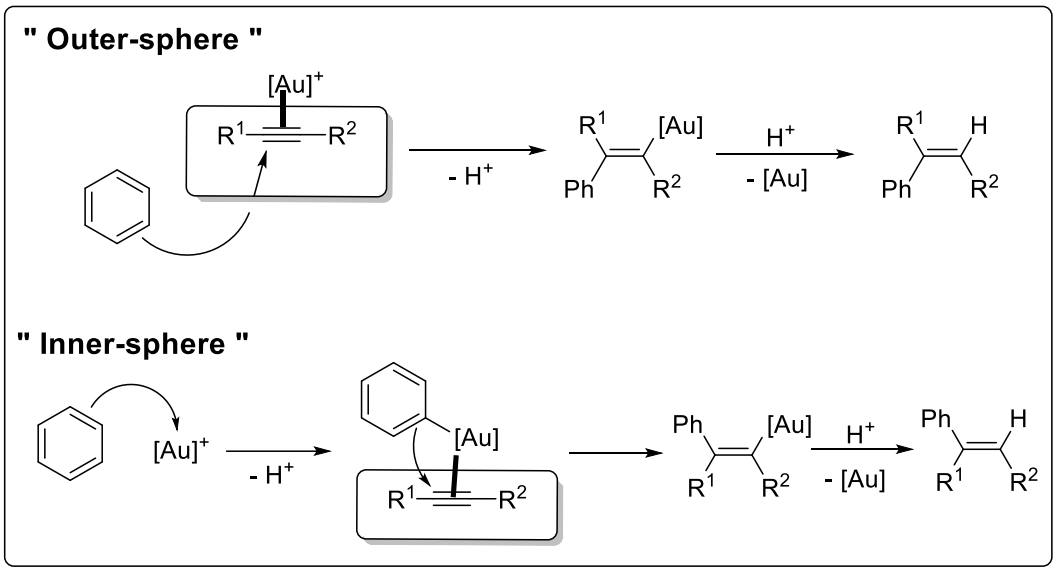
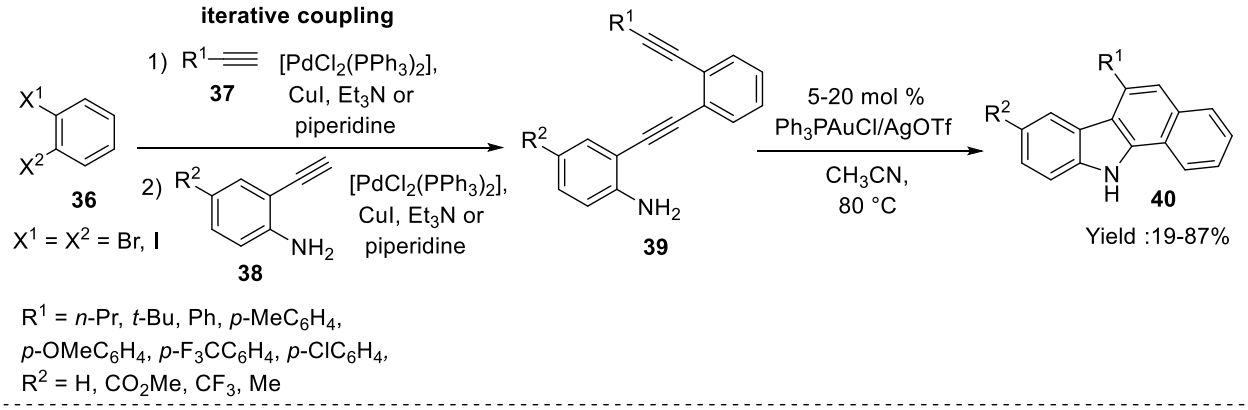
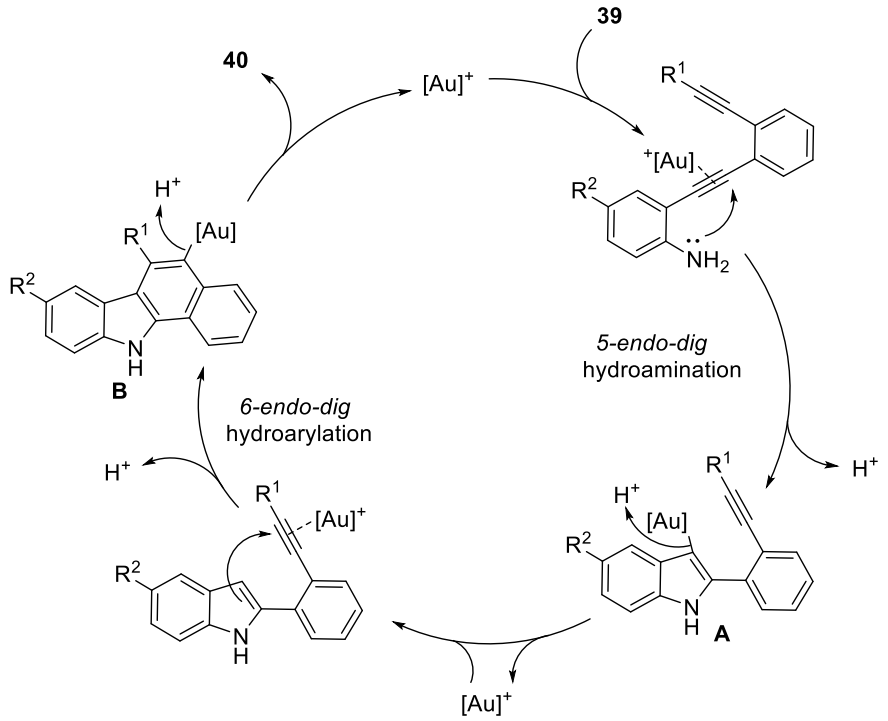


Figure 3.2: Outer (*Anti*) and inner (*syn*) sphere mechanism in gold-catalyzed arene functionalization

Ohno and co-workers reported gold catalyzed $Ph_3PAuCl/AgOTf$ (5-20 mol %) cascade reaction strategy for the synthesis of indole-annulated[*a*]carbazole scaffold **40** *via* intramolecular *5-endo-dig* hydroamination followed by *6-endo-dig* hydroarylation of aniline substituted diethynylarenes **39.** The aniline substituted diethynylarenes were obtained by iterative Sonogashira reactions of 1,2-dihalobenzenes **36** with substituted acetylenes **37** and ethynylanilines **38** (the order depending on the substrate) without producing undesirable indoles (**Scheme 3.12**).[65]

The substrates **39** having electron-deficient aryl groups such as *p*-ClC_6H_4 and *p*-$F_3CC_6H_4$ as the R^1 substituents with 5 mol % catalyst gave **40** in good yields 84% and 81%, respectively.



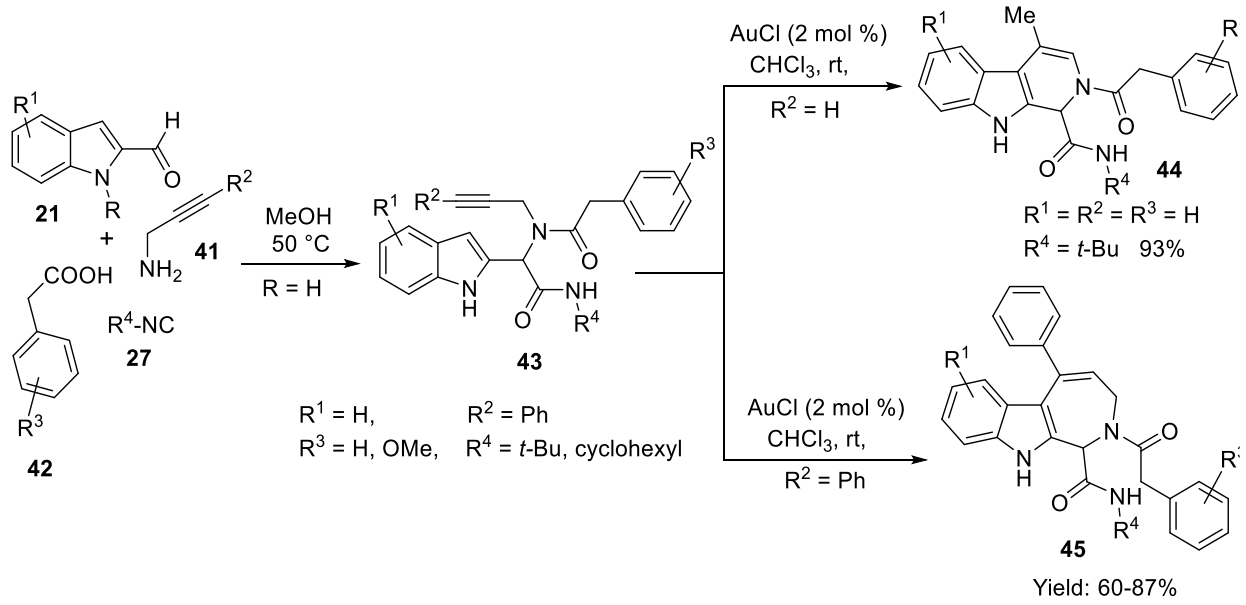


Scheme 3.12: Complete synthetic route with proposed mechanism for the synthesis of indole-annulated[*a*]carbazoles **40**

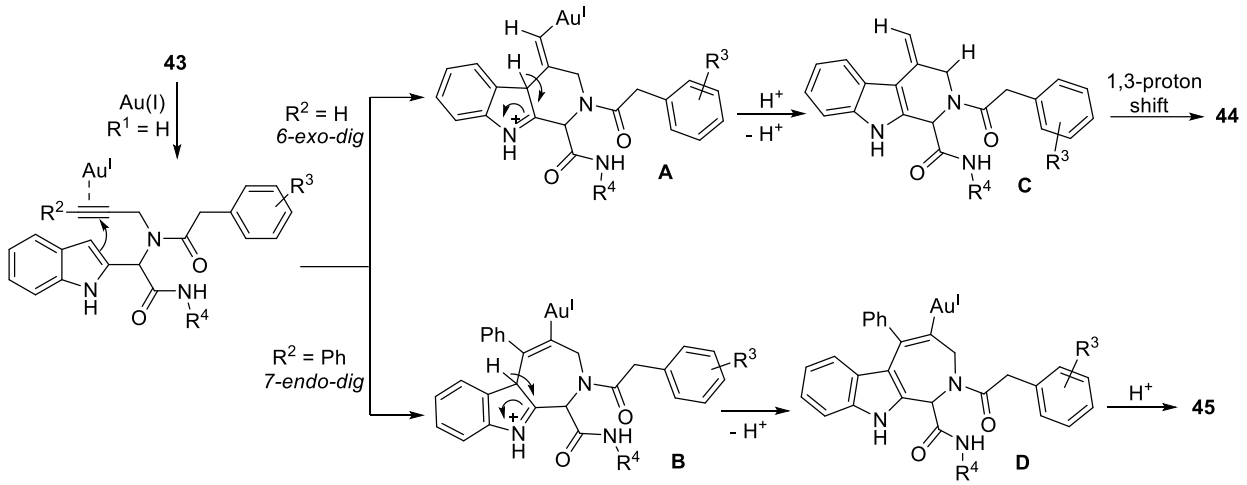
In contrast, substrates **40** with electron-rich aryl groups such as *p*-MeC_6H_4 and *p*-$MeOC_6H_4$ resulted in low yields 42% and 29%, respectively. The yield were slightly improved by increasing the catalyst loading. Several substituents on alkyne terminus were well tolerated for the cascade cyclization, compound with *tert*-butyl group on alkyne terminus gave low yield (19%) of the product presumably due to the steric repulsion of the *tert*-butyl group and the gold

complex on the second cyclization as well as the formation of a sterically congested product. Compound **39** with either electron-withdrawing group (-CF_3) or electron-releasing group (-Me) on the aminoaryl ring (R^2) afforded desired carbazoles **40** in good yields by using 20 mol % catalyst.

Van der Eycken and coworkers elaborated gold(I)-catalyzed diversity-oriented sequential post-Ugi intramolecular hydroarylation approach for the synthesis of pyridoindoles **44** and azepinoindoles **45** by (**Scheme 3.13a**).[66] The Ugi four-component reaction involved the reaction of 2-formylindoles (**21**), propargylamines (**41**), phenylacetic acids (**42**) and isocyanides (**27**) in methanol at 50 ºC. The Ugi adducts **43** were subjected to intramolecular hydroarylation reaction in the presence of AuCl (2 mol %) as catalyst in chloroform at room temperature. In the case of terminal alkynes of substrates **43**, the products **44** were obtained *via 6-exo-dig* cyclization whereas phenyl substituted alkynes of substrates **43** afforded **45** in a very good yield *via 7-endo-dig* cyclization reaction (**Scheme 3.13b**).

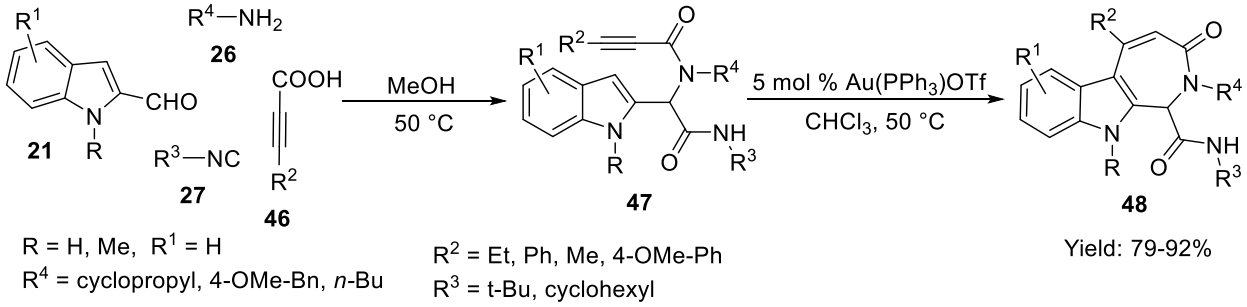


Scheme 3.13a: Gold (I) catalyzed post-Ugi intramolecular hydroarylation reaction of **43** for the synthesis of indole-annulated compounds **44** and **45**



Scheme 3.13b: Proposed mechanism for the synthesis of pyridoindoles **44** and azepinoindoles **45**

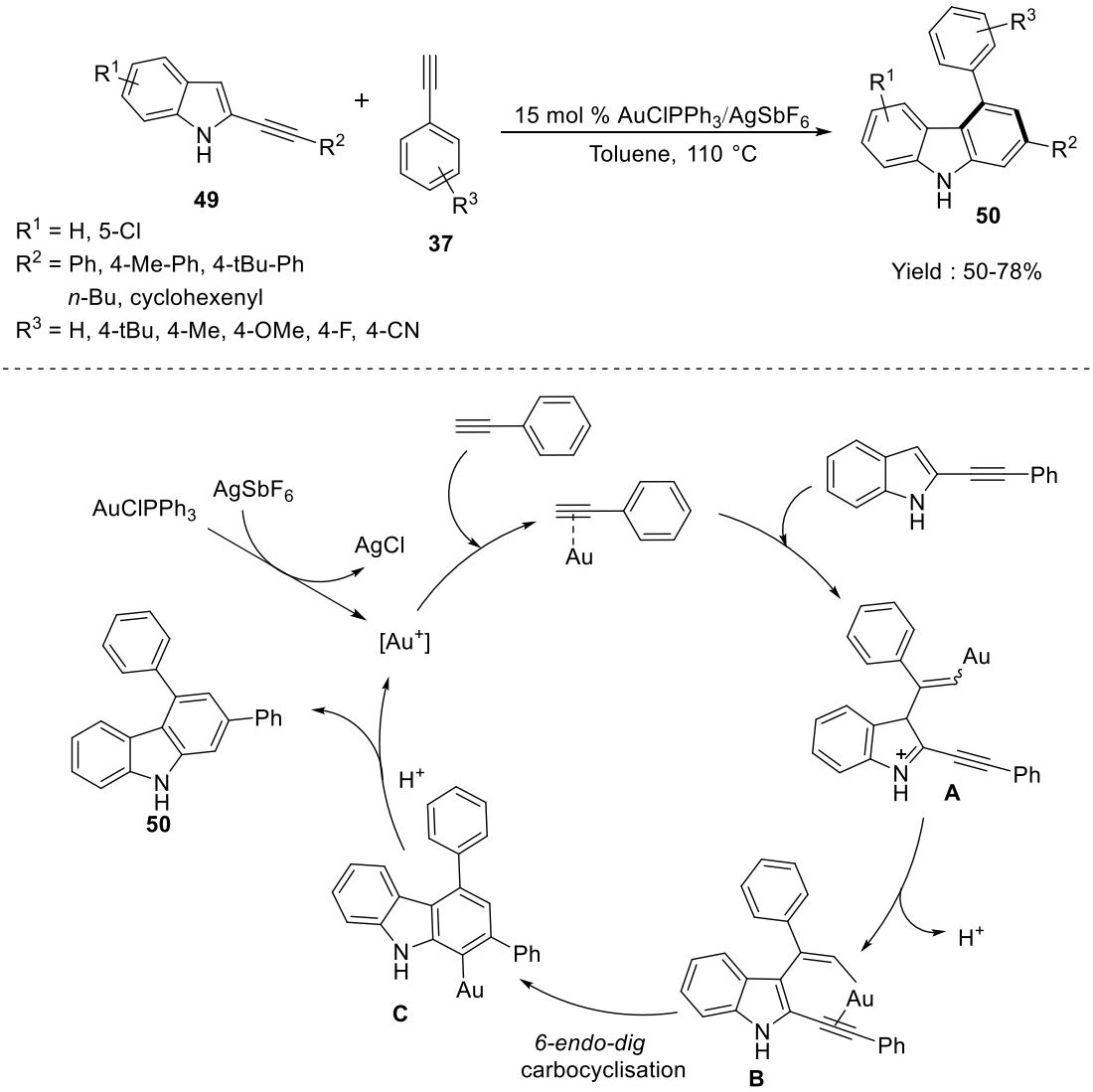
In another report, Eycken group synthesized azepinones by gold catalyzed hydroarylation of Ugi four-component product **47**. The Ugi-adduct **47** was obtained by the reaction of 2-formylindole (**21**) with an amine (**26**), alkynoic acid (**46**) and isonitriles (**27**) in methanol at 50 °C. The Ugi-adducts **47** were treated with 5 mol % $Au(PPh_3)OTf$ in chloroform, only 7-membered ring formation was observed *via 7-endo-dig* attack of the aromatic ring on the activated alkyne resulting in the formation of azepinoindoles **48** (**Scheme 3.14**).[67] The desired azepinones **48** were obtained in excellent yield even though a bulky substituent like a phenyl group was present on the alkyne of substrates **47**.



Scheme 3.14: Synthesis of azepinoindoles **48** *via* post-Ugi Au(I)-catalyzed intramolecular hydroarylation

Kundu and co-workers reported the one-pot synthesis of carbazoles **50** involving the reaction of 2-alkynylindoles **49** with aryl acetylenes **37** in the presence of 15 mol % $AuClPPh_3/AgSbF_6$ in toluene at 110 °C. This strategy comprises tandem gold-catalyzed reactions leading to two C-C

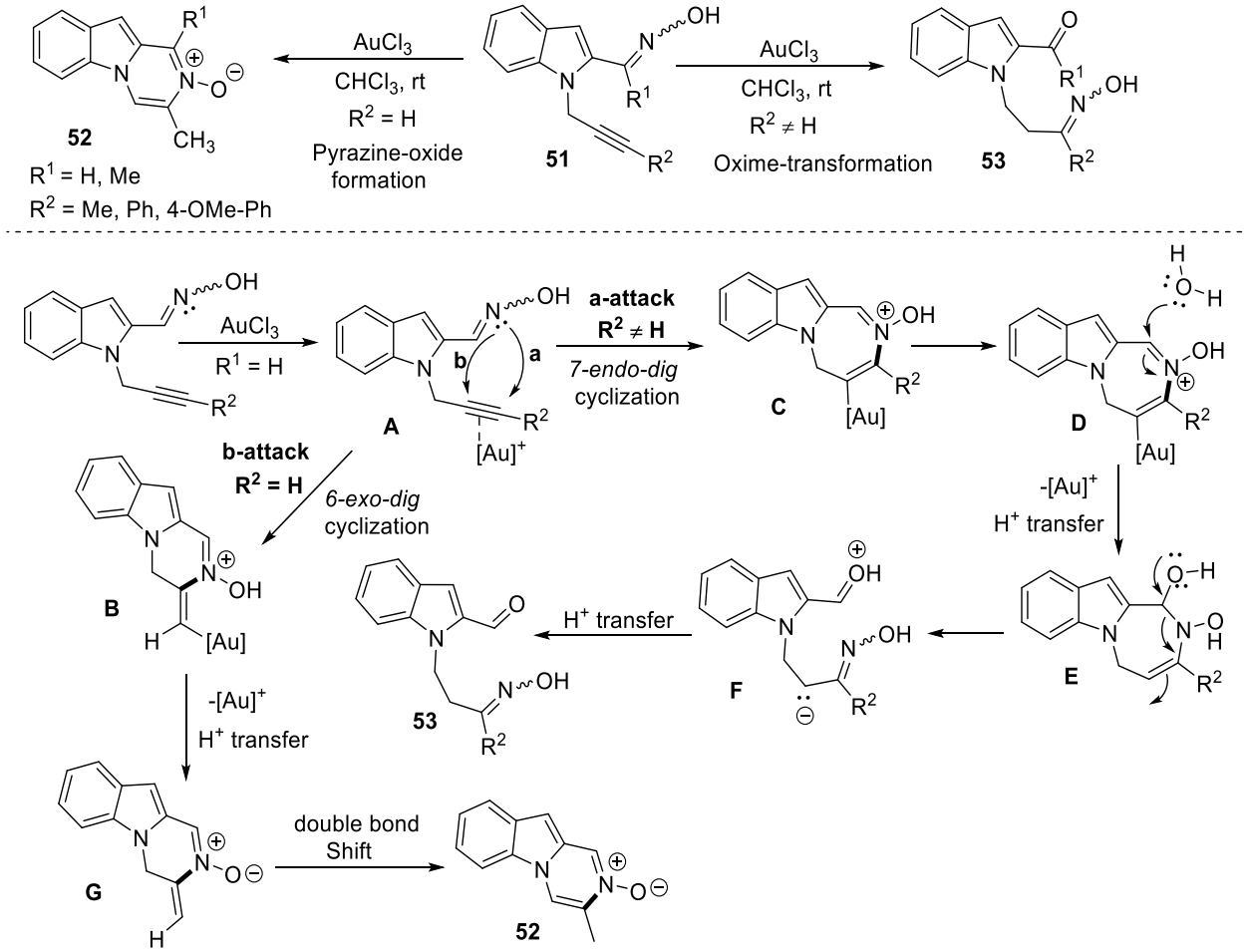
bonds forming *via* sequential hydroarylation of the alkyne and *6-endo-dig* carbocyclization reactions (**Scheme 3.15**).[68]



Scheme 3.15: Gold-catalyzed one pot synthesis of NH-carbazoles **50**.

Aryl alkynes (**37**) bearing both electron withdrawing and electron donating groups were found to be suitable substrates for the cyclization and gave the corresponding products in moderate to excellent yields. Replacing phenylacetylenes **37** with aliphatic terminal alkynes failed to give desired products. Similarly, indoles **49** with R^2 as aryl substituent gave corresponding carbazoles in good yields whereas with R^2 as aliphatic substituents (*n*-butyl and cyclohexenyl) gave corresponding carbazoles in moderate yield. On the other hand substituent on indole ring R^1 had no effect on the yield of the corresponding carbazoles **50**.

Balci and co-workers demonstrated $AuCl_3$ gold(III) catalyzed reaction of various *N*-propargylated indole oximes **51** to give pyrazine *N*-oxides (**52**) and rearranged oximes **53** (**Scheme 3.16**).[69] The substrates **51** with terminal alkynes underwent *6-exo-dig* cyclization reaction giving rise to pyrazine *N*-oxides **52.** However, in the case of substituted alkynes, the reaction proceeded in a completely different way forming an intermediate **D** with a seven-membered ring, which transfered the oxime functionality intramolecularly from one carbon to another *via 7-endo-dig* cyclization process and resulted in the formation of **53**. This type of rearrangement is unprecedented in the literature and represents a new rearrangement, the oxime−oxime rearrangement.

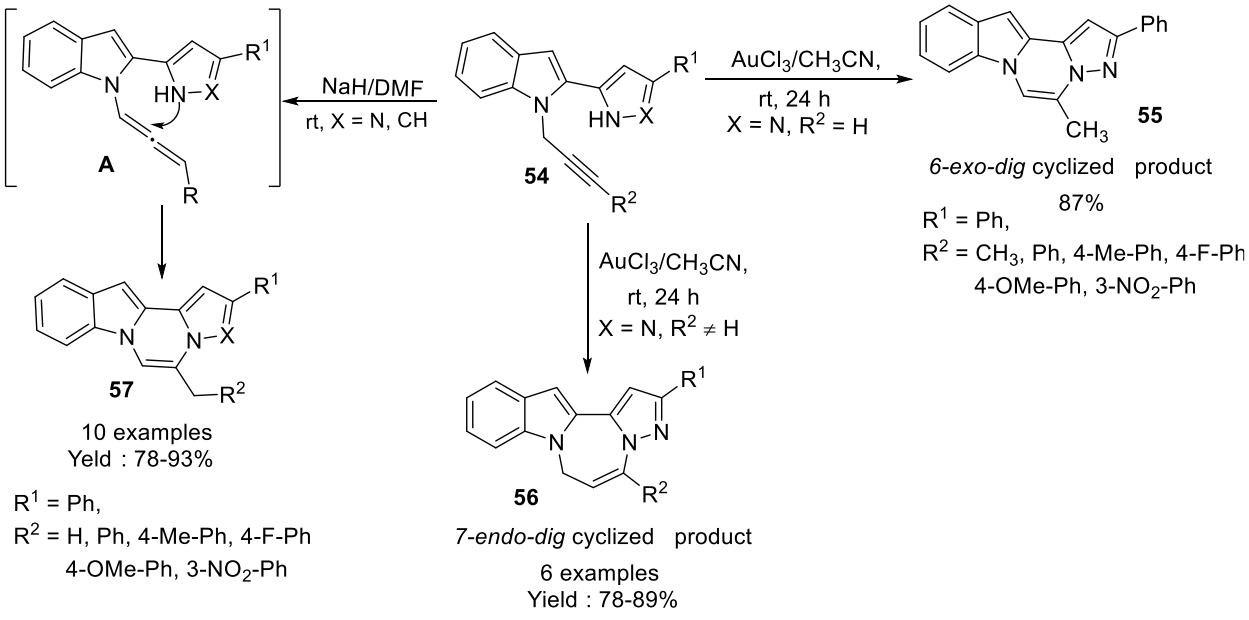


Scheme 3.16: Gold-catalyzed synthesis of pyrazine oxides **52** and oxime **53**

Very recently, Balci group extended their work and reported gold-catalyzed as well as NaH-supported cyclizations to provide a versatile approach to the synthesis of new heterocycles such as pyrazolodiazepinoindoles (**56**), pyrazolopyrazinoindoles (X = N, **57** and **55**) and pyrrolo-

pyrazinoindole (X = CH, **57**). $AuCl_3$ catalyzed intramolecular cyclization of **54** (X = N, R^2 = H) having a terminal alkyne afforded the *6-exo-dig* cyclization product **55** at room temperature.[70] However, the exclusive formation of *7-endo-dig* cyclization product **56** was observed with internal alkynes. In case of **54** (X = CH) either *6-exo-dig* or *7-endo-dig* cyclization products were not observed. On the other hand, cyclization with NaH resulted in the formation of *6-exo-dig* cyclization products **57** regardless of the substitution of the alkyne functionality. As there was no trace of *7-endo-dig* cyclization products observed, it's believed that the cascade process relies on the interception of allene intermediates followed by an H-shift.

With our interest in the synthesis of novel indole-annulated sulfur heterocycles using transition metal catalyzed C-H functionalizations. In this chapter, we have taken up to develop novel synthetic methods for the synthesis of benzothiazino[3,2-*a*]indoles, dihydroisothiochromeno[3,4-*b*]indoles and dihydrothiopyrano[2,3-*b*]indoles employing copper, palladium and gold transition metals catalysis.



Scheme 3.17: Gold-catalyzed and NaH supported intramolecular cyclization of **54**

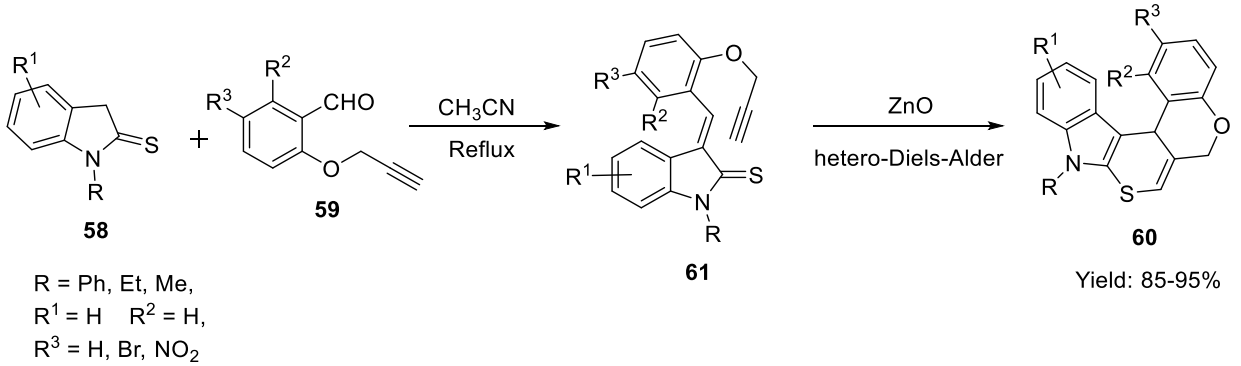
Chapter III

PART-A

Synthesis of Indole-annulated Sulfur Heterocycles using Copper Catalyzed C–N Coupling and Palladium Catalyzed Direct Arylation

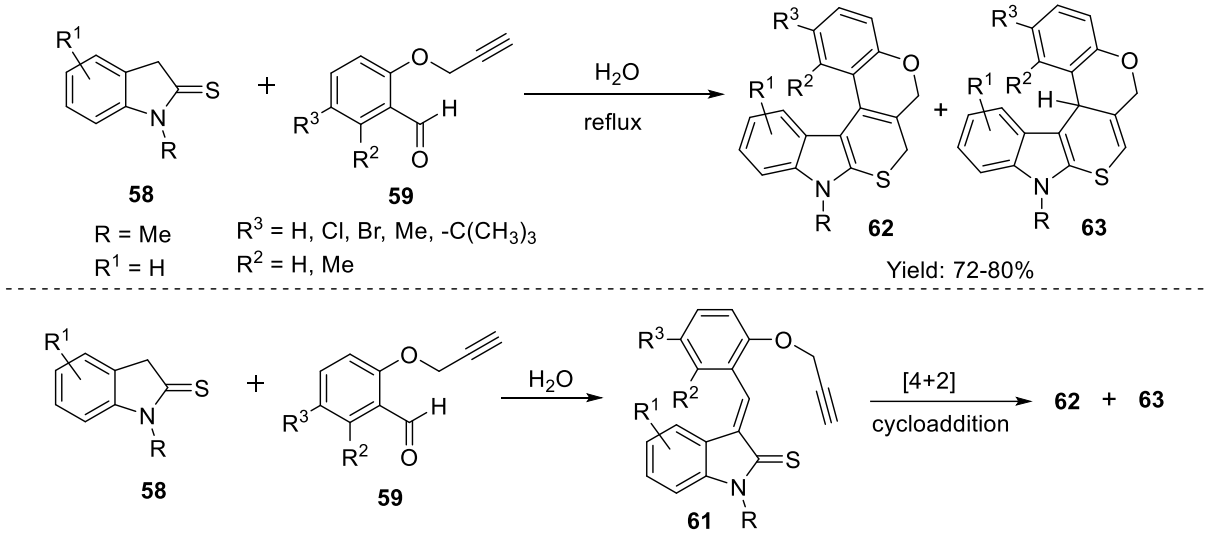
3.2 Introduction

The indole ring system is a prominent and privileged structural subunit present in many biologically active natural and synthetic molecules.[71-74] Polyheterocyclic derivatives of indole have received significant attention in recent years due to their high biological and medicinal importance. More specifically, indole-annulated heterocycles containing one or two sulfur atoms are found in several cruciferous phytoalexins, e.g. cyclobrassinin and spirobrassinin.[75-78] Furthermore, these types of sulfur-containing heterocycles have been found to exhibit numerous biological activities such as HIF-1 inhibition,[79] selective estrogen receptor modulators[80] LTB4 production inhibition[81] etc. In particular, tetrahydrothiopyrano[2,3-*b*]indole and tetrahydrothiopyrano[3,2-*b*]indole derivatives are known to possess analgesic, psychoanaleptic and nootropic activity.[82, 83] Although several synthetic methods have been developed for the assembly of indole-annulated polyheterocyclic compound containing nitrogen and oxygen atoms, there are relatively few examples known in the literature for the synthesis of indole-annulated sulfur heterocycles. For example, Moghaddam group reported an efficient ZnO-catalyzed synthesis of novel indole-annulated thiopyrano-chromene derivatives (**60**) *via* domino Knoevenagel-hetero-Diels-Alder reaction of indoline-2-thiones (**58**) and *o*-propargylated salicylaldehydes (**59**) in acetonitrile (**Scheme 3.18**).[84] The *o*-propargylated salicylaldehydes (**59**) were prepared from the reaction of salicylaldehydes and propargyl bromide in the presence of anhydrous potassium carbonate in dry DMF at room temperature. The major advantage of this reaction is the simple work up during which the products can be isolated without chromatography in good to excellent yields.



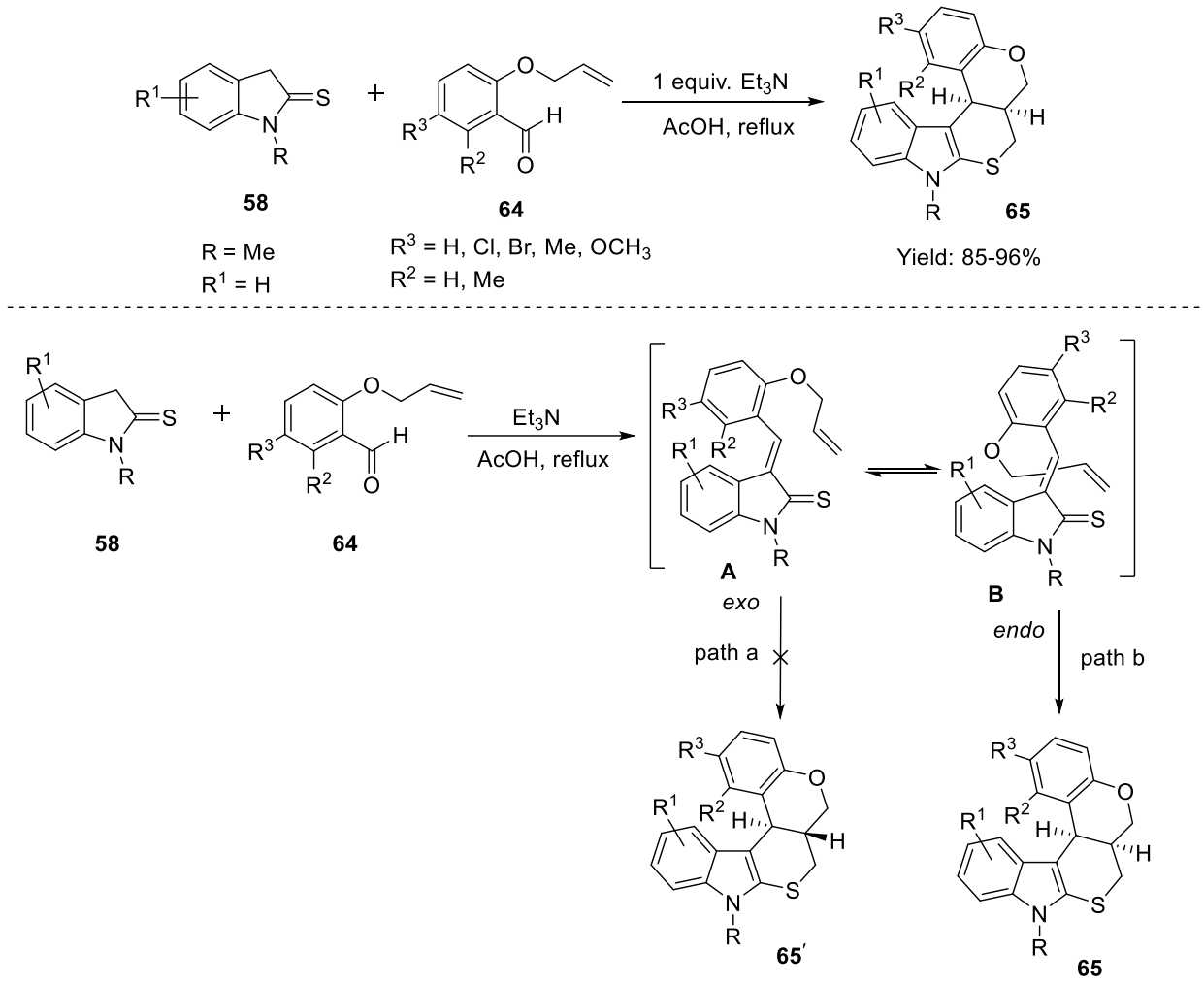
Scheme 3.18: ZnO-catalyzed synthesis of indole-annulated thiopyrano-chromene derivatives **60**

K.C. Majumdar group[85] also reported an efficient one-step synthesis of indole-annulated [6,6]fused-thiopyranobenzopyran derivatives **(62)** in excellent yields *via* domino Knoevenagel-hetero-Diels-Alder reaction of unactivated terminal acetylene in the absence of Lewis acid (**Scheme 3.19**). When indoline-2-thione (**58**) and *o*-propargylated salicylaldehydes **(59)** was treated in aqueous media at reflux condition, afforded either product **63** or **64** due to the substituent effect of *ortho*-position (-R^2) with respect to the aldehyde group. The fact that substituent in *ortho*-position (-R^2) led to unconjugated products **63** clearly indicates peri-hindrance, which is substantially diminished in case of a sp^3-hybridized angular carbon while the substrates without a substituent in *ortho*-position (-R^2) yielded conjugated products **64** involving a 1,3-prototropic shift of the intermediates **63**.



Scheme 3.19: Synthesis of indole-annulated [6,6]fused-thiopyranobenzopyran derivatives *via* domino-Knoevengel-hetero-Diels-Alder reaction of **58** and **59** in aqueous media.

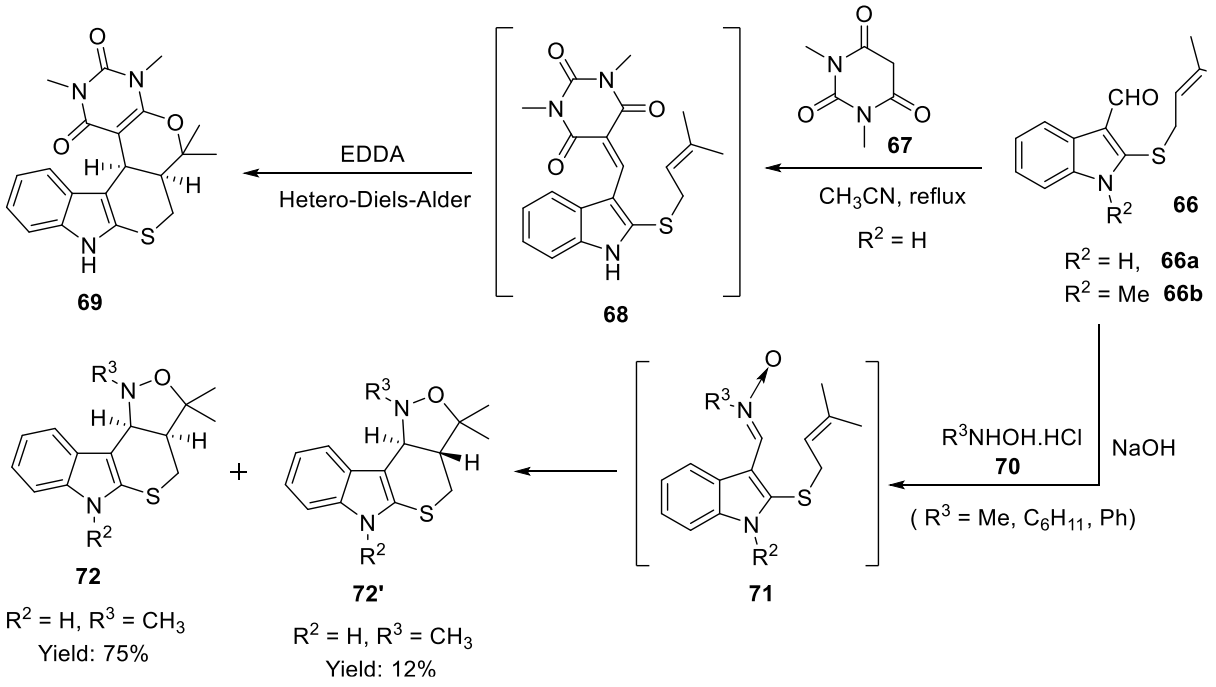
In another report, Majumdar group achieved synthesis of *cis*-[6,6]-fused thiopyranobenzopyran derivatives (**65**) by the reaction of indoline-2-thione (**58**) with *o*-allyl salicylaldehydes (**64**) in the presence of triethylamine (1 equiv.) in acetic acid at reflux condition (**Scheme 3.20**).[86] The stereochemistry of the product **65** was confirmed by single crystal XRD data. The authors were unable to isolate the intermediate heterodiene **A.** *cis*-Stereochemistry of the product **65** is believed due to endo attack during cycloaddition as shown in **Scheme 3.20**.



Scheme 3.20: Synthesis of *cis*-[6,6]-fused thiopyranobenzopyran derivatives from **58** and **65**

Majumder and co-workers synthesized some novel polycyclic thiopyrano[2,3-*b*]indole derivatives *via* Knoevengel condensation of 2-thioprenyl indolo-3-carbaldehyde (**66**) with *N*,*N*-dimethyl barbituric acid (**67**) followed by intramolecular hetero-Diels-Alder reaction in the presence of EDDA in CH_3CN (**Scheme 3.21**).[87, 88] They have also prepared tetrahydro-isoxazolo[3'4':4,5]thiopyrano[2,3-*b*]indole (**72**) by reacting 2-thioprenylindolo-3-carbaldehyde (**66a**) with *N*-methylhydroxyamine hydrochloride (**70a**) and *N*-cyclohexylhydroxylamine hydrochloride (**70b**) in presence of NaOH using ethanol as solvent under refluxing conditions (**Scheme 3.21**). Two isomers **72** (*cis*) and **72'** (*trans*) tetrahydroisoxazolo[3'4':4,5]thiopyrano-[2,3-*b*]indole were obtained in 75% and 12% yields, respectively through intramolecular 1,3-

dipolar cycloaddition reaction of nitrone intermediate **71**. In the case of phenylhydroxylamine, the nitrone **71** was formed but has not given the cyclised product.

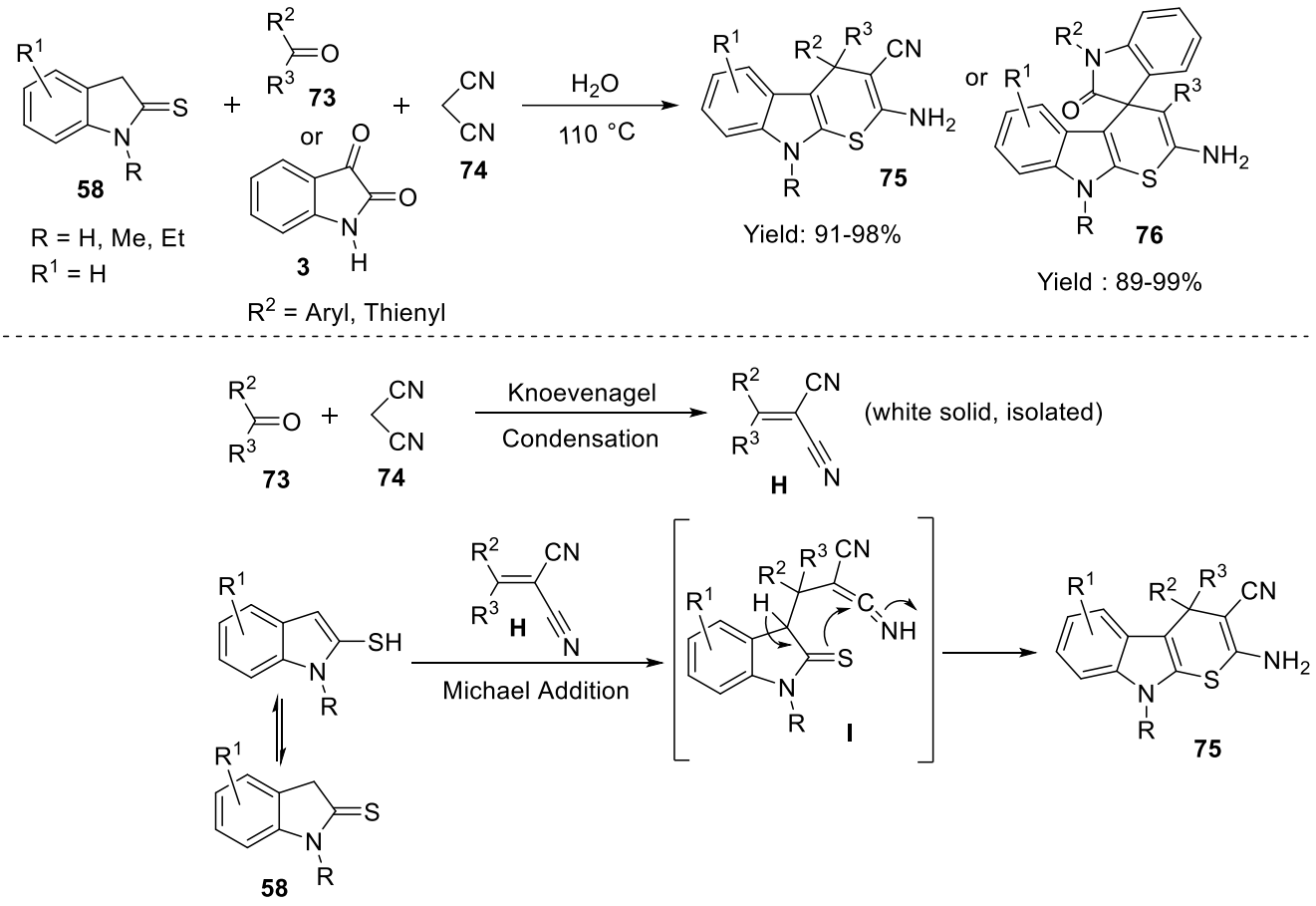


Scheme 3.21: Synthesis of some novel polycyclic thiopyrano[2,3-*b*]indole derivatives

The electron withdrawing nature of the aromatic group might have prevented the cyclization while the electron donating nature of the methyl and the cyclohexyl groups might have facilitated the cyclization process to afford thiopyrano[2,3-*b*]indole derivatives **72.**

Synthesis of thiopyrano[2,3-*b*]indole-3-carbonitrile and spiro[indoline-3,4'-thiopyrano[2,3-*b*]indole] derivatives have been achieved *via* one-pot multicomponent reaction (**Scheme 3.22**).[89, 90] Reaction of various indoline-2-thione (**58**), aromatic aldehyde (**73**), malononitrile (**74**) in water at 100 °C gave excellent yield (91–98%) of **75** without any additional reagent or catalyst (**Scheme 3.22**).[89] When aromatic aldehyde was replaced by isatin (**3**) and reaction was performed in ethanol corresponding spiro[indoline-3,4'-thiopyrano[2,3-*b*]indole] derivatives (**76**) were obtained in excellent yields (89-99%). The formation of thiopyrano[2,3-*b*]indole-3-carbonitrile product **75** may be rationalized by the initial formation of Knoevengel product **H** followed by Michael addition of indoline-2-thione (**58**) with **H** to give intermediate **I** (not isolable) which on further intramolecular cyclization afforded the product **75**.

The involvement of an intermediate cyanoolefin **H** in this green reaction was also verified by carrying out the separate reaction of intermediate **H** with indoline-2-thione (**58)** which gives desired product **75**.

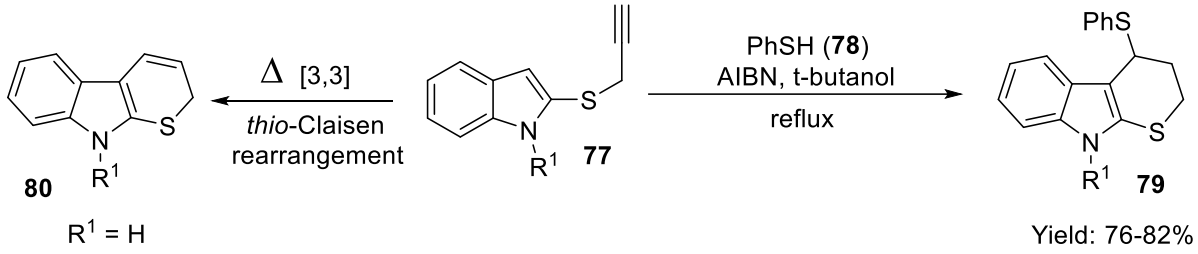


Scheme 3.22: Synthesis of thiopyrano[2,3-*b*]indole-3-carbonitrile (**75**) and spiro[indoline-3,4'-thiopyrano[2,3-*b*]indole] (**76**) derivatives

In addition to indoline-2-thione, K. C. Majumdar group reported the regioselective synthesis of indole-annulated sulfur heterocycles such as tetrahydro-thiopyrano[2,3-*b*]indole (**96**) and benzo[*c*]thiopyrano[2,3-*b*]indole (**85**) *via* radical cyclization reactions.[91]

The exclusive synthesis of 4-thiophenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole derivatives (**79**) has been achieved from the indole-2-yl-prop-2-ynyl sulfides (**77**), under thiophenol (**78**) mediated alkenyl radical cyclization conditions using AIBN as radical initiator (**Scheme 3.23**). To avoid the synthesis of *thio*-Claisen rearrangement product **80**, the all indole-2-yl-prop-2-ynyl

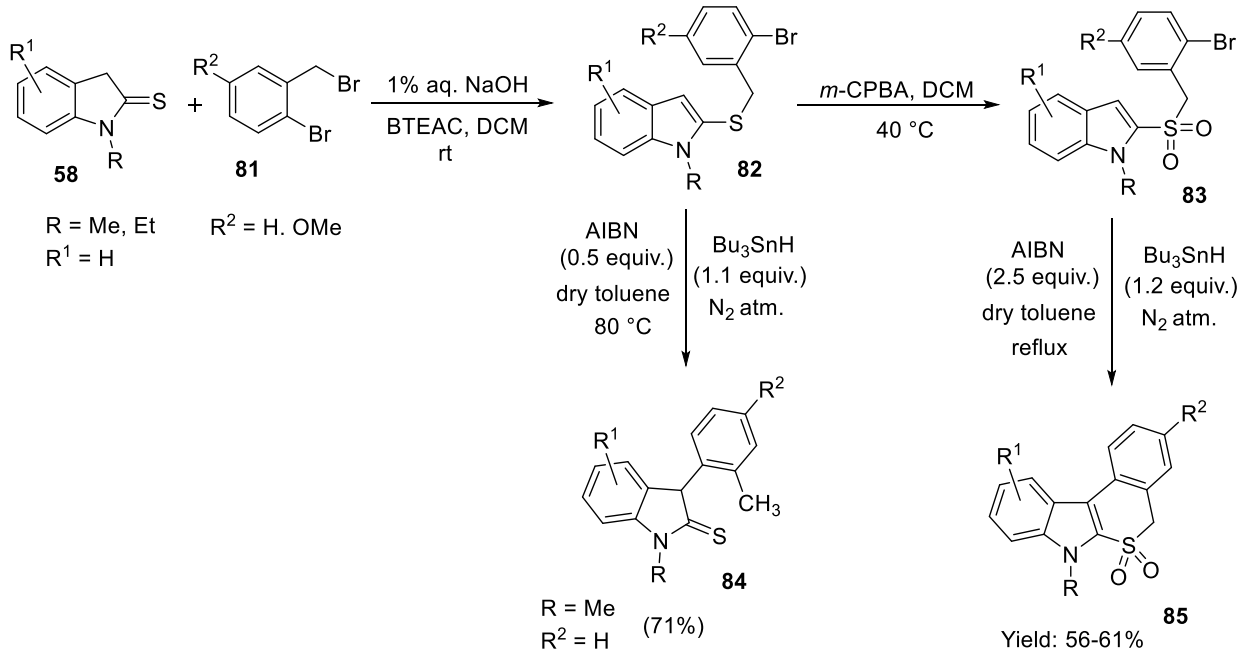
sulfides (**77**) were purified at room temperature. However, under the similar reaction conditions *thio*-Claisen rearrangement product **80** did not give **79** even after 5 h.



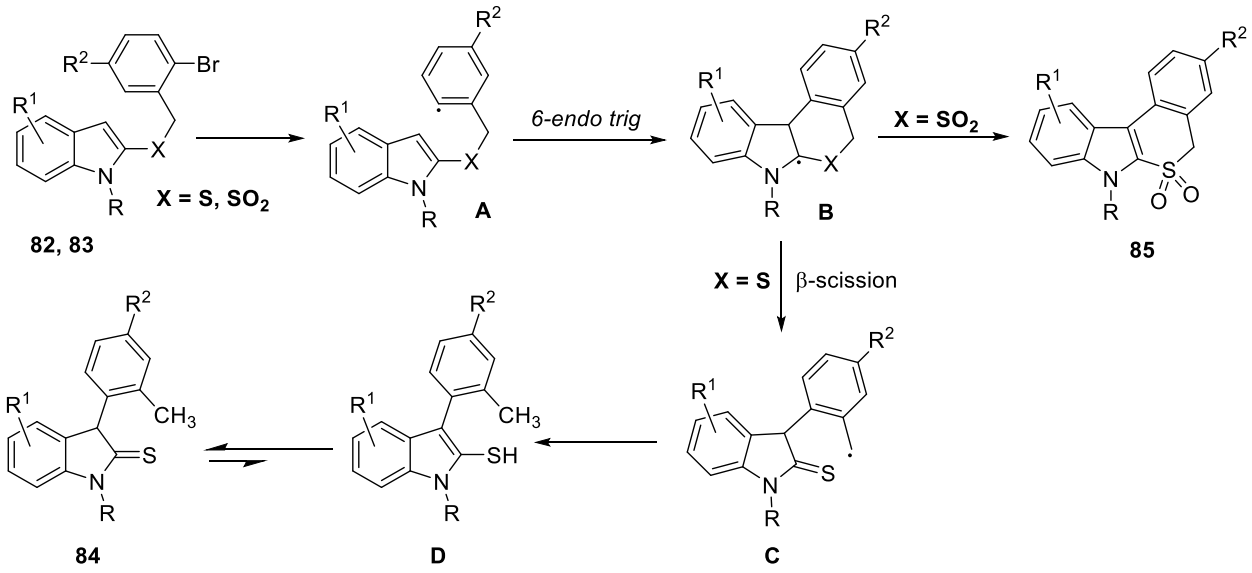
Scheme 3.23 : Synthesis of 4-thiophenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole and 3-thiophenylmethyl-2,3,8-trihydrothieno[2,3-*b*]indoles derivatives

The regioselective synthesis of benzo[*c*]thiopyrano[2,3-*b*]indole derivatives (**85**) was gained through Bu_3SnH mediated aryl radical cyclization of 2-[(2-bromobenzyl)sulfonyl]indoles (**83**) in 56-61% yields. The required precursor 2-[(2-bromobenzyl)sulfonyl]indoles (**83**) were synthesized in two steps in 70-90% yields. Initially, the reaction of indoline-2-thiones (**58**) with 2-bromobenzyl bromides (**81**) in dichloromethane and 1% aq. NaOH solution in the presence of benzyltriethylammonium chloride (BTEAC) at room temperature yielded 2-[(2-bromobenzyl)sulfanyl]indoles (**82**) which on further oxidation with *m*-CPBA (2.5 equiv.) in dichloromethane at 40 °C afforded **85** (**Scheme 3.24a**).[92] Cyclization of **82** to corresponding isothio-chromeno[3,4-*b*]indoles was unsuccessful. The reaction of **82** in the presence of Bu_3SnH (1.1 equiv.), AIBN (0.5 equiv.) at 80 °C for 1 h gave 1-methyl-3-(2-methylphenyl)-2-indolinethione (**84**) instead of cyclized product.

The formation of products **84** and **85** may be explained by the generation of an aryl radical **A.** The aryl radical **A** may undergo *6-endo-trig* cyclization at the double bond of the pyrrole ring of the indole moiety to produce intermediate radical **B.** Oxidative elimination of hydrogen from **B** may afford **85** when X = SO_2 , In the case of X = S, the intermediate **B** may lead to the *β*-scission to give product **84** *via* radical intermediate **C** (**Scheme 3.24b**).



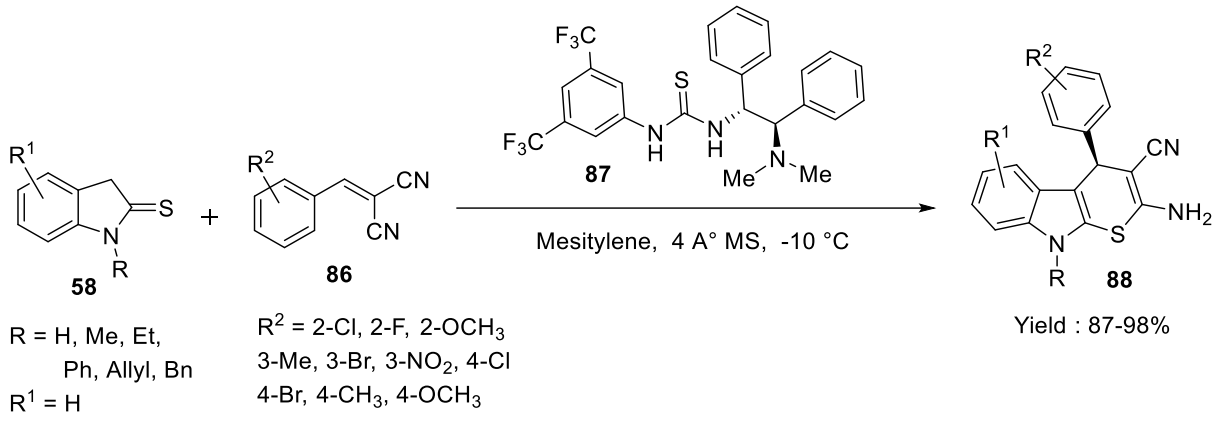
Scheme 3.24a: Synthesis of benzo[*c*]thiopyrano[2,3-*b*]indole and 1-methyl-3-(2-methylphenyl)-2-indolinethione



Scheme 3.24b: Proposed radical mechanism for the synthesis of **84** and **85**

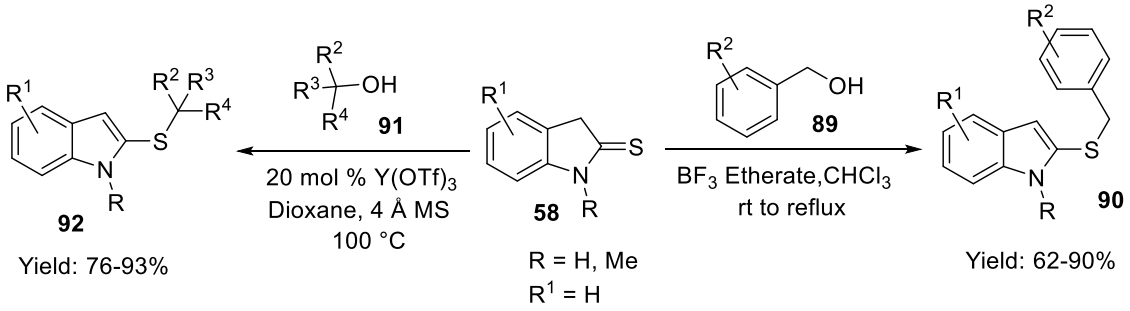
Recently, Wang group constructed optically active thiopyrano[2,3-*b*]indole-3-carbonitrile derivatives (**88**) in 87-98% yields with excellent enantioselectivities *via* a formal thio[3 + 3]-cyclization reaction between indoline-2-thiones (**58**) and 2-benzylidenemalononitrile (**86**). The

reaction was catalyzed by (1R, 2R)-1,2 diphenylethane-1,2-diamine (DPEN)-derived chiral thiourea-tertiary amine catalyst **87** (**Scheme 3.25**).[93]



Scheme 3.25: Synthesis of optically active thiopyrano[2,3-*b*]indole-3-carbonitrile derivatives *via* organocatalytic [3+3]-cascade reaction.

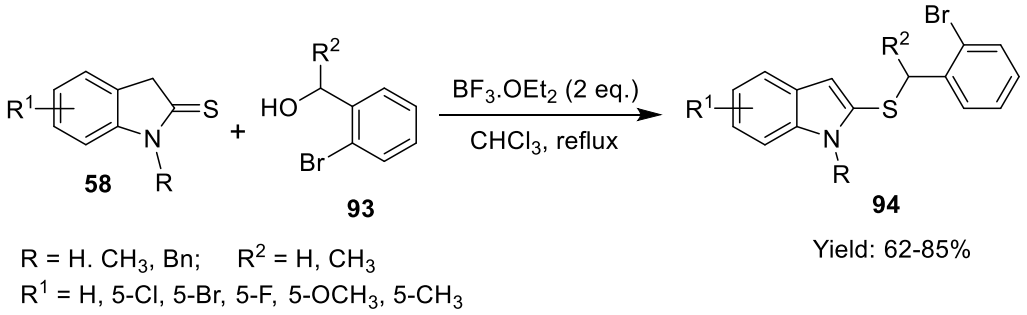
In recent years, our group has reported an efficient Lewis acid–catalyzed chemoselective S-benzylation process leading to indole-based sulfides.[94, 95]



Scheme 3.26: Lewis acid catalyzed chemoselective *S*-benzylation of indoline-2-thiones

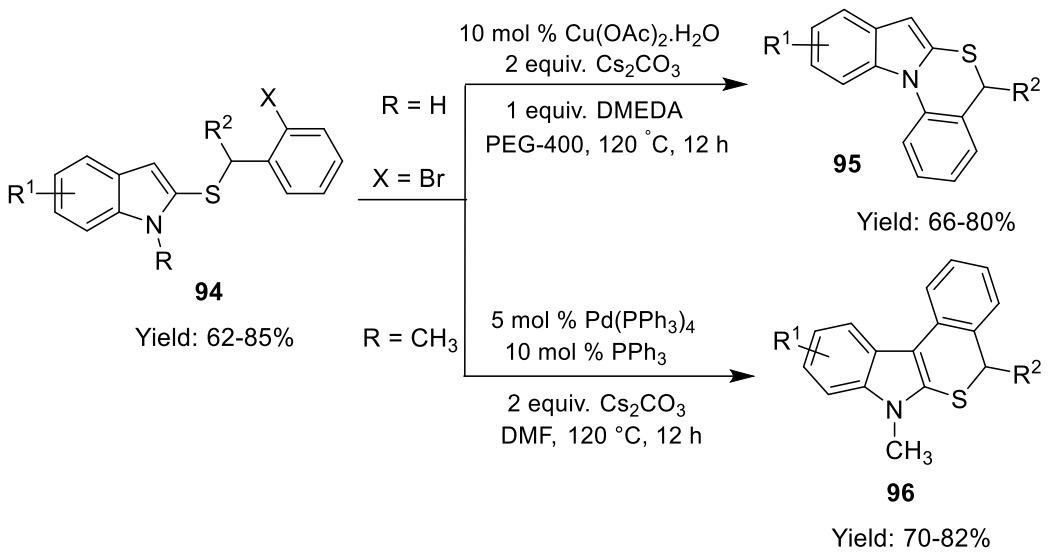
We have developed Lewis acid BF_3-etherate catalyzed chemoselective S-benzylation of indoline-2-thiones (**58**) using benzyl alcohols (**89**) under mild conditions (**Scheme 3.26**). Benzyl alcohols possessing electron-donating groups reacted quite rapidly at room temperature with indoline-2-thiones (**58**) while unsubstituted benzyl alcohol reacted slowly and required additional heating and the electron-withdrawing $–NO_2$ group bearing alcohol did not afford any product. It is worthwhile to mention that under these reaction conditions *ortho* and *p*ara-hydroxylated benzyl alcohols also reacted efficiently with indoline-2-thione without requiring any additional protection/deprotection steps.

Later, we implement $Y(OTf)_3$ as an efficient, inexpensive, and environmentally benign catalyst over previously reported BF_3-etherate for the chemoselective S-benzylation of indoline-2-thiones (**58**) using a variety of benzyl alcohols (**91**) (**Scheme 3.26**). The reaction condition required low catalyst loading (20 mol %) compared to BF_3-etherate (2 equiv.) in the previous report. In addition, we employed a variety of 2-bromo benzyl alcohols (**93**) with varying degree of substitutions (primary, secondary and tertiary) at benzylic position reacted quite effectively with indolin-2-thiones (**58**) under optimized reaction conditions to obtain 2-((2-bromobenzyl)thio)indoles (**94**) (**Scheme 3.27**). Mechanistically, in all the cases the exclusive formation of S-benzylated products supports the involvement of resonance stabilized benzylic carbocation as the reaction intermediate.



Scheme 3.27: BF_3 etherate catalyzed synthesis of 2-((2-bromobenzyl)thio)indoles (**94**)

Lately, transition metal catalyzed cross-coupling reactions have given significant impetus to produce polyheterocyclic compounds from simple precursors.[96-100] Considering the importance of indole-annulated sulfur heterocycles for their potential bioactivities and to continue our interest in developing innovative synthetic methodologies for novel polyheterocyclic molecular structures.[101-108] We envisaged 2-((2-bromobenzyl)thio)indoles (**94**) as key intermediates to synthesize indole-fused thiazines and dihydroisothiochromenes. In this part of chapter III, we have developed a novel method for the synthesis of 5*H*-benzo[4,5][1,3]thiazino[3,2-*a*]indoles (**95**) and dihydroisothiochromeno[3,4-*b*]indoles (**96**) *via* intramolecular C-N coupling and direct arylation reactions (**Scheme 3.28**).



Scheme 3.28 : Synthesis of benzo[4,5][1,3]thiazino[3,2-*a*]indoles (**95**) and isothio-chromeno[3,4-*b*]indoles (**96**) derivatives

3.3 Results and discussion

As depicted in **Scheme 3.27**, the required precursors, substituted 2-((2-bromobenzyl)thio)indoles (**94aa-ib**), for the present study were prepared by the reaction of differently substituted indoline-2-thiones (**58a-k**) with (2-bromophenyl)methanol (**93a**) or 1-(2-bromophenyl)ethanol (**93b**) following a methodology previously reported by our group (**Scheme 3.26**).[94] During the current study, we noted that the yields for S-benzylation reaction were unaffected by the type of thiones used but were profoundly affected by the degree of substitution at the benzylic position of benzyl alcohols (Table 3.1). For example, the reaction of secondary benzyl alcohol (**93b**) required lesser time for completion and gave better yield of corresponding 2-((2- bromobenzyl)thio)indoles (Table 3.1, entries 7-10 & 16-18) as compared to primary benzyl alcohols. These results are in agreement with the previously proposed mechanism, which is believed to involve resonance stabilized benzylic carbocation as the reaction intermediate. The structures of all 2-((2-bromobenzyl)thio)indoles were confirmed by ^{1}H NMR, ^{13}C NMR and mass data. Representative ^{1}H NMR and ^{13}C NMR of **94aa** is shown in **Figure 3.3**.

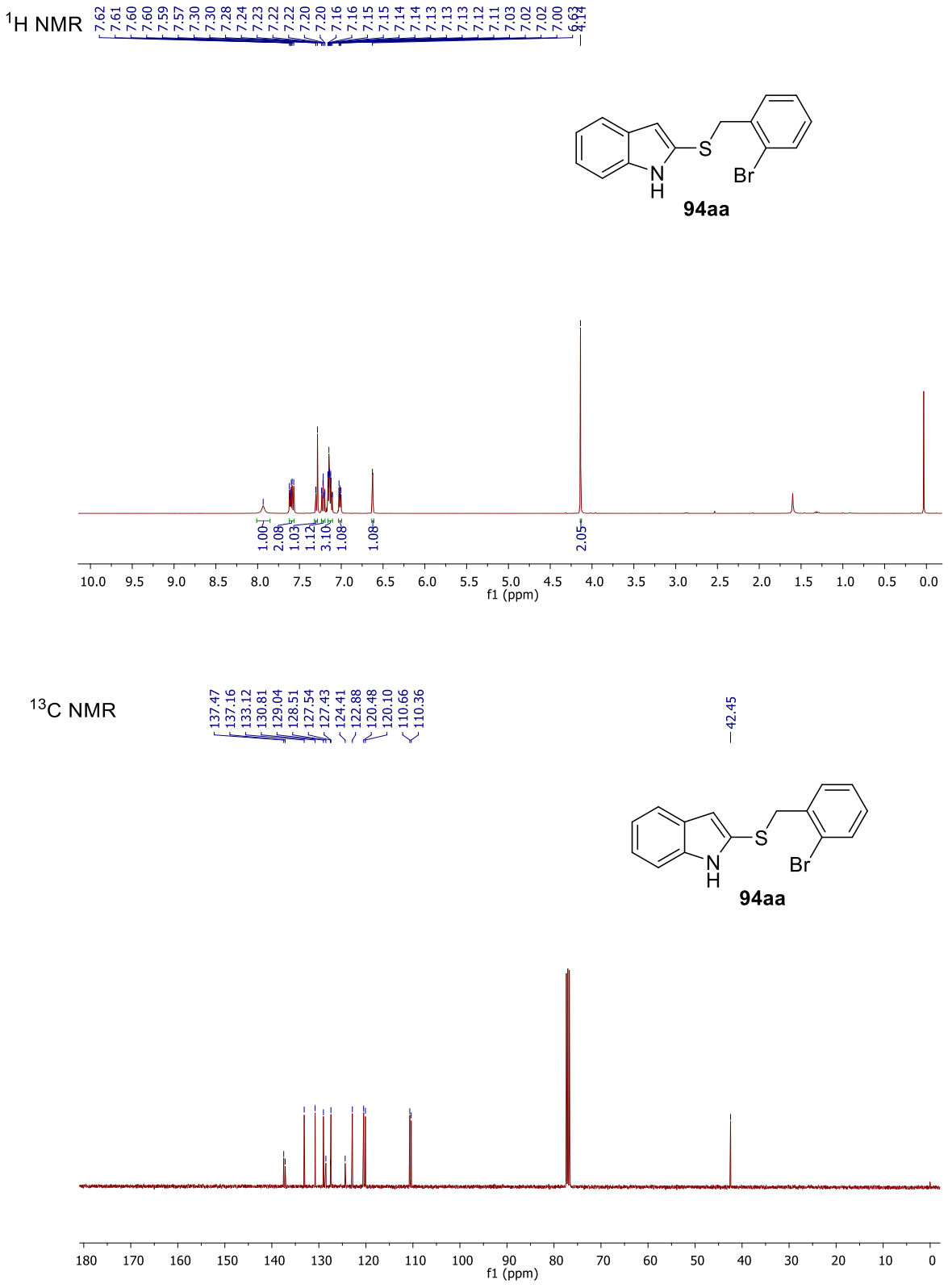
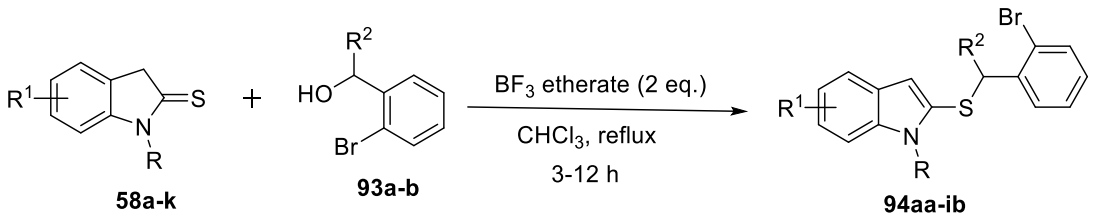
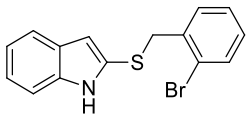
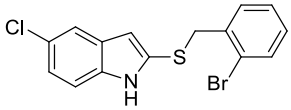
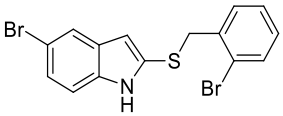
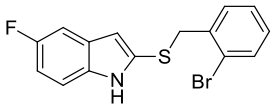
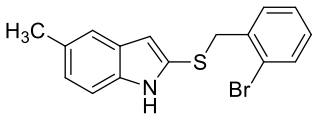
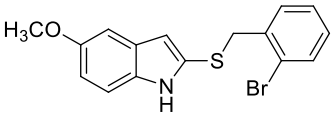
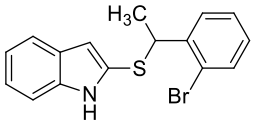
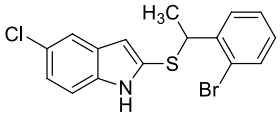
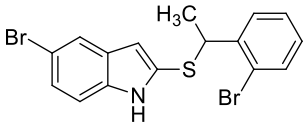
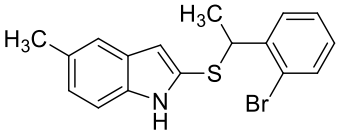
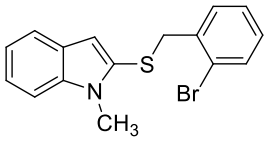
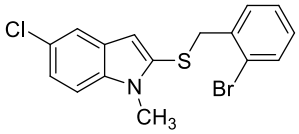
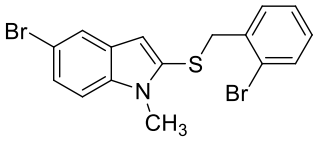
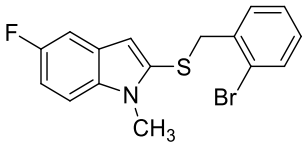
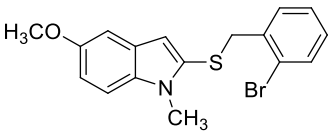
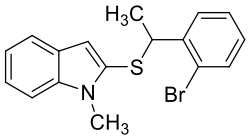
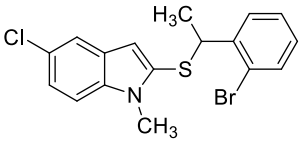
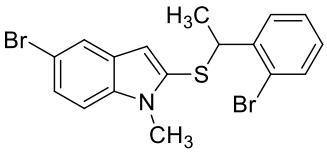


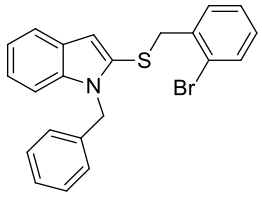
Figure 3.3: ^{1}H and ^{13}C NMR spectra of 2-((2-Bromobenzyl)thio)-1*H*-indole **(94aa)** in $CDCl_3$

Table 3.1: S-Benzylation of indoline-2-thiones (**58a-k**) using benzyl alcohol (**93a-b**).[a]



Entry	R	R^1	R^2	Product		Time (h)	Yield (%)[b]
1	H	H	H		**94aa**	12	74
2	H	5-Cl	H		**94ba**	12	66
3	H	5-Br	H		**94ca**	12	68
4	H	5-F	H		**94da**	12	64
5	H	5-CH_3	H		**94ea**	12	70
6	H	5-OCH_3	H		**94fa**	12	72
7	H	H	CH_3		**94ab**	3	84
8	H	5-Cl	CH_3		**94bb**	3	78

9	H	5-Br	CH_3		**94cb**	3	80
10	H	5-CH_3	CH_3		**94eb**	3	76
11	CH_3	H	H		**94ga**	12	72
12	CH_3	5-Cl	H		**94ha**	12	64
13	CH_3	5-Br	H		**94ia**	12	65
14	CH_3	5-F	H		**94ja**	12	62
15	CH_3	5-OCH_3	H		**94ka**	12	70
16	CH_3	H	CH_3		**94gb**	3	85
17	CH_3	5-Cl	CH_3		**94hb**	3	80
18	CH_3	5-Br	CH_3		**94ib**	3	78

19	$PhCH_2$	H	H		**94la**	12	76

[a]Reaction conditions: **58** (1.0 mmol), **93** (1.1 mmol), BF_3-etherate (2.0 mmol), chloroform (10.0 mL), reflux. [b]Isolated yield.

After having all the desired substituted 2-((2-bromobenzyl)thio)-1*H*-indoles and 2-((1-(2-bromophenyl)ethyl)thio)-1*H*-indoles in our hand, we attempted the transition metal-catalyzed Ullmann type C-N coupling reaction to produce the indole-fused sulfur-containing cyclized products. Initially, 2-((2-bromobenzyl)thio)-1*H*-indole (**94aa**) was chosen as a model reactant to study the intramolecular C-N coupling reaction. The reaction of **94aa** using CuI (10 mol %), Cs_2CO_3 (2 equiv) and ligand L-proline (1 equiv) in DMSO afforded the C-N coupled product, 5*H*-benzo[4,5][1,3]thiazino[3,2-*a*]indole (**95aa**) in 24% yield (Table 3.2, entry 1). The structure of **95aa** was ascertained by its NMR and mass spectral data. Encouraged by the success of the desired cyclization, we proceeded to further screen various copper-based catalysts, ligand, and solvents to improve the yield of the product **95aa.** The examination of ligands such as 1,10-phenanthroline, 8-hydroxyquinoline and *N*,*N*′-dimethylethylenediamine (DMEDA) suggested that DMEDA is a most suitable ligand for the present methodology, which afforded **95aa** in 47% yield (Table 3.2, entry 4). Next, we screened different solvents *viz.* toluene, DMF, DMSO and ethylene glycol for the model reaction using CuI as a catalyst. The highest yield of 60% for **95aa** was obtained with ethylene glycol (Table 3.2, entry 7). Screening of various potential copper catalysts such as CuI, CuBr, CuCl, CuO, $Cu(OTf)_2$, $CuSO_4.5H_2O$, $CuCl_2$ and $Cu(OAc)_2.H_2O$ for the model reaction in ethylene glycol revealed that $Cu(OAc)_2.H_2O$ was the most efficient catalyst to result in **95aa** in 74% yield (Table 3.2, entry 14). Finally, changing the solvent from ethylene glycol to PEG-400 led to further improvement in the yield (80%) of **95aa** (Table 3.2, entry 15). It is worthwhile to mention that the use of ligand appears to be essential for this reaction, as in the absence of ligand only trace amount of **95aa** was obtained (Table 3.2, entry 16).

Table 3.2: Optimization of reaction condition for C-N coupling of **94aa** to produce **95aa**.[a]

S. No.	R	Catalyst	Ligand	Solvent	Yield (%)[b]
1	H	CuI	L-Proline	DMSO	24
2	H	CuI	1,10-Phen[c]	DMF	27
3	H	CuI	8-HQ[d]	DMF	36
4	H	CuI	DMEDA	DMF	47
5	H	CuI	DMEDA	DMSO	54
6	H	CuI	DMEDA	Toluene	56
7	H	CuI	DMEDA	Ethylene glycol	60
8	H	CuBr	DMEDA	Ethylene glycol	67
9	H	CuCl	DMEDA	Ethylene glycol	47
10	H	CuO	DMEDA	Ethylene glycol	40
11	H	$Cu(OTf)_2$	DMEDA	Ethylene glycol	54
12	H	$CuSO_4.5H_2O$	DMEDA	Ethylene glycol	64
13	H	$CuCl_2.2H_2O$	DMEDA	Ethylene glycol	67
14	H	$Cu(OAc)_2.H_2O$	DMEDA	Ethylene glycol	74
15	**H**	**$Cu(OAc)_2.H_2O$**	**DMEDA**	**PEG-400**	**80[e,f]**
16	H	$Cu(OAc)_2.H_2O$	-	PEG-400	Trace

[a]Reaction conditions: **94aa** (0.25 mmol), Cu-catalyst (0.025 mmol), Cs_2CO_3 (0.5 mmol), Ligand (0.25 mmol), solvent (2.0 mL); [b]Isolated yield; [c]1,10-Phen=1,10-Phenanthroline, [d]8-HQ = 8 Hydroxyquinoline, [e]Optimized reaction conditions, [f]The yield of **95aa** was 73 and 81% by using catalyst loading of 5 and 15 mol %.

With the optimal reaction conditions in hand, we next examined the substrate scope for the synthesis of various indole-fused benzothiazines. As shown in **Figure 3.5**, differently substituted 2-((2-bromobenzyl)thio)-1*H*-indoles (**94aa-fa**) and 2-((1-(2-bromophenyl)-ethyl)thio)-1*H*-indoles (**94ab-eb**) resulted in corresponding indole fused benzothiazines (**95aa-eb**) in good to excellent yield (66-80%). Our results indicate that substituents such as methyl, methoxy, chloro, bromo etc. on the indole nucleus were tolerated well in the reaction under investigation. The ability to incorporate halogen substituents makes the method attractive for synthetic chemists, as these substituents can be utilized for further synthetic manipulations. The structure of all the compounds was ascertained by IR, NMR, and HRMS data. Representative ^{1}H NMR and ^{13}C NMR of **95aa** are shown in **Figure 3.4.**

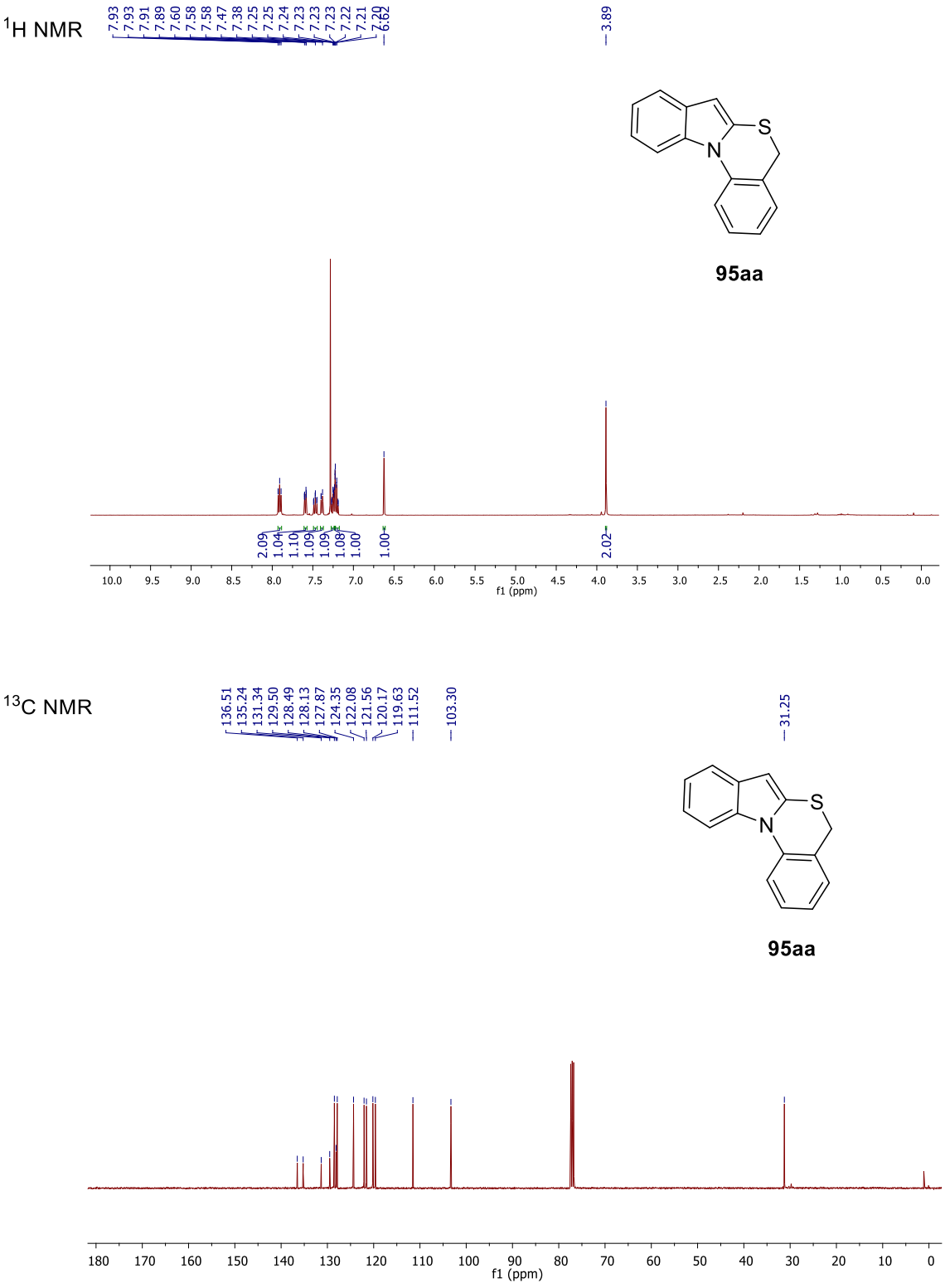


Figure 3.4: ^{1}H and ^{13}C NMR spectra of 5*H*-benzo[4,5][1,3]thiazino[3,2-*a*]indole **(95aa)** in $CDCl_3$

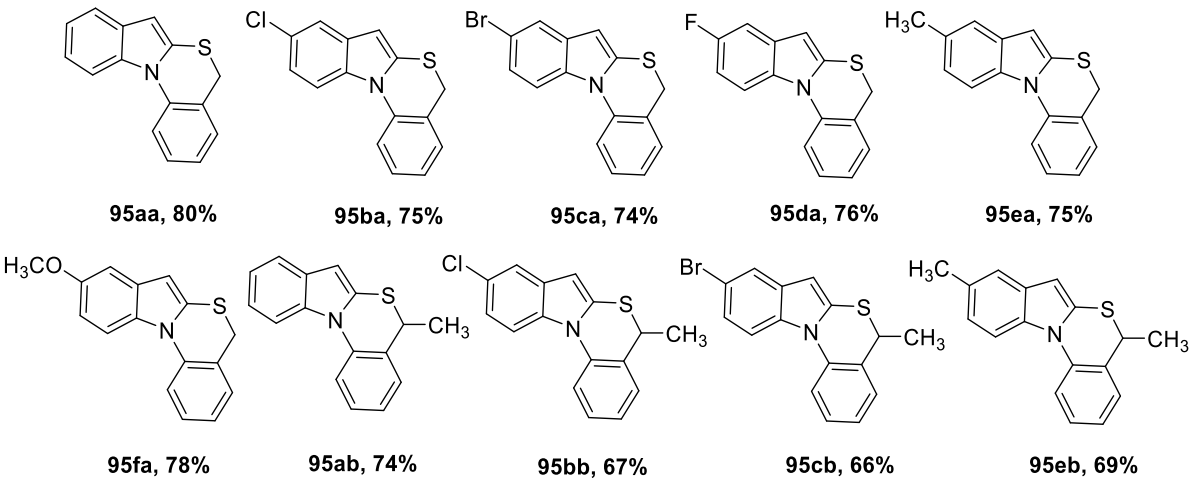


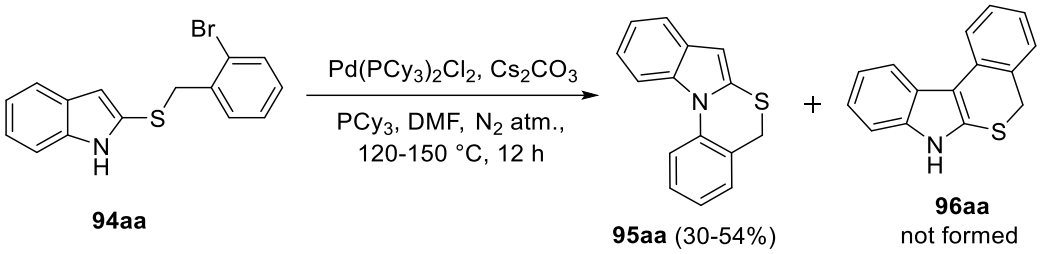
Figure 3.5: Synthesis of 5*H*-benzo[4,5][1,3]thiazino[3,2-*a*]indoles (**95**) using copper catalysed intramolecular C-N coupling.

Next, we turned our attention to synthesize 5,7- dihydroisothiochromeno[3,4-*b*]indole (**96aa**), a C-C coupled product from **94aa** using palladium catalysis. The reaction of **94aa** in the presence of $Pd(PCy_3)_2Cl_2$ (5 mol %), PCy_3 (10 mol %) and Cs_2CO_3 (2 equiv) in *N*,*N*-dimethylformamide (DMF) under nitrogen atmosphere after 12 h at 120 °C resulted **95aa** in 30% yield instead of required **96aa** (**Scheme 3.28**). Attempts to further change the palladium source, bases and ligands were also futile in yielding the desired C-C coupled product, the instead formation of **95aa** or a complex TLC was observed. To circumvent the issue of C-N coupling we resorted to using *N*-methylated substrate **94ga**. Gratifyingly, the reaction of **94ga** in the presence of $Pd(PPh_3)_4$ (5 mol %), PPh_3 (10 mol %) and Cs_2CO_3 (2 equiv) in DMF under N_2 atmosphere resulted in the formation of desired C-C coupled product, 5,7-dihydroisothiochromeno[3,4-*b*]indole (**96ga**). As summarized in Table 3.3, a quick screening of the potential catalysts, bases, and solvents led to the optimal conditions to yield **96ga** in 82% (Table 3.3, entry 6). Structure of **96ga** was accertained by NMR and mass analysis. NMR of **94ga** and **96ga** are shown in **Figure 3.6** and **Figure 3.7**, respectively.

Table 3.3: Optimization of reaction condition for C-C coupling to give **96ga**.

Entry	Catalyst	Base	Ligand	Solvent	Yield (%)[b]
1	$Cu(OAc)_2.H_2O$	Cs_2CO_3	DMEDA	PEG-400	NR
2	$Pd(PPh_3)_4$	K_2CO_3	PPh_3	1,4-Dioxane	15
3	$Pd(OAc)_2$	CsOAc	PPh_3	DMA	Traces
4	$Pd(PPh_3)_4$	Cs_2CO_3	PPh_3	DMA	46
5	$Pd(PPh_3)_4$	Cs_2CO_3	PPh_3	DMSO	70
6	**$Pd(PPh_3)_4$**	**Cs_2CO_3**	**PPh_3**	**DMF**	**82**

[a]Reaction conditions: **94ga** (0.5 mmol), catalyst (0.025 mmol), base (1.0 mmol), Ligand (0.05 mmol), solvent (2.0 mL); [b]Isolated yield.



Scheme 3.28: Intramolecular cyclization of **94aa**

Next, as outlined in **Figure 3.8**, the synthetic worth of C-C coupling method was demonstrated by varying the substrates for the reaction. In all the cases, reactions underwent a smooth conversion to afford the corresponding 5,7-dihydroisothiochromeno[3,4-*b*]indoles **96ga-la** in good to excellent (70-82%) yields (**Figure 3.8**). Intramolecular cyclization of *N*-benzylated indole derivative **94la** gave corresponding of isothiochromeno[3,4-*b*]indole derivative **96la** in 76% yield which can be deprotected to give corresponding unprotected derivative.

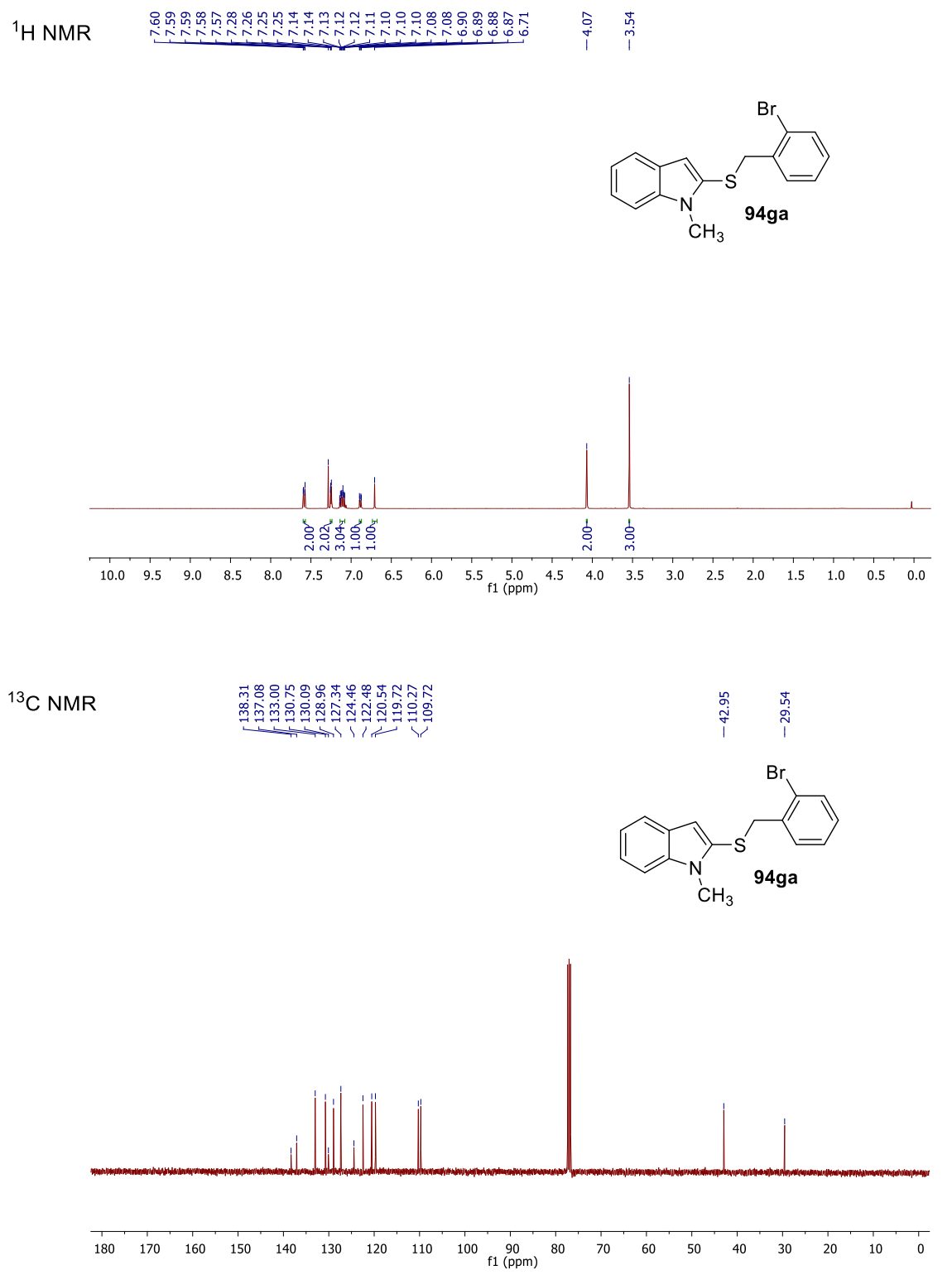


Figure 3.6: ^{1}H and ^{13}C NMR spectra of 2-((2-Bromobenzyl)thio)-1-methylindole **(94ga)** in $CDCl_3$

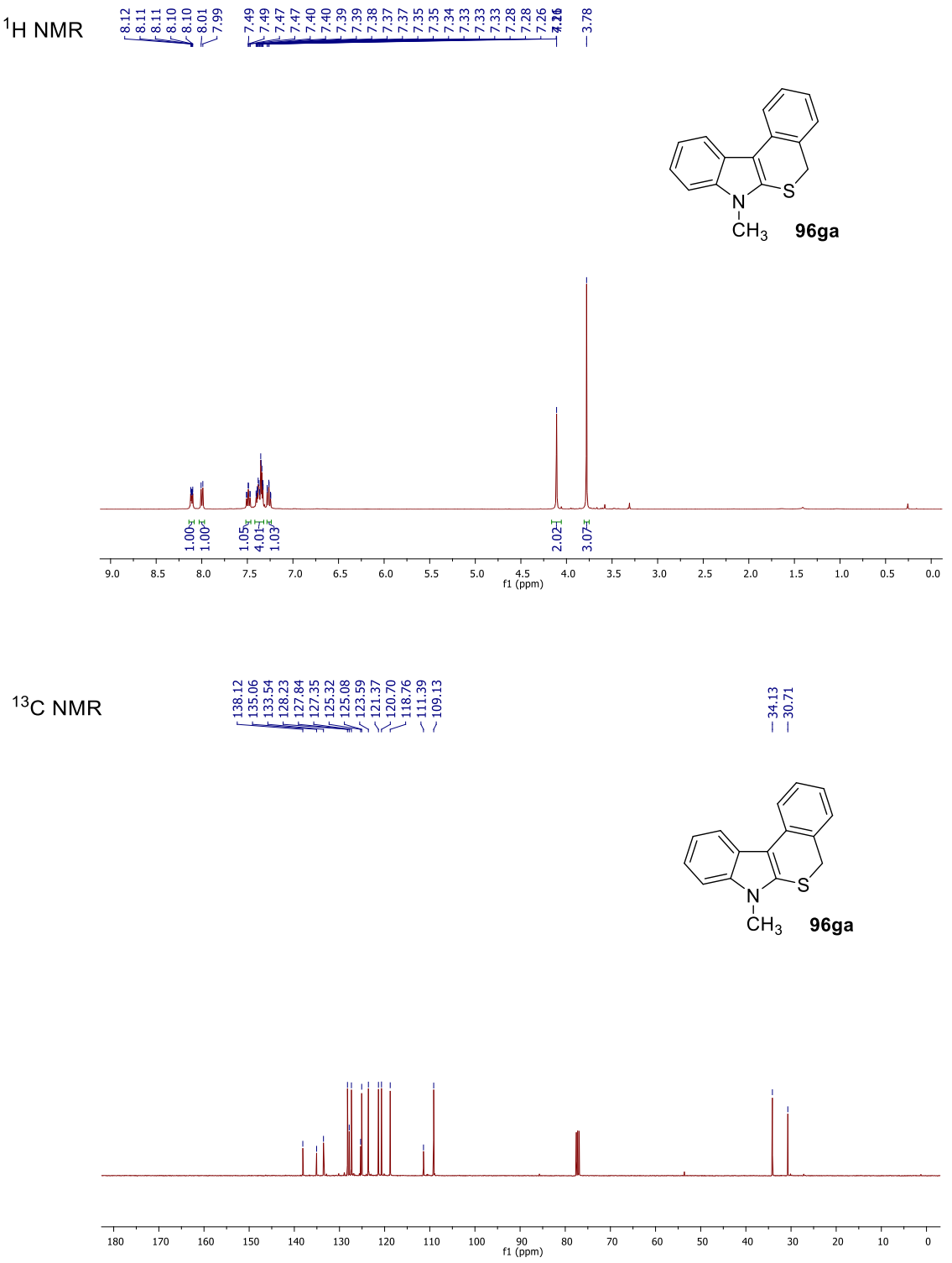


Figure 3.7: ^{1}H and ^{13}C NMR spectra of 7-Methyl-5,7-dihydroisothiochromeno[3,4-*b*]indole **(96ga)** in $CDCl_3$

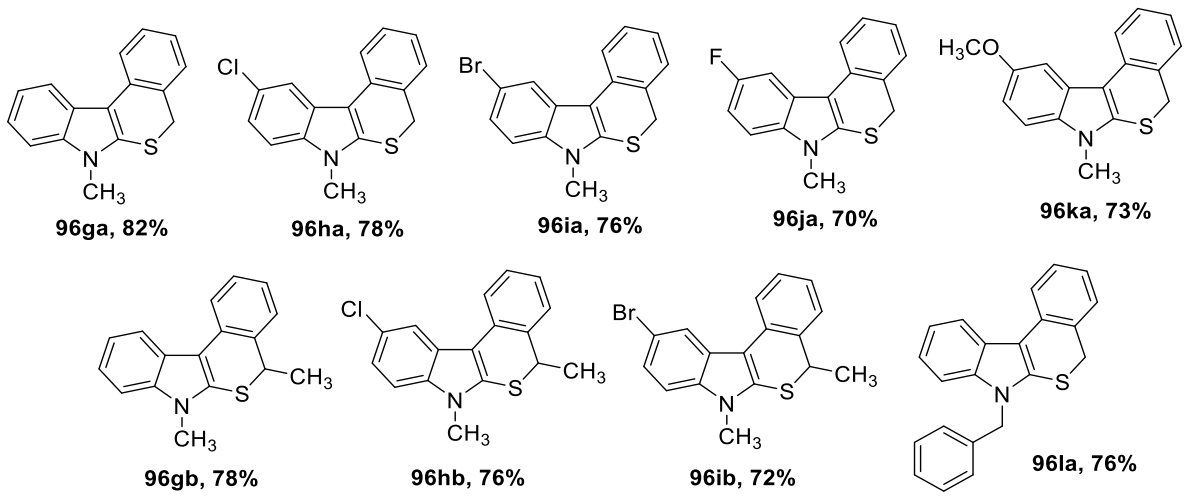
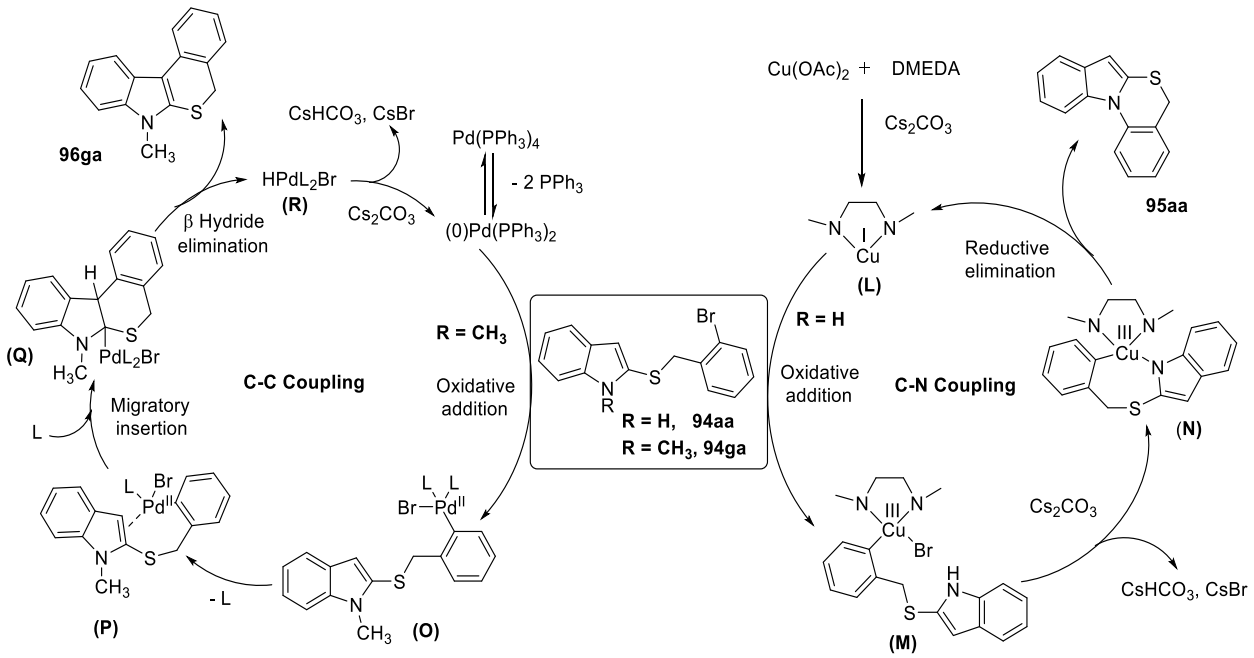


Figure 3.8: Synthesis of 5,7-dihydroisothiochromeno[3,4-*b*]indoles (**96**).

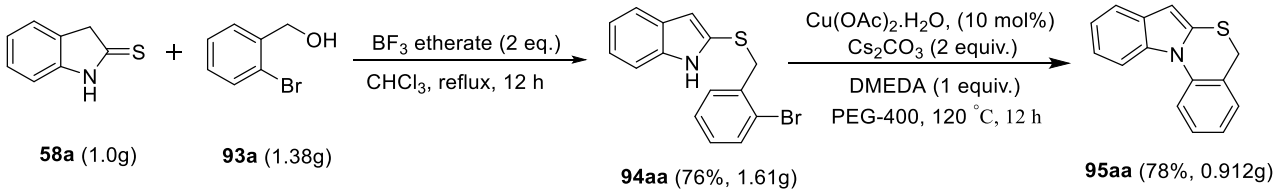
Based on the structure of the products obtained and previous literature reports on Ullmann type C-N Coupling[13, 109, 110] and direct arylation reactions,[111-114] a plausible mechanism of the reaction is presented in **Scheme 3.28**. It is believed that C-N coupling reaction proceeds *via* initial formation of complex **L** when $Cu(OAc)_2$ and DMEDA were heated in the presence of a base. Complex **L** appears to be highly reactive species toward the oxidative addition of **94aa** to form complex **M.**

It is noteworthy that similar four coordinated Cu(III) intermediate has been proposed by other groups.[33, 35, 115, 116] Replacement of Br in **M** with an internal nucleophile (NH) may lead to the formation of intermediate **N** which on reductive elimination affords **95aa**. On the other side, the neutral pathway of the direct arylation may begin with the oxidative addition of **94ga** to form the complex **O**. Dissociation of a phosphine ligand followed by coordination of the pendant unsaturated group (C2-C3 double bond) of **94ga** provides complex **P**, and migratory insertion of this double bond into the carbon palladium bond establishes the key C-C bond. After insertion, β-hydride elimination provides C-C coupled product **96ga** and palladium(0) to complete the catalytic cycle.



Scheme 3.28: A plausible mechanism for the synthesis of **95** and **96**.

Finally, to further demonstrate the practicality and efficiency of the developed methodology, a gram-scale reaction was performed. As shown in **Scheme 3.29**, **95aa** could be readily synthesized in 0.942 g from **58a** (1.0 g) in a gram-scale synthesis.



Scheme 3.29: Gram-scale synthesis of **95aa**.

3.4 Conclusions

In conclusion, we have demonstrated a highly efficient and straightforward approach for the synthesis of 5*H*-benzo[4,5][1,3]thiazino[3,2-*a*]indole and 5,7-dihydroisothiochromeno[3,4-*b*]indole derivatives *via* copper-catalysed intramolecular Ullmann type C-N coupling of 2-(2-bromobenzylthio)-1*H*-indoles and palladium-catalysed direct arylation reaction of 2-(2-bromobenzylthio)-1-methyl-1*H* indoles, respectively. The substrates for this transformation have been synthesized from indoline-2-thiones and 2-bromobenzyl alcohols. The developed protocol

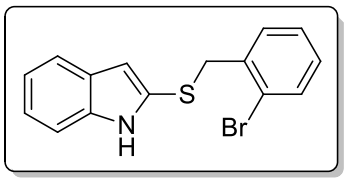
offers a valuable method for the synthesis of these potential bioactive scaffolds and would find wide applications in organic synthesis and medicinal chemistry.

3.5 Experimental

Melting points were determined in open capillary tubes on an automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates. The chemical structures of final products were determined by their NMR spectra (^{1}H and ^{13}C NMR) using 400 MHz spectrometer. ^{13}C NMR spectra are fully decoupled. High-resolution mass spectra (HRMS) were carried out using a quadrupole time-of-flight (qTOF) mass spectrometer. All other chemicals were obtained from the commercial suppliers and used without further purification.

General procedure for the synthesis of 2-(2-bromobenzylthio)-1*H*-indoles (94): BF_3-etherate (2.0 mmol) was added dropwise to a stirred solution of appropriate indolin-2-thione (1.0 mmol) and 2-bromobenzyl alcohol (1.1 mmol) in chloroform (10.0 mL) at the ice-cold condition. Then, the reaction mixture was kept at reflux condition (for reaction time see Table 1). After the reaction was a complete excess of chloroform was evaporated by rotary evaporator. The residue was subjected to column chromatography (1% EtOAc in hexane) to obtain pure 2-(2-bromobenzylthio)-1*H*-indoles (**94aa-la**).

2-((2-Bromobenzyl)thio)-1*H*-indole (94aa): Yellow solid (74%, 236 mg); mp 83-85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.63 – 7.55 (m, 2H), 7.31 – 7.28 (m, 1H), 7.22 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.17 – 7.10 (m, 3H), 7.04 – 6.99 (m, 1H), 6.63 (s, 1H), 4.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 137.2, 133.1, 130.9, 129.0, 128.5, 127.5, 127.4, 124.4, 122.9, 120.5, 120.1, 110.7, 110.4, 42.4; FT-IR ν_{max} (neat): 3373, 1567, 1439, 1226, 1089, 1043, 734, 657; ESI-TOF *m/z* Calcd for $C_{15}H_{13}BrNS^{+}$ 317.9947, found 317.9940 $[M + H]^{+}$ and 319.9897 $[M + H + 2]^{+}$.



2-((2-Bromobenzyl)thio)-5-chloro-1*H*-indole (94ba): Pale yellow liquid (66%, 233 mg);[1]H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.49 – 7.45 (m, 1H), 7.40 (dt, *J* = 1.6, 0.7 Hz, 1H), 7.05 – 6.99 (m, 4H), 6.89 – 6.84 (m, 1H), 6.41 (s, 1H), 4.01 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 135.4, 133.1, 130.8, 129.5, 129.3, 129.2, 127.5, 125.8, 124.4, 123.2, 119.8, 111.7, 109.7, 42.2; FT-IR ν_{max} (neat): 3382, 2924, 1565, 1319, 1221, 1065, 1025, 767, 735; ESI-TOF *m/z* Calcd for $C_{15}H_{12}BrClNS^+$ 351.9557, found 351.9563 $[M + H]^+$ and 353.9527 $[M + H + 2]^+$.

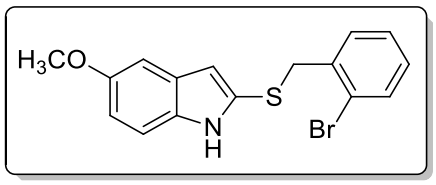
5-Bromo-2-((2-bromobenzyl)thio)-1*H*-indole (94ca): Greenish liquid (68%, 270 mg)**;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.70 – 7.68 (m, 1H), 7.60 (dd, *J* = 5.4, 3.8 Hz, 1H), 7.29 (dd, *J* = 6.0, 2.6 Hz, 1H), 7.14 (ddd, *J* = 4.8, 2.5, 1.1 Hz, 3H), 7.01 – 6.97 (m, 1H), 6.53 (s, 1H), 4.13 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 135.6, 133.1, 130.8, 130.1, 129.2, 127.5, 125.7, 124.4, 122.8, 113.3, 112.1, 109.5, 42.2; FT-IR ν_{max} (neat): 3383, 3049, 1565, 1316, 1221, 1090, 766, 733; FD-TOF *m/z* Calcd for $C_{15}H_{11}Br_2NS^+$ 394.8979, found 394.8967 $[M]^+$, 396.8946 $[M + 2]^+$ and 398.8923 $[M + 4]^+$.

2-((2-Bromobenzyl)thio)-5-fluoro-1*H*-indole (94da): Liquid (64%, 215 mg)**;** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.60 (dd, *J* = 6.8, 2.3 Hz, 1H), 7.17 (ddd, *J* = 9.7, 7.1, 2.0 Hz, 4H), 7.04 – 6.90 (m, 2H), 6.56 (s, 1H), 4.14 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.4 (d, $J_{C\text{-}F}$ = 274.6 Hz), 133.1, 130.8, 129.5, 129.1, 128.8 (d, $J_{C\text{-}F}$ = 9.9 Hz), 127.5, 124.4, 111.5, 111.3, 111.2 (d, $J_{C\text{-}F}$= 3.4 Hz), 110.1, 105.1 (d, $J_{C\text{-}F}$ = 23.4 Hz)., 42.3; FT-IR ν_{max} (neat): 3388, 2928, 2855, 1568, 1466, 1433, 1140, 1025, 756, 738; FD-TOF *m/z* Calcd for $C_{15}H_{11}BrFNS^+$ 334.9780, found 334.9782 $[M]^+$ and 336.9761 $[M + 2]^+$.

2-((2-Bromobenzyl)thio)-5-methyl-1*H*-indole (94ea): Greenish liquid (70%, 233 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.63 – 7.59 (m, 1H), 7.36 (d, *J* = 0.8 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 7.16 – 7.13 (m, 2H), 7.05 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.01 – 6.98 (m, 1H), 6.55 (s, 1H), 4.12 (s, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 135.5, 133.1, 130.8, 129.3, 129.0, 128.8, 127.4, 127.4, 124.6, 124.4, 120.0, 110.3, 110.0, 42.5, 21.5; FT-IR ν_{max} (neat): 3378, 2916, 2852, 1565, 1465, 1435, 1025,

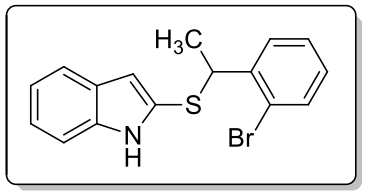
761, 723; ESI-TOF *m/z* Calcd for $C_{16}H_{15}BrNS^+$ 332.0103, found 332.0111 $[M + H]^+$ and 334.0075 $[M + H + 2]^+$.

2-((2-Bromobenzyl)thio)-5-methoxy-1*H*-indole (94fa): Liquid (72%, 251 mg); ^{1}H NMR (300



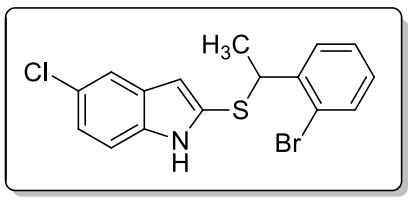
MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.59 (dd, *J* = 5.2, 2.3 Hz, 1H), 7.21 – 7.10 (m, 3H), 7.00 (d, *J* = 7.5 Hz, 2H), 6.90 – 6.84 (m, 1H), 6.54 (s, 1H), 4.11 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 137.5, 133.1, 132.3, 130.8, 129.0, 128.9, 127.9, 127.4, 124.4, 113.4, 111.4, 110.1, 101.7, 55.8, 42.5; FT-IR ν_{max} (neat): 3393, 3322, 1566, 1507, 1154, 1023, 753, 727; ESI-TOF *m/z* Calcd for $C_{16}H_{15}BrNOS^+$ 348.0052, found 348.0063 $[M + H]^+$ and 350.0029 $[M + H + 2]^+$.

2-((1-(2-Bromophenyl)ethyl)thio)-1*H*-indole (94ab): Greenish liquid (84%, 279 mg);^{1}H NMR



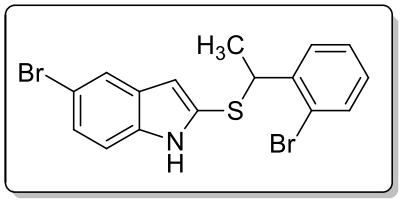
(400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.65 – 7.59 (m, 2H), 7.36 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.30 (dt, *J* = 4.1, 1.9 Hz, 2H), 7.25 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.18 – 7.12 (m, 2H), 6.69 (s, 1H), 4.79 (q, *J* = 7.0 Hz, 1H), 1.69 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 137.3, 133.0, 128.8, 128.4, 128.0, 127.7, 94.3, 124.3, 122.9, 120.5, 120.1, 111.5, 110.7, 47.5, 21.4; FT-IR ν_{max} (neat): 3396, 3052, 2966, 1565, 1468, 1436, 1020, 796, 747; ESI-TOF *m/z* Calcd for $C_{16}H_{15}BrNS^+$ 332.0103, found 332.0117 $[M + H]^+$ and 334.0086 $[M + H + 2]^+$.

2-((1-(2-Bromophenyl)ethyl)thio)-5-chloro-1*H*-indole (94bb): Greenish liquid (78%, 286 mg);



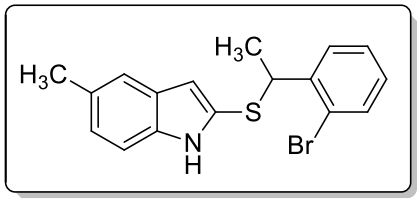
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.60 – 7.54 (m, 2H), 7.34 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.28 (td, *J* = 7.6, 1.1 Hz, 1H), 7.18 (d, *J* = 1.3 Hz, 2H), 7.16 – 7.12 (m, 1H), 6.57 (s, 1H), 4.80 (q, *J* = 7.0 Hz, 1H), 1.67 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 135.5, 133.0, 129.3, 128.9, 128.1, 127.9, 127.8, 125.7, 124.3, 123.2, 119.8, 111.7, 110.8, 47.5, 21.4; FT-IR ν_{max} (neat): 3417, 3057, 2968, 1565, 1434, 1092, 1021, 755, 724; FD-TOF *m/z* Calcd for $C_{16}H_{13}BrClNS^+$ 364.9641, found 364.9631 $[M]^+$ and 366.9610 $[M + 2]^+$.

5-Bromo-2-((1-(2-bromophenyl)ethyl)thio)-1*H*-indole (94cb): Greenish liquid (80%, 329 mg);



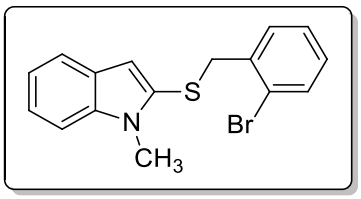
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.70 (d, *J* = 1.8 Hz, 1H), 7.57 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.35 – 7.25 (m, 3H), 7.17 – 7.10 (m, 2H), 6.55 (s, 1H), 4.78 (q, *J* = 7.0 Hz, 1H), 1.66 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 135.7, 133.0, 130.0, 128.9, 127.9, 127.9, 127.7, 125.7, 124.3, 122.9, 113.3, 112.1, 110.6, 47.5, 21.3; FT-IR ν_{max} (neat): 3413, 3058, 2966, 1563, 1468, 1436, 1185, 1020, 753, 723; FD-TOF *m/z* Calcd for $C_{16}H_{13}Br_2NS^+$ 408.9135, found 408.9135 $[M]^+$, 410.9112 $[M + 2]^+$, 412.9095 $[M + 4]^+$.

2-((1-(2-Bromophenyl)ethyl)thio)-5-methyl-1*H*-indole (94eb): Greenish liquid (76%, 263 mg);



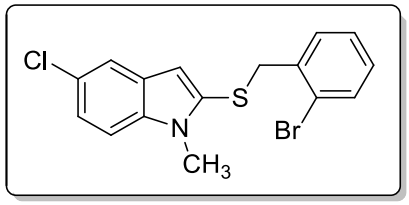
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.59 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.39 (d, *J* = 0.7 Hz, 1H), 7.33 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 7.14 (ddd, *J* = 7.9, 7.2, 1.9 Hz, 1H), 7.06 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.58 (s, 1H), 4.75 (q, *J* = 7.0 Hz, 1H), 2.47 (s, 3H), 1.66 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 135.6, 133.0, 129.3, 128.7, 128.6, 127.9, 127.7, 94.0, 124.6, 124.3, 120.0, 111.1, 110.4, 47.5, 21.5, 21.3; FT-IR ν_{max} (neat): 3392, 3053, 2960, 1587, 1468, 1436, 1020, 754, 724; FD-TOF *m/z* Calcd for $C_{17}H_{16}BrNS^+$ 345.0187, found 345.0173 $[M]^+$ and 347.0151 $[M + 2]^+$.

2-((2-Bromobenzyl)thio)-1-methyl-1*H*-indole (94ga):White solid (72%, 239 mg); mp 72-74 °C



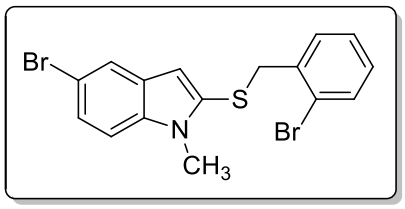
(lit.[12b] mp 76-78 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.56 (m, 2H), 7.26 – 7.24 (m, 2H), 7.15 – 7.07 (m, 3H), 6.88 (dd, *J* = 7.2, 2.1 Hz, 1H), 6.71 (s, 1H), 4.07 (s, 2H), 3.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.1, 133.0, 130.7, 130.1, 129.0, 127.3, 124.5, 122.5, 120.5, 119.7, 110.3, 109.7, 42.9, 29.5; FT-IR ν_{max} (neat): 3048, 1566, 1312, 1230, 1024, 745, 724; ESI-TOF *m/z* Calcd for $C_{16}H_{15}BrNS^+$ 332.0103, found 332.0103 $[M + H]^+$, 334.0063 $[M + H + 2]^+$.

2-((2-Bromobenzyl)thio)-5-chloro-1-methyl-1*H*-indole (94ha): Yellow liquid (64%, 235 mg);



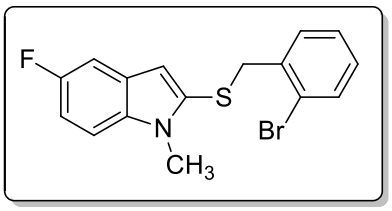
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.56 (m, 1H), 7.54 (d, *J* = 1.9 Hz, 1H), 7.21 – 7.05 (m, 4H), 6.88 – 6.83 (m, 1H), 6.62 (s, 1H), 4.07 (s, 2H), 3.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 136.6, 133.0, 131.8, 130.7, 129.0, 128.2, 127.4, 125.5, 124.5, 122.7, 119.8, 110.7, 109.5, 42.7, 29.7; FT-IR ν_{max} (neat): 3057, 1566, 1320, 1227, 1053, 1024, 757, 726; ESI-TOF *m/z* Calcd for $C_{16}H_{14}BrClNS^+$ 365.9713, found 365.9721 $[M + H]^+$ and 367.9682 $[M + H + 2]^+$.

5-Bromo-2-((2-bromobenzyl)thio)-1-methyl-1*H*-indole (94ia): Yellow liquid (65%, 267 mg);



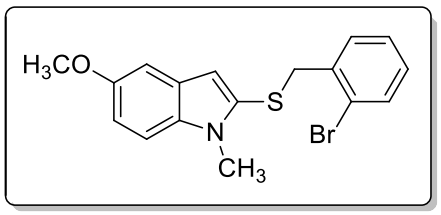
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 1.6 Hz, 1H), 7.58 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.32 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.13 – 7.07 (m, 3H), 6.85 (dd, *J* = 7.3, 1.9 Hz, 1H), 6.62 (s, 1H), 4.07 (s, 2H), 3.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 136.8, 133.0, 131.6, 130.7, 129.1, 128.8, 127.4, 125.2, 124.4, 122.9, 113.0, 111.1, 109.4, 42.7, 29.7; FT-IR ν_{max} (neat): 3054, 1566, 1319, 1044, 1024, 787, 737; FD-TOF *m/z* Calcd for $C_{16}H_{13}Br_2NS^+$ 408.9135, found 408.9124 $[M]^+$, 410.9104 $[M + 2]^+$ and 412.9083 $[M + 4]^+$.

2-((2-Bromobenzyl)thio)-5-fluoro-1-methyl-1*H*-indole (94ja): Pale yellow liquid (62%, 217



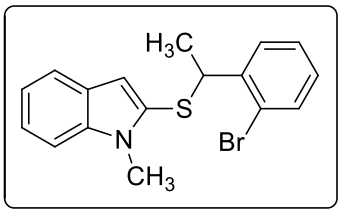
mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 9.4 Hz, 1H), 7.18 – 7.07 (m, 3H), 7.01 (t, *J* = 9.1 Hz, 1H), 6.87 (d, *J* = 7.0 Hz, 1H), 6.66 (s, 1H), 4.07 (s, 2H), 3.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9 (d, $J_{C\text{-}F}$ = 147.9 Hz), 133.0, 132.6, 131.8, 130.7, 129.1, 127.4, 127.2, 124.5, 111.2, 110.8, 110.4 (d, $J_{C\text{-}F}$ = 9.6 Hz), 109.9 (d, $J_{C\text{-}F}$ = 4.8 Hz), 105.1 (d, $J_{C\text{-}F}$ = 23.3 Hz), 42.8, 29.7; FT-IR ν_{max} (neat): 3051, 3011, 2927, 1454, 1414, 1183, 1023, 750, 722; ESI-TOF *m/z* Calcd for $C_{16}H_{14}BrFNS^+$ 350.0009, found 349.9997 $[M + H]^+$ and 351.9974 $[M + H + 2]^+$.

2-((2-Bromobenzyl)thio)-5-methoxy-1-methyl-1*H*-indole (94ka): White solid (70%, 254 mg);



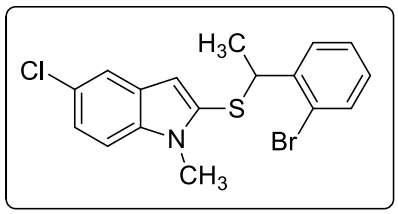
mp 102-103 °C;^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.0 Hz, 1H), 7.16 – 7.03 (m, 4H), 6.95 – 6.90 (m, 1H), 6.88 – 6.83 (m, 1H), 6.64 (s, 1H), 4.05 (s, 2H), 3.87 (s, 3H), 3.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 137.1, 133.7, 133.0, 130.7, 130.1, 129.0, 127.5, 127.3, 124.4, 113.1, 110.5, 109.8, 101.6, 55.8, 43.1, 29.6; FT-IR ν_{max} (neat): 3048, 2999, 2927, 1566, 1458, 1439, 1150, 1023, 756, 723; ESI-TOF *m/z* Calcd for $C_{17}H_{17}BrNOS^+$ 362.0209, found 362.0199 $[M + H]^+$ and 364.0172 $[M + H + 2]^+$.

2-((1-(2-Bromophenyl)ethyl)thio)-1-methyl-1*H*-indole (94gb): Pale yellow liquid (85%, 295



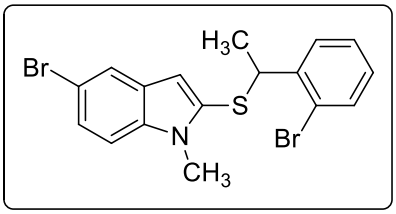
mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.57 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.27 – 7.23 (m, 2H), 7.22 – 7.17 (m, 2H), 7.16 – 7.10 (m, 2H), 6.74 (s, 1H), 4.68 (q, *J* = 7.0 Hz, 1H), 3.55 (s, 3H), 1.66 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 138.5, 132.9, 132.4, 128.6, 127.8, 127.6, 127.1, 124.2, 122.5, 120.5, 119.7, 111.8, 109.8, 47.1, 29.6, 21.0; FT-IR ν_{max} (neat): 3055, 2962, 2924, 1589, 1458, 1319, 1026, 748, 663; ESI-TOF *m/z* Calcd for $C_{17}H_{17}BrNS^+$ 346.0260, found 346.0261 $[M + H]^+$ and 348.0236 $[M + H + 2]^+$.

2-((1-(2-Bromophenyl)ethyl)thio)-5-chloro-1-methyl-1*H*-indole (94hb): White solid (80%,

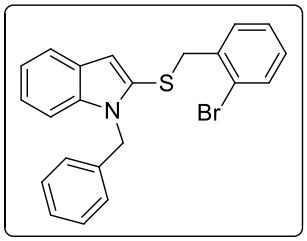


305 mg); mp100-102 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dt, *J* = 5.5, 1.1 Hz, 2H), 7.21 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.19 – 7.17 (m, 2H), 7.16 – 7.13 (m, 1H), 7.10 (ddd, *J* = 7.9, 7.0, 2.1 Hz, 1H), 6.62 (s, 1H), 4.69 (q, *J* = 7.0 Hz, 1H), 3.51 (s, 3H), 1.66 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 136.8, 132.9, 130.1, 128.7, 127.9, 127.8, 127.6, 125.4, 124.2, 122.8, 119.8, 111.0, 110.7, 47.1, 29.7, 21.0; FT-IR ν_{max} (neat): 3071, 2961, 1563, 1451, 1437, 1052, 1019, 760, 725; ESI-TOF *m/z* Calcd for $C_{17}H_{16}BrClNS^+$ 379.9870, found 379.9878 $[M + H]^+$ and 381.9833 $[M + H + 2]^+$.

5-Bromo-2-((1-(2-bromophenyl)ethyl)thio)-1-methyl-1H-indole (94ib): Gummy mass (78%, 338 mg);[1]H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 1.6 Hz, 1H), 7.54 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.31 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.15 – 7.09 (m, 4H), 6.62 (s, 1H), 4.68 (q, *J* = 7.0 Hz, 1H), 3.49 (s, 3H), 1.65 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 137.0, 132.9, 129.8, 128.7, 128.6, 127.7, 127.6, 125.3, 124.2, 122.9, 113.0, 111.2, 110.9, 47.1, 29.7, 21.0; FT-IR ν_{max} (neat): 3071, 2961, 1563, 1451, 1437, 1052, 1019, 760, 725; FD-TOF *m/z* Calcd for $C_{17}H_{15}Br_2NS^+$ 422.9292, found 422.9304 $[M]^+$, 424.9280 $[M + 2]^+$ and 426.9257 $[M + 4]^+$.

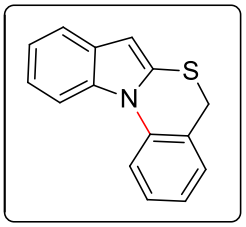


1-Benzyl-2-((2-bromobenzyl)thio)-1*H*-indole (94la): White solid (76%, 292 mg); mp 106-108 °C; 1H NMR (400 MHz, CDCl3) δ 7.67 – 7.57 (m, 2H), 7.32 – 7.27 (m, 3H), 7.25 – 7.23 (m, 2H), 7.19 – 7.09 (m, 3H), 7.08 (d, *J* = 7.3 Hz, 2H), 6.95 – 6.88 (m, 1H), 6.77 (s, 1H), 5.39 (s, 2H), 3.97 (s, 2H); 13C NMR (100 MHz, CDCl3) δ 138.0, 136.8, 133.0, 130.9, 130.2, 129.0, 128.7, 128.5, 128.3, 127.6, 127.3, 126.4, 124.5, 122.7, 120.6, 120.0, 110.9, 110.4, 46.7, 42.7; FT-IR νmax (neat): 3024, 2924, 1497, 1250, 1196, 1018, 725, 648 cm-1. ESI-TOF *m/z* Calcd for C22H19BrNS+ 408.0416, found 408.0422 $[M + H]^+$.

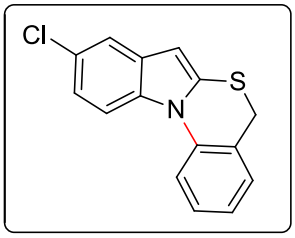


General procedure for the synthesis of 5*H* benzo[4,5][1,3]thiazino[3,2-*a*]indoles (95): A clean oven dried 10 mL RB flask was charged with appropriate 2-(2-bromobenzylthio)-1*H*-indoles (**3**) (0.25 mmol), $Cu(OAc)_2.H_2O$ (0.025 mmol), Cs_2CO_3 (0.5 mmol), DMEDA (0.25 mmol) and PEG-400 (2.0 mL). The reaction mixture was stirred at 120 °C for 12 h. After completion of the reaction, the reaction mass was allowed to cool to ambient temperature, diluted with water (10.0 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude material was purified by column chromatography to obtain 5*H*-benzo[4,5][1,3]thiazino[3,2-*a*]indoles (**95aa-eb**).

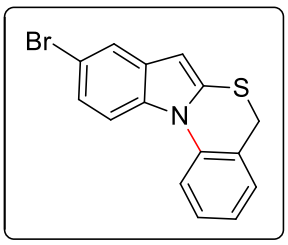
5H-Benzo[4,5][1,3]thiazino[3,2-*a*]indole (95aa): Pale yellow liquid (80%, 48 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 10.9, 3.9 Hz, 2H), 7.61 – 7.57 (m, 1H), 7.47 (td, *J* = 8.0, 1.6 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.27 – 7.24 (m, 1H), 7.23 (dd, *J* = 2.2, 1.5 Hz, 1H), 7.20 (dd, *J* = 7.1, 1.1 Hz, 1H), 6.62 (s, 1H), 3.89 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 135.2, 131.3, 129.5, 128.5, 128.1, 127.9, 124.3, 122.1, 121.6, 120.2, 119.6, 111.5, 103.3, 31.2; FT-IR ν_{max} (neat): 3047, 2962, 1497, 1450, 1103, 779, 741; ESI-TOF *m/z* Calcd for $C_{15}H_{12}NS^+$ 238.0685, found 238.0692 $[M + H]^+$.



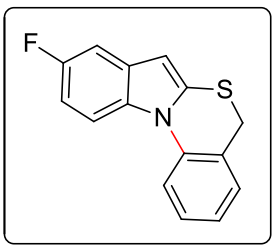
9-Chloro-5H-benzo[4,5][1,3]thiazino[3,2-*a*]indole (95ba): Pale yellow liquid (75%, 51 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.47 (td, *J* = 8.0, 1.5 Hz, 1H), 7.41 – 7.38 (m, 1H), 7.24 (td, *J* = 7.5, 1.0 Hz, 1H), 7.19 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.56 (s, 1H), 3.89 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 133.6, 133.1, 130.6, 129.1, 129.0, 128.6, 128.0, 127.0, 124.7, 122.1, 119.5, 112.4, 102.6, 31.0; FT-IR ν_{max} (neat): 2916, 2854, 1497, 1443, 1203, 1072, 756; FD-TOF *m/z* Calcd for $C_{15}H_{10}ClNS^+$ 271.0222, found 271.0214 $[M]^+$ and 273.0184 $[M + 2]^+$.



9-Bromo-5H-benzo[4,5][1,3]thiazino[3,2-*a*]indole (95ca): Yellow liquid (74%, 59 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 1.8 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 7.3 Hz, 1H), 7.32 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 6.55 (s, 1H), 3.88 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 133.9, 133.0, 131.2, 128.6, 128.0, 128.0, 124.7, 124.7, 122.6, 119.5, 114.7, 112.8, 102.5, 31.0; ESI-TOF *m/z* Calcd for $C_{15}H_{11}BrNS^+$ 315.9790, found 315.9786 $[M + H]^+$ and 317.9774 $[M + H + 2]^+$.

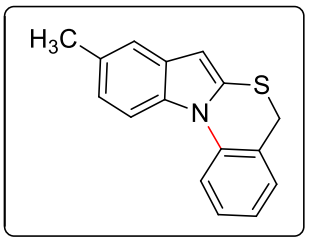


9-Fluoro-5H-benzo[4,5][1,3]thiazino[3,2-*a*]indole (95da): Pale yellow liquid (76%, 49 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.6 Hz, 1H), 7.81 – 7.75 (m, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.01 – 6.91 (m, 1H), 6.56 (s, 1H), 3.88 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7 (d, $J_{C\text{-}F}$ = 237.1 Hz), 136.3, 133.3, 131.7, 130.2, 130.1, 128.6, 127.9 (d, $J_{C\text{-}F}$ = 7.5 Hz), 124.6, 119.3, 112.1 (d, $J_{C\text{-}F}$ = 9.5 Hz), 109.8 (d, $J_{C\text{-}F}$ = 25.8 Hz), 105.2 (d, $J_{C\text{-}F}$ = 23.8 Hz), 103.0 (d, $J_{C\text{-}F}$= 4.3 Hz), 31.0; FT-IR

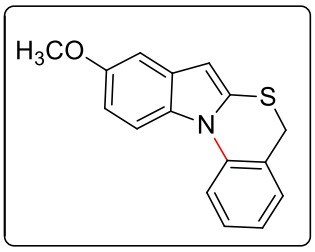


ν_{max} (neat): 3067, 3046, 2954, 1587, 1490, 1452, 1150, 1099, 755, 730; HRMS (FD-TOF) (*m/z*) Calcd for $C_{15}H_{10}FNS^+$ 255.0518, found 255.0510 $[M]^+$.

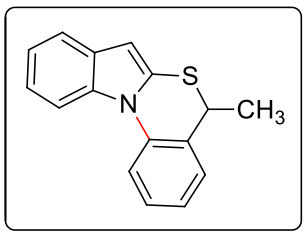
9-Methyl-5H-benzo[4,5][1,3]thiazino[3,2-a]indole (95ea): Yellow liquid (75%, 47 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.46 (td, *J* = 8.0, 1.5 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.21 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.07 (dd, *J* = 8.5, 1.3 Hz, 1H), 6.54 (s, 1H), 3.87 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 133.5, 132.5, 130.9, 129.7, 129.1, 128.5, 127.8, 124.1, 123.4, 119.9, 119.4, 111.2, 102.8, 31.2, 21.3; FT-IR ν_{max} (neat): 2924, 2854, 1489, 1458, 1350, 755; ESI-TOF *m/z* Calcd for $C_{16}H_{14}NS^+$ 252.0841, found 252.0845 $[M + H]^+$.



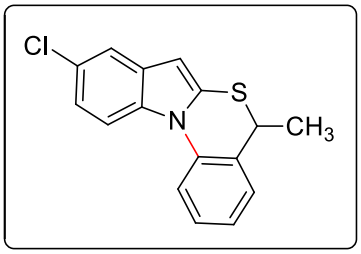
9-Methoxy-5H-benzo[4,5][1,3]thiazino[3,2-a]indole (95fa): Liquid (78%, 52 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.05 (s, 1H), 6.92 – 6.83 (m, 1H), 6.53 (s, 1H), 3.89 (s, 3H), 3.87 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 136.5, 133.7, 131.7, 130.2, 128.5, 127.8, 127.6, 124.1, 119.2, 112.3, 111.3, 102.9, 102.2, 55.8, 31.1; FT-IR ν_{max} (neat): 2992, 2923, 1586, 1490, 1430, 1161, 754, 729; ESI-TOF *m/z* Calcd for $C_{16}H_{14}NOS^+$ 268.0791, found 268.0800 $[M + H]^+$.



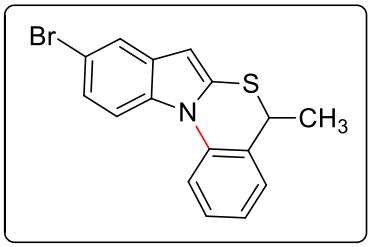
5-Methyl-5H-benzo[4,5][1,3]thiazino[3,2-a]indole (95ab): Pale yellow liquid (74%, 47 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.4, 2.5 Hz, 1H), 7.73 – 7.68 (m, 1H), 7.54 – 7.48 (m, 1H), 7.41 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.33 (dtd, *J* = 14.0, 7.4, 1.3 Hz, 3H), 6.76 (s, 1H), 4.14 (q, *J* = 7.0 Hz, 1H), 1.63 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 135.1, 132.9, 129.9, 129.6, 128.3, 94.2, 124.6, 122.1, 121.6, 120.2, 119.9, 111.6, 104.5, 39.4, 20.3; FT-IR ν_{max} (neat): 3055, 2970, 2924, 1497, 1450, 1111, 741; ESI-TOF *m/z* Calcd for $C_{16}H_{14}NS^+$ 252.0841, found 252.0840 $[M + H]^+$.



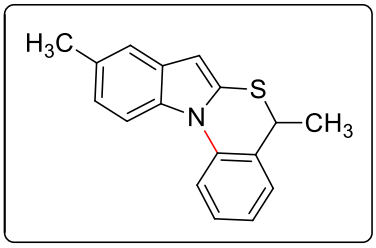
9-Chloro-5-methyl-5H-benzo[4,5][1,3]thiazino[3,2-a]indole (95bb): Liquid (67%, 48 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.38 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.19 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.60 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 1H), 1.57 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 133.4, 132.7, 130.6, 128.3, 127.3, 127.0, 94.2, 124.9, 122.0, 119.7, 119.4, 112.3, 103.7, 39.3, 20.2; FT-IR ν_{max} (neat): 2970, 2924, 1489, 1443, 1203, 1072, 756; ESI-TOF *m/z* Calcd for $C_{16}H_{13}ClNS^+$ 286.0452, found 286.0461 [M + H]+, 288.0453 $[M + H + 2]^+$.



9-Bromo-5-methyl-5H-benzo[4,5][1,3]thiazino[3,2-a]indole (95cb): Gummy mass (66%, 55 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 1.9 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.33 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.60 (s, 1H), 4.11 (q, *J* = 7.0 Hz, 1H), 1.57 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 133.7, 132.8, 131.6, 131.2, 128.3, 94.1, 124.9, 124.6, 122.5, 119.8, 114.6, 112.7, 103.6, 39.3, 20.2; FT-IR ν_{max} (neat): 3041, 2963, 1507, 1437, 1352, 1183, 1056, 751; ESI-TOF *m/z* Calcd for $C_{16}H_{13}BrNS^+$ 329.9947, found 329.9953 $[M + H]^+$ and 331.9935 $[M + H + 2]^+$.



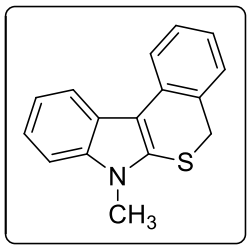
5,9-Dimethyl-5H-benzo[4,5][1,3]thiazino[3,2-a]indole (95eb): Yellow liquid (69%, 46 mg);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.42 – 7.40 (m, 1H), 7.37 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.24 (td, *J* = 7.5, 1.1 Hz, 1H), 7.09 (dd, *J* = 8.5, 1.3 Hz, 1H), 6.60 (s, 1H), 4.10 (q, *J* = 7.0 Hz, 1H), 2.50 (s, 3H), 1.57 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 133.3, 132.6, 130.8, 129.8, 129.6, 128.2, 94.0, 124.3, 123.4, 119.9, 119.7, 111.2, 104.0, 39.3, 21.4, 20.3; FT-IR ν_{max} (neat): 3024, 2970, 2924, 1497, 1458, 1165, 756, 687; ESI-TOF *m/z* Calcd for $C_{17}H_{16}NS^+$ 266.0998, found 266.1003 $[M + H]^+$.



General procedure for the synthesis of 5,7-dihydroisothiochromeno[3,4-*b*]indoles (96)

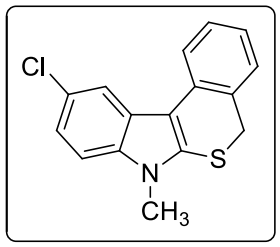
Under an N_2 atmosphere, a mixture of appropriate 2-(2-bromobenzylthio)-1*H*-indoles (**3**) (0.25 mmol), PPh_3 (0.1 mmol), Cs_2CO_3 (2.0 mmol), $Pd(PPh_3)_4$ (0.05 mmol) and DMF (2.0 mL) were charged to a clean oven dried 10 mL RB flask and stirred at 120 °C for 12 h. On completion, the reaction mass was cooled to room temperature and then diluted with water (10.0 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, the residue was purified by column chromatography to give 5,7-dihydroisothiochromeno[3,4-*b*]indoles (**96ga-96ib**).

7-Methyl-5,7-dihydroisothiochromeno[3,4-b]indole (96ga): Pale yellow liquid (82%, 52 mg);



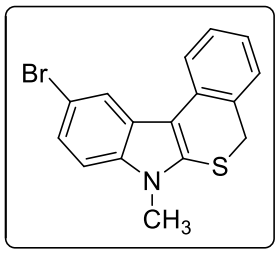
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.08 (m, 1H), 8.00 (d, *J* = 7.7 Hz, 1H), 7.49 (td, *J* = 7.6, 1.2 Hz, 1H), 7.41 – 7.32 (m, 4H), 7.26 (td, *J* = 7.4, 1.0 Hz, 1H), 4.11 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 135.1, 133.5, 128.2, 127.8, 127.3, 125.3, 125.1, 123.6, 121.4, 120.7, 118.8, 111.4, 109.1, 34.1, 30.7; FT-IR ν_{max} (neat): 3030, 2968, 1596, 1534, 1498, 1454, 1136, 1074, 746; FD-TOF *m/z* Calcd for $C_{16}H_{13}NS^+$ 251.0769, found 251.0759 $[M]^+$.

10-Chloro-7-methyl-5,7-dihydroisothiochromeno[3,4-*b*]indole (96ha): Pale yellow liquid



(78%, 56 mg) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.81 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.42 (td, *J* = 7.6, 1.4 Hz, 1H), 7.31 (dd, *J* = 7.5, 0.7 Hz, 1H), 7.24 – 7.17 (m, 3H), 4.05 (s, 2H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 136.4, 132.8, 128.3, 127.7, 127.4, 94.4, 94.1, 125.4, 123.4, 121.3, 118.2, 111.0, 109.9, 34.0, 30.8; FT-IR ν_{max} (neat): 3056, 1594, 1286, 1154, 1072, 734; FD-TOF *m/z* Calcd for $C_{16}H_{12}ClNS^+$ 285.0379, found 285.0371 $[M]^+$ and 287.0343 $[M + 2]^+$.

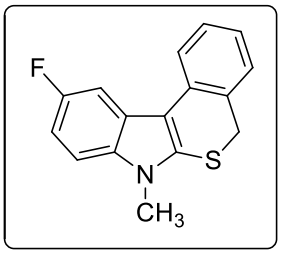
10-Bromo-7-methyl-5,7-dihydroisothiochromeno[3,4-*b*]indole (96ia): Yellow liquid (76%, 63



mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 1.8 Hz, 1H), 7.81 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.41 (ddd, *J* = 5.4, 4.6, 1.4 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.23 – 7.18 (m, 2H), 4.06 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 136.4, 132.8, 128.3, 127.7, 127.3, 125.4, 123.9, 123.5, 121.1, 118.7, 114.1, 110.3, 109.0, 34.0, 30.8; FT-IR ν_{max} (neat):

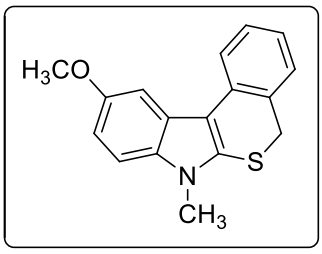
3053, 1596, 1294, 1141, 1077, 736; FD-TOF *m/z* Calcd for $C_{16}H_{12}BrNS^+$ 328.9874, found 328.9864 $[M]^+$ and 330.9844 $[M + 2]^+$.

10-Fluoro-7-methyl-5,7-dihydroisothiochromeno[3,4-b]indole (96ja): Liquid (70%, 47 mg);



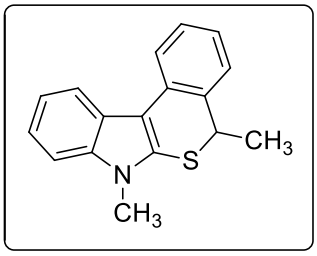
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 10.0 Hz, 1H), 7.41 (t, *J* = 6.5 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.26 – 7.15 (m, 2H), 6.98 (ddd, *J* = 9.0, 5.7, 2.4 Hz, 1H), 4.05 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6 (d, $J_{C\text{-}F}$= 153.0 Hz), 133.0, 128.2, 127.8, 127.6, 127.3, 125.2, 123.2, 111.2 (d, $J_{C\text{-}F}$ = 4.2 Hz), 109.5, 109.4, 109.3, 108.9, 104.09 (d, $J_{C\text{-}F}$ = 24.7 Hz), 34.0, 30.9; FT-IR ν_{max} (neat): 3057, 3026, 2921, 1506, 1468, 1420, 194, 757; FD-TOF *m/z* Calcd for $C_{16}H_{12}FNS^+$ 269.0674, found 269.0673 $[M]^+$.

10-Methoxy-7-methyl-5,7-dihydroisothiochromeno[3,4-b]indole (96ka): Off white solid



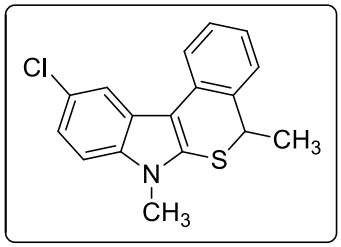
(73%, 51 mg); mp 98-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.1 Hz, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.43 (td, *J* = 7.6, 1.3 Hz, 1H), 7.32 (d, *J* = 6.8 Hz, 1H), 7.24 (d, *J* = 8.9 Hz, 1H), 7.19 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.93 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.07 (s, 2H), 3.97 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 135.4, 133.5, 133.4, 128.1, 127.8, 127.3, 125.6, 124.9, 123.1, 111.0, 110.4, 109.6, 101.7, 56.1, 34.1, 30.8; FT-IR ν_{max} (neat):3051, 2951, 1596, 1567, 1417, 1270, 1228, 715; ESI-TOF *m/z* Calcd for $C_{17}H_{16}NOS^+$ 282.0947, found 282.0938 $[M + H]^+$.

5,7-Dimethyl-5,7-dihydroisothiochromeno[3,4-b]indole (96gb): White solid (78%, 52 mg);



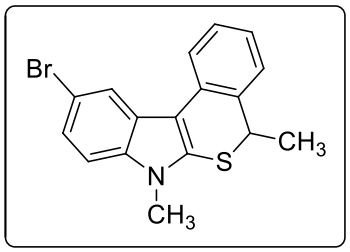
mp 114-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.06 (m, 1H), 8.01 (d, *J* = 7.7 Hz, 1H), 7.44 (td, *J* = 7.6, 1.5 Hz, 1H), 7.39 (dt, *J* = 7.2, 3.2 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.30 – 7.28 (m, 1H), 7.28 – 7.23 (m, 1H), 4.28 (q, *J* = 7.0 Hz, 1H), 3.79 (s, 3H), 1.64 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 133.1, 132.9, 132.1, 127.8, 125.9, 125.2, 124.0, 121.1, 120.5, 118.8, 110.1, 109.0, 42.2, 30.6, 21.6; FT-IR ν_{max} (neat): 3045, 2961, 1508, 1465, 1420, 1080, 727; ESI-TOF *m/z* Calcd for $C_{17}H_{16}NS^+$ 266.0998, found 266.1001 $[M + H]^+$.

10-Chloro-5,7-dimethyl-5,7-dihydroisothiochromeno[3,4-b]indole (96hb): Yellow solid



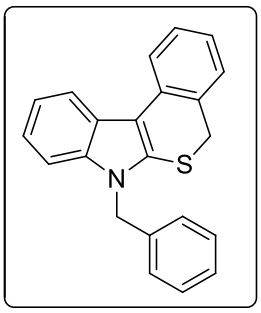
(76%, 57 mg); mp 94-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 1.8 Hz, 1H), 7.88 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.42 (td, *J* = 7.5, 1.5 Hz, 1H), 7.30 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.26 – 7.22 (m, 2H), 7.20 (dd, *J* = 8.6, 1.9 Hz, 1H), 4.26 (q, *J* = 7.0 Hz, 1H), 3.74 (s, 3H), 1.61 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 134.5, 133.0, 131.5, 127.9, 94.3, 94.0, 125.9, 125.6, 123.9, 121.1, 118.2, 109.8, 109.7, 42.2, 30.7, 21.6; FT-IR ν_{max} (neat): 2958, 2915, 1505, 1464, 1296, 1067, 785, 758; ESI-TOF *m/z* Calcd for $C_{17}H_{15}ClNS^+$ 300.0608, found 300.0595 $[M + H]^+$.

10-Bromo-5,7-dimethyl-5,7-dihydroisothiochromeno[3,4-b]indole (96ib): Yellow liquid



(72%, 62 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 1.8 Hz, 1H), 7.87 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.41 (td, *J* = 7.5, 1.5 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.23 (ddd, *J* = 11.3, 6.2, 2.5 Hz, 2H), 4.26 (q, *J* = 7.0 Hz, 1H), 3.75 (s, 3H), 1.59 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 134.4, 133.1, 132.4, 127.9, 94.7, 125.9, 125.6, 123.9, 123.7, 121.2, 113.9, 110.3, 109.6, 42.2, 30.7, 21.6; FT-IR ν_{max} (neat): 3043, 2954, 1508, 1466, 1294, 1068, 776, 754; FD-TOF *m/z* Calcd for $C_{17}H_{14}BrNS^+$ 343.0030, found 343.0039 $[M]^+$ and 345.0020 $[M + 2]^+$.

7-Benzyl-5,7-dihydroisothiochromeno[3,4-*b*]indole (96la): White solid (74%, 148 mg); mp



96-97 °C; 1H NMR (400 MHz, CDCl3) δ 8.08 (d, *J* = 5.8 Hz, 1H), 7.97 (d, *J* = 5.8 Hz, 1H), 7.44 – 7.21 (m, 11H), 5.42 (s, 2H), 4.09 (s, 2H); 13C NMR (100 MHz, CDCl3) δ 137.6, 137.0, 134.7, 133.3, 128.8, 128.2, 127.9, 127.6, 127.3, 94.7, 125.5, 125.2, 123.7, 121.5, 120.8, 118.8, 111.9, 109.6, 47.9, 34.2; FT-IR νmax (neat): 3055, 2916, 1597, 1512, 1450, 1188, 741, 694 cm-1; FD-TOF *m/z* Calcd for C22H18NS$^+$ 328.1154 [M + H]$^+$, found 328.1146.

Chapter III

PART-B

Synthesis of Dihydrothiopyrano[2,3-*b*]indoles *via* Gold Catalyzed Sequential Hydroarylation and Rearrangements

3.6 Introduction

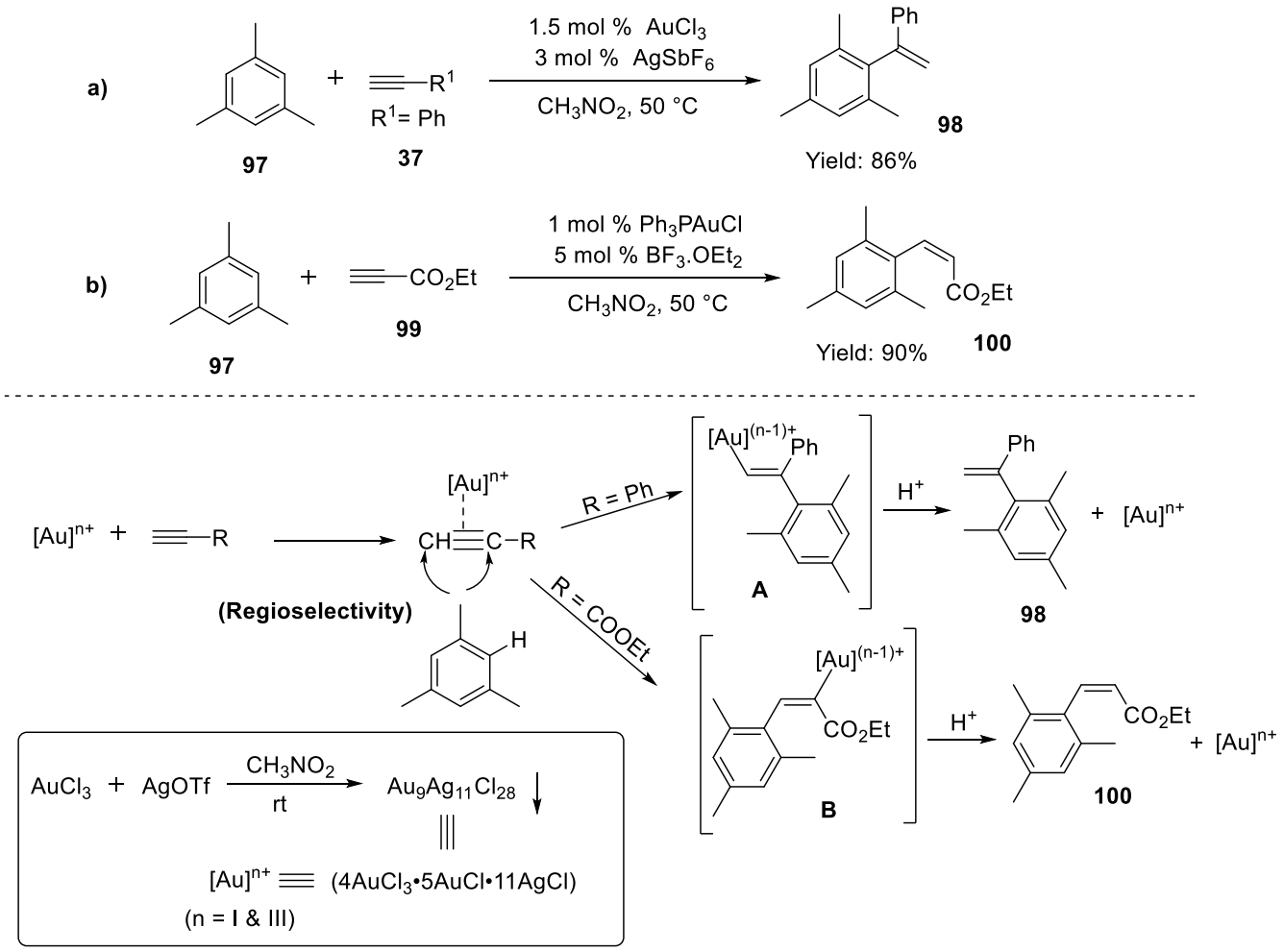
Transition-metal-catalyzed hydroarylation reactions have received considerable attention in recent years as an atom-economical approach for the functionalization of arenes, as well as for the creation of complex molecular architectures.[117, 118] This ever-developing area has witnessed a remarkable growth in gold-catalyzed methodologies involving the addition of a wide variety of nucleophiles (C/N/O) to internal or terminal alkynes in an intra/intermolecular fashion.[64, 119-122] Not surprisingly, this strategy has also emerged as a highly useful tool for the synthesis of novel heterocycles.[123]

3.6.1 Gold-catalyzed inter/intramolecular hydroarylation reactions of alkynes

3.6.1.1 Intermolecular hydroarylation reactions

Since Hashmi's first report in 2000 gold-catalyzed hydroarylation has been explored with various substrates by several research groups. Because of the strong Lewis acidity of gold(III), it is difficult to determine the reaction mechanism that involves a direct *auration* of arene form an aryl-gold(III) species versus a gold π-activation of alkyne followed by Friedel-Crafts type reaction.[53]

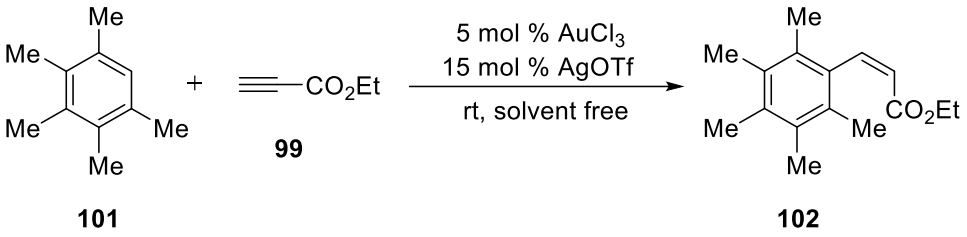
Reetz and Sommer reported a gold(III)-catalyzed hydroarylation reaction of normal alkynes and electron deficient alkynes with mesitylene. Hydroarylation of phenylacetylene with electron rich arene such as mesitylene is catalyzed by $AuCl_3$ activated by silver salt e.g. $AgSbF_6$ in nitromethane to give 1-mesityl-1-phenylethene (**98**) in 86% yield (**Scheme 3.30a**).[124] Nitromethane was chosen as a solvent because it dissolves $AuCl_3$ and most silver salts. On the other hand, the hydroarylation of electron deficient alkynes such as ethyl propiolate is effectively catalyzed by Ph_3AuCl activated with $BF_3.OEt_2$ to give **100** in 90% yield (**Scheme 3.30b**).



Scheme 3.30: Gold-catalyzed hydroarylation of **37** and **99** with mesitylene

The reaction is believed to proceed *via* generation of catalytically active species $[Au]^{n+}$ possessing both n = (I) and (III) oxidation state, generated from the reaction of $AuCl_3$ and silver salt. Thus active species coordinates to the alkyne followed by nucleophilic attack of the arene from the opposite side leads to the formation of a vinyl gold intermediate **A** or **B** depending on the substituent R of the alkyne. Further, H^+ protonation of intermediate **A** and **B** stereospecifically affords product **98** and **100** respectively (**Scheme 3.30**). The regioselectivity is determined by the electronic factors.

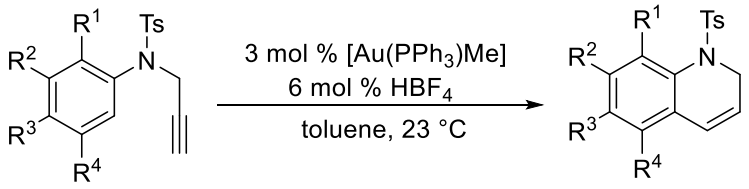
$AuCl_3$-catalyzed hydroarylation of electron-deficient alkynes can be also conducted under solvent-free conditions. The $AuCl_3$ (5 mol %) and AgOTf (15 mol %) couple afforded product in good to excellent yield, with significant regioselectivity, under mild reaction conditions. Pentamethylbenzene reacted with ethyl propiolate at room temperature to afford the hydroarylation product in 99% yield (**Scheme 3.31**).[125]



Scheme 3.31: $AuCl_3$/AgOTf catalyzed coupling of pentamethylbenzene and ethyl propiolate

3.6.1.2 Intramolecular hydroarylation reactions

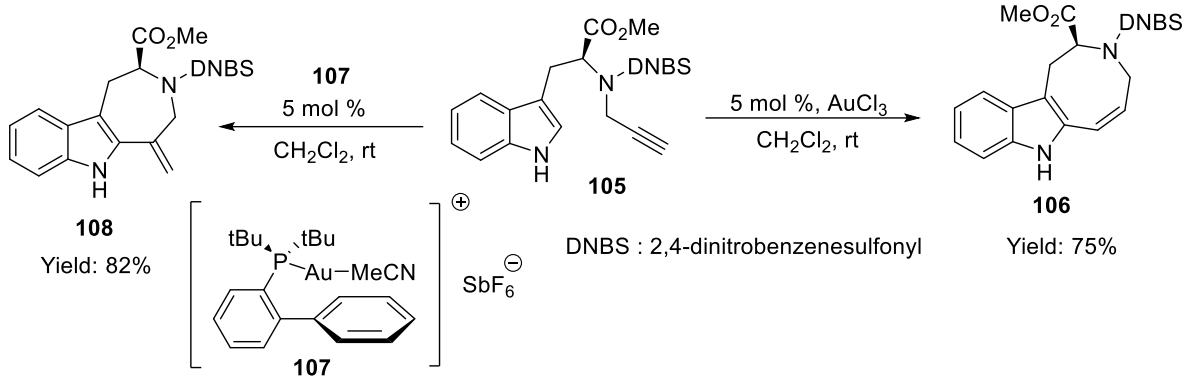
Echavarren and co-workers reported the gold-catalysed annulation of 6 to 8 membered rings on indoles, *via* intramolecular *endo* or *exo dig* cyclization (**Scheme 3.32a** and **Scheme 3.32b**).[126-128] Intramolecular hydroarylation of *N*-propargyl-*N*-tosyl anilines proceeds in the presence of cationic Au^I catalyst formed in situ from [Au(PPh_3)Me] and HBF_4, which presumably formed [Au(PPh_3)]BF_4 in toluene at reflux to afford 6-*endo-dig* cyclization product, *N*-tosyl-1,2-dihydroquinolines in good yields (**Scheme 3.32a**). Satisfactory results are also obtained with catalysts formed from the combination of [Au(PPh_3)Cl] (3 mol %) with $AgBF_4$ or $AgSbF_6$ (3 mol %) in dichloromethane as a solvent.



$R^1 = R^4 = OMe$, $R^2 = R^3 = H$ 71%
$R^1 = R^4 = H$, $R^2 = R^3 = OMe$ 71%
$R^1 = H$, $R^2 = R^3 = R^4 = OMe$ 92%

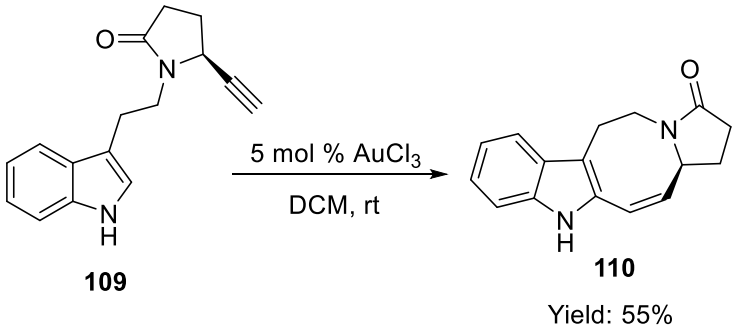
Scheme 3.32a: Synthesis of 1,2-dihydroquinolines catalyzed by the cationic gold catalyst.

The selective formation of 7- or 8-membered ring compounds, from the same substrate, is achieved through regiochemical control exhibited by the oxidation state of the gold center. The treatment of tryptophan derivative **105** with 5 mol % $AuCl_3$ Au(III) catalyst at room temperature furnished indoloazocine **106** in 75% yield *via* an interesting 8-*endo-dig* cyclization. When Au(I) triphenylphosphine complex **107** was used as a catalyst a 7-*exo-dig* cyclization product azepino[4,5-*b*]indole **108** was obtained in 82% yield (**Scheme 3.32b**).



Scheme 3.32b: Au(I) and Au(III) catalyzed intramolecular hydroarylation of **105**

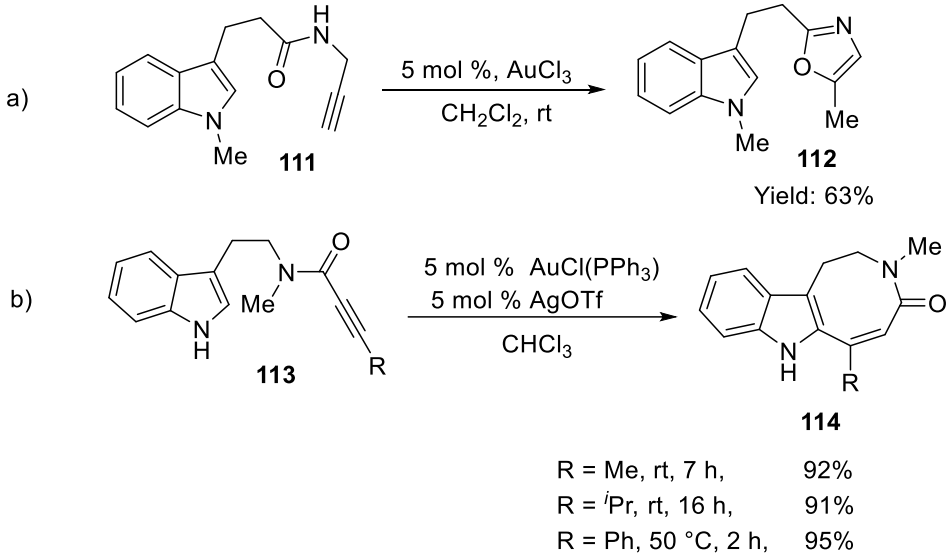
Echavarren and co-workers extended the scope of intramolecular hydroarylation and synthesized indoloazocine **110** by the 8-*endo-dig* cyclization of substrate **109** using 5 mol % $AuCl_3$ as a catalyst in CH_2Cl_2 at room temperature in 55% isolated yield (**Scheme 3.33**). [129]



Scheme 3.33: Regioselective synthesis of azacino[5,4-*b*]indole derivative **110** *via* $AuCl_3$ catalyzed cyclization of **109**

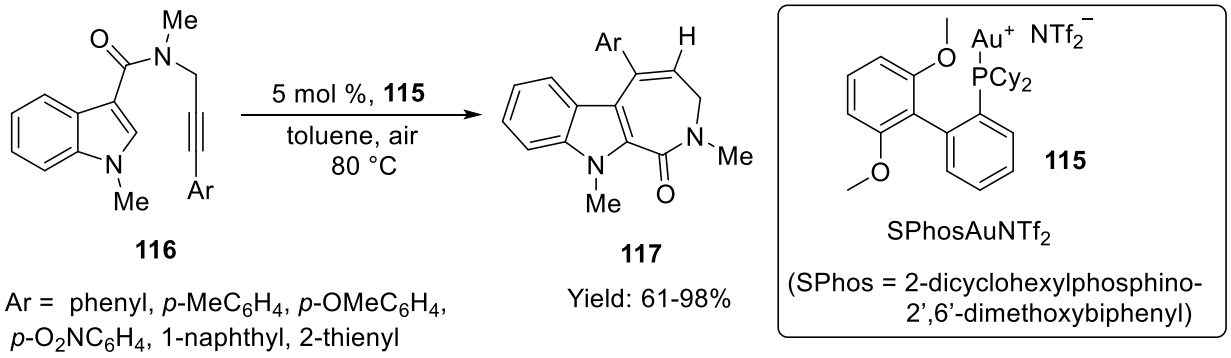
Padwa and coworkers reported that indole-substituted *N*-propargylamides **111** undergoes gold(III)-catalyzed cyclization to give oxazoles **112** *via* 5-*exo-dig* cyclization. However, they failed to obtain the 8-*exo-dig* cyclization product from indole derivative **111** (**Scheme 3.34a**).[130, 131]

In contrast, Van der Eycken and coworkers reported that on treatment with a cationic gold (I) catalyst, which was generated from $AuCl(PPh_3)$ and AgOTf, tryptamine-derived propionamides **113** underwent 8-*endo-dig* cyclization to selectively afford indole-fused azocinones **114** in high yields (**Scheme 3.34b**).[130, 131]

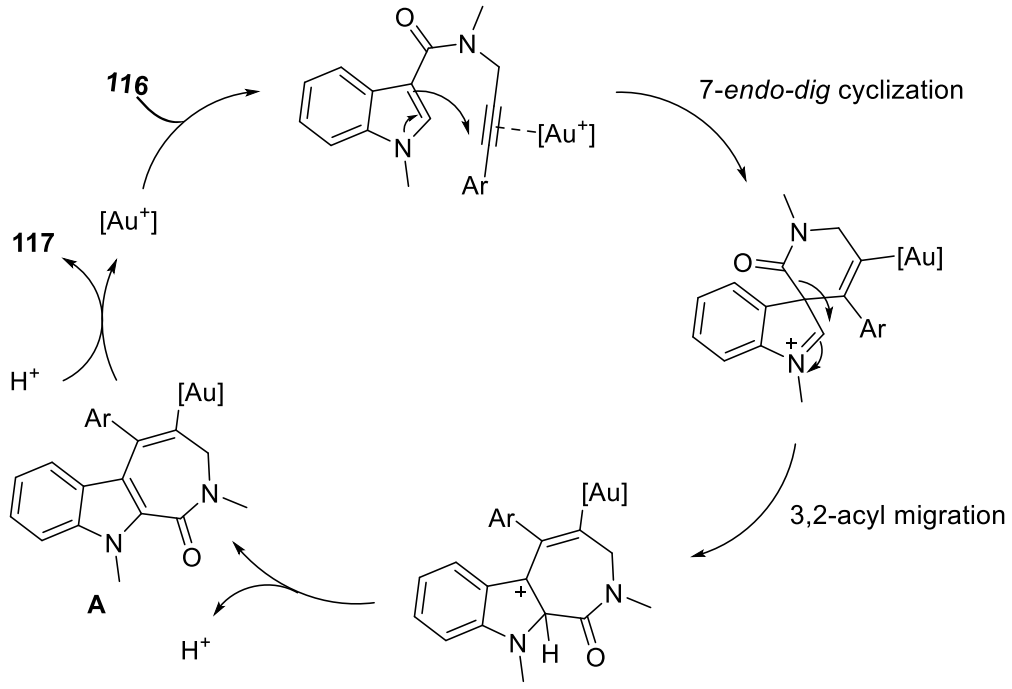


Scheme 3.34: Gold-catalyzed synthesis of **112** and **114**

Hashmi and co-workers reported reactions of alkyne-substituted indole-3-carboxamides **116** in the presence of 5 mol % $SPhosAuNTf_2$ in toluene at 80 °C without an inert atmosphere. The reaction proceeded *via* 7-*endo-dig* cyclization involving 3,2-acyl migration independent of the substituents on the aryl terminal group, affording azepino[3,4-*b*]indol-1-ones **117** in good to excellent yield (**Scheme 3.35**). [132]



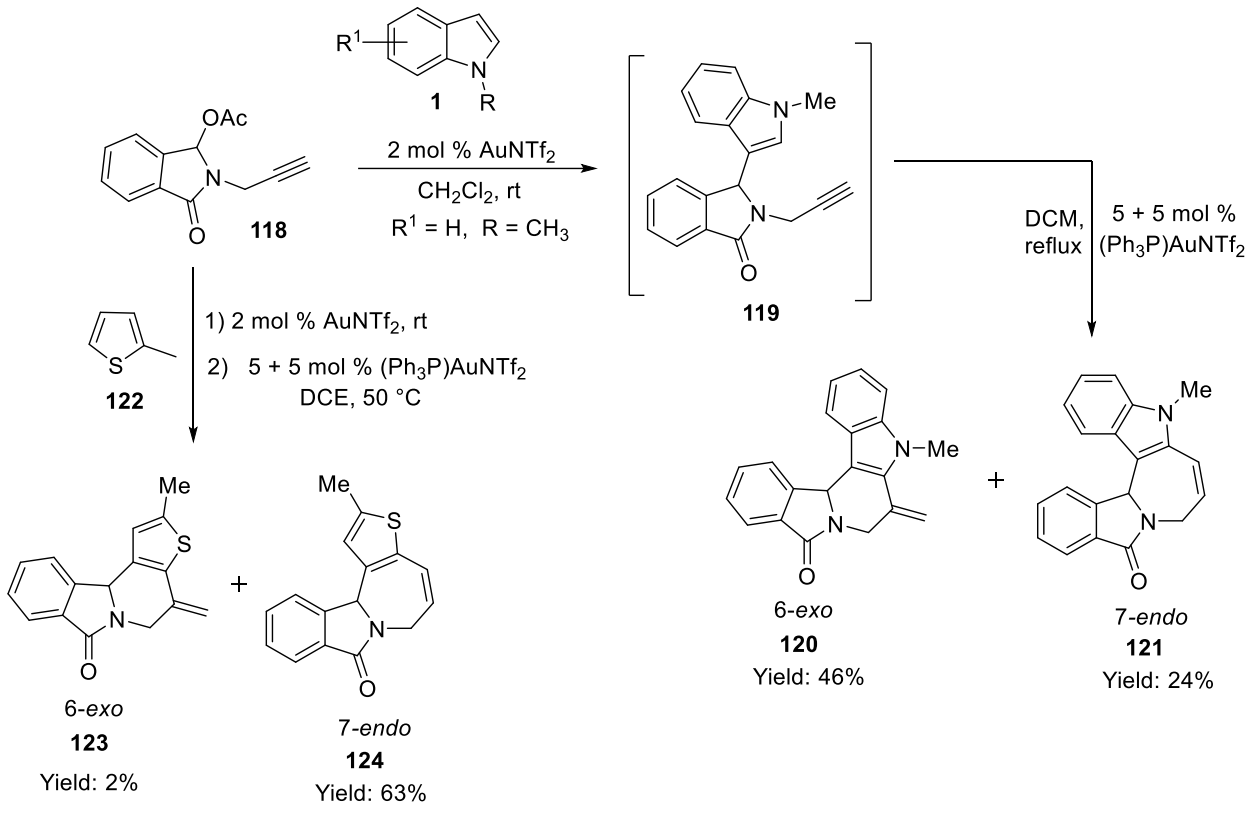
Scheme 3.35a: $SPhosAuNTf_2$ gold(I) catalyzed synthesis of **117** from **116**



Scheme 3.35b: Tentative mechanism for the synthesis of **117**

Dalla and Othman reported one pot gold-catalyzed coupling of *N*-propargylacetoxylactam (**118**) with *N*-methylindole (**1**) *via* α-amidoalkylation/intramolecular hydroarylation sequence. However, the product selectivity of this method was not high (**Scheme 3.36**).[133] Initially, it is Friedel-Crafts alkylation of *N*-Methylindole (**1**) with an *N*-acyliminium ion derived from *N,O*-acetal **118** resulted intermediate **119** which then underwent intramolecular hydroarylation in the presence of 5 mol % $(Ph_3P)AuNTf_2$ to give the 6-*exo-dig* cyclization product **120** in 46% yield, along with the 7-*endo-dig* cyclization product **121** in 24% yield. In contrast, the use of 2-

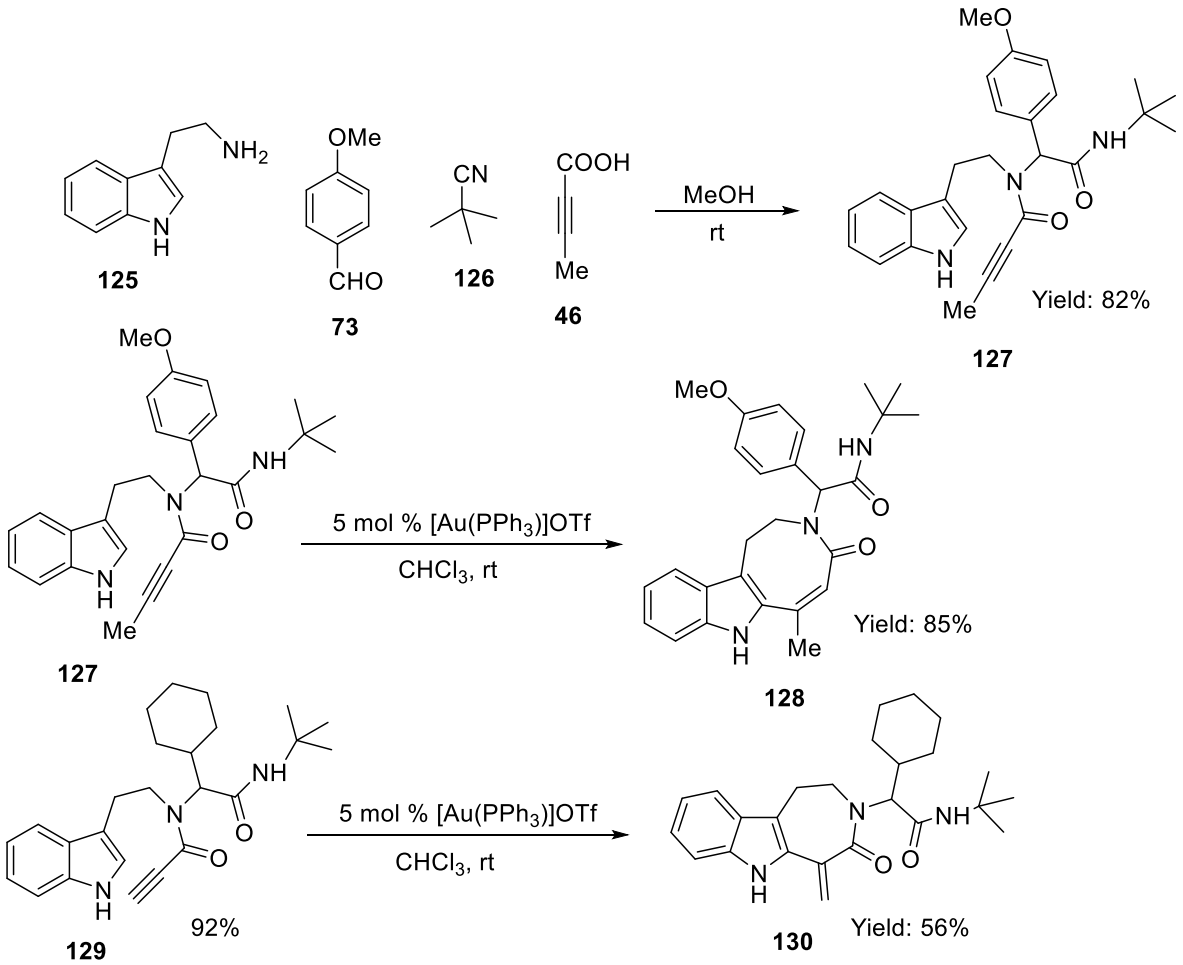
methylthiophene **(122)** instead of *N*-methylindole (**1**) selectively furnished the 7-*endo-dig* cyclization product **124** in 63% yield, along with the 6-*exo-dig* cyclization product **123** in trace amount.



Scheme 3.36: Gold catalyzed α-amidoalkylation/hydroarylation of **118** with various nucleophiles

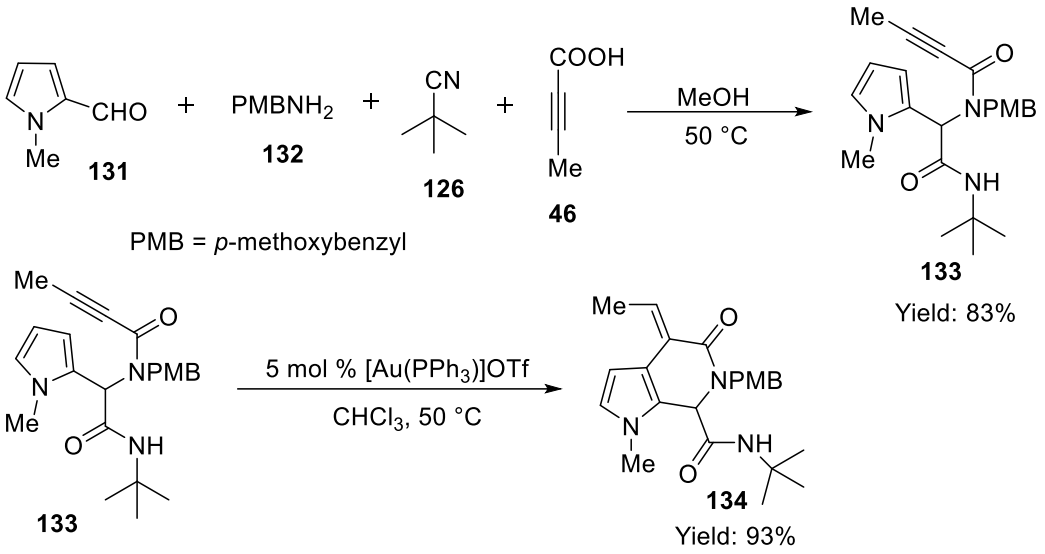
Van der Eycken and co-workers extended the gold-catalyzed intramolecular hydroarylation to the diversity-oriented synthesis of indoloazocines involving substrate preparation using the four-component Ugi reaction. For example, the Ugi coupling of tryptamine (**125**), *p*-anisaldehyde (**73**), *tert*-butylisonitrile (**126**) and 2-butynoic acid (**46**) was carried out in MeOH at room temperature, successfully producing **127** in 82% yield (**Scheme 3.37a**).[134] Subsequent cyclization of **127** was carried out in the presence of cationic gold(I) catalyst [Au(PPh_3)]OTf, in chloroform at room temperature for 8 h, affording the desired indoloazocinone **128** in 85% yield *via* 8-*endo-dig* cyclization of **127** (**Scheme 3.37b**). When cyclohexanecarboxyaldehyde and propiolic acid were used instead of *p*-anisaldehyde and 2-butynoic acid respectively, substrate **129** was obtained in 92% yield. Consequently, **129** with a terminal alkyne moiety was subjected

to the same reaction conditions, affording 7-*exo-dig* cyclization product **130** in 56% yield (**Scheme 3.37a**).



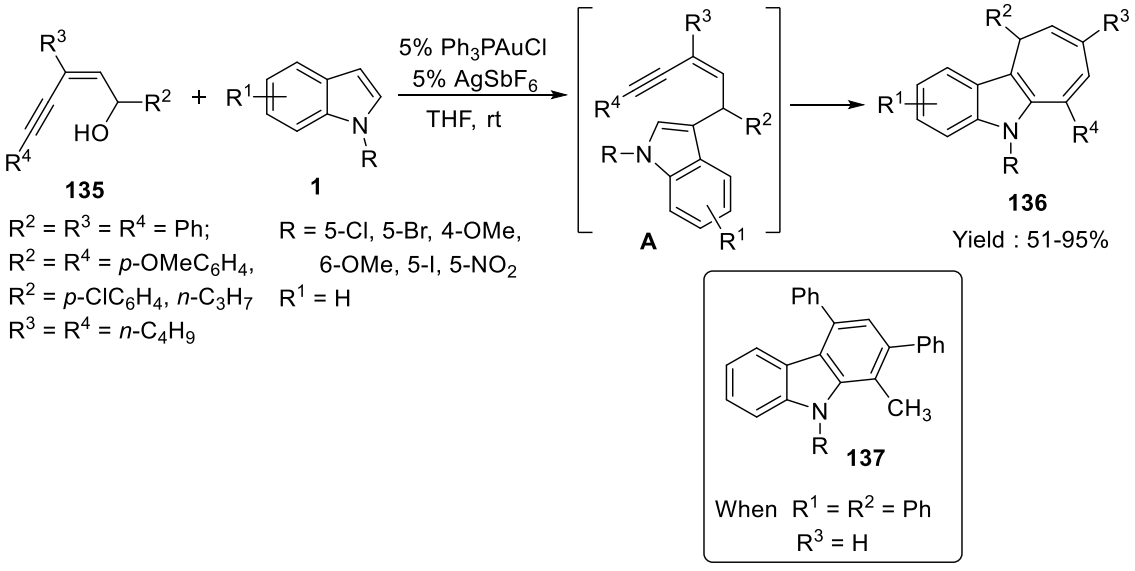
Scheme 3.37: Synthesis of **128** and **130** *via* gold(III) catalyzed hydroarylation.

In a similar manner, Ugi four-component reaction of 2-formyl-*N*-methylpyrrole (**131**), *p*-methoxybenzylamine (**132**), *t*-butylisonitrile (**126**) and 2-butynoic acid (**46**) in methanol at 50 °C furnished the corresponding Ugi-adduct **133** in 83% yield which was further used for the intramolecular hydroarylation reaction. The substrate **133** was treated with 5 mol % [Au(PPh$_3$)]OTf in chloroform at 50 °C for 3 h, affording pyrrolopyridinone **134** in 93% yield as a result of selective 5-*exo-dig* cyclization (**Scheme 3.38**).[135]



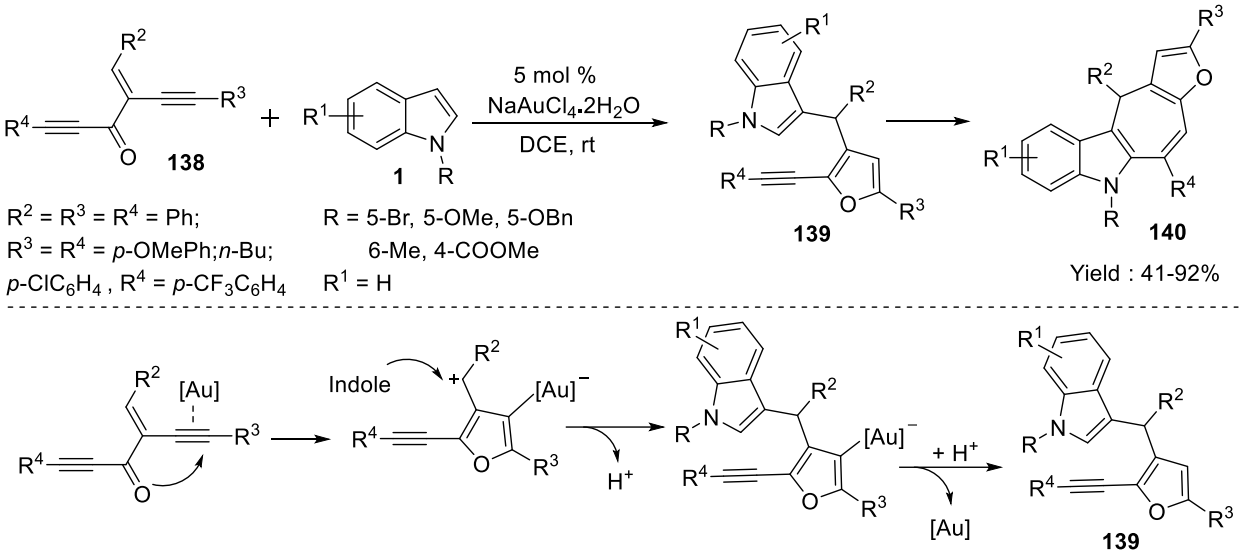
Scheme 3.38: Gold(I) catalyzed post-Ugi intramolecular hydroarylation reaction of **133**

The various one-pot sequential processes consisting of indole alkylations and subsequent carbocyclizations *via* intramolecular hydroarylation have been explored. Liu and co-workers described the domino approach for the synthesis of dihydrocyclohepta[*b*]indoles **136** through the reaction of (Z)-enynols **135** with 1.5 equiv. indoles **1** at room temperature in THF using 5 mol % $(Ph_3P)AuCl$ and 5 mol % $AgSbF_6$ as catalysts *via* Friedel-Crafts/hydroarylation reactions. Interestingly, when terminal alkyne (R^3 = H) was used 1- methyl-2,4-diphenyl-9H-carbazole **137** was obtained in 76% yield. [136]



Scheme 3.39: Gold-catalyzed one-pot synthesis of dihydrocyclohepta[*b*]indoles **136**

Liu group extended their work and developed a one-pot synthesis of indole polycyclic systems **140** *via* 5 mol % $NaAuCl_4.2H_2O$ gold-catalyzed tandem annulation reaction of 1,2-*bis*(alkynyl)-2-en-1-ones **138** with 2.0 equiv. indoles **1** in dichloroethane at room temperature. The process is recognized through a cascade carbonyl-yne cyclization/Friedel-Crafts/indole-yne cyclization sequence catalyzed by the single-pot catalyst of gold (**Scheme 3.40**).[136]



Scheme 3.40: Synthesis of **140** through cascade reaction

Being structural constituents of several natural products, agrochemicals, pharmaceuticals, and organic materials, heterocycles with diverse substitution patterns are highly sought-after chemical entities. In particular, chemicals possessing an indole core are an extremely desirable subclass of heterocycles due to a wide range of biological activities associated with them.[137] A survey of the literature suggests the chemistry of *S*-containing heterocycles, thiopyran, and fused-thiopyrans has not been explored to the same extent as that of their pyran analogs. Recent reports have associated substituted thiopyran and fused-thiopyran scaffolds to anti-inflamatory, antibacterial, anti hyperplasia, antipsychotic, analgesic, estrogen receptor modulator, and anticancer activities.[90] Certain thiopyran-fused indoles and their pharmaceutically acceptable salts have been shown to possess psychoanaleptic and nootropic effects.[82]

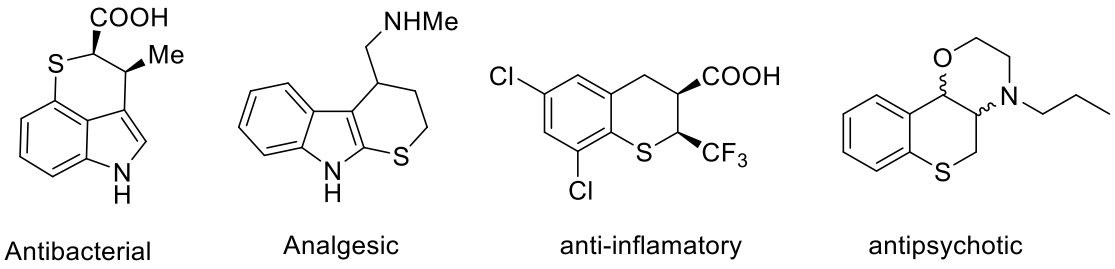


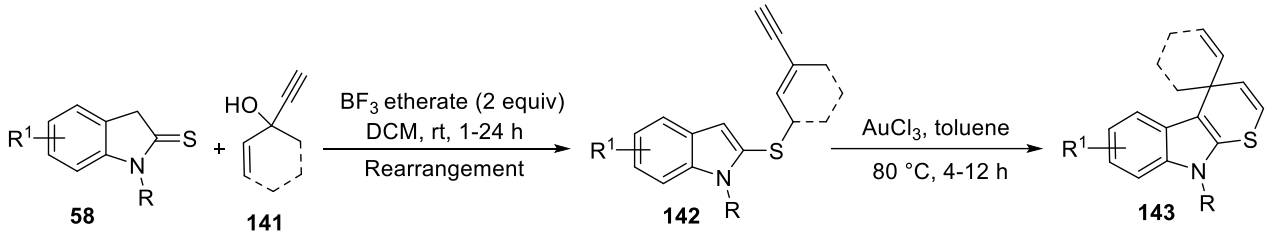
Figure 3.9: Some bioactive fused-thiopyran and thiopyran-fused indole derivatives

Considering the importance of functionalized indoles, developing an efficient synthetic process remains an area of interest. In a continuation of our efforts toward developing synthetic strategies to access diversely substituted indoles[102-104, 138-140] we explored the application of 2-(2-alkenylthio)indoles to the construction of indole-fused *S*-containing ring structures. We have recently reported an efficient process for chemoselective *S*-benzylation of indoline-2-thiones using benzyl alcohols in the presence of a catalytic amount of Lewis acids, leading to biologically relevant indole-based sulfides[94, 95] (**Scheme 3.25**). Mechanistically, the methodology supports the involvement of a resonance-stabilized benzylic carbocation in the *S*-benzylation process. On the basis of these results, we envisaged that unsaturated aliphatic alcohol capable of producing resonance-stabilized carbocations may also undergo *S*-alkylation similar to the *S*-benzylation process to produce 2-(2-alken/ynylthio)indoles. Furthermore, an intramolecular hydroarylation carbocyclization with the 3-position of the indole core may lead to an indole-fused S-containing ring system. Herein, we wish to report an efficient two-step methodology for the synthesis of indole-fused dihydrothiopyrans starting from indoline-2-thiones via sequential rearrangements.

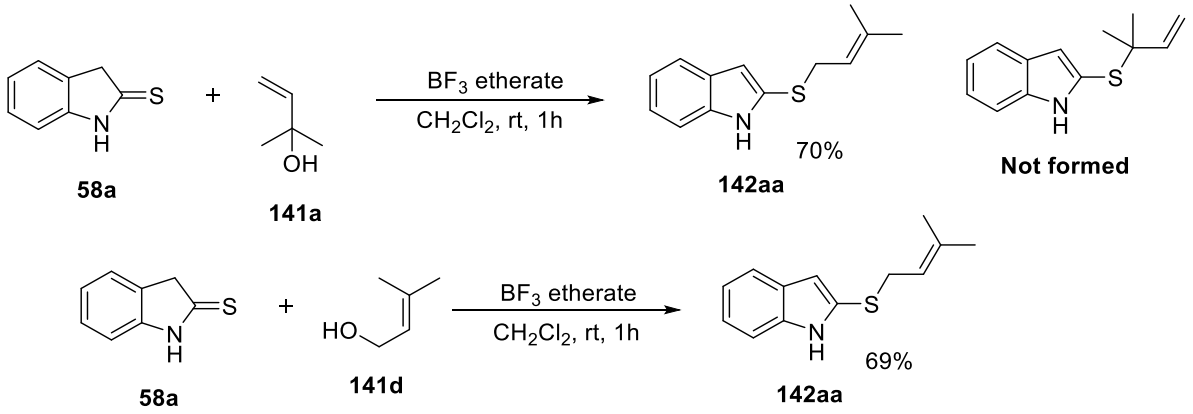
3.7 Results and discussion

To the best of our knowledge, the use of unsaturated aliphatic alcohols in the synthesis of *S*-alkenylated sulfides has not yet been reported. Hence, our initial investigation focused on the *S*-alkylation of indoline-2-thiones with the aid of unsaturated aliphatic alcohols. Inspired by our *S*-benzylation work, we first employed rare earth metal triflates as a potential catalyst for the *S*-alkylation of indoline-2-thione (**58a**) with 2-methylbut-3-en-2-ol (**141a**).

Even after multiple attempts, the desired *S*-(2-alkenyl)indole could not be obtained under these conditions. Gratifyingly, the use of excess BF_3-etherate in the reaction facilitated the formation of desired indole sulfide **142aa** in good yield. Interestingly, a rearrangement in the allyl side chain was observed in the isolated product (**Scheme 3.42**). It appears that the thermodynamically more stable, highly substituted alkene is the favored product under these conditions.



Scheme 3.41: Synthesis of indole-fused dihydrothiopyrans starting from indoline-2-thiones *via* sequential rearrangements



Scheme 3.42: BF_3 etherate-mediated alkylation of indoline-2-thione **(58a)** using 2-methylbut-3-en-2-ol **(141a)** and prenyl alcohol **(141d)**

Encouraged by these results, we then proceeded to screen a range of substituted/unsubstituted allylic or propargylic alcohols with varying degrees of substitution (1°/2°/3° alcohols) for the *S*-alkylation reaction. As presented in table 3.4, only a select group of unsaturated alcohols, primarily substituted allyl alcohols, yielded *S*-(2-alkenylated) products (**142**). No reaction was observed in the cases of unsubstituted allyl/propargyl alcohols. Interestingly, the regioisomer of **141a**, prenyl alcohol (**141d**), when reacted with thione **58a**, also resulted in 2-(3-methylbut-2-enylthio)-indole (**142aa**) in 69% yield **(Scheme 3.42)**.

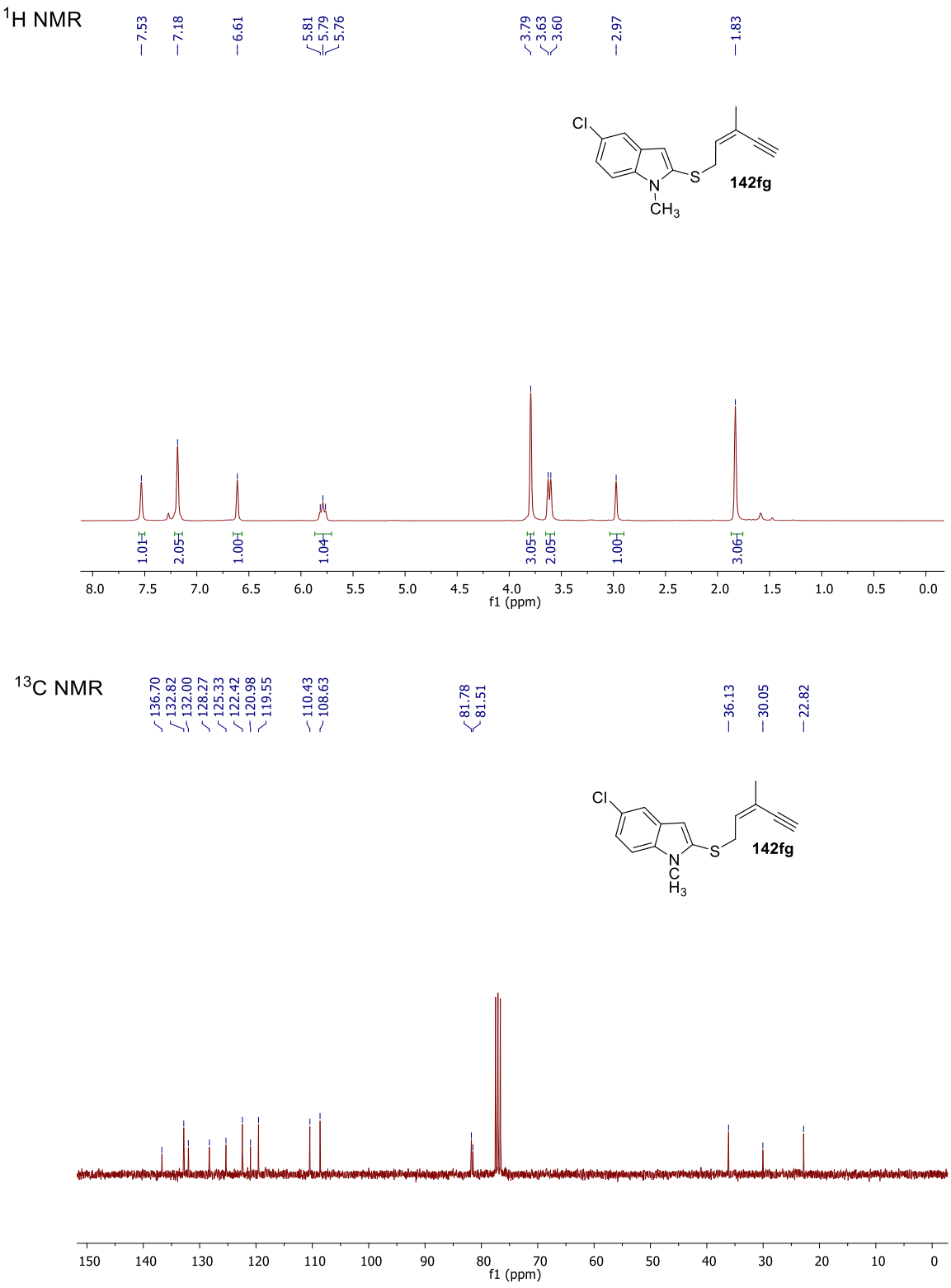
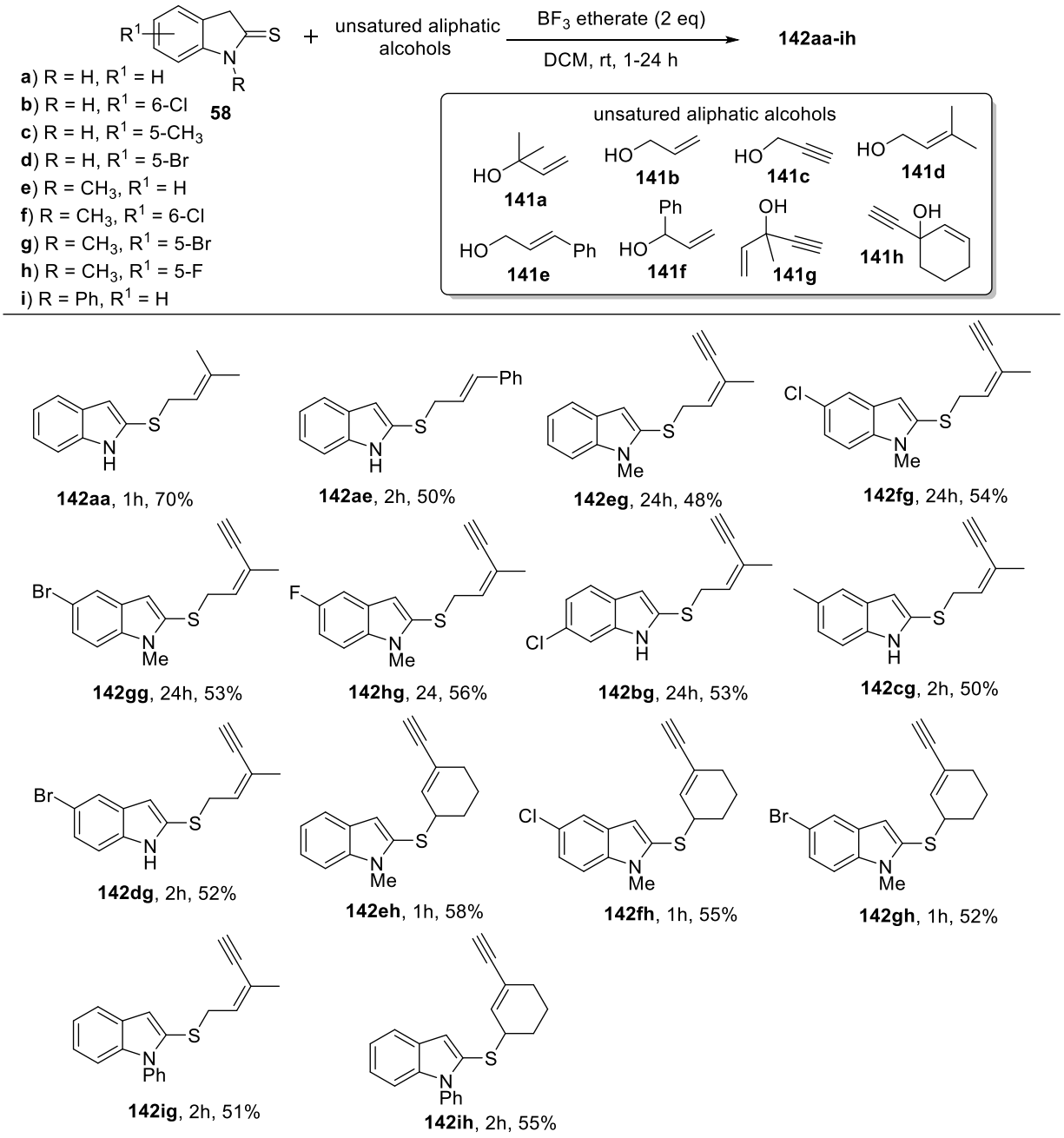


Figure 3.10: ^{1}H and ^{13}C NMR spectra of 5-Chloro-1-methyl-2-(3-methylpent-2-en-4-ynylthio)-1*H*-indole **(142fg)** in $CDCl_3$

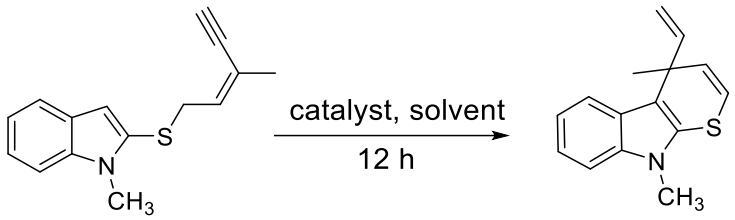
These results were further corroborated using isomeric alcohols **141e** and **141f**, both of which resulted in sulfide **142ae** in ~50% yield. Furthermore, irrespective of the degree of substitution of the reactant alcohol, we observed a consistent trend of rearrangement in the reactions of all of the substituted allyl alcohols, including 3-methylpent-1-en-4-yn-3-ol **(141g)** and 1-ethynylcyclohex-2-enol **(141h)**[141] under these conditions, in the synthesis of sulfides **142aa−ih** (Table 3.4). The sulfides obtained from alcohols **141g** and **141h** are of particular importance because they possess a conjugated ene-yne unsaturated system, which can be synthetically manipulated for further chemical transformations.

Table 3.4: BF_3 Etherate-mediated alkylation of indoline-2-thiones using unsaturated aliphatic alcohols[a]



[a]Reaction conditions: **58** (1.0 mmol), **141** (1.0 mmol), BF_3 etherate (2.0 mmol) and dichloromethane (40 mL) at rt; yields are based on the amounts of starting materials utilized in the reaction and are unoptimized.

Table 3.5: Optimization of metal-catalyzed hydroarylation reaction[a]



142eg **143a**

Entry	Catalyst (mol %)	Solvent	Temperature (°C)	Yield (%)
1	AuCl (5)	toluene	80	55
2	CuCl (5)	toluene	80	[b]
3	$FeCl_3$ (5)	toluene	80	[b]
4	$PdCl_2$ (5)	toluene	80	[b]
5	$AuCl_3$ (5)	toluene	80	62
6	$NiCl_2$ (5)	toluene	80	[b]
7	$ZnCl_2$ (5)	toluene	80	46
8	$AuCl_3$ (5)	toluene	110	45
9	$AuCl_3$ (5)	acetonitrile	80	50
10	$AuCl_3$ (5)	DMF	80	55
11	$AuCl_3$ (5)	DMSO	80	40
12	$AuCl_3$ (5)	1,4-dioxane	80	26
13	$AuCl_3$ (2)	toluene	80	50
14	$ZnCl_2$	toluene	80	32
15	$AuCl_3.PPh_3$ (2)	toluene	80	48
16	$AuCl(PPh_3)$/AgOTf (5/5)	toluene	80	54
17	**$AuCl_3$ (10)**	**toluene**	**80**	**76**

[a]Reaction conditions: **142eg** (40 mg, 0.16 mmol), catalyst (2−10 mol %), solvent (2 mL), 80 °C, 12 h.
[b]No reaction

After acquiring all of the desired 2-(2-alkenylthio)indoles (**142aa−ih**), we attempted the metal-catalyzed hydroarylation reaction to produce the indole-fused S-containing cyclized products. Initially, 2-(3-methylpent-2-en-4-ynylthio)-N-methylindole **142eg** was chosen as a model reactant to study the intramolecular cyclization reaction with the prospect of producing annulated products I and/or II as depicted in **Scheme 3.43**. As shown in table 3.5, the desired C−H activated carbocyclization step was screened using a range of potential metal catalysts in toluene at 80 °C. Initially, only reactions attempted with AuCl, $AuCl_3$, and $ZnCl_2$ resulted in product formation (Table 3.5, entries 1, 5 and 7).

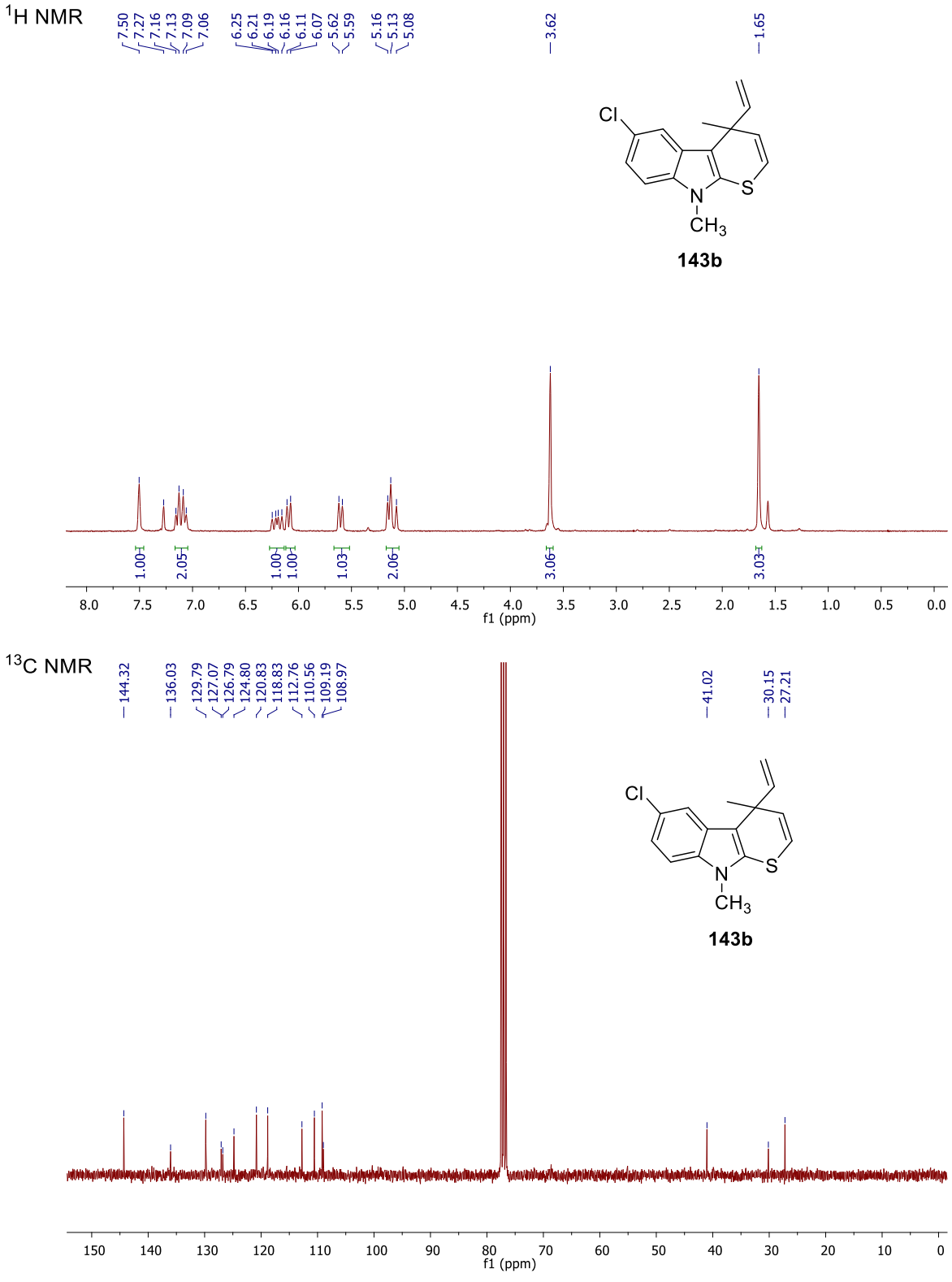


Figure 3.11: ^{1}H and ^{13}C NMR spectra of 6-Chloro-4,9-dimethyl-4-vinyl-4,9-dihydrothiopyrano[2,3-*b*]- indole **(143b)** in $CDCl_3$

^{1}H and ^{13}C NMR analysis of the product (liquid) revealed that the possible structure of the product may be dihydrothiopyrano[2,3-*b*]-*N*-methylindole.

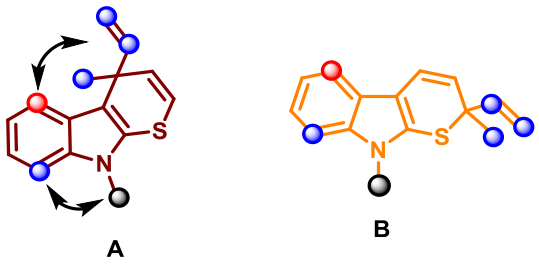
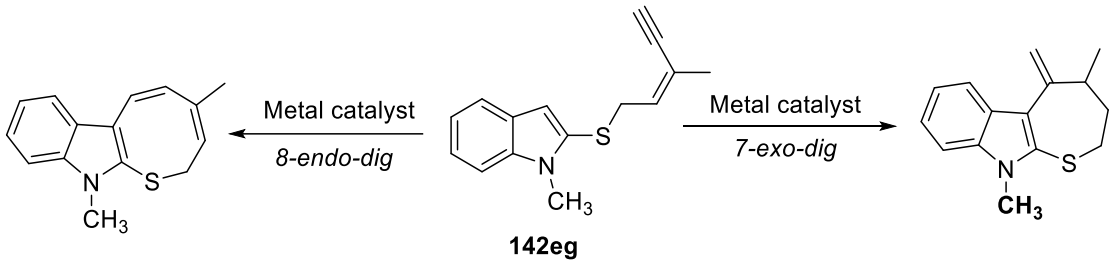


Figure 3.12: Possible regioisomers of compound **143a.**

The exact positions of the substituents were established using 1D NOESY experiments. The two possible regioisomers of **143a** are shown in **Figure 3.12** (A and B). The perturbations of the phenyl proton at position 5 (red dot) showed a strong NOE to the methyl and vinyl groups at position 4 (blue dot). This evidence supported regioisomer A. In addition, negative evidence was obtained by the perturbation of N-CH_3 protons (black dot), which showed only an NOE response to the phenyl proton at position 8 of the skeleton. Thus, on the basis of 1D NOESY experiments, the structure of **143a** was unambiguously assigned as 4,9-dimethyl-4-vinyl-4,9-dihydrothiopyrano[2,3-*b*]indole (regioisomer A).



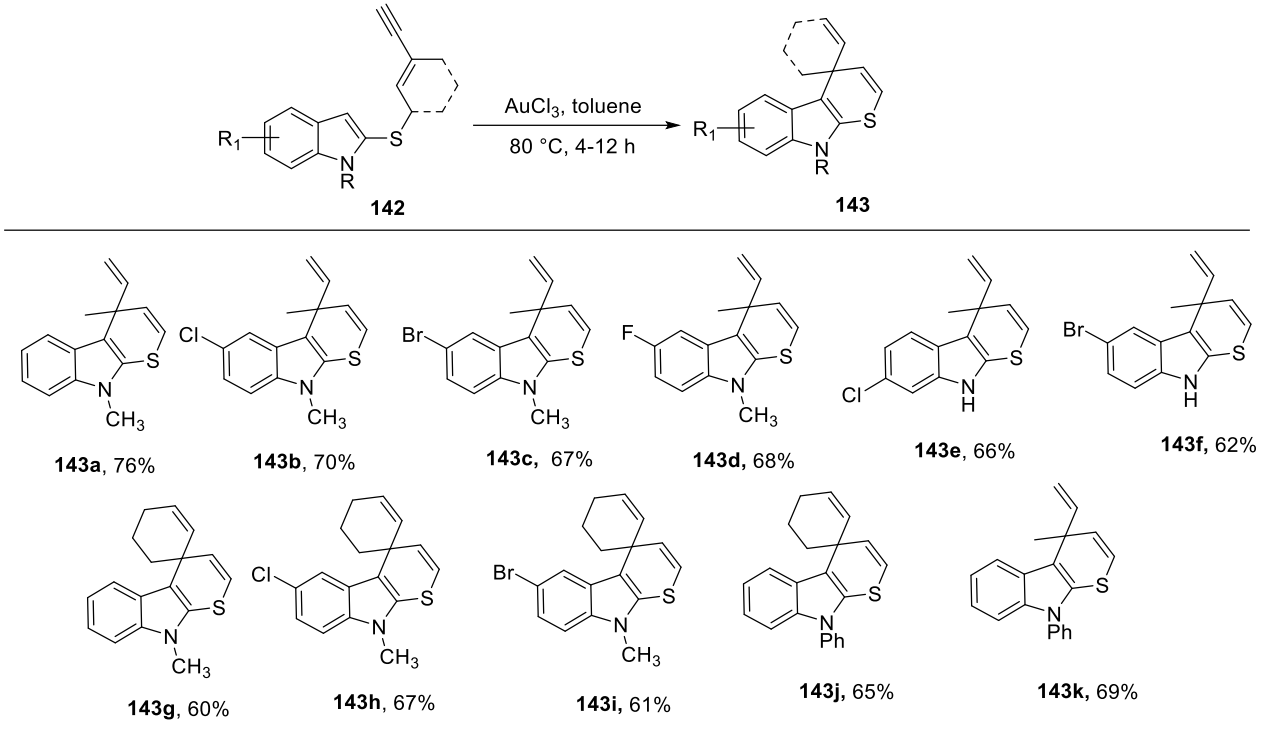
Scheme 3.43: Chemical structures of the expected annulation products from sulfide **142eg**

Once the isolated product was fully characterized, the effect of a cocatalyst on the product yield was studied. On the basis of literature reports,[66, 135] a combination of $AuCl(PPh_3)$ and AgOTf was employed as a catalyst for our desired cyclization. However, this isolated yield of **1a** was found to be lower than that of $AuCl_3$ alone (Table 3.5, entry 16). These results led us to select $AuCl_3$ as the catalyst of choice for the cyclization step and set out to optimize other reaction parameters, such as temperature, solvent, and catalyst concentration. A loss in yield of **143a** was

observed when the reaction temperature was increased to 110 °C (Table 3.5, entry 8). Changing the solvent of the reaction did not appear to have a significant impact on the product yields.

In general, reactions performed in toluene provided superior results among the tested solvents (Table 3.5, entries 9−12). Catalyst loading had a profound impact on the reaction outcome. The use of 2 mol % of $AuCl_3$ resulted in 50% yield of cyclized product **143a**, whereas the use of 10 mol % of $AuCl_3$ provided 76% of **143a** (Table 3.5, entries 5, 13 and 14). Overall, after a thorough screening, we determined that 10 mol % of $AuCl_3$ in toluene at 80 °C is the optimal condition for the synthesis of **143a** from **142eg**.

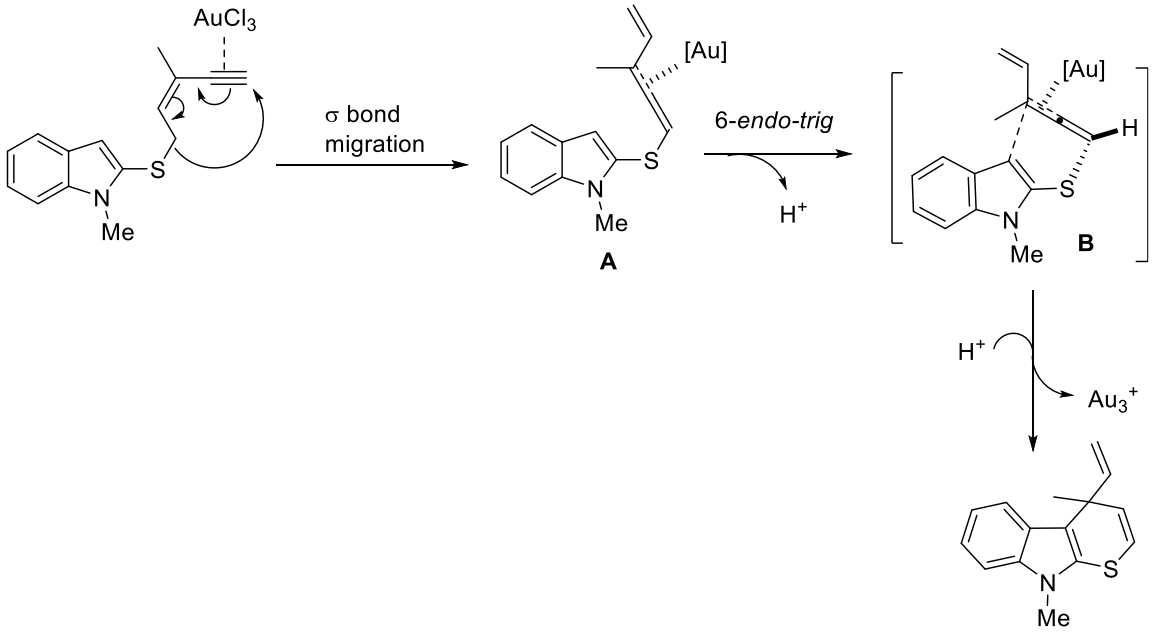
Table 3.6: Synthesis of dihydrothiopyrano[2,3-*b*]indoles from 2-(2-alkenylthio)indoles[a]



[a]Reaction conditions: **142** (0.16 mmol), $AuCl_3$ (10 mol %), toluene (2 mL), 80 °C.

Next, the optimized conditions were used to study the scope of the C−H activation-mediated carbocyclization reaction. As shown in table 3.6, differently substituted 2-(2-alkenylthio)-indoles (**142**) were subjected to these conditions to obtain diverse indole-fused dihydrothiopyrans (**143**). Among the various substrates studied, no specific substitution effects were observed in the reaction outcome, and all dihydrothiopyran derivatives were prepared in

good yields (54−76%). Owing to the nucleophilic nature of position 1 of the indole core in the case of unsubstituted 2-(2-alkenylthio)indoles (e.g., **142bg**), a competition between position 1 and 3 was anticipated in the cyclization process. In the past, gold-catalyzed reactions of indoles have been preferred using *N*-alkylated substrates to circumvent such issues.[142, 143] Remarkably, no interference of indole nitrogen was observed in the current investigation. The synthesis of *N*-unsubstituted analogs of indole-fused dihydrothiopyrans (**143e−f**) was achieved directly without requiring additional protection and deprotection steps, reflecting the regioselective nature of the reaction. Furthermore, under the optimized reaction conditions, cyclization was only feasible from substrates possessing a conjugated ene-yne side chain. Prenyl-substituted sulfide (2-(3-methylbut-2-enylthio)- indole, **142aa**) was found to be unreactive in these conditions. Overall, the new synthesis of functionalized tricyclic indole derivatives appears to be quite general in nature. Further, chemical manipulations at positions 1, 5, and 6 can be conveniently performed using the strategically placed vital functional groups (nitrogen, methyl, bromine, and chlorine) at these sites in compound **142**. These transformations could easily lead to analogs of biologically active carbazole alkaloids. In addition, the vinyl group of product **143** could also be exploited for the creation of new C−C bonds.[144]



Scheme 3.44: Proposed mechanism for $AuCl_3$-mediated formation of dihydrothiopyrano[2,3-*b*]indoles

The actual mechanism for the formation of product **143** might be complicated. A simplified mechanism for the observed *6-endo-trig* carbocyclization is outlined in **Scheme 3.44**. Typically, gold-catalyzed intramolecular hydroarylation of alkynes begins with the nucleophilic attack at the alkynic/allenic carbon activated with cationic gold. The apparent formation of an *S*-containing six-membered ring in **143a−k** suggested that, prior to the hydroarylation step, rearrangement of the conjugated ene-yne manifold present on sulfur takes place, as depicted in **Scheme 3.44**. In addition to 1D NOESY correlations, the creation of a spiro ring in products **143g−j** provide further evidence in favor of the proposed rearrangement. We are currently investigating in detail the different aspects of the rearrangement of a conjugated ene-yne side chain under these conditions.

The structure of the indole-fused thiopyran product **143k** was confirmed by using X-ray crystallographic data as shown in **Figure 3.13**

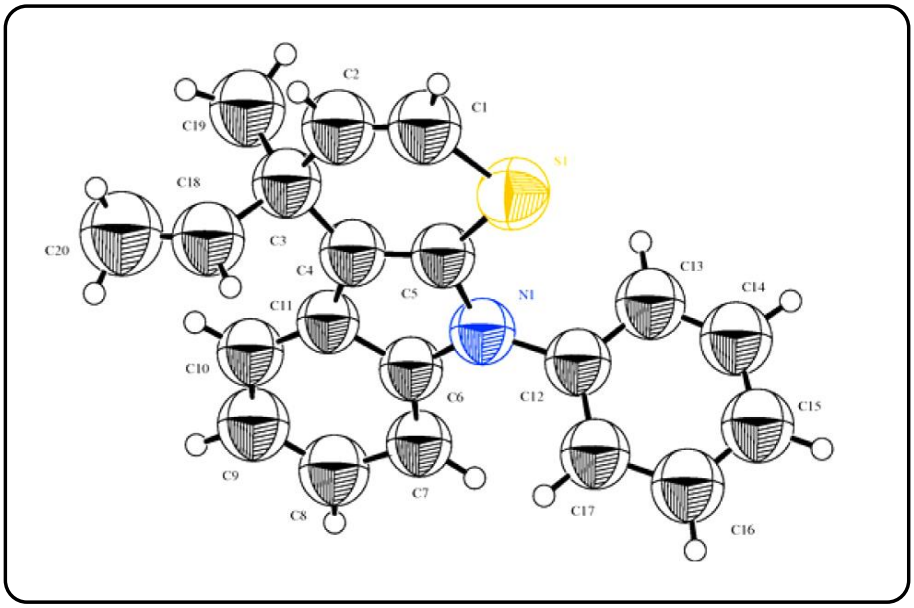


Figure 3.13: ORTEP plot of **143k** (ellipsoids are drawn at 40%). The compound data of **143k** is available at **CCDC No**. **1057877**.

3.8 Conclusions

In conclusion, we have developed an efficient methodology for the formation of a dihydrothiopyrano[2,3-*b*]indole skeleton starting from indoline-2-thione in two steps. First, a regioselective BF_3 etherate-catalyzed alkylation of indoline-2-thione using unsaturated alcohols results in 2-(2-alkenylthio)indole. Subsequently, an Au(III)-mediated reaction of 2-(2-alkenylthio)-indole allowed access to an indole-fused dihydrothiopyran framework via sequential rearrangement of the ene-yne side chain and intramolecular hydroarylation at the C-3 position of the indole core.

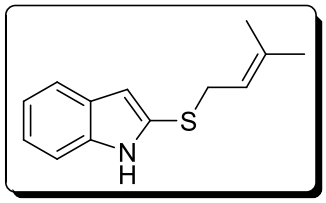
3.9 Experimental

General. All reagents and solvents were used as supplied by commercial sources without further purification. Melting points were measured using an MEL-TEMP II apparatus and are uncorrected. Precoated fluorescent silica gel TLC plates were used to monitor the progress of the reactions. The ^{1}H and ^{13}C NMR spectra were obtained by a 300 MHz FT-NMR spectrometer. Chemical shifts of the ^{1}H NMR spectra are reported in parts per million (ppm) downfield from tetramethylsilane. IR spectra were recorded on an FT-IR spectrometer, and the values are expressed in cm^{-1}. HRMS spectra were obtained using a qTOF mass analyzer and ESI positive ionization source.

General Procedure for the Synthesis of Compounds 142aa−142ih

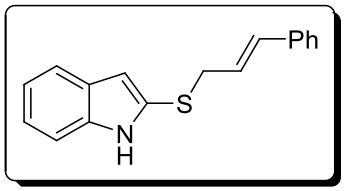
BF_3 etherate (2.01 mmol) was added dropwise to a solution of appropriate indolin-2-thione (1.0 mmol) and alcohol (1.0 mmol) in dichloromethane (40 mL). The reaction mixture was stirred at room temperature (see Table 3.6 for reaction times). Excess dichloromethane was evaporated using rotavap after the reaction was complete. The residue was subjected to column chromatography (2% ethyl acetate in hexanes) to obtain compounds **142aa−ih**.

2-(3-Methylbut-2-enylthio)-1H-indole (142aa)



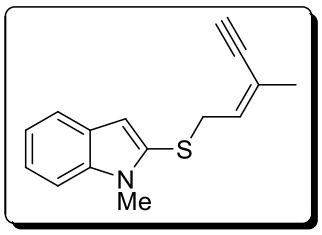
Light yellow liquid (70%, 153 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.3 Hz, 1H), 6.65 (s, 1H), 5.36 (t, *J* = 7.4 Hz, 1H), 3.48 (d, *J* = 7.9 Hz, 2H), 1.74 (s, 3H), 1.47 (s, 3H); 13C NMR (75 MHz, $CDCl_3$) δ 137.1, 136.8, 128.9, 128.6, 122.5, 120.2, 120.0, 119.9, 110.5, 109.0, 35.1, 25.7, 17.5; FT-IR ν_{max} (neat) 3396, 2965, 2912, 1439, 1337, 1226, 741 cm^{-1}; HRMS *m/z* calcd for $C_{13}H_{15}NS$ 218.0998 $[M + H]^+$, found 218.0997.

2-(Cinnamylthio)-1H-indole (142ae)



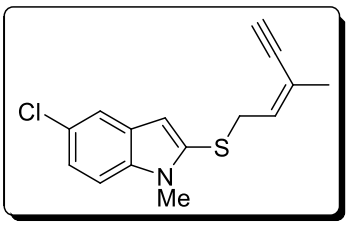
Colorless oil (50%, 134 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.37−7.11 (m, 8H), 6.74 (s, 1H), 6.35 (s, 2H), 3.64 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 136.7, 133.1, 128.7, 128.6, 128.2, 127.8, 94.4, 125.6, 122.7, 120.4, 120.1, 110.7, 109.7, 39.9; FT-IR ν_{max} (neat) 3393, 1487, 1435, 1337, 1228, 962, 736, 696 cm^{-1}; HRMS *m/z* calcd for $C_{17}H_{16}NS$ 266.0998 $[M + H]^+$, found 266.0985.

(Z)-1-Methyl-2-(3-methylpent-2-en-4-ynylthio)-1H-indole (142eg)



Pale yellow liquid (48%, 116 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 6.4 Hz, 2H), 6.70 (s, 1H), 5.81 (t, *J* = 7.6 Hz, 1H), 3.83 (s, 3H), 3.61 (d, *J* = 7.7 Hz, 2H), 3.00 (s, 1H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 133.1, 130.2, 127.4, 122.23, 120.7, 120.3, 119.6, 109.51, 109.4, 81.8, 81.6, 36.4, 29.9, 22.8; FT-IR ν_{max} (neat) 3276, 3049, 2921, 1706, 1610, 1457, 1323, 735 cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{15}NS$ 242.0998 $[M + H]^+$, found 242.0986.

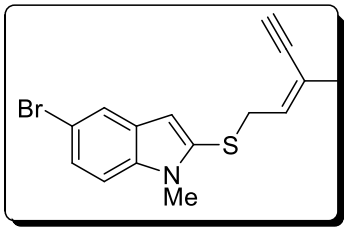
(Z)-5-Chloro-1-methyl-2-(3-methylpent-2-en-4-ynylthio)-1H-indole (142fg)



Colorless liquid (54%, 150 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.18 (s, 2H), 6.61 (s, 1H), 5.79 (t, *J* = 7.5 Hz, 1H), 3.79 (s, 3H), 3.61 (d, *J* = 7.7 Hz, 2H), 2.97 (s, 1H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 132.8, 132.0, 128.3, 125.3, 122.4, 121.0, 119.5, 110.4, 108.6, 81.8, 81.5, 36.1, 30.1, 22.8; FT-IR ν_{max} (neat)

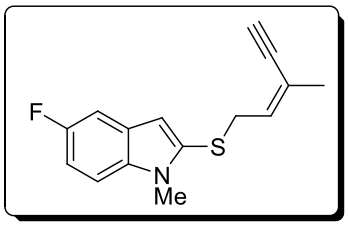
3286, 2920, 1452, 1320, 788 cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{14}ClNS$ 276.0608 $[M + H]^+$, found 276.0619.

(Z)-5-Bromo-1-methyl-2-(3-methylpent-2-en-4-ynylthio)-1H-indole (142gg)



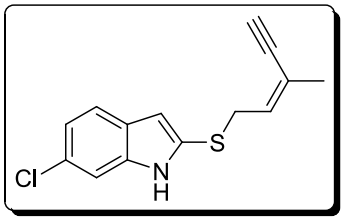
Liquid (53%, 171 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 6.61 (s, 1H), 5.79 (t, *J* = 7.5 Hz, 1H), 3.78 (s, 3H), 3.62 (d, *J* = 7.7 Hz, 2H), 2.98 (s, 1H), 1.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 132.8, 131.9, 128.9, 124.9, 122.6, 121.0, 112.9, 110.9, 108.5, 81.8, 81.5, 36.1, 30.0, 22.8; FT-IR ν_{max} (neat) 3283, 2919, 1714, 1606, 1455, 1318, 786 cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{14}BrNS$ 320.0103 $[M + H]^+$, found 320.0101.

(Z)-5-Fluoro-1-methyl-2-(3-methylpent-2-en-4-ynylthio)-1H-indole (142hg)



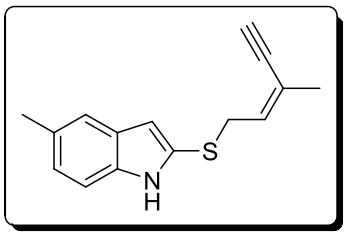
Yellow liquid (56%, 146 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J* = 9.1 Hz, 2H), 6.99 (t, *J* = 8.8 Hz, 1H), 6.64 (s, 1H), 5.80 (t, *J* = 7.6 Hz, 1H), 3.81 (s, 3H), 3.62 (d, *J* = 7.6 Hz, 2H), 2.99 (s, 1H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9 (d, J_{C-F} = 234.5 Hz), 135.0, 132.9, 132.1, 127.5 (d, J_{C-F} = 10.2 Hz), 120.9, 110.6 (d, J_{C-F} = 26.4 Hz), 110.06 (d, J_{C-F} = 9.6 Hz), 108.9 (d, J_{C-F} = 4.8 Hz), 104.9 (d, J_{C-F} = 23.3 Hz), 81.8, 81.5, 36.2, 30.1, 22.8; FT-IR ν_{max} (neat) 3290, 2922, 1620, 1456, 1328, 844, 786 cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{14}FNS$ 260.0904 $[M + H]^+$, found 260.0892.

(Z)-6-Chloro-2-(3-methylpent-2-en-4-ynylthio)-1H-indole (142bg)



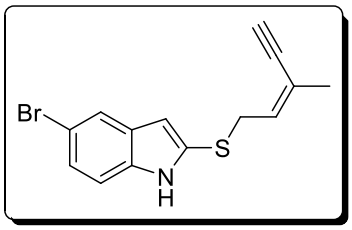
Colorless liquid (53%, 140 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.31 (s, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.60 (s, 1H), 5.83 (t, *J* = 7.7 Hz, 1H), 3.69 (d, *J* = 7.7 Hz, 2H), 3.07 (s, 1H), 1.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 133.6, 128.8, 128.4, 127.2, 121.0, 120.8, 120.7, 110.4, 109.1, 82.2, 81.6, 36.0, 22.84; FT-IR ν_{max} (neat) 3403, 3284, 2919, 1608, 1435, 1333, 807 cm^{-1}; HRMS *m/z* calcd for $C_{14}H_{12}ClNS$ 262.0452 $[M + H]^+$, found 262.0448.

(Z)-5-Methyl-2-(3-methylpent-2-en-4-ynylthio)-1H-indole (142cg)



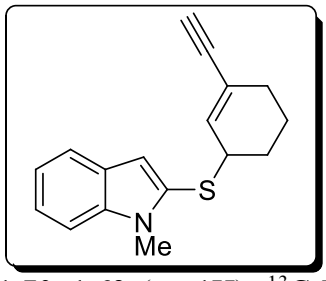
Pale yellow liquid (50%, 122 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.37 (s, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.58 (s, 1H), 5.85 (t, *J* = 7.5 Hz, 1H), 3.69 (d, *J* = 7.6 Hz, 2H), 3.10 (s, 1H), 2.46 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 133.9, 129.3, 128.9, 127.8, 124.2, 120.4, 119.8, 110.2, 108.7, 82.2, 81.8, 36.2, 22.8, 21.5; FT-IR ν_{max} (neat) 3392, 3281, 2918, 1442, 1325, 793 cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{15}NS$ 242.0998 $[M + H]^+$, found 242.0991

(Z)-5-Bromo-2-(3-methylpent-2-en-4-ynylthio)-1H-indole (142dg)



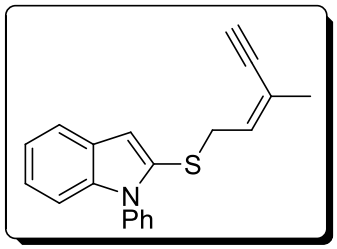
Pale yellow liquid (52%, 160 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.68 (s, 1H), 7.22 (dd, *J* = 25.5, 8.0 Hz, 2H), 6.56 (s, 1H), 5.83 (t, *J* = 7.3 Hz, 1H), 3.70 (d, *J* = 7.7 Hz, 2H), 3.07 (s, 1H), 1.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 133.5, 130.3, 129.7, 125.3, 122.6, 120.8, 113.2, 111.9, 108.1, 82.3, 81.6, 35.9, 22.8; FT-IR ν_{max} (neat) 3193, 2964, 1435, 1021, 793 cm^{-1}. HRMS *m/z* calcd for $C_{14}H_{13}BrNS$ 305.9952 $[M + H]^+$, found 305.9947.

2-((3-Ethynylcyclohex-2-en-1-yl)thio)-1-methyl-1H-indole (142eh).



Yellow liquid (58%, 145 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.60 (m, 1H), 7.34 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.28 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.15 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 6.80 (d, *J* = 0.8 Hz, 1H), 3.86 (s, 3H), 3.71−3.64 (m, 1H), 2.94 (s, 1H), 2.22−2.14 (m, 3H), 1.97−1.90 (m, 1H), 1.89−1.84 (m, 1H), 1.83−1.76 (m, 1H), 1.70−1.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 134.6, 129.9, 127.3, 123.0, 122.5, 120.5, 119.8, 110.4, 109.7, 84.49, 76.8, 46.4, 29.9, 29.0, 27.6, 19.2; HRMS *m/z* calcd for $C_{17}H_{18}NS$ 268.1160 $[M + H]^+$, found 268.1154.

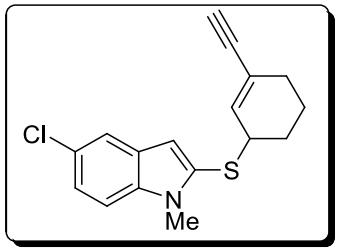
(Z)-2-(3-Methylpent-2-en-4-ynylthio)-1-phenyl-1H-indole (142ig)



Pale yellow liquid (51%, 156 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ7.58−7.43 (m, 5H), 7.17 (s, 4H), 6.81 (s, 1H), 5.68 (t, *J* = 7.6 Hz, 1H), 3.48 (d, *J* = 7.7 Hz, 2H), 3.04 (s, 1H), 1.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 137.4, 133.3, 131.6, 129.1, 128.5, 128.0,

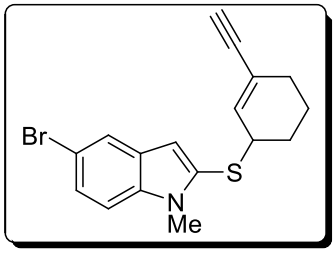
127.7, 122.5, 120.4, 120.3, 120.0, 110.3, 109.1, 82.1, 81.7, 35.6, 22.8; FT-IR ν_{max} (neat) 3278, 3046, 2920, 1496, 741, 695 cm^{-1}; HRMS *m/z* calcd for $C_{20}H_{18}NS$ 304.1160 $[M + H]^+$, found 304.1154.

2-(3-Ethynylcyclohex-2-enylthio)-1-phenyl-1H-indole (142fh)



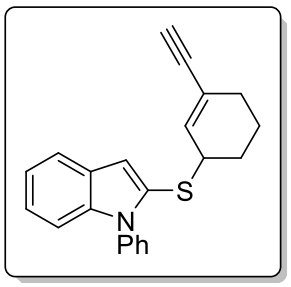
Pale yellow liquid (55%, 167 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.60− 7.41 (m, 6H), 7.17 (d, *J* = 6.0 Hz, 3H), 6.89 (s, 1H), 5.94 (d, *J* = 3.8 Hz, 1H), 3.46 (s, 1H), 2.88 (s, 1H), 1.79−1.43 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 137.3, 134.4, 130.7, 129.1, 128.6, 127.9, 127.5, 122.8, 120.5, 120.2, 111.0, 110.6, 84.4, 77.2, 45.6, 28.9, 27.4, 18.9; FT-IR ν_{max} (neat) 3291, 3011, 2942, 1472, 772 cm^{-1}; HRMS *m/z* calcd for $C_{22}H_{20}NS$ 330.1316 $[M + H]^+$, found 330.1311.

5-Bromo-2-((3-ethynylcyclohex-2-en-1-yl)thio)-1-methyl-1H-indole (142gh)



Colorless oil (55%, 189 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.73−7.71 (m, 1H), 7.34 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 6.70 (d, *J* = 0.8 Hz, 1H), 3.82 (s, 3H), 3.71−3.67 (m, 1H), 2.93 (s, 1H), 2.21−2.16 (m, 3H), 1.93−1.84 (m, 2H), 1.81−1.73 (m, 1H), 1.72−1.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 134.3, 131.6, 128.8, 125.2, 123.3, 122.8, 113.1, 111.1, 109.3, 84.3, 76.9, 46.3, 30.1, 28.9, 27.6, 19.1; HRMS *m/z* calcd for $C_{17}H_{17}BrNS$ 346.0256 $[M + H]^+$, found 346.0260.

5-Chloro-2-(3-ethynylcyclohex-2-enylthio)-1-methyl-1H-indole (142ih)

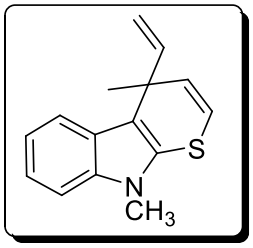


Colorless liquid (55%, 182 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.21 (s, 2H), 6.70 (s, 1H), 6.20 (s, 1H), 3.82 (s, 3H), 2.92 (s, 1H), 2.18 (s, 2H), 1.99−1.56 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 134.3, 131.7, 128.1, 125.6, 123.3, 122.7, 119.7, 110.7, 109.5, 84.3, 77.2, 46.3, 30.2, 29.0, 27.7, 19.2; FT-IR ν_{max} (neat) 3287, 2931, 1451, 1220, 790 cm^{-1}; HRMS *m/z* calcd for $C_{17}H_{17}ClNS$ 302.0765 $[M + H]^+$, found 302.0755.

General Procedure for the Synthesis of Compounds 143a−143k

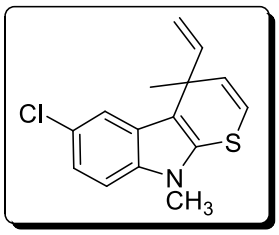
$AuCl_3$ (10 mol %, 0.016 mmol) was added to a solution of the appropriate indole sulfide (0.16 mmol) in toluene. The reaction mixture was stirred at 80 °C for 4−12 h. After the reaction was complete, excess toluene was evaporated using rotavap. The residue was subjected to column chromatography (2% ethyl acetate in hexanes) to obtain compounds **143a−k**.

4,9-Dimethyl-4-vinyl-4,9-dihydrothiopyrano[2,3-b]indole (143a)



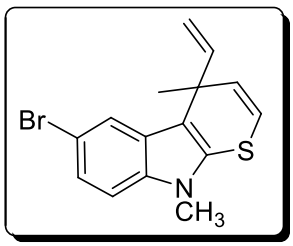
Light yellow liquid (76%, 30.5 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.26 (t, *J* = 7.4 Hz 1H), 7.18 (t, *J* = 7.1 Hz, 1H), 6.38 (dd, *J* = 16.8, 10.7 Hz, 1H), 6.19 (d, *J* = 9.9 Hz, 1H), 5.71 (d, *J* = 9.9 Hz, 1H), 5.28−5.18 (m, 2H), 3.71 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 137.6, 129.8, 94.1, 124.9, 120.7, 119.5, 119.1, 112.3, 110.8, 109.3, 108.3, 41.2, 29.9, 27.7; FT-IR ν_{max} (neat) 2962, 2923, 1613, 1462, 1405, 1326, 992, 914, 735 cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{15}NS$ 242.0998 $[M + H]^+$, found 242.0987.

6-Chloro-4,9-dimethyl-4-vinyl-4,9-dihydrothiopyrano[2,3-b]- indole (143b)



Colorless liquid (70%, 31.5 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.11 (dd, *J* = 20.8, 8.6 Hz, 2H), 6.20 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.09 (d, *J* = 10.1 Hz, 1H), 5.60 (d, *J* = 9.8 Hz, 1H), 5.12 (t, *J* = 12.4 Hz, 2H), 3.62 (s, 3H), 1.65 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 136.0, 129.8, 127.1, 94.8, 124.8, 120.8, 118.8, 112.7, 110.5, 109.2, 108.9, 41.0, 30.1, 27.2; FT-IR ν_{max} (neat) 2924, 1615, 1463, 1423, 1362, 1330, 995, 914, 710 cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{14}ClNS$ 276.0608 $[M + H]^+$, found 276.0614.

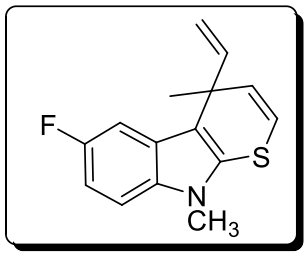
6-Bromo-4,9-dimethyl-4-vinyl-4,9-dihydrothiopyrano[2,3-b]- indole (143c)



Pale yellow liquid (67%, 35 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.20 (dd, *J* = 17.3, 10.5 Hz, 1H), 6.09 (d, *J* = 10.1 Hz, 1H), 5.60 (d, *J* = 10.1 Hz, 1H), 5.12 (t, *J* = 13.0 Hz, 2H), 3.62 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 136.3, 129.8, 127.7, 94.7, 123.4, 121.8, 112.8, 112.3, 110.5, 109.6, 108.9, 41.0, 30.1, 27.2; FT-IR ν_{max} (neat) 2961, 2922, 1613, 1461, 1422, 1363,

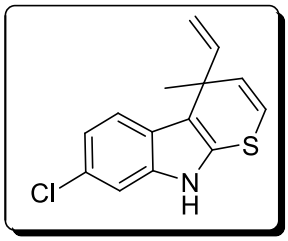
1329, 992, 922, 713 cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{14}BrNS$ 320.0103 $[M + H]^+$, found 320.0103.

6-Fluoro-4,9-dimethyl-4-vinyl-4,9-dihydrothiopyrano[2,3-b]- indole (143d)



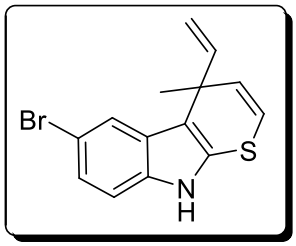
Pale yellow liquid (68%, 28.6 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 10.1 Hz, 1H), 7.17−7.10 (m, 1H), 6.87 (t, *J* = 9.0 Hz, 1H), 6.20 (dd, *J* = 17.0, 10.5 Hz, 1H), 6.10 (d, *J* = 9.8 Hz, 1H), 5.61 (d, *J* = 9.9 Hz, 1H), 5.17−5.06 (m, 2H), 3.63 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 157.3 (d, J_{C-F} = 234.2 Hz), 144.3, 134.2, 129.7, 94.9, 94.3 (d, J_{C-F} = 10.2 Hz), 112.5, 110.6, 109.2, 108.8 (d, J_{C-F} = 3.2 Hz), 108.6 (d, J_{C-F} = 13.0 Hz), 104.6 (d, J_{C-F} = 24.4 Hz); FT-IR ν_{max} (neat) 2967, 2919, 1619, 1573, 1473, 1425, 1334, 989, 918, 712 cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{14}FNS$ 260.0904 $[M + H]^+$, found 260.0916.

7-Chloro-4-methyl-4-vinyl-4,9-dihydrothiopyrano[2,3-b]indole (143e)



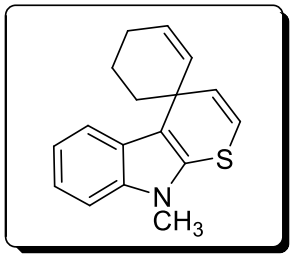
Pale yellow liquid (66%, 27.8 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.25 (s, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.19 (dd, *J* = 17.4, 10.4 Hz, 1H), 6.07 (d, *J* = 9.9 Hz, 1H), 5.59 (d, *J* = 9.9 Hz, 1H), 5.11 (t, *J* = 12.3 Hz, 2H), 1.66 (s, 3H); 13C NMR (75 MHz, $CDCl_3$) δ 144.2, 136.7, 129.5, 129.4, 127.2, 124.9, 123.0, 120.2, 112.7, 110.9, 110.9, 110.2, 40.7, 27.0; FT-IR ν_{max} (neat) 2965, 2925, 1737, 1697, 1608, 1446, 1406, 1367, 1320, 991, 918, 719 cm^{-1}; HRMS *m/z* calcd for $C_{14}H_{12}ClNS$ 262.0452 $[M + H]^+$, found 262.0441.

6-Bromo-4-methyl-4-vinyl-4,9-dihydrothiopyrano[2,3-b]indole (143f).



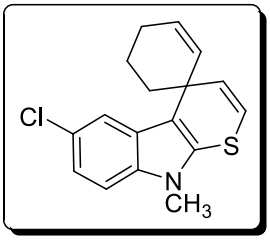
Yellow liquid (62%, 30.4 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.64 (s, 1H), 7.16 (dd, *J* = 17.1, 8.8 Hz, 2H), 6.19 (dd, *J* = 16.9, 10.7 Hz, 1H), 6.06 (d, *J* = 9.8 Hz, 1H), 5.59 (d, *J* = 10.3 Hz, 1H), 5.13 (t, *J* = 13.8 Hz, 2H), 1.65 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 144.0, 135.0, 129.5, 128.1, 124.0, 123.8, 121.9, 113.0, 112.9, 111.56 110.8, 110.5, 40.6, 27.0; FT-IR ν_{max} (neat) 3193, 2964, 1435, 1042, 793 cm^{-1}; HRMS *m/z* calcd for $C_{14}H_{13}BrNS$ 305.9952 $[M + H]^+$, found 305.9947.

9′-Methyl-9′H-spiro[cyclohex[2]ene-1,4′-thiopyrano[2,3-*b*]- indole] (143g)



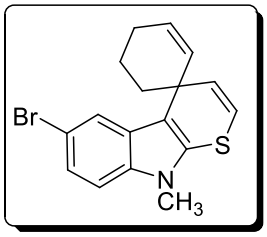
Pale yellow liquid (60%, 24.5 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.2 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.16 (t, *J* = 6.8 Hz, 1H), 7.07 (d, *J* = 6.9 Hz, 1H), 6.11 (d, *J* = 9.7 Hz, 1H), 5.99−5.84 (m, 3H), 3.66 (s, 1H), 2.37−2.16 (m, 3H), 2.06−1.69 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 134.1, 129.7, 94.3, 125.9, 125.3, 120.6, 119.3, 118.9, 110.8, 110.3, 108.2, 38.7, 36.8, 29.9, 24.7, 18.6; FT-IR ν_{max} (neat) 3005, 2926, 1606, 1463, 1424, 1325, 727 cm^{-1}; HRMS *m/z* calcd for $C_{17}H_{17}NS$ 268.1154 $[M + H]^+$, found 268.1161.

6′-Chloro-9′-methyl-9′H-spiro[cyclohex[2]ene-1,4′-thiopyrano- [2,3-*b*]indole] (143h)



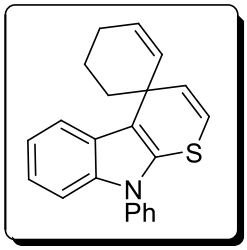
Colorless liquid (67%, 32.4 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.18−7.01 (m, 2H), 6.08 (d, *J* = 8.6 Hz, 1H), 5.97−5.78 (m, 3H), 3.61 (s, 3H), 2.32−2.07 (m, 3H), 2.02−1.67 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 133.6, 129.8, 127.2, 94.5, 124.7, 120.7, 118.6, 110.6, 110.1, 109.1, 38.5, 36.7, 30.1, 24.6, 18.5; FT-IR ν_{max} (neat) 3018, 2930, 2850, 1609, 1462, 1421, 1329, 730 cm^{-1}; HRMS *m/z* calcd for $C_{17}H_{16}ClNS$ 302.0765 $[M + H]^+$, found 302.0766.

6′-Bromo-9′-methyl-9′H-spiro[cyclohex[2]ene-1,4′-thiopyrano- [2,3-b]indole] (143i)



Pale yellow liquid (61%, 34.2 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.20 (d, *J* = 8.6 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.09 (d, *J* = 9.9 Hz, 1H), 5.87 (dd, *J* = 26.0, 10.4 Hz, 3H), 3.62 (s, 3H), 2.29−2.06 (m, 3H), 2.01−1.67 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 133.59, 129.9, 127.89 127.1, 94.5, 123.3, 121.7, 112.4, 110.63, 110.0, 109.5, 38.5, 36.8, 30.1, 24.6, 18.5; FT-IR ν_{max} (neat) 3022, 2929, 1462, 1237, 786 cm^{-1}; HRMS *m/z* calcd for $C_{17}H_{17}BrNS$ 346.0265 $[M + H]^+$, found 346.0260.

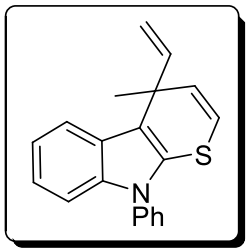
9′-Phenyl-9′H-spiro[cyclohex[2]ene-1,4′-thiopyrano[2,3-b]indole] (143j)



Pale yellow liquid (65%, 34.5 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74−7.65 (m, 1H), 7.60−7.51 (m, 2H), 7.47 (d, *J* = 7.2 Hz, 3H), 7.25−7.16 (m, 1H), 7.09 (dd, *J* = 6.0, 3.2 Hz, 2H), 6.05 (d, *J* = 9.9 Hz, 1H), 5.97−5.87 (m, 3H), 2.44−2.18 (m, 3H), 2.10−1.76 (m, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 138.1, 136.7, 134.0, 129.5, 129.1, 128.0, 127.3, 94.7, 94.1, 125.5, 121.2, 119.7, 119.4, 111.9, 111.5, 109.4, 38.7, 36.6, 24.7, 18.6; FT-IR ν_{max} (neat) 3044, 2926, 1497, 1447, 736, 695 cm^{-1}; HRMS *m/z* calcd for $C_{22}H_{20}NS$ 330.1316 $[M + H]^+$, found 330.1311.

4-Methyl-9-phenyl-4-vinyl-4,9-dihydrothiopyrano[2,3-b]indole (143k)



Pale yellow liquid (69%, 34.5 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 6.0, 3.2 Hz, 1H), 7.54 (d, *J* = 6.8 Hz, 2H), 7.50−7.44 (m, 3H), 7.19 (dt, *J* = 7.3, 3.7 Hz, 1H), 7.13−7.06 (m, 2H), 6.34 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.07 (d, *J* = 10.0 Hz, 1H), 5.61 (d, *J* = 10.0 Hz, 1H), 5.19 (dd, *J* = 13.9, 6.3 Hz, 2H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.7, 138.1, 136.7, 129.5, 129.2, 128.1, 127.4, 94.5, 125.2, 121.3, 119.8, 119.6, 112.4, 111.5, 110.8, 109.5, 41.2, 27.1; FT-IR ν_{max} (neat) 3045, 2962, 2922, 1594, 1497, 1447, 737, 696 cm^{-1}; HRMS *m/z* calcd for $C_{20}H_{18}NS$ 304.1160 $[M + H]^+$, found 304.1154.

❖ X-ray crystallographic data of compound **143k** is as follows

A. Crystal Data

Empirical Formula	$C_{20}H_{18}NS$
Formula Weight	304.43
Crystal Color, Habit	faint-yellow, blobs
Crystal Dimensions	0.31mm × 0.27mm × 0.24 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Indexing Images	180 oscillations @ 4.0 seconds
Detector Position	127.40 mm
Pixel Size	0.100 mm

Lattice Parameters	a = 8.8800(16) Å b = 10.855(3) Å c = 16.771(3) Å V = 1616.6(6) Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.251 g/cm^3
F_{000}	644.00
⎾(MoK ⟨)	1.961 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku RAXIS-UNKNOWN
Radiation	MoK ⟨ (⎿ = 0.71075 Å) graphite monochromated
Data Images	36 exposures
⏋ Oscillation Range	20.0 - 200.0º
Exposure Rate	360.0 sec./º
Detector Position	127.40 mm
Pixel Size	0.100 mm
2⟍max	53.7º
No. of Reflections Measured	Total: 3458 Unique: 3455 (R_{int} = 0.000) Friedel pairs: 1471
Corrections	Lorentz-polarization Absorption (trans. factors: 0.381 - 0.954)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELX97)
Refinement	Full-matrix least-squares on F^2
Function Minimized	©w $(Fo^2 - Fc^2)^2$
Least Squares Weights parameters	Chebychev polynomial with 3
2\max cutoff	21914.0000,30640.1000,9474.9600, 53.7°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00 ⌠(I))	495
No. Variables	94
Reflection/Parameter Ratio	5.27
Residuals: R^1 (I>3.00 ⌠(I))	0.0764
Residuals: wR^2 (I>3.00 ⌠(I))	0.0822
Goodness of Fit Indicator	1.168
Flack Parameter (Friedel pairs = 1471)	0.121
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.28 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.30 $e^-/Å^3$

3.10 References

[1] Echavarren, A. M.; Cárdenas, D. J., Mechanistic Aspects of Metal-Catalyzed C,C- and C,X-Bond-Forming Reactions. In *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH Verlag GmbH: **2008**; pp 1.

[2] Negishi, E. *Accounts of Chemical Research* **1982,** *15*, 340.

[3] Erdik, E. *Tetrahedron* **1992,** *48*, 9577.

[4] Wang, Z., Buchwald-Hartwig Amination. In *Comprehensive Organic Name Reactions and Reagents*, John Wiley & Sons, Inc.: **2010**.

[5] Guram, A. S.; Buchwald, S. L. *Journal of the American Chemical Society* **1994,** *116*, 7901.

[6] Paul, F.; Patt, J.; Hartwig, J. F. *Journal of the American Chemical Society* **1994,** *116*, 5969.

[7] Heck, R. F., Palladium-Catalyzed Vinylation of Organic Halides. In *Organic Reactions*, John Wiley & Sons, Inc.: **2004**.

[8] Suzuki, A., In *Pure and Applied Chemistry*, **1991**; Vol. 63, p 419.

[9] Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002,** *58*, 9633.

[10] Milstein, D.; Stille, J. K. *Journal of the American Chemical Society* **1979,** *101*, 4981.

[11] Milstein, D.; Stille, J. K. *Journal of the American Chemical Society* **1979,** *101*, 4992.

[12] Milstein, D.; Stille, J. K. *The Journal of Organic Chemistry* **1979,** *44*, 1613.

[13] Monnier, F.; Taillefer, M. *Angewandte Chemie International Edition* **2009,** *48*, 6954.

[14] Nakao, Y.; Hiyama, T. *Chemical Society Reviews* **2011,** *40*, 4893.

[15] S. M. Bronner, G. Y. J. I., N. K. Garg, *Heterocycles in Natural Product Synthesis*. Wiley-VCH Verlag GmbH & Co. KGaA: , **2011**.

[16] Torborg, C.; Beller, M. *Advanced Synthesis & Catalysis* **2009,** *351*, 3027.

[17] Akita, Y.; Itagaki, Y.; Takizawa, S.; Ohta, A. *Chemical and Pharmaceutical Bulletin* **1989,** *37*, 1477.

[18] Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990,** *46*, 4003.

[19] Grigg, R.; Fretwell, P.; Meerholtz, C.; Sridharan, V. *Tetrahedron* **1994,** *50*, 359.

[20] Burwood, M.; Davies, B.; Diaz, I.; Grigg, R.; Molina, P.; Sridharan, V.; Hughes, M. *Tetrahedron Letters* **1995,** *36*, 9053.

[21] Kozikowski, A. P.; Ma, D. *Tetrahedron Letters* **1991,** *32*, 3317.

[22] Mérour, E. D. a. J.-Y. *Heterocycles* **1995,** *41*, 1987.

[23] Campeau, L.-C.; Fagnou, K. *Chemical Communications* **2006**, 1253.

[24] Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *Journal of the American Chemical Society* **2006,** *128*, 581.

[25] Chu, X.-Q.; Zi, Y.; Lu, X.-M.; Wang, S.-Y.; Ji, S.-J. *Tetrahedron* **2014,** *70*, 232.

[26] Bressy, C.; Alberico, D.; Lautens, M. *Journal of the American Chemical Society* **2005,** *127*, 13148.

[27] Monnier, F.; Taillefer, M. *Angewandte Chemie International Edition* **2008,** *47*, 3096.

[28] Evano, G.; Blanchard, N.; Toumi, M. *Chemical Reviews* **2008,** *108*, 3054.

[29] Evano, G.; Toumi, M.; Coste, A. *Chemical Communications* **2009**, 4166.

[30] Bender, T. P.; Graham, J. F.; Duff, J. M. *Chemistry of Materials* **2001,** *13*, 4105.

[31] Goodbrand, H. B.; Hu, N.-X. *The Journal of Organic Chemistry* **1999,** *64*, 670.

[32] Antilla, J. C.; Klapars, A.; Buchwald, S. L. *Journal of the American Chemical Society* **2002,** *124*, 11684.

[33] Zhang, H.; Cai, Q.; Ma, D. *The Journal of Organic Chemistry* **2005,** *70*, 5164.

[34] Chandrasekhar, S.; Sultana, S. S.; Yaragorla, S. R.; Reddy, N. R. *Synthesis* **2006,** 839.

[35] Swapna, K.; Murthy, S. N.; Nageswar, Y. V. D. *European Journal of Organic Chemistry* **2010,** *2010*, 6678.

[36] Zhang, Q.; Luo, J.; Wei, Y. *Synthetic Communications* **2012,** *42*, 114.

[37] Xu, Z.-L.; Li, H.-X.; Ren, Z.-G.; Du, W.-Y.; Xu, W.-C.; Lang, J.-P. *Tetrahedron* **2011,** *67*, 5282.

[38] Zhao, F.; Zhang, L.; Liu, H.; Zhou, S.; Liu, H. *Beilstein Journal of Organic Chemistry* **2013,** *9*, 2463.

[39] Zhang, L.; Zheng, M.; Zhao, F.; Zhai, Y.; Liu, H. *ACS Combinatorial Science* **2014,** *16*, 184.

[40] Barbero, N.; SanMartin, R.; Domínguez, E. *Tetrahedron Letters* **2009,** *50*, 2129.

[41] Hashmi, A. S. K. *Chemical Reviews* **2007,** *107*, 3180.

[42] Garcia, P.; Malacria, M.; Aubert, C.; Gandon, V.; Fensterbank, L. *ChemCatChem* **2010,** *2*, 493.

[43] Arcadi, A. *Chemical Reviews* **2008,** *108*, 3266.

[44] Li, Z.; Brouwer, C.; He, C. *Chemical Reviews* **2008,** *108*, 3239.

[45] Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angewandte Chemie International Edition* **2000,** *39*, 2285.

[46] Teles, J. H.; Brode, S.; Chabanas, M. *Angewandte Chemie International Edition* **1998,** *37*, 1415.

[47] Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angewandte Chemie International Edition* **2002,** *41*, 4563.

[48] Casado, R.; Contel, M.; Laguna, M.; Romero, P.; Sanz, S. *Journal of the American Chemical Society* **2003,** *125*, 11925.

[49] Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Organic Letters* **2005,** *7*, 5409.

[50] Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *Journal of the American Chemical Society* **2005,** *127*, 9976.

[51] Arcadi, A.; Giuseppe, S. D.; Marinelli, F.; Rossi, E. *Advanced Synthesis & Catalysis* **2001,** *343*, 443.

[52] Gorin, D. J.; Davis, N. R.; Toste, F. D. *Journal of the American Chemical Society* **2005,** *127*, 11260.

[53] Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *Journal of the American Chemical Society* **2000,** *122*, 11553.

[54] Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *Journal of the American Chemical Society* **2004,** *126*, 4526.

[55] Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angewandte Chemie International Edition* **2004,** *43*, 5350.

[56] Zhang, L.; Kozmin, S. A. *Journal of the American Chemical Society* **2004,** *126*, 11806.

[57] Zhang, L.; Kozmin, S. A. *Journal of the American Chemical Society* **2005,** *127*, 6962.

[58] Gagosz, F. *Organic Letters* **2005,** *7*, 4129.

[59] Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *Journal of the American Chemical Society* **2006,** *128*, 3112.

[60] Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *Journal of the American Chemical Society* **2002,** *124*, 12650.

[61] Kim, N.; Kim, Y.; Park, W.; Sung, D.; Gupta, A. K.; Oh, C. H. *Organic Letters* **2005,** *7*, 5289.

[62] Yao, X.; Li, C.-J. *Organic Letters* **2006,** *8*, 1953.

[63] Morita, N.; Krause, N. *Angewandte Chemie International Edition* **2006,** *45*, 1897.

[64] Bandini, M. *Chemical Society Reviews* **2011,** *40*, 1358.

[65] Hirano, K.; Inaba, Y.; Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Advanced Synthesis & Catalysis* **2010,** *352*, 368.

[66] Kumar, A.; Vachhani, D. D.; Modha, S. G.; Sharma, S. K.; Parmar, V. S.; Van der Eycken, E. V. *European Journal of Organic Chemistry* **2013,** *2013*, 2288.

[67] Kumar, A.; Vachhani, D. D.; Modha, S. G.; Sharma, S. K.; Parmar, V. S.; Van der Eycken, E. V. *Synthesis* **2013,** *45*, 2571.

[68] Samala, S.; Mandadapu, A. K.; Saifuddin, M.; Kundu, B. *The Journal of Organic Chemistry* **2013,** *78*, 6769.

[69] Guven, S.; Ozer, M. S.; Kaya, S.; Menges, N.; Balci, M. *Organic Letters* **2015,** *17*, 2660.

[70] Basceken, S.; Kaya, S.; Balci, M. *The Journal of Organic Chemistry* **2015,** *80*, 12552.

[71] Sharma, V.; Kumar, P.; Pathak, D. *Journal of Heterocyclic Chemistry* **2010,** *47*, 491.

[72] Fernando Rodrigues de Sa, A.; Eliezer, J. B.; Carlos Alberto Manssour, F. *Mini-Reviews in Medicinal Chemistry* **2009,** *9*, 782.

[73] Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Current Opinion in Chemical Biology* **2010,** *14*, 347.

[74] Kaushik, N.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C.; Verma, A.; Choi, E. *Molecules* **2013,** *18*, 6620.

[75] Takasugi, M.; Katsui, N.; Shirata, A. *Journal of the Chemical Society, Chemical Communications* **1986**, 1077.

[76] Takasugi, M.; Monde, K.; Katsui, N.; Shirata, A. *Bulletin of the Chemical Society of Japan* **1988,** *61*, 285.

[77] Takasugi, M.; Monde, K.; Katsui, N.; Shirata, A. *Chemistry Letters* **1987,** *16*, 1631.

[78] Pedras, M. S. C.; Jha, M.; Ahiahonu, P. W. K. *Current Organic Chemistry* **2003,** *7*, 1635.

[79] Staab, A.; Loeffler, J.; Said, H. M.; Diehlmann, D.; Katzer, A.; Beyer, M.; Fleischer, M.; Schwab, F.; Baier, K.; Einsele, H.; Flentje, M.; Vordermark, D. *BMC Cancer* **2007,** *7*, 1.

[80] Ji, Q.; Gao, J.; Wang, J.; Yang, C.; Hui, X.; Yan, X.; Wu, X.; Xie, Y.; Wang, M.-W. *Bioorganic & Medicinal Chemistry Letters* **2005,** *15*, 2891.

[81] Kuehm-Caubère, C.; Caubère, P.; Jamart-Grégoire, B.; Pfeiffer, B.; Guardiola-Lemaître, B.; Manechez, D.; Renard, P. *European Journal of Medicinal Chemistry* **1999,** *34*, 51.

[82] Takada, S.; Makisumi, Y. *Chemical and Pharmaceutical Bulletin* **1984,** *32*, 872.

[83] Takada, S.; Ishizuka, N.; Sasatani, T.; Makisumi, Y.; Jyoyama, H.; Hatakeyama, H.; Asanuma, F.; Hirose, K. *Chemical and Pharmaceutical Bulletin* **1984,** *32*, 877.

[84] Kiamehr, M.; Moghaddam, F. M. *Tetrahedron Letters* **2009,** *50*, 6723.

[85] Majumdar, K. C.; Taher, A.; Ponra, S. *Tetrahedron Letters* **2010,** *51*, 147.

[86] Majumdar, K. C.; Taher, A.; Ray, K. *Tetrahedron Letters* **2009,** *50*, 3889.

[87] Majumder, S.; Bhuyan, P. J. *Tetrahedron Letters* **2012,** *53*, 137.

[88] Majumder, S.; Bhuyan, P. J. *Tetrahedron Letters* **2012,** *53*, 762.

[89] Majumdar, K. C.; Ponra, S.; Ghosh, T. *RSC Advances* **2012,** *2*, 1144.

[90] Majumdar, K. C.; Ponra, S.; Nandi, R. K. *Tetrahedron Letters* **2012,** *53*, 1732.

[91] Majumdar, K. C.; Debnath, P.; Alam, S.; Maji, P. K. *Tetrahedron Letters* **2007,** *48*, 7031.

[92] Majumdar, K. C.; Debnath, P.; Alam, S.; Islam, R. *Journal of Sulfur Chemistry* **2008,** *29*, 467.

[93] Chen, X.; Qi, Z.-H.; Zhang, S.-Y.; Kong, L.-P.; Wang, Y.; Wang, X.-W. *Organic Letters* **2015,** *17*, 42.

[94] Jha, M.; Enaohwo, O.; Marcellus, A. *Tetrahedron Letters* **2009,** *50*, 7184.

[95] Jha, M.; Enaohwo, O.; Guy, S. *Tetrahedron Letters* **2011,** *52*, 684.

[96] Nakamura, I.; Yamamoto, Y. *Chemical Reviews* **2004,** *104*, 2127.

[97] Geissler, H.; Beller, M.; Bolm, C., Transition Metal—Catalyzed Cross Coupling Reactions. In *Transition Metals for Organic Synthesis*, Wiley-VCH Verlag GmbH: **2008**; pp 158.

[98] Thansandote, P.; Lautens, M. *Chemistry – A European Journal* **2009,** *15*, 5874.

[99] Seregin, I. V.; Gevorgyan, V. *Chemical Society Reviews* **2007,** *36*, 1173.

[100] Dyker, G. *Angewandte Chemie International Edition* **1999,** *38*, 1698.

[101] Rao, V. K.; Shelke, G. M.; Tiwari, R.; Parang, K.; Kumar, A. *Organic Letters* **2013,** *15*, 2190.

[102] Jha, M.; Edmunds, M.; Lund, K.-l.; Ryan, A. *Tetrahedron Letters* **2014,** *55*, 5691.

[103] Jha, M.; Davis, C.; Fazzari, J.; Vitali, M. *Tetrahedron Letters* **2014,** *55*, 7043.

[104] Jha, M.; Guy, S.; Chou, T.-Y. *Tetrahedron Letters* **2011,** *52*, 4337.

[105] Pericherla, K.; Khedar, P.; Khungar, B.; Kumar, A. *Chemical Communications* **2013,** *49*, 2924.

[106] Pericherla, K.; Kaswan, P.; Khedar, P.; Khungar, B.; Parang, K.; Kumar, A. *RSC Advances* **2013,** *3*, 18923.

[107] Pericherla, K.; Jha, A.; Khungar, B.; Kumar, A. *Organic Letters* **2013,** *15*, 4304.

[108] Nandwana, N. K.; Pericherla, K.; Kaswan, P.; Kumar, A. *Organic & Biomolecular Chemistry* **2015,** *13*, 2947.

[109] Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. *Chemical Society Reviews* **2014,** *43*, 3525.

[110] Sperotto, E.; van Klink, G. P. M.; van Koten, G.; de Vries, J. G. *Dalton Transactions* **2010,** *39*, 10338.

[111] Gibson, S. E.; Middleton, R. J. *Contemporary Organic Synthesis* **1996,** *3*, 447.

[112] Amatore, C.; Azzabi, M.; Jutand, A. *Journal of the American Chemical Society* **1991,** *113*, 8375.

[113] Amatore, C.; Jutand, A.; Suarez, A. *Journal of the American Chemical Society* **1993,** *115*, 9531.

[114] Cabri, W.; Candiani, I. *Accounts of Chemical Research* **1995,** *28*, 2.

[115] Zhang, S.; Zhang, D.; Liebeskind, L. S. *The Journal of Organic Chemistry* **1997,** *62*, 2312.

[116] Zhang, Y.; Yang, X.; Yao, Q.; Ma, D. *Organic Letters* **2012,** *14*, 3056.

[117] Kitamura, T. *European Journal of Organic Chemistry* **2009,** *2009*, 1111.

[118] Bandini, M.; Emer, E.; Tommasi, S.; Umani-Ronchi, A. *European Journal of Organic Chemistry* **2006,** *2006*, 3527.

[119] Hashmi, A. S. K., Gold-Catalyzed Organic Reactions. In *Inventing Reactions*, Gooßen, J. L., Ed. Springer Berlin Heidelberg: Berlin, Heidelberg, **2013**; pp 143.

[120] Boorman, T. C.; Larrosa, I. *Chemical Society Reviews* **2011,** *40*, 1910.

[121] Gilmore, K.; Alabugin, I. V. *Chemical Reviews* **2011,** *111*, 6513.

[122] Andreatta, J. R.; McKeown, B. A.; Gunnoe, T. B. *Journal of Organometallic Chemistry* **2011,** *696*, 305.

[123] Yamamoto, Y. *Chemical Society Reviews* **2014,** *43*, 1575.

[124] Reetz, Manfred T.; Sommer, K. *European Journal of Organic Chemistry* **2003,** *2003*, 3485.

[125] Shi, Z.; He, C. *The Journal of Organic Chemistry* **2004,** *69*, 3669.

[126] Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angewandte Chemie International Edition* **2004,** *43*, 2402.

[127] Nevado, C.; Echavarren, A. M. *Chemistry – A European Journal* **2005,** *11*, 3155.

[128] Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chemistry – A European Journal* **2007,** *13*, 1358.

[129] Ferrer, C.; Escribano-Cuesta, A.; Echavarren, A. M. *Tetrahedron* **2009,** *65*, 9015.

[130] Verniest, G.; England, D.; De Kimpe, N.; Padwa, A. *Tetrahedron* **2010,** *66*, 1496.

[131] Peshkov, V. A.; Pereshivko, O. P.; Eycken, E. V. V. d. *Advanced Synthesis & Catalysis* **2012,** *354*, 2841.

[132] Hashmi, A. S. K.; Yang, W.; Rominger, F. *Advanced Synthesis & Catalysis* **2012,** *354*, 1273.

[133] Boiaryna, L.; El Mkaddem, M. K.; Taillier, C.; Dalla, V.; Othman, M. *Chemistry – A European Journal* **2012,** *18*, 14192.

[134] Modha, S. G.; Vachhani, D. D.; Jacobs, J.; Van Meervelt, L.; Van der Eycken, E. V. *Chemical Communications* **2012,** *48*, 6550.

[135] Modha, S. G.; Kumar, A.; Vachhani, D. D.; Sharma, S. K.; Parmar, V. S.; Van der Eycken, E. V. *Chemical Communications* **2012,** *48*, 10916.

[136] Lu, Y.; Du, X.; Jia, X.; Liu, Y. *Advanced Synthesis & Catalysis* **2009,** *351*, 1517.

[137] Blanchard, D.; Cameron, T. S.; Jha, M. *Molecular Diversity* **2013,** *17*, 827.

[138] Jha, M.; Blunt, B. *Tetrahedron Letters* **2009,** *50*, 6044.

[139] Jha, M.; Chou, T.-Y.; Blunt, B. *Tetrahedron* **2011,** *67*, 982.

[140] Jha, M.; Shelke, G. M.; Kumar, A. *European Journal of Organic Chemistry* **2014,** *2014*, 3334.

[141] Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. *Angewandte Chemie International Edition* **2006,** *45*, 7591.

[142] Qiu, Y.; Kong, W.; Fu, C.; Ma, S. *Organic Letters* **2012,** *14*, 6198.

[143] Liu, C.; Widenhoefer, R. A. *Organic Letters* **2007,** *9*, 1935.

[144] Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. *Angewandte Chemie International Edition* **2012,** *51*, 5915.

Chapter IV

Conclusions

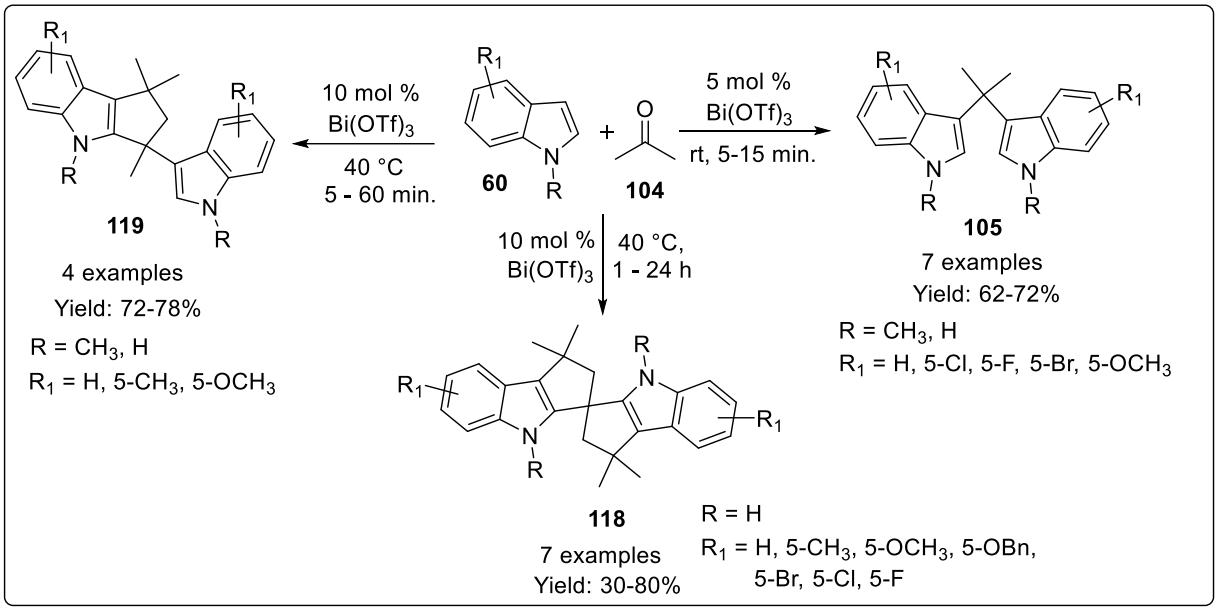
4.1 General conclusions

In the field of modern synthetic chemistry developing atom-economical synthetic strategies has become a foremost priority of synthetic chemists. The synthesis of indole derivatives continues to be a topic of research interest for well over a century. In this context, the importance of indole and indole core containing heterocycles such as isatin, oxindole and indoline-2-thione are described in the introduction section of each chapter of this thesis. Further, new synthetic methodologies have been developed to explore the chemistry of indole and it's derivatives where traditional Lewis acids (such as $InCl_3$, $AlCl_3$, BF_3, $SnCl_4$ etc.) are replaced by metal triflates and the transition metal-catalysts are used for the construction of potent diverse heterocyclic motifs by employing C-C and C-heteroatom bond formation *via* cross-coupling reactions with high efficiencies, high functional group tolerance and excellent regioselectivities.

The current thesis entitled **"Development of Synthetic Methods for Selected Indole-Based Heterocyclic Compounds from Indole, Isatin and Indoline-2-thione"** deals with the syntheses of some selected heterocycles such as bisindolyl scaffolds, oxindoles and indole annulated sulfur heterocycles by using metal triflates and transition metal catalysts. The thesis is divided into three chapters.

4.2 Specific conclusions

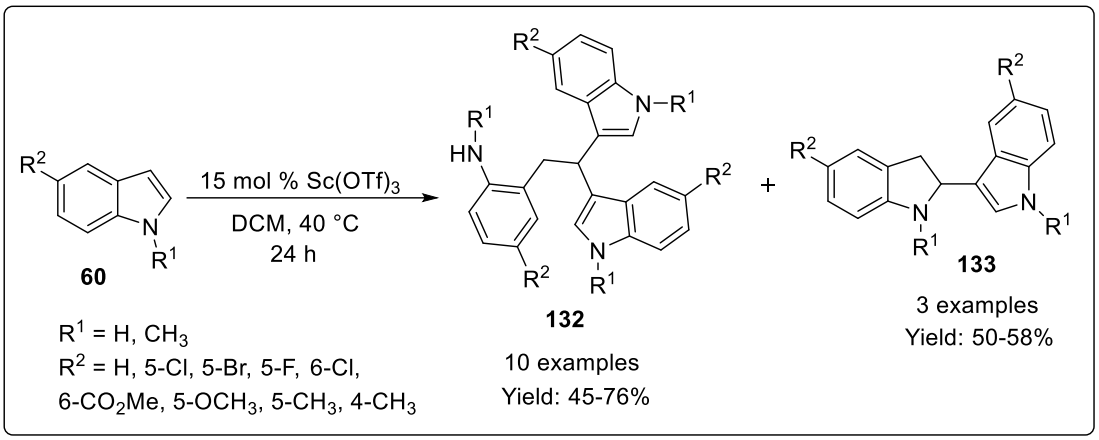
The first chapter of the thesis described the brief history of indole along with the importance of metal triflates in the synthesis of indole derivatives including some advanced examples. This chapter is mainly focused on the synthesis of *bis*(indolyl) compounds using metal triflate catalyzed reactions. The chapter is divided into two parts. In **part-A**, an efficient one-pot condensation reaction of indole and acetone was investigated using $Bi(OTf)_3$ as a catalyst. The reaction furnished good to excellent yields of spirobi[cyclopenta[*b*]indoles (**118**), *N*-methylindolyl-cyclopenta[*b*]indoles (**119**) and bis(*N*-methylindolyl)propanes (**105**) as shown in **Scheme 4.1**. The product formation of the reaction was found to be dependent on the reaction conditions and electronic effect of the indole ring.



Scheme 4.1: $Bi(OTf)_3$ catalyzed condensation of indole with acetone

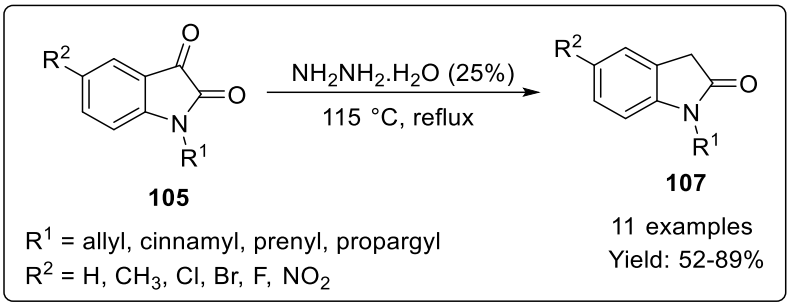
A series of spirobi[cyclopenta[*b*]indoles were prepared from the corresponding indoles in the presence of 10 mol % $Bi(OTf)_3$ and 3 mL volume of acetone at 40 °C under reflux condition however, in case of *N*-Methylindole with electron donating groups gave corresponding *N*-methylindolyl-cyclopenta[*b*]indole derivatives, whereas *N*-Methylindole with electron withdrawing groups it afforded *bis*(*N*-methylindolyl)-propanes. The mechanism of the reaction is believed to be similar to that reported by Bergman group. The present reaction conditions for the synthesis of spirobi[cyclopenta[*b*]indoles are benign and takes lesser time to complete the reaction with improved yield compared to previously reported conditions using protic acids.

In **part-B,** we have studied $Sc(OTf)_3$ catalyzed polymerization of indole and found that the product distribution is dependent on the substituent present on the indole ring. Indole with electron withdrawing or donating groups at the C-5 or C-6 position gave corresponding 3,3′-(*o*-aminophenethylidene)di-indole **132** (indole-3,3′-trimer), except 4-methylindole which afforded corresponding indolylindoline **133** (indole-dimer). In the case of *N*-methylindole with electron withdrawing groups at the C-5 position indole-3,3′-trimer **132** was obtained whereas *N*-methylindole with electron donating group at C-5 position afforded indole-dimer **133** in fairly good yield. We have synthesized three new dimer and six new trimer compounds using $Sc(OTf)_3$ as a catalyst as shown in **Scheme 4.2**. Structure of all the compounds have been confirmed by NMR (^1H and ^{13}C) and mass analysis.



Scheme 4.2: $Sc(OTf)_3$ catalyzed synthesis of substituted 3,3′-(*o*-aminophenethylidene)di-indole **132** and 3-(indolin-2-yl)indole **133**

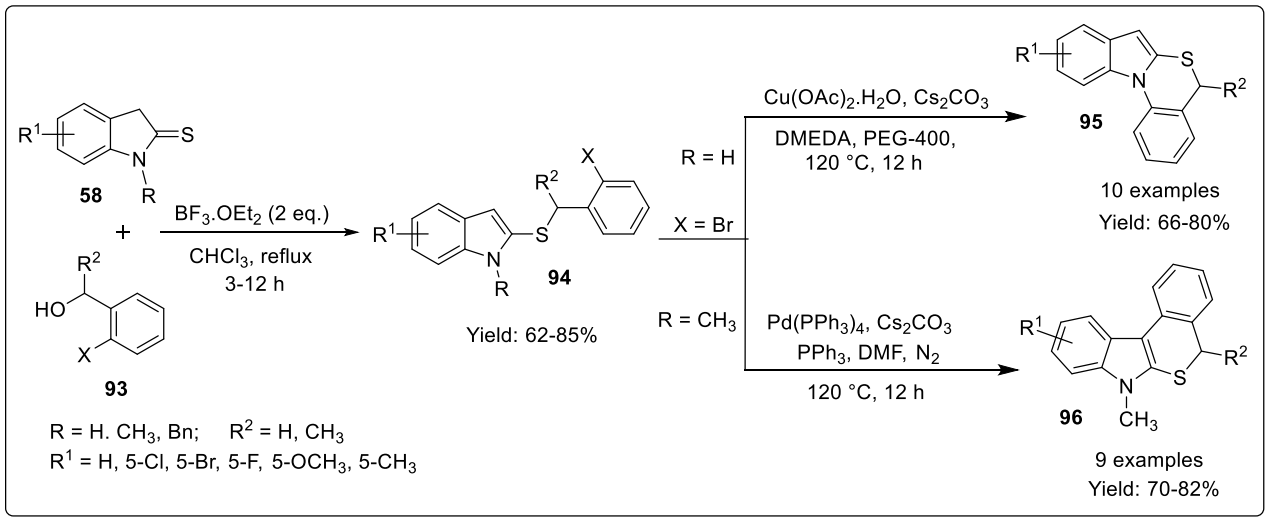
The second chapter of the thesis commences with the classification of different synthetic approaches for the synthesis of oxindole derivatives based on the use of starting materials and type of bond formation. The classical approach for the synthesis of substituted oxindoles involves one step Wolff-Kishner reduction of isatin in the presence of hydrazine hydrate. Hydrazine hydrate is a very powerful reducing agent, which reduces many functional groups such as alkenes, alkynes, carbonyl and nitro groups under mild reaction conditions. On these points here, for the first-time, we developed one-pot tandem reduction of oxo and *N*-ene/-yne substituted isatins using hydrazine hydrate (25% in H_2O) at reflux condition **(Scheme 4.3)**. Fourteen different substrates were taken to generalize the reaction. The reaction conditions tolerated various functionalities such as methyl, chloro, fluoro and bromo. Structures of the synthesized compounds have been confirmed by NMR and mass analysis.



Scheme 4.3: Tandem reduction of oxo- and ene-/yne-substituted isatins by $NH_2NH_2.H_2O$

A gram-scale reaction has been performed to demonstrate the potency of optimized procedure for the scale-up processes. This reaction offers clean conversion of the *N*-(2-alkenyl)/propargylisatins to *N*-alkyl-2-oxindoles in excellent yields (52-89%). This methodology substantially expands the scope of the Wolff-Kishner reduction procedure to prepare substituted 2-oxindoles.

The third chapter of the thesis begins with the significance of transition metal catalyzed C−H bond functionalization reactions for the synthesis of diverse indole annulated heterocyclic molecules. In this chapter, benzo-thiazino[3,2-*a*]indoles, 5,7-dihydro-isothiochromeno[3,4-*b*]indoles and dihydro-thiopyrano[2,3-*b*]indoles have been synthesized using transition metal catalyzed intramolecular cross-coupling and hydroarylation reactions. The chapter is divided into two parts. In **part-A**, copper-catalyzed intramolecular Ullmann type C-N coupling of 2-(2-bromobenzylthio)-1*H*-indoles and palladium-catalysed direct C-H arylation reaction of 2-(2-bromobenzylthio)-1-methyl-1*H* indoles were successfully applied for the construction of benzo-thiazino[3,2-*a*]indoles **(95)** and isothiochromeno[3,4-*b*]indoles **(96),** respectively **(Scheme 4.4)**.

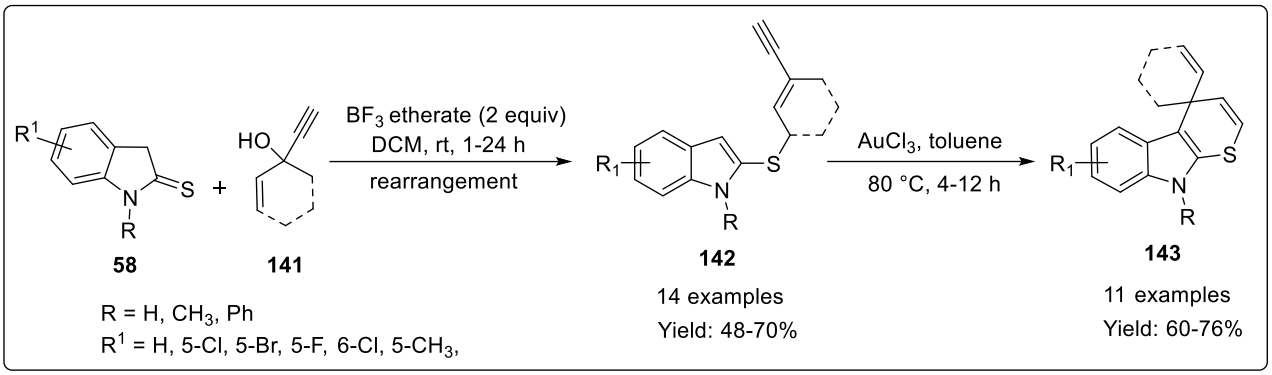


Scheme 4.4: Synthesis of benzo-thiazino[3,2-*a*]indoles (**95**) and isothio-chromeno [3,4-*b*]indoles (**96**) derivatives

The required substrates 2-(2-bromobenzylthio)-1*H*-indoles and 2-(2-bromobenzylthio)-1-methyl-1*H* indoles were prepared by the reaction of substituted indoline-2-thiones and 2-bromobenzyl alcohols in presence of BF_3.etherate in chloroform. The reaction mechanism for the coupling product was expected to proceeds *via* oxidative addition and reductive elimination reaction

pathway. An array of benzo-thiazino[3,2-*a*]indoles and 5,7-dihydro-isothiochromeno[3,4-*b*]indoles have been prepared in good to excellent yields (66-82%). All the synthesized compounds have been confirmed with ^{1}H NMR, ^{13}C NMR and mass analysis. The optimized method efficiently tolerated reactive functionalities such as methyl, methoxy, bromo, fluoro and chloro. The practicality and efficiency of the developed method was validated by gram-scale synthesis of 5*H*-Benzo[4,5][1,3]thiazino[3,2-*a*]indole (**95aa**)

In **part-B**, we have demonstrated regioselective Au(III)-catalyzed synthesis of dihydrothiopyrano[2,3-*b*]indoles *via* rearrangement of the ene-yne side chain of 2-(2-alkenylthio)-indoles followed by intramolecular hydroarylation at the C-3 position of the indole core **(Scheme 4.5)**.



Scheme 4.5: Synthesis of indole-fused dihydrothiopyrans **143** starting from indoline-2-thiones **58** and unsaturated aliphatic alcohols **141**

The required precursor 2-(2-alkenylthio)-indoles were synthesized by the reaction of indoline-2-thione with unsaturated aliphatic alcohols in presence of excess of BF_3.etherate in dichloromethane. The two possible regioisomers **A** and **B** of compound **143a** are shown in **Figure 4.1**. On the basis of 1D NOESY experiments, the correct structure of **143a** was assigned as regioisomer **A**. In addition, dihydrothiopyrano[2,3-*b*]indole was unambiguously confirmed by an X-ray crystallographic data of **143k** (CCDC No. 1057877)

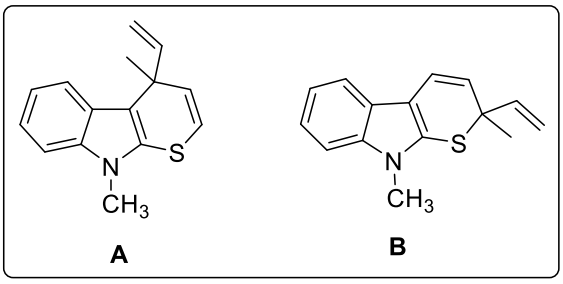


Figure 4.1: Two possible regioisomers of compound **143a**

The reaction shows high generality, functional group tolerance and no specific substituent effects. All dihydrothiopyrano[2,3-*b*]indoles were prepared in good yields (60-76%). Remarkably, *N*-unsubstituted dihydrothiopyrano[2,3-*b*]indoles were achieved directly without any protection and deprotection steps, which reflecting the regioselective nature of the reaction. All the compounds were analyzed by ^{1}H NMR, ^{13}C NMR and mass data.

4.3 Future scope of the research work

In recent years, the major concern in organic synthesis is to access the potent heterocyclic organic structures involving fewer synthetic steps from simple and readily available precursors. In this direction, the use of Lewis acids such as metal triflates and transition metal catalyzed C−H activation, C−C and C−heteroatom bond formation is undoubtedly a valuable tool for the construction of these heterocyclic compounds. As many natural products in addition to pharmacologically active molecules contains fused heterocyclic compounds as their central frameworks, synthesis of these molecules by means of aforementioned hybrid methodologies is an attractive alternative to traditional linear syntheses approaches.

The indole-fused sulfur containing heterocyclic structures have been synthesized while utilizing transition metal catalyzed C−H functionalizations. As the synthesized molecules are the hybrid structures of two potent bioactive molecules such as indole-fused benzothiazine, indole-fused isothiochromene compounds, we can expect to perceive a good bioactivity compared to the parent drug molecules in the developed procedures **(Figure 4.2)**

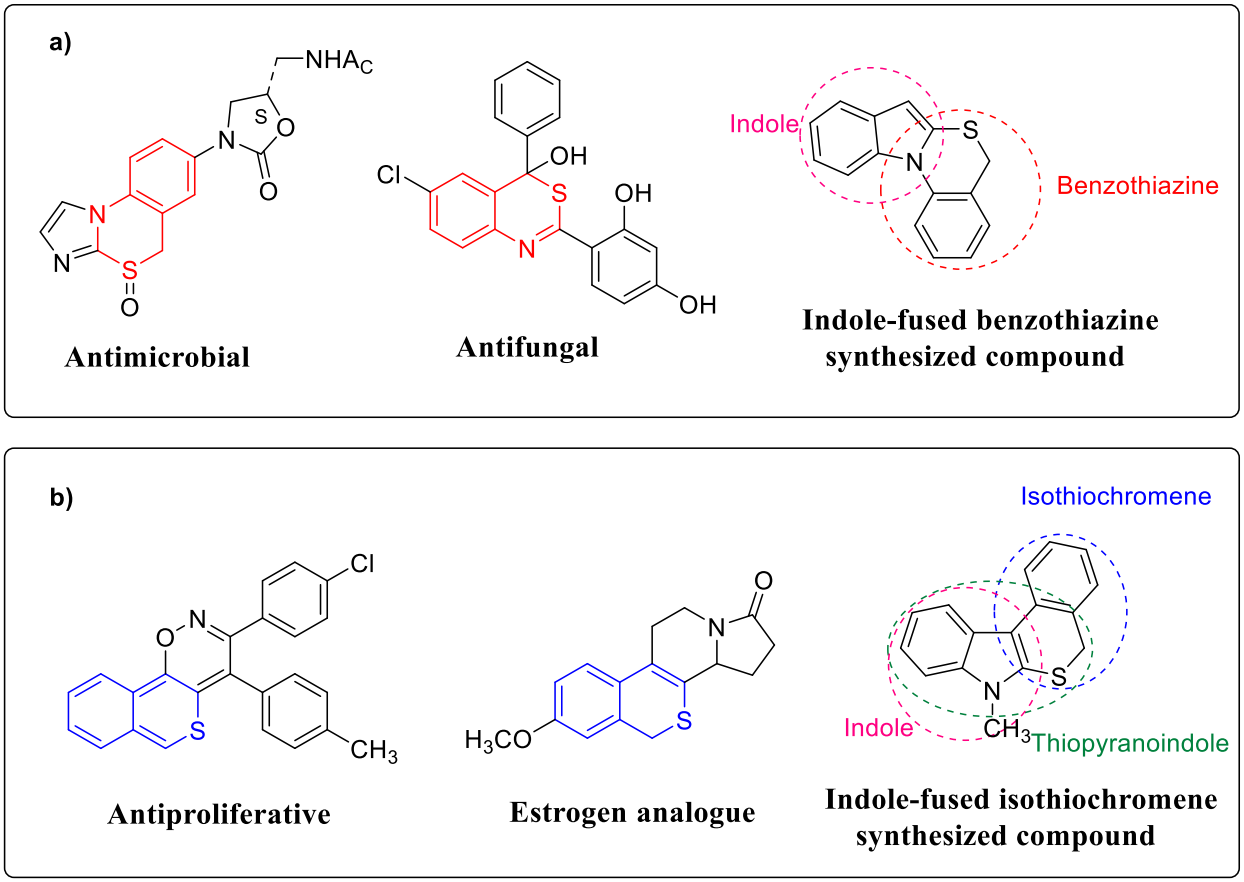


Figure 4.2: Some biologically important compounds containing a) benzothiazine b) isothiochromene motifs

The developed strategies in the thesis can be employed for the synthesis of a diverse range of bioactive heterocyclic molecules for biological screenings. The synthetic methodologies and novel indole-fused heterocyclic compounds provided in the thesis will be a fine and adoptable example for the systematic construction of fused heterocycles for biological activities and for material chemistry.

Appendices

Appendices

List of Publications *[A-1]*

1. **Ganesh M. Shelke**, M Jha, A Kumar, "Synthesis of indole-annulated sulfur heterocycles using copper-catalyzed C-N coupling and palladium-catalysed direct arylation" *Org. Biomol. Chem.* **2016**, *14*, 3450-3458.
2. M Jha, **Ganesh M. Shelke**, TS Cameron, A Kumar, "Access to substituted dihydro thiopyrans[2,3-*b*]indoles *via* sequential rearrangements during S-alkylation and Au-catalyzed hydroarylation on indoline-2-thiones" *J. Org. Chem.* **2015**, *80*, 5272-5278.
3. **Ganesh M. Shelke**, VK Rao, M Jha, TS Cameron, A Kumar, "Microwave assisted catalyst-free synthesis of substituted 1,2,4-triazoles" *Synlett* **2015**, *26*, 404-407.
4. M Jha, **Ganesh M. Shelke**, K Pericherla, A Kumar, "Microwave assisted copper triflate catalyzed rapid hydration of aryl acetylenes" *Tetrahedron Lett.* **2014**, *55*, 4814-4816.
5. M Jha, **Ganesh M. Shelke**, A Kumar, "Catalyst- free one- pot tandem reduction of oxo and ene/yne functionalities by hydrazine: synthesis of substituted oxindoles from isatins" *Eur. J. Org. Chem*. **2014**, *16*, 3334-3336.
6. **Ganesh M. Shelke**, VK Rao, K Pericherla, A Kumar, "An efficient and facile synthesis of vinyl sulfones *via* microwave-assisted copper triflate catalyzed hydro-sulfonylation of alkynes" *Synlett* **2014**, *25*, 2345-2349.
7. **Ganesh M. Shelke**, VK Rao, RK Tiwari, BS Chhikara, K Parang, A Kumar, "Bismuth triflate catalyzed condensation of indoles with acetone" *RSC Adv.* **2013**, *3*, 22346-22352.
8. VK Rao, **Ganesh M. Shelke**, R Tiwari, K Parang, A Kumar, "A simple and efficient synthesis of 2,3-diarylnaphthofurans using sequential hydroarylation/heck oxyarylation" *Org. Lett.* **2013**, *15*, 2190-2193.
9. A Kumar, Saroj Budania, **Ganesh M. Shelke**, "Synthesis of 3-alkenylated indole and bis(indol-3-yl) derivatives catalyzed by sulfonic acid functionalized ionic liquid under ultrasound irradiation" (Synth. Commun. Accepted)
10. P Kaswan, **Ganesh M. Shelke**, VK Rao, A Kumar, "Hydroxy group-facilitated vinylic iodination of ortho-vinylnaphthols using molecular iodine" *Synlett* **2016**, *27*, 2553-2556.

11. K Pericherla, **Ganesh M. Shelke**, YC Kothari, A Kumar, "$Yb(OTf)_3$ catalyzed Mannich reaction of imidazo[1,2-*a*]pyridine and pyrazolo[1,5-*a*]pyrimidines" *Indian J. Chem., Sect B* **2015**, *54B*, 290-300.
12. Noorullah Baig, **Ganesh M. Shelke,** AK Sah, A Kumar, "Selective synthesis of *bis*(indolyl)methanes under solvent-free condition using glucopyranosylamine derived cis-dioxo Mo(VI) complex as an efficient catalyst" *Catal. Lett.* **2016**, 333-337.
13. RP Singh, **Ganesh M. Shelke,** A Kumar, PN Jha, "Biochemistry and genetics of ACC deaminase: a weapon to stress ethylene produced in plants" *Front. Microbiol.* **2015,** 6, 1-14.
14. NK Nandwana, S Dhiman, **Ganesh M. Shelke,** A Kumar, "Copper-catalyzed tandem Ullmann type C–N coupling and dehydrative cyclization: synthesis of imidazo[1,2-c]quinazolines" *Org. Biomol. Chem*. **2016**, 14, 1736-1741.
15. VK Rao, P Kaswan, **Ganesh M. Shelke**, A Ryan, M Jha, A Kumar, "Iodine-mediated microwave assisted synthesis of 2-arylnaphthofurans *via* cyclization of 1-(1′-arylvinyl)-2-naphthols" *Synthesis* **2015**, *47*, 3990-3996.
16. M Kumar Muthyala, S Choudhary, K Pandey, **Ganesh M. Shelke**, M Jha, A Kumar, "Synthesis of ionic liquid- supported diaryliodonium salts" *Eur. J. Org. Chem.* **2014**, *11*, 2365-2370.

List of Oral/poster presented in conferences *[A-2]*

Oral presentations

1. **Ganesh M. Shelke**, M Jha, A Kumar, "Facile access to substituted dihydrothiopyrano[2,3-*b*]indoles *via* sequential rearrangements during S-alkylation and Au-catalyzed hydroarylation on indoline-2-thiones" at 21st Indian Society of Chemists and Biologists (ISCBC), CDRI Lucknow, February 25-28, 2015.

Poster presentations

1. **Ganesh M. Shelke**, A Kumar, M Jha, "Synthesis of indole-annulated sulfur heterocycles using copper-catalysed C–N coupling and palladium-catalysed direct arylation" at Organic Chemistry in Sustainable Development (OCSD), Birla Institute of Technology and Science Pilani, Rajasthan, August 29-30, 2016.
2. **Ganesh M. Shelke**, A Kumar, M Jha, "Synthesis of substituted benzothiazino[3,2-*a*]indoles and dihydroisothiochromeno[3,4-*b*]indoles *via* intramolecular C-N and C-C coupling" at Current Challenges in Drug Discovery Research (CCDDR), Malaviya National Institute of Technology Jaipur, Rajasthan, November 23-25, 2015.
3. **Ganesh M. Shelke**, A Kumar, M Jha, "Synthesis of substituted benzothiazino[3,2-*a*]indoles and dihydroisothiochromeno[3,4-*b*]indoles *via* intramolecular C-N and C-C coupling" at Nascent Developments in Chemical Sciences (NDCS), Birla Institute of Technology and Science Pilani, Rajasthan, October 16-18, 2015.
4. **Ganesh M. Shelke**, M Jha, A Kumar, "Synthesis of substituted oxindoles from isatins by one-pot tandem reduction of oxo- and ene-/yne- functionalities by hydrazine hydrate" at Deenbandhu Chhotu Ram University of Science and Technology, Murthal, March 14, 2014.
5. **Ganesh M. Shelke**, M Jha, A Kumar, "Synthesis of substituted oxindoles from isatins by one-pot tandem reduction of oxo- and ene-/yne- functionalities by hydrazine hydrate" at 20th ISCBC, University of Delhi, New Delhi, March 1-4, 2014.
6. **Ganesh M. Shelke,** VK Rao and A Kumar, "Bismuth triflate catalyzed the condensation of indole with acetone under different reaction conditions" at 19th ISCBC, Mohanlal Sukhadia University, Udaipur, March 2-5, 2013.

Ganesh Mahadeorao Shelke obtained his master degree in Organic Chemistry from Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, India during 2007-09. In June 2010, he cleared the Joint CSIR-UGC NET for Lectureship (LS) by CSIR, New Delhi. In March 2011, he joined Department of Chemistry, BITS Pilani, Pilani Campus under the guidance of Dr. Anil Kumar with the financial assistance from the UGC project. Later, in August 2011 he cleared the Ph.D. entrance exam and joined as a Ph.D. research scholar. During the Ph.D. tenure, he visited Prof. Mukund Jha's lab, Nippising University, Canada with the financial support from the Natural Sciences and Engineering Research Council of Canada (NSERC), Nipissing University and the Canada Foundation for Innovation (CFI) during May 2013 to November 2013. In Prof. Jha's group, he was involved in the synthesis of indole annulated sulfur heterocycles such as substituted dihydro-thiopyrano-indoles, dihydro-isothiochromenoindoles etc. which were synthesized through multi-step processes. In october 2014, he was awarded Senior Research Fellowship (SRF) for two years. He has published sixteen research articles in peer reviewed international journals and presented papers in two national and five international conferences.

His research interest lies in the development of new methods for the synthesis of bioactive indole-fused heterocyclic motifs using C−H activation/functionalizations and the application of metal triflates over the traditional Lewis acids.

Dr. Anil Kumar is Associate Professor of Chemistry at the Birla Institute of Technology and Science, Pilani. He obtained his Ph.D degree from Department of Chemistry, University of Delhi, Delhi, India under the supervision of Prof. S. M. S. Chauhan in 2004. Dr. Anil Kumar worked on development of heterogeneous catalyst for organic synthesis with emphasis on green chemistry for his doctoral studies. During May 2004 to April 2006, he worked in Prof. Keykavous Parang's group as postdoctoral fellow at Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, USA. He joined Department of Chemistry, Birla Institute of Technology and Science, Pilani, India as Assistant Professor in 2006 and was promoted to Associate Professor in February 2013. He served as Head of Department of Chemistry from September 2014 - August 2016. He has visited University of Rhode Island, Kingston, USA and Chapman University as visiting scientist and Acadia University, Wolfville, Canada as Harrison McCain visiting Professor.

Dr. Kumar is recipient of Harrison McCain Foundation award from Acadia University, Canada for 2012, ISCB Young Scientist award in Chemical Sciences from Indian Society of Chemists and Biologists, Lucknow for 2013 and Dr. Aravind Kumar memorial award from Indian Council of Chemist for 2014. He has 16 year of research experience and 10 year of teaching experience. He has published over 135 research papers in international journals of repute and contributed two book chapters and one US patent. He has participated in more than 75 national and international symposia/conferences and delivered about 30 invited lectures. He has guided four Ph.D students and currently supervising 10 Ph.D students. He is editor for Canadian Chemical Transactions and member of editorial advisory board for The Open Catalysis Journal. He has completed three research projects as Principle Investigator and one as Co-PI sponsored by DST, CSIR and UGC. Currently, he has one research project from CSIR and one industry project from Ranbaxy in collaboration with Prof. Dalip Kumar. He is member of American Chemical Society and life member of Chemical Research Society of India, Bangalore; Indian Society of Chemists and Biologists, Lucknow and Indian Council of Chemists, Agra.

His research interest lies in transition metal catalyzed C−H activation, green chemistry, ionic liquids and medicinal chemistry.

Dr. Mukund Jha is a Full Professor of Organic Chemistry in the Department of Biology and Chemistry at Nipissing University, Canada. He received his B.Sc (Honours) and M.Sc. (Organic Chemistry) degrees from University of Delhi, India, in the years 1998 and 2000 respectively. Subsequently, he obtained his Ph.D. degree from the Department of Chemistry, University of Saskatchewan, SK, Canada in 2006 under the tutelage of Prof M. S. C. Pedras studying plant pathogen interactions. In particular he was interested in developing safer plant protecting agents using the tools of organic chemistry during his doctoral research. From 2006-2008 he pursued his Postdoctoral research in the Department of Chemistry at Queen's University, Kingston, ON, Canada with Prof Derek Pratt, where he was involved in the exploration of mechanistic studies of biologically relevant peroxyl radical reactions, synthesis of novel antioxidants and heterologous expression enzymes, their purification and function studies. In 2008 he assumed a position of Assistant Professor of Organic Chemistry in the Department of Biology and Chemistry at Nipissing University, ON, Canada. He was promoted to Associate Professor in 2012 and recently to the rank of Full Professor at Nipissing University in 2016.

Dr. Jha has been a recipient of Ichikizaki Fund for Young Chemist, awarded by the Canadian Society of Chemistry, in the years 2012 and 2013. He was awarded Research Achievement Award by Nipissing University in 2012. Dr Jha has over 16 years of research and over 8 years of teaching experience. Over the years, Dr Jha has published more than 30 peer reviewed research articles in journals of high standings and contributed over 30 presentations in various international conferences. He has also delivered 14 invited lectures at various national and international forums. Dr. Jha has co-supervised 3 Masters level students and supervised over 16 BSc Honours thesis students. He has also supervised a postdoctoral fellow and 3 research interns and technicians. Financial support for research activities in Dr. Jha's laboratory mainly comes from NSERC, CFI, Industry Canada, and Industrial collaborators. Presently, Dr Jha is also serving as a scientific advisor to two regional companies of Ontario, Canada namely, Life4ce Bio-Botinical and Greenfoot.

Dr Jha's current interests include organic synthesis, methodology development, heterocyclic synthesis, metal-catalyzed reactions and medicinal mushrooms.