Development of novel metal-free multicomponent and oxidative reaction methodologies for the construction of biologically relevant molecules

Thesis Submitted to AcSIR for the Award of the Degree of

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in Chemical Sciences

By

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Dedicated to my beloved

Grandma

DECLARATION

I hereby declare that the Ph.D. thesis entitled "**Development of novel metal-free multicomponent and oxidative reaction methodologies for the construction of biologically relevant molecules"** is an independent work carried out by me under the supervision of **Dr. Ravi Shankar Lankalapalli** at the Organic Chemistry Section, CSTD, CSIR-NIIST, Thiruvananthapuram and it has not been submitted anywhere else for any other degree or diploma.

In keeping the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

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CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled "**Development of novel metal-free multicomponent and oxidative reaction methodologies for the construction of biologically relevant molecules**" submitted by **Mr. CH Chandrasekhar** to Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of Doctor of Philosophy in Chemical Sciences, embodies original research work under my supervision/guidance. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table, etc. used in the thesis from other sources have been duly cited and acknowledged.

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Dr. Ravi Shankar Lankalapalli (Thesis Supervisor)

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CH Chandrasekhar

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ABBREVIATIONS

Å	:	Angstrom
Ac_2O	:	Acetic anhydride
AcOH	:	Acetic acid
Ac	:	Acety
aq	:	aqueous
All	:	Allyl
app t	:	apparent triplet
app d	:	apparent doublet
Ar	:	Aryl
$AlCl_3$	:	Aluminium chloride
AIBN	:	2,2′-Azobis(2-methylpropionitrile)
AcOOH	:	Peracetic acid
$BF_3.OEt_2$	:	Boron trifluoride diethyl etherate
Bn	:	Benzyl
OBn	:	Benzyloxy
OBz	:	Benzoyloxy
Boc	:	*t*-Butoxycarbonyl
BuOH	:	Butanol
^{13}C NMR	:	Carbon-13 nuclear magnetic resonance
calcd	:	Calculated
cat	:	Catalytic
CAN	:	Ceric Ammonium Nitrate

CR	:	Component reaction
$CDCl_3$	:	Deuterated chloroform
CH_2Cl_2	:	Dichloromethane
CH_3CN	:	Acetonitrile
$Cu(OTf)_2$	:	Copper(II) triflate
CuCl	:	Copper(I) chloride
CF_3	:	Trifluoromethyl
COSY	:	Correlation spectroscopy
Cs_2CO_3	:	Cesium carbonate
Conc.	:	Concentrated
CDC	:	Cross Dehydrogenative Coupling
CCDC	:	The Cambridge Crystallographic Data Centre
CT	:	Charge transfer
d	:	doublet
dd	:	doublet of doublets
dt	:	doublet of triplet
ddd	:	doublet of doublet of doublet
DFT	:	Density Functional Theory
DBU	:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	:	Dichloroethane
DCM	:	Dichloromethane
DIM	:	Diindolylmethane
DIPM	:	Diindolyl phenyl methane
DIBM	:	Diindolyl biaryl methane
DDQ	:	2,3-Dichloro 5,6-dicyano 1,4-benzoquinone

DEPT-135°	:	Distortionless Enhancement of Polarization Transfer using a 135 degree decoupler pulse
DIPEA	:	N,N-Diisopropylethylamine
DMAP	:	4-(Dimethylamino) pyridine
DMF	:	Dimethylformamide
DMP	:	Dess-Martin periodinane
DMSO	:	Dimethyl sulfoxide
D_2O	:	Deuterium oxide
DOS	:	Diversity Oriented Synthesis
DHP	:	Dihydropyridine
dppp	:	1,3-Bis(diphenylphosphino)propane
Equiv	:	equivalent
EWG	:	electron withdrawing group
EDG	:	electron donating group
ESI	:	Electrospray ionization
Et_3N	:	Triethylamine
Et_3SiH	:	Triethylsilane
Et_2O	:	Diethyl ether
EtOAc	:	Ethyl acetate
EtOH	:	Ethanol
FDA	:	Food and drug administration
FG	:	Functional group
^1H NMR	:	Proton nuclear magnetic resonance
HCl	:	Hydrochloric acid
HCOOH	:	Formic acid

HMBC	:	Heteronuclear multiple bond correlation spectroscopy
HSQC	:	Heteronuclear single quantum correlation spectroscopy
HRMS	:	High resolution mass spectrometry
HIR	:	Hypervalent Iodine Reagent
Hg	:	Mercury
HMDS	:	Hexamethyldisilazane
HFIP	:	1,1,1,3,3,3-hexafluoro-2-propanol
$HNTf_2$	:	Trifluoromethanesulfonimide
H_5IO_6	:	Periodic acid
h	:	Hour
Hz	:	Hertz
IC_{50}	:	Inhibition concentration 50%
$InCl_3$	:	Indium(III) chloride
IBX	:	2-Iodoxybenzoic acid
IUPAC	:	International Union for Pure and Applied Chemistry
IDC	:	Intermolecular dehydrogenative coupling
I_2	:	Molecular iodine
IMCR	:	Isocyanide based Multicomponent Reaction
I_L	:	Left side indole
I_R	:	Right side indole
K_2CO_3:	:	Potassium carbonate
KO*t*Bu	:	Potassium tert-butoxide
$LiNTf_2$	:	Bis(trifluoromethane)sulfonimide lithium salt
LD_{50}	:	Lethal Dose 50
m	:	multiplet

m-CPBA	:	*meta*-Chloroperoxybenzoic acid
MnO_2	:	Manganese dioxide
MCR	:	Multicomponent reaction
MS	:	Molecular sieves
MW	:	Microwave
MsOH	:	Methane sulfonic acid
Me_3Si	:	Trimethyl silyly
mM	:	Millimolar
μL	:	Microliter
MeOH	:	Methanol
Me	:	Methyl
MTBE	:	Methyl *tert*-butyl ether
$Mn(OAc)_3$	:	Manganese(III) acetate
m/*z*	:	Mass to charge ratio
mmol	:	millimole
$NaBH_4$	:	Sodium borohydride
NaCl	:	Sodium chloride
n-Bu_4NI	:	Tetrabutylammonium iodide
$NaHCO_3$	:	Sodium bicarbonate
Na_2SO_4	:	Sodium sulfate
$Na_2S_2O_3$	:	Sodium thiosulfate
NBS	:	N-Bromosuccinimide
NH_3	:	Ammonia
n.d.	:	not detected
$Ni(COD)_2$	:	Bis(1,5-cyclooctadiene)nickel(0)

NIS	:	*N*-Iodosuccinimide
NMR	:	Nuclear magnetic resonance
OTs	:	Tosyloxy
OTBS	:	Tert-butyl silyloxy
OMe	:	Methoxy
$OSiMe_3$	:	Trimethyl silyloxy
ppm	:	Parts per million
Ph	:	Phenyl
PPh_3	:	Triphenyl phosphine
PAH	:	Polyaromatic hydrocarbon
Ph_2CuLi	:	Lithium diphenylcuprate
Ph_2IF	:	Diphenyliodonium fluoride
PIDA	:	Phenyliodine diacetate
PIFA	:	Phenyliodine bis(trifluoroacetate)
$PhI(OPiv)_2$	:	Bis(*tert*-butylcarbonyloxy)iodobenzene
PhI(OH)OTs	:	Hydroxy(tosyloxy)iodobenzene
$PhICl_2$:	:	Iodobenzene dichloride
PMP	:	*para*-methoxyphenyl
PMB	:	*para*-methoxybenzyl
$Pd[(o\text{-tol})_3P]_2$	:	Bis[tris(2-methylphenyl)phosphine]palladium
PPh_3AuNTf_2	:	[Bis(trifluoromethanesulfonyl)imidate](triphenylphosphine)gold(I)
p-TsOH	:	*p*-Toluenesulfonic acid
PCl_5	:	Phosphorous pentachloride
Quant	:	quantitative
q	:	quartet

rt	:	Room temperature
R_f	:	Retention factors
$[Rh(coe)_2Cl]_2$	:	Chlorobis(cyclooctene)rhodium(I),dimer
$[Rh(COD)Cl]_2$	:	Chloro(1,5-cyclooctadiene)rhodium(I) dimer
s	:	singlet
SET	:	Single Electron Transfer
$SnCl_2$	:	Tin(II) chloride
SMD	:	Solvent Model based on Density
SF_6	:	Sufur hexafluoride
t	:	triplet
TBDMS	:	tert-Butyldimethylsilane
TBDMSCl	:	tert-Butyldimethylsilane chloride
TMSOTf	:	Trimethylsilyl trifluoromethane sulfonate
TFA	:	Trifluoroacetic acid
TCA	:	Trichloroacetic acid
TBHP	:	Tert-butyl hydroperoxide
TEMPO	:	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TfOH	:	Triflic acid
THF	:	Tetrahydrofuran
TLC	:	Thin layer chromatography
TBAF	:	Tetrabutylammonium fluoride
t-Bu	:	Tert-butyl
TFE	:	2,2,2-Trifluoroethanol
TMS-EBX	:	1-[(Trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one
TIPS-EBX	:	1-[(Triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one

td	:	Triplet of doublet
TS	:	Transition state
W	:	Watts
XRD	:	X-Ray Diffraction
XeF_4	:	Xenon tetrafluoride
$Zn(NTf_2)_2$	:	Zinc di[bis(trifluoromethylsulfonyl)imide]

Chapter-1: Introduction

1.1. A brief history of multicomponent reactions (MCRs)

Organic synthesis is considered as a cornerstone of molecular science. Prof. K. C. Nicolaou from Rice University explained the importance of organic synthesis in his several research articles. In one of his recent article, he stated "*One of the most vital and valued sub-disciplines of chemistry is the science of organic synthesis, without which much of science and industry would have remained paralyzed and sterile. This is the discipline that provides the myriad molecules from which emerge our most precious new material goods and gadgets, whether they are instruments to cure disease and promote wellness or tools that help us build machines, communicate, travel, and entertain ourselves, not to mention advance education and science, and achieve sustainability*".[1] Advent of sophisticated analytical and separation techniques necessitates the need for ideal synthesis.[2] Ideal synthesis calls for the target molecule to be assembled from readily available starting materials in a simple, safe, economical, and efficient operation (Figure 1.1A).[3] In this context, multicomponent reactions (MCRs) satisfy majority of the criteria of ideal synthesis. MCRs are defined as reactions with three and more starting materials where majority of the atoms of the starting materials are incorporated into the product.[4] Unlike multi-step total synthesis, MCRs generate the products in time and resource economical manner along with more complexity and diversity in a single-pot operation (Figure 1.1B).[5] In MCRs, all the starting materials do not react simultaneously in one-step to deliver the product rather they react sequentially in several elementary steps (domino process) in a programmed manner.

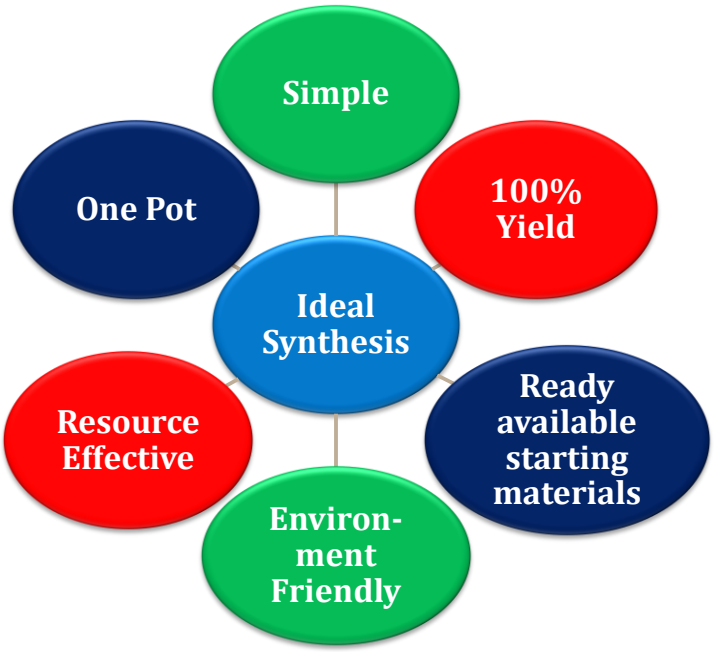


Figure 1.1A. Criteria for ideal synthesis

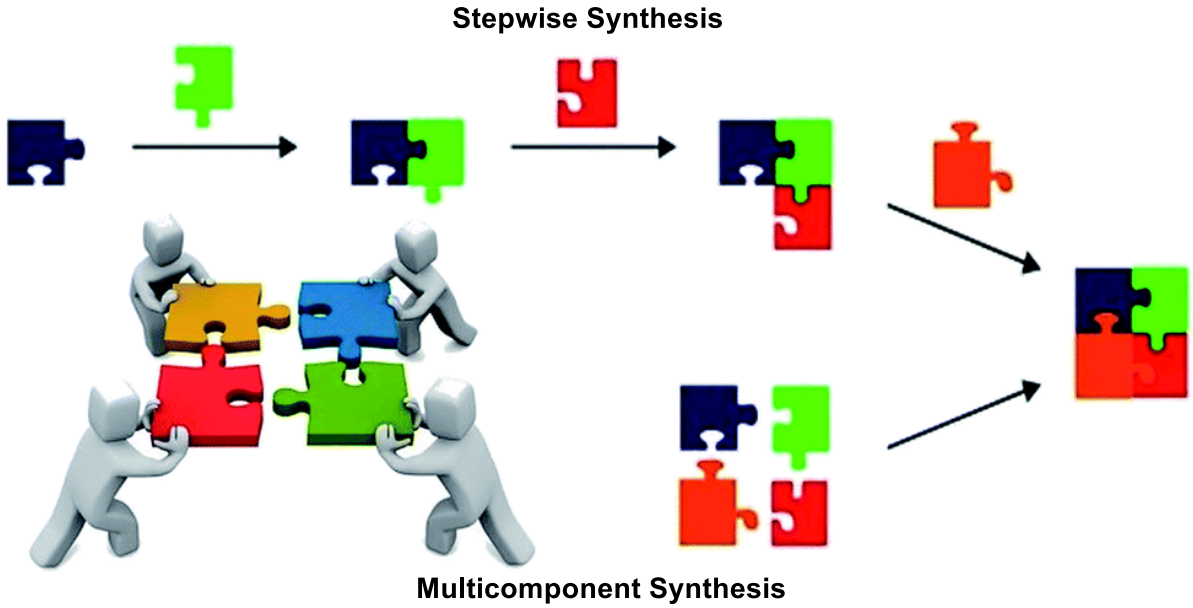


Figure 1.1B. Stepwise linear synthesis *vs* multicomponent synthesis

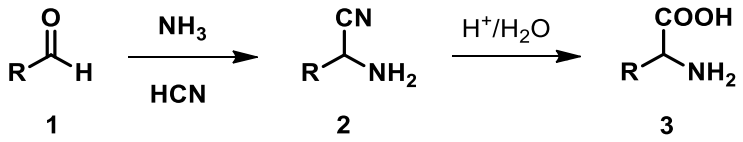
MCRs have enormous advantages over conventional two-component reactions (2CRs) and multi-step total synthesis in contemporary organic synthesis.

Advantages of MCRs:

- Multiple new bond formations in one-pot operation

- No intermediate isolation or change in reaction conditions
- Time, atom, economic and energy efficient
- Exhibits broad substrate scope
- Generates products with more complexity and diversity
- Highly sustainable and convergent

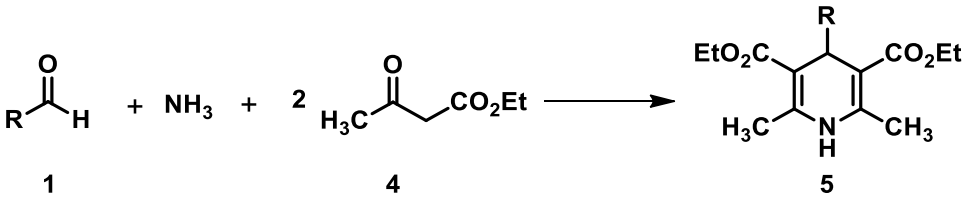
Most of the basic/classical MCRs are named reactions, and the chemistry of some of these MCRs are briefly explained in this chapter. Strecker reported α-amino acid **3** synthesis in 1850 by condensation of aldehyde **1**, ammonia and hydrogen cyanide.[6] The reaction proceeds via α-cyano amine intermediate **2** which upon hydrolysis generates α-amino acid **3** (Scheme 1.1i). This reaction is considered as the first ever reported MCR. Interestingly, twelve years ago, Gerhard and Laurent observed the formation of cyanohydrin imine as a poorly soluble compound from bitter almond oil and ammonia.[7]



1 2 3

Scheme 1.1i. Strecker synthesis of α-amino acid

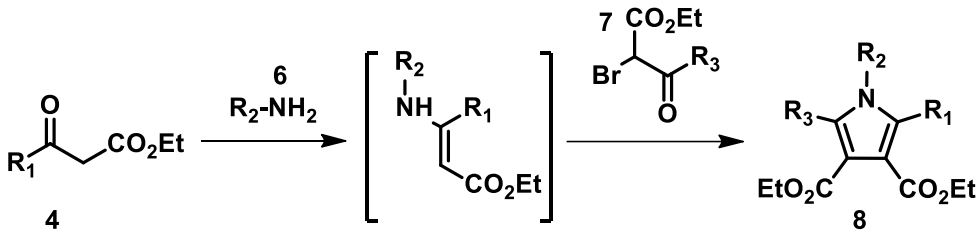
In 1882, significant progress in MCRs was made by Hantzsch involving the synthesis of dihydropyridine as a four-component reaction (4CR).[8] Hantzsch synthesized 1,4-dihydropyridine (1,4-DHP) **5** from aldehyde **1**, ammonia and two equivalents of β-ketoester **4** (Scheme 1.1ii).



1 4 5

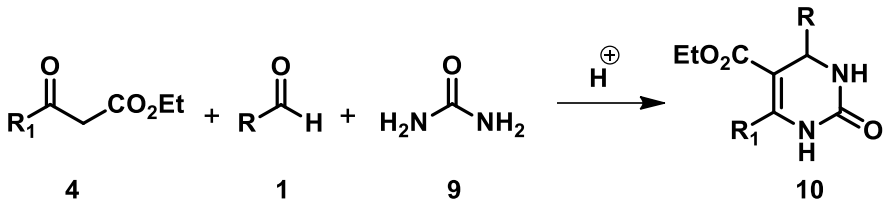
Scheme 1.1ii. Hantzsch-4CR for the synthesis of 1,4-dihydropyridine

Hantzsch further contributed to MCRs by synthesizing fully substituted pyrroles in 1890.[9] This 3CR involves the synthesis of pyrrole **8** by the reaction of β-ketoester **4** with amine **6** and α-halo β-ketoester **7** (Scheme 1.1iii).



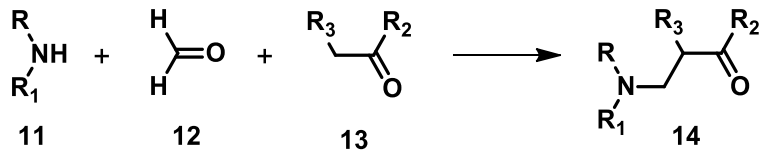
Scheme 1.1iii. Hantzsch-3CR for the synthesis of pyrrole

Later in 1891, Biginelli replaced the amine component in Hantzsch 1,4-DHP synthesis with urea to access dihydropyrimidine.[10] It is an acid catalyzed cyclocondensation of β-ketoester **4**, aldehyde **1** and urea **9** to synthesize dihydropyrimidine **10** (Scheme 1.1iv).



Scheme 1.1iv. Biginelli-3CR for the synthesis of dihydropyrimidine

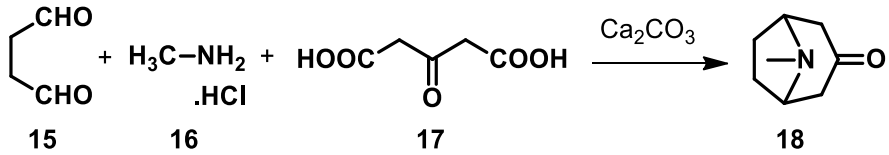
One of the best-known MCR is Mannich's 3CR in 1912.[11] This is a condensation reaction between an amine **11** and formaldehyde **12** to generate an imine intermediate which further reacts with an active methylene compound **13** to afford β-aminocarbonyl compound **14** (Scheme 1.1v).



Scheme 1.1v. Mannich-3CR for the synthesis of β-aminocarbonyl compound

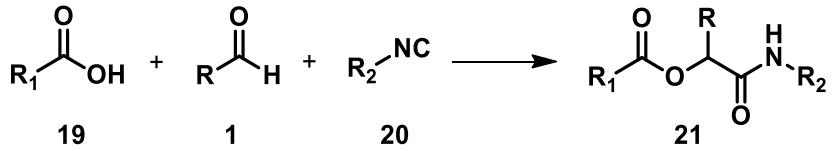
In 1917, the first application of MCR was shown by Robert Robinson for the synthesis of tropinone alkaloid by a double Mannich reaction.[12] Robinson's synthesis involves the

reaction of succinaldehyde **15** with methylamine hydrochloride **16** and acetone dicarboxylic acid **17** under physiological conditions to generate tropinone **18** (Scheme 1.1vi).



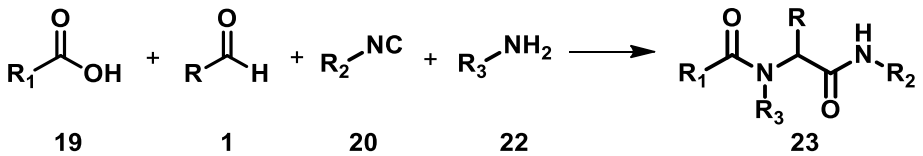
Scheme 1.1vi. Robinson's synthesis of tropinone by a double Mannich-3CR

It is noteworthy that introduction of isocyanide component has brought revolution in MCRs. The isocyanide based MCRs (IMCRs) have great potential compared to other classes of MCRs due to their excellent bond forming capacity and functional group tolerance.[13] Isocyanide possesses exceptional reactivity and a unique property involving reaction with both nucleophiles and electrophiles at the same carbon atom.[13a] The first IMCR was reported by Mario Passerini in 1921 for the synthesis of α-acyloxycarboxamide **21** from aldehyde **1**, carboxylic acid **19** and isocyanide **20** in a three-component approach (Scheme 1.1vii).[14]



Scheme 1.1vii. Passerini-3CR for the synthesis of α-acyloxycarboxamide

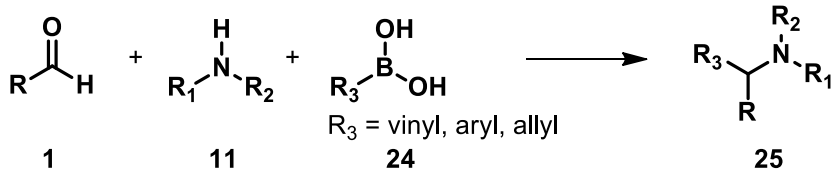
MCRs took a major leap in 1959 with the invention of Ugi-4CR.[13a, 15] Prof. I. Ugi developed a 4CR by introducing an additional amine component **22** in Passerini 3CR components viz. aldehyde **1**, carboxylic acid **19** and isocyanide **20** to synthesize bis-amide (α-aminoacyl amide) derivative **23** (Scheme 1.1viii).



Scheme 1.1viii. Ugi-4CR for the synthesis of bis-amides

Ugi-4CR is the most versatile and most famous MCR in multicomponent history.

In 1993, Nicos A. Petasis reported a three component coupling reaction which includes aldehyde **1**, amine **11** and boronic acid **24** to synthesize allyl, vinyl, aryl and alkynyl amines **25** (Scheme 1.1ix).[16] The Petasis reaction is considered as a variation of Mannich reaction.



Scheme 1.1ix. Petasis-3CR for the synthesis of various amines

1.1.1. Applications of MCRs

The easily automated one-pot MCRs have found applications in various fields. Especially, the isocyanide based MCRs (IMCRs) were well explored and being employed in drug discovery, natural products synthesis, diversity-oriented synthesis (DOS) and material applications.[15a-c]

1.1.1A. MCRs in drug discovery

In the post-genomic era, medicinal chemistry added combinatorial synthesis and high-speed parallel synthesis in lead discovery and optimization in order to meet the vast need for diverse library of compounds by pharmaceutical industries.[17] In this context, MCRs are considered as a powerful technology for the convergent synthesis of a diverse library of small molecule drugs. Utilizing MCR technology several protease inhibitors (e.g., serine, aspartyl, metallo and cysteine proteases), kinase inhibitors, phosphatase inhibitors, and G-protein coupled receptor ligands were synthesized.[18] Some of the representative drugs synthesized by using MCRs are listed in the figure 1.1C.

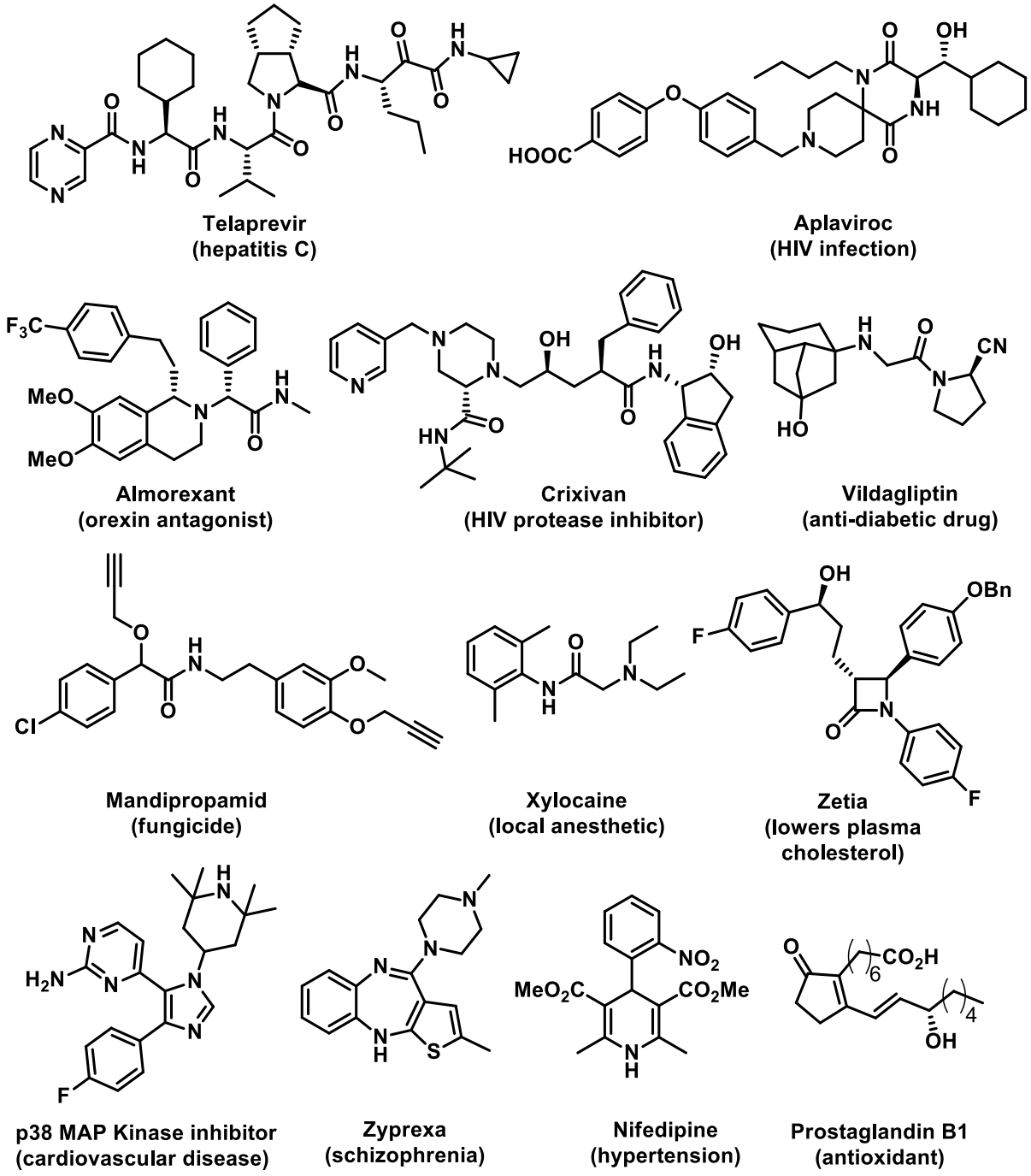


Figure 1.1C. Examples of MCR derived marketed drugs

1.1.1B. MCRs in synthesis of natural products

Initially, Robinson's synthesis of tropinone alkaloid by a double Mannich reaction (Scheme 1.1.vi) laid the foundation for natural product synthesis using MCRs. Since then MCRs were underexploited in natural products synthesis for several decades, but recently MCRs experienced renaissance by the advent of combinatorial chemistry.[19] Several

complex natural products were synthesized by using MCRs as a key reaction strategy, and some of them are listed in the figure 1.1D.

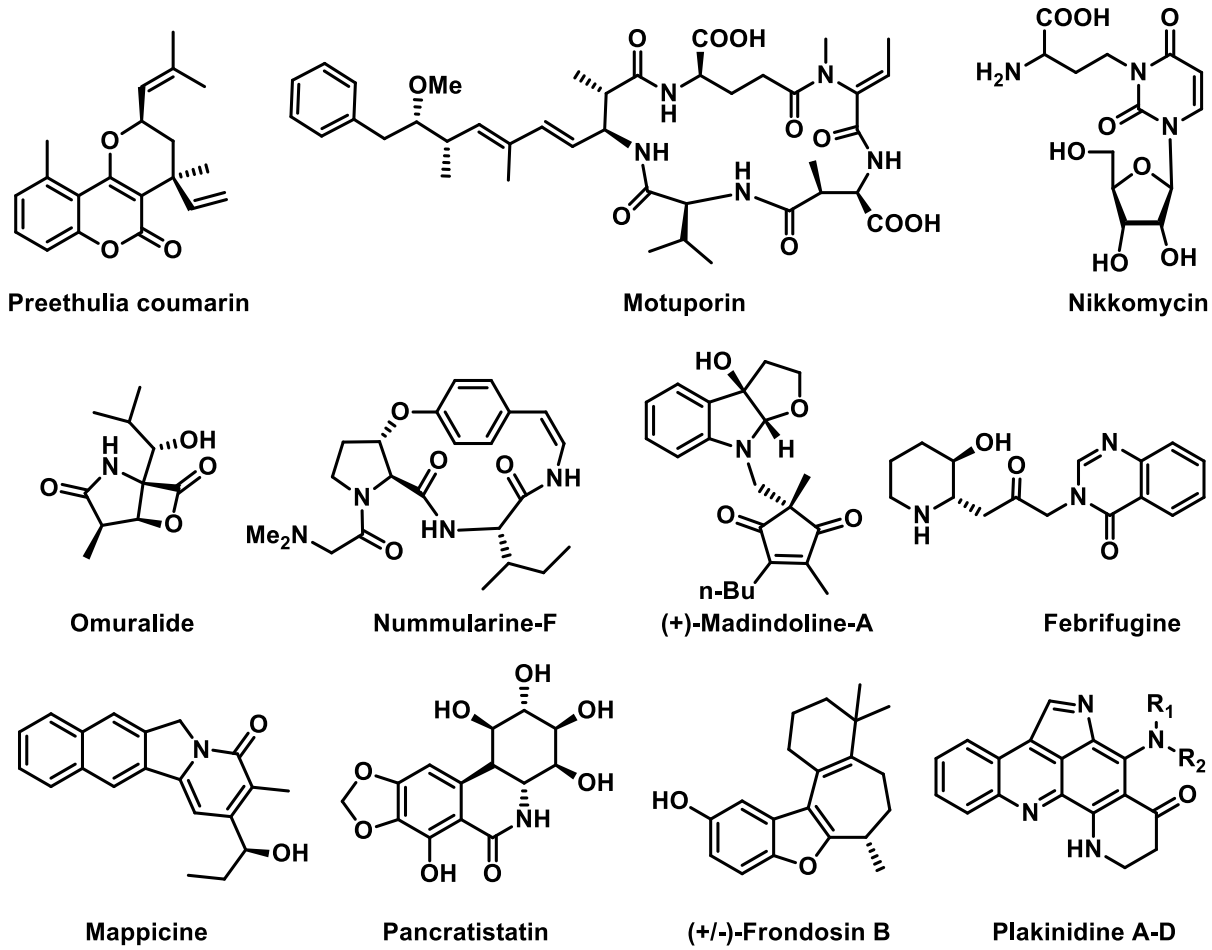
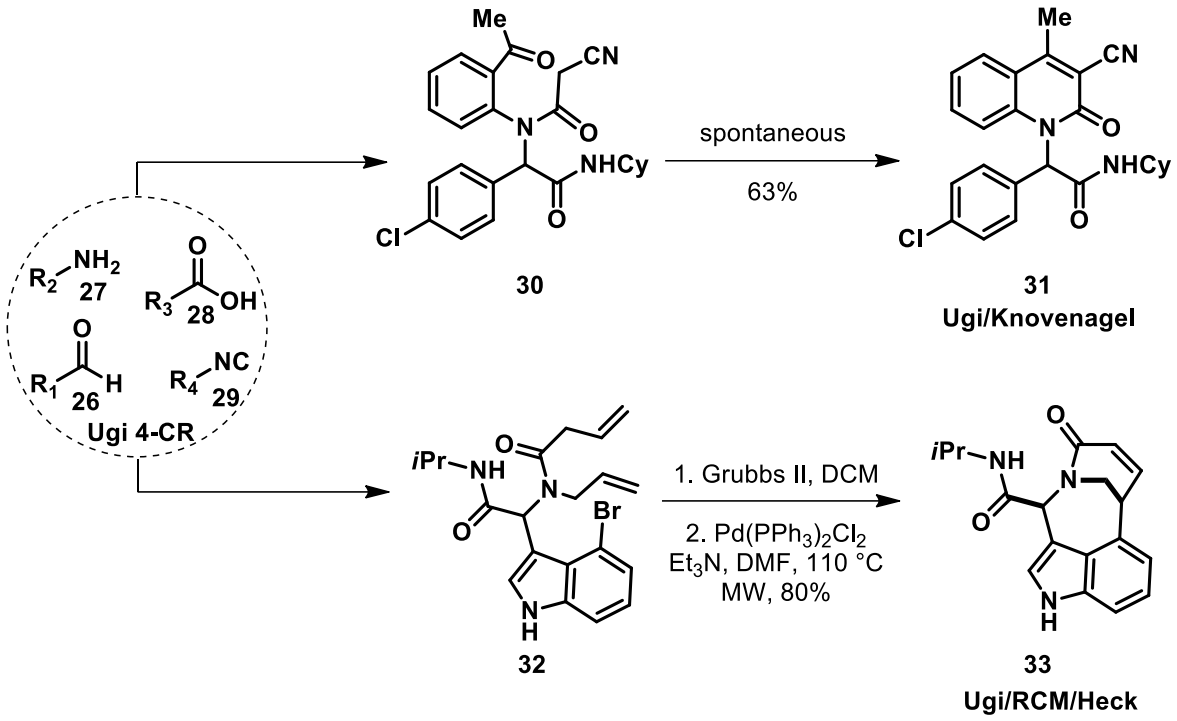


Figure 1.1D. Targeted natural products using MCRs

1.1.1C. MCRs in synthesis of diverse heterocycles

Heterocycle sub-unit represents the vast majority of natural products and drug-like molecules. MCR is the best technology for the collection of structurally and stereochemically diverse heterocycles by diversity-oriented synthesis (DOS).[20] The best way to generate functionalized heterocyclic scaffolds is to perform the post-chemical transformations on MCR products. In this context, Ugi-4CR products were well utilized in several post-functionalization reactions to access diverse heterocyclic scaffolds. For

instance, post-functionalization of some Ugi products such as **30** and **32** leading to the corresponding heterocycles **31** and **33** were highlighted in scheme 1.1x



Scheme 1.1x. Post-functionalization of Ugi adducts leading to heterocycles

1.1.1D. MCRs in synthesis of functional chromophores

Chromophores are molecules endowed with π-electron systems with wide applications including organic light-emitting diodes (OLEDs), dye-sensitized solar cells (DSSCs) and organic photovoltaics (OPVs).[21a] MCRs were well explored in the synthesis of several chromophoric materials either by "scaffold approach" in which one of the starting components contain a chromophore or by the "chromophore approach" where MCR generates chromophore from non-chromophoric reactants.[21b] Some of the chromophores that were synthesized by using MCRs are listed in figure 1.1E.

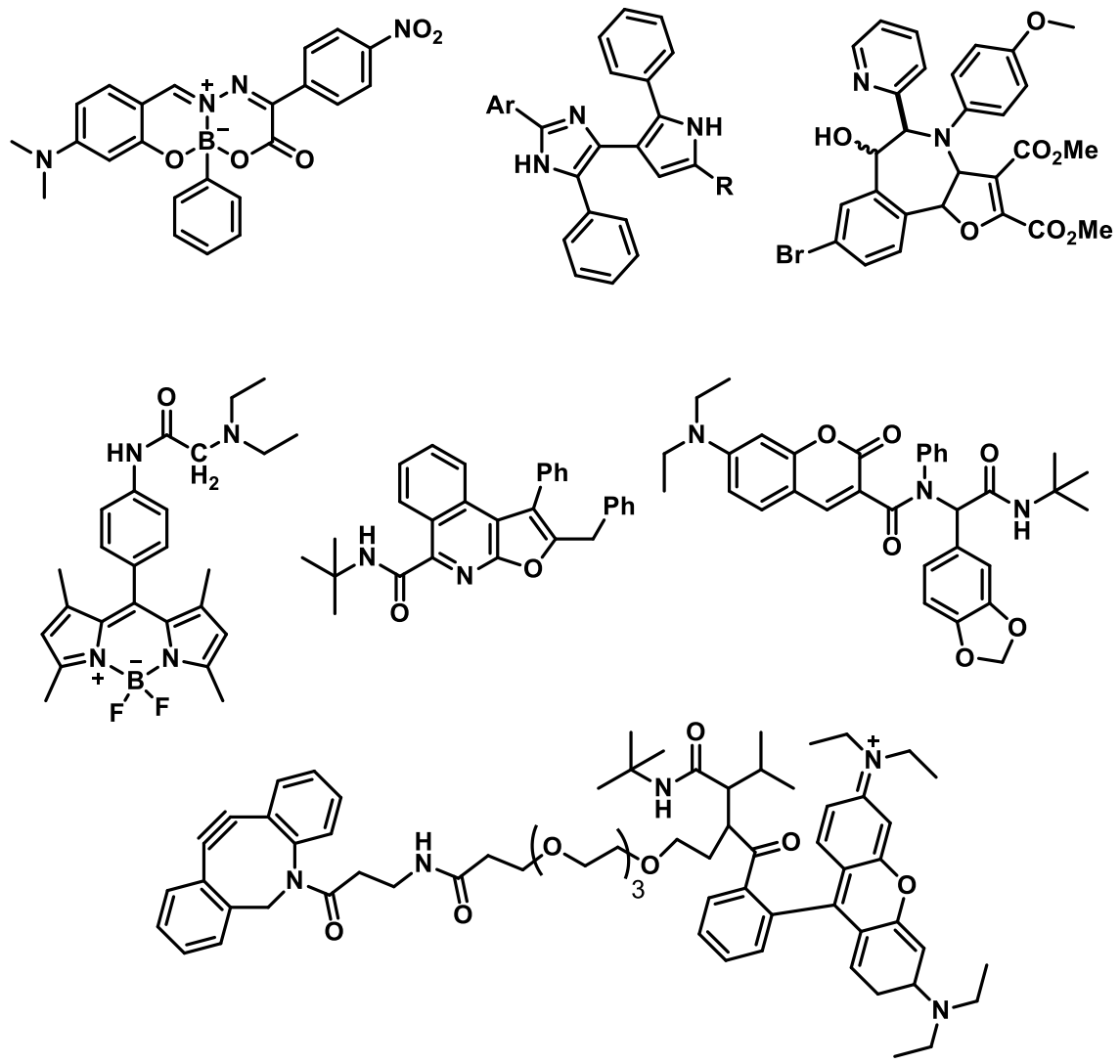
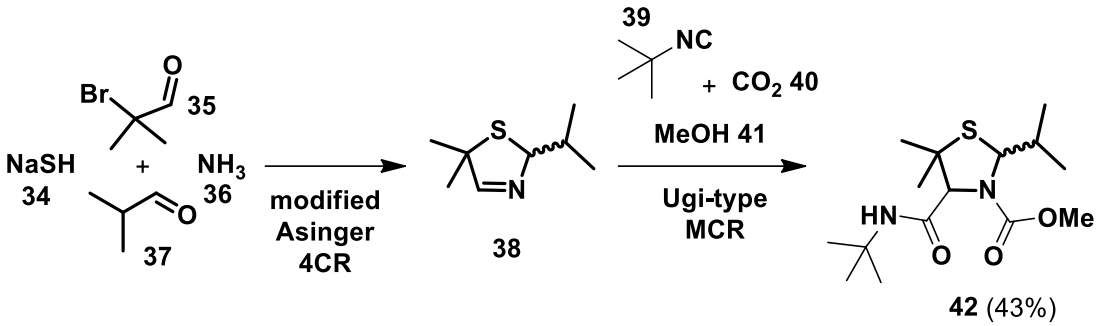


Figure 1.1E. Examples of MCR derived fluorophores

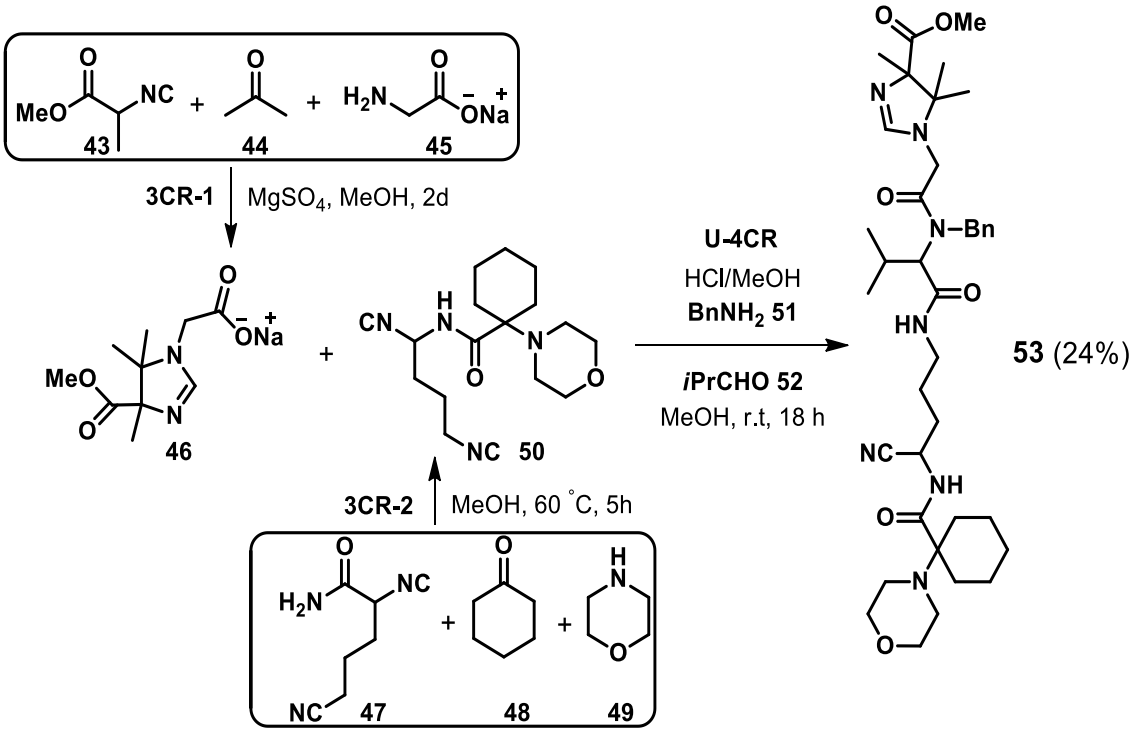
1.1.2. State-of-the-art of MCRs

In order to enhance the scope and also to develop novel MCRs, transition metal catalysts were recently introduced. Prof. Ugi and Prof. Domling first coined the term 'union of MCRs' which means that the combination of two or more MCRs in a single vessel to generate the product with increased complexity and diversity.[22] In this context, Ugi et al. first developed a seven-component reaction (7CR) by uniting modified Asinger-4CR and Ugi type-3CR (Scheme 1.1xi).[23] In this 7CR, NaSH **34**, a α-halo aldehyde **35**, NH_3 **36**, another aldehyde **37**, an isocyanide **39**, CO_2 **40**, and a primary alcohol **41** (solvent) are combined to afford a complex thiazolidines **42** in 43% yield.



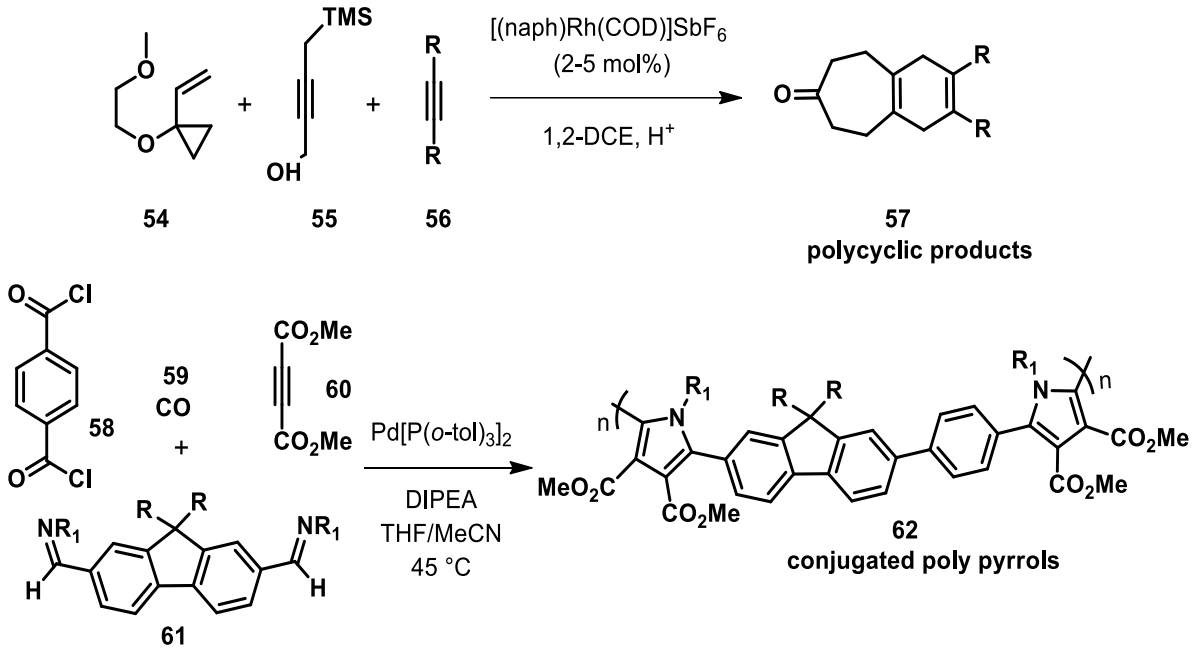
Scheme 1.1xi. Ugi's seven component reaction (7CR)

Recently, Orru et al. reported an eight-component reaction (8CR) by combining three MCRs. In this reaction, the first set of three components viz. **43**, **44** and **45** (3CR-1) generates a carboxylate intermediate **46**, whereas the second set of three components viz. **47**, **48** and **49** react to form an isocyanide intermediate **50**. In the final step, addition of an amine **51** and aldehyde **52** into the same reaction vessel containing intermediates **46** and **50** led to the formation of a Ugi adduct **53** in 24% yield in a one-pot operation. (Scheme 1.1xii).[24]



Scheme 1.1xii. Orru's eight component reaction (8CR)

On the other hand, transition metal catalyzed reactions can offer the desired products in more efficient and versatile manner. Recently, transition metals are being employed in post-functionalization of MCRs and also in the development of new MCRs for the synthesis of diverse scaffolds.[25] Some of the recent and most significant transition metal catalyzed MCRs are presented in scheme 1.1xiii.[26a-b]



Scheme 1.1xiii. Rh and Pd catalyzed MCRs

1.2. A brief introduction to hypervalent iodine reagents (HIRs)

The term 'hypervalent' was first introduced by Jeremy Musher in 1969.[27] According to Musher hypervalent molecules are those that formed by the non-metals of groups V-VIII (15-18) of the periodic table in any of their valences other than their lowest stable valency of 3, 2, 1 and 0, respectively.[28] The simplest definition of a hypervalent molecule is "a molecule which does not obey octet rule by possessing more than four pairs of electrons in its conventional Lewis structure" (e.g., PCl_5, SF_6, XeF_4).[28] The German chemist Willgerodt prepared the first polyvalent organic iodine (hypervalent iodine) compound $PhICl_2$ in 1886.[29] But only after 100 years, i.e. since the early 1980s hypervalent iodine

reagents (HIRs) experienced a renaissance in organic synthesis.[31a] The major factors leading to resurgence of interest in HIR are:

1. HIRs chemical properties and reactivities are quite similar to heavy toxic metal oxidants such as Hg(III), Tl(III), Pb(IV) but without the toxicity and other environmental issues.

2. Operates under mild reaction conditions and easy to handle

3. Commercial availability with enough stability

The chemistry of HIRs was well documented in several books[30] and comprehensive reviews.[31]

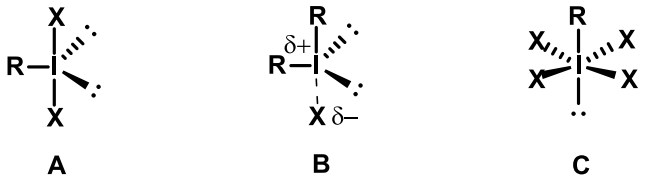
1.2.1. Nomenclature and Structural aspects of HIRs

Hypervalent iodine compounds are commonly named according to *N-X-L* nomenclature also called Martin-Arduengo designation.[32] where

N = Number of valence electrons assigned to the central atom

X = Symbol of the central atom from the periodic table

L = Number of ligands bonded to central atom



R = carbon ligand; X = halogen/oxygen/nitrogen ligand

N-X-L Designation	10-I-3	8-I-2	12-I-5
IUPAC Nomenclature*	Aryl λ^3 iodane	Aryl λ^3 iodane	Aryl λ^5 iodane
* In λ^3/λ^5, where 3/5 is the oxidation state of central iodine atom			

Figure 1.2A. Major classes and nomenclature of HIR

According to IUPAC recommendations, 'λ' is used as a non-standard bonding. All known HIRs can be classified into two classes based on their structures: (1) iodine(III) compounds **A** and **B** (iodonium salts) also called iodanes and (2) iodine(V) compounds **C** also called periodanes (Figure 1.2A).[33]

The structural features and bonding in iodine(III) compounds are explained by a hypervalent model which was proposed by Musher in 1969[34] and recently employed by Martin.[35] Iodane **A** has a total of 10 electrons with a distorted trigonal bipyramidal geometry (T-shaped structure). Two heteroatom ligands X occupies the apical position, whereas least electronegative carbon ligand R and other two lone pairs of electrons reside in equatorial position [e.g., $PhI(OAc)_2$ (PIDA)]. Iodonium salt **B** is also having similar pseudo-trigonal bipyramidal geometry (T-shaped structure) with two carbon ligands and a closely associated anionic part (e.g., $Ph_2I^+ {}^-OTf$). Most of the reported λ^3 iodanes **A** & **B** structures were unambiguously confirmed by single crystal X-ray analysis. Periodanes **C** exist in distorted octahedral geometry with carbon ligand R and a lone pair of electrons in apical positions and the remaining four X ligands in equatorial position (e.g., Dess-Martin periodinane). In the hypervalent model of RIX_2 (**A**), iodine uses its nonhybridized 5p orbitals in X-I-X bond formation. The carbon ligand R attached to iodine by forming a normal covalent bond with singly occupied equatorial 5p orbital of iodine, whereas the other two X ligands attached to the lobes of doubly occupied axial 5p orbital of iodine which results in a linear three-center four-electron (3c-4e) bond. Such bonds are termed as 'hypervalent bonds' and are highly polarized, longer and weaker compared to a normal covalent bond between two atoms. This hypervalent bond is responsible for high electrophilicity of λ^3 iodanes, and also the leaving group ability of –IRX group in λ^3 iodanes is 10^6 times greater than that of triflate leaving group. Out of four electrons in a hypervalent 3c-4e bond, only two electrons occupy bonding orbitals and other two

electrons present in non-bonding orbitals (Figure 1.2B). In λ^5 iodanes **C**, a covalent bond is present between carbon ligand R and iodine atom, whereas four X ligands are accommodated by two orthogonal hypervalent 3c-4e bonds.

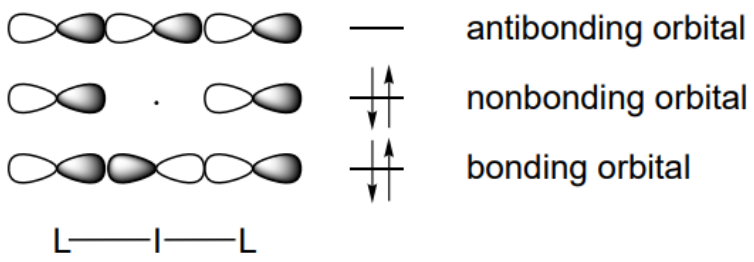


Figure 1.2B. Hypervalent molecular orbitals

In general, λ^3 and λ^5 iodanes with R group as aryl or heteroaryl substituents are quite stable and isolable. Even, λ^3 iodanes stabilized with strong electron withdrawing groups (eg., perfluoro-alkyl) were isolated but simple alkyl groups containing λ^3 iodanes do not exist in the literature.

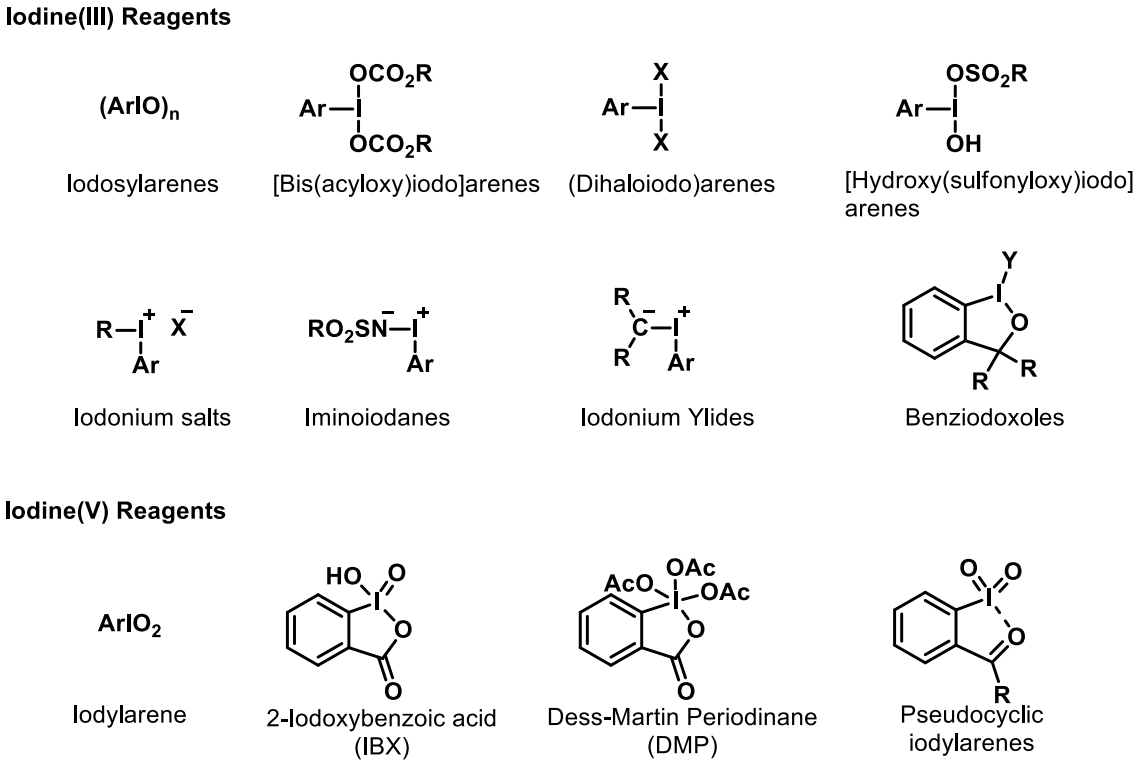
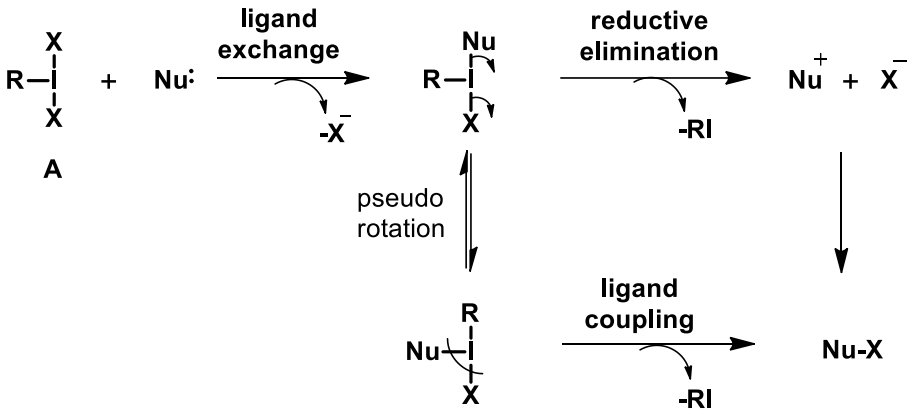


Figure 1.2C. Frequently used HIRs in organic synthesis

The structural aspects of HIRs were studied by various computational,[36] X-ray,[37] NMR and LC-MS[38] methods in both solid and solution states. The most commonly used HIRs in organic synthesis are presented in figure 1.2C.[39]

1.2.2. General reactivity patterns of HIRs

HIRs reactivity pattern was comprehensively reviewed by Ochiai in a book chapter.[39a] In general, most HIRs exhibit three typical reactivity patterns: (1) ligand exchange, (2) reductive elimination, and (3) ligand coupling (Scheme 1.2i).[39b]



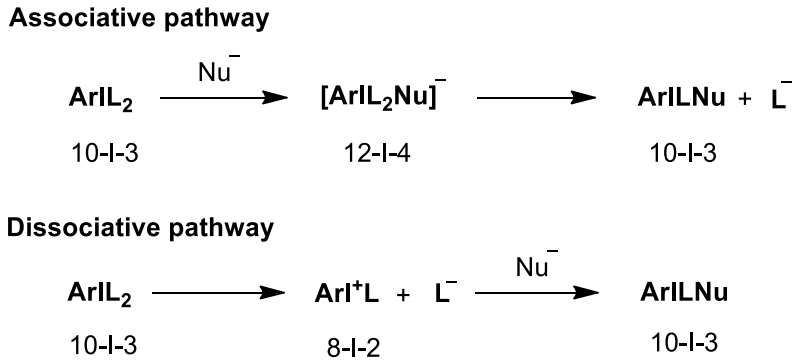
Scheme 1.2i. General reaction mechanism of λ^3 iodanes **A**

1.2.2A. Ligand exchange

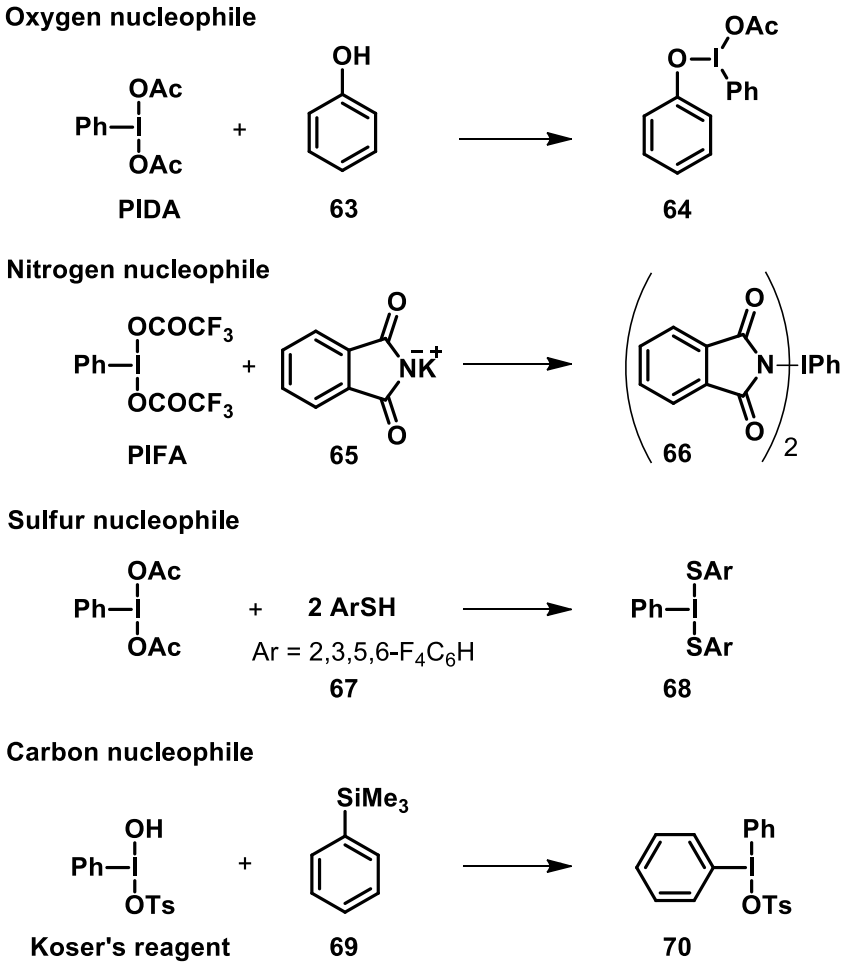
In λ^3 iodanes, heteroatom ligands are readily exchanged with external nucleophiles. This process is believed to undergo either by associative mechanism or by dissociative mechanism and many experimental evidences support associative mechanism (Scheme 1.2ii).[40] Several oxygen (**63**),[41] nitrogen (**65**),[42] sulfur (**67**)[43] and carbon (**69**)[44] nucleophiles were successfully employed in HIR ligand exchange process (Scheme 1.2iii).

1.2.2B. Reductive elimination

Reductive elimination of λ^3 iodanes to generate their monovalent iodine species is the most important mode of reaction. This reaction is highly energy favourable and also does not require any external reagent assistance. This reduction reaction converts hypervalent



Scheme 1.2ii. Possible pathways for λ^3 iodanes ligand exchange

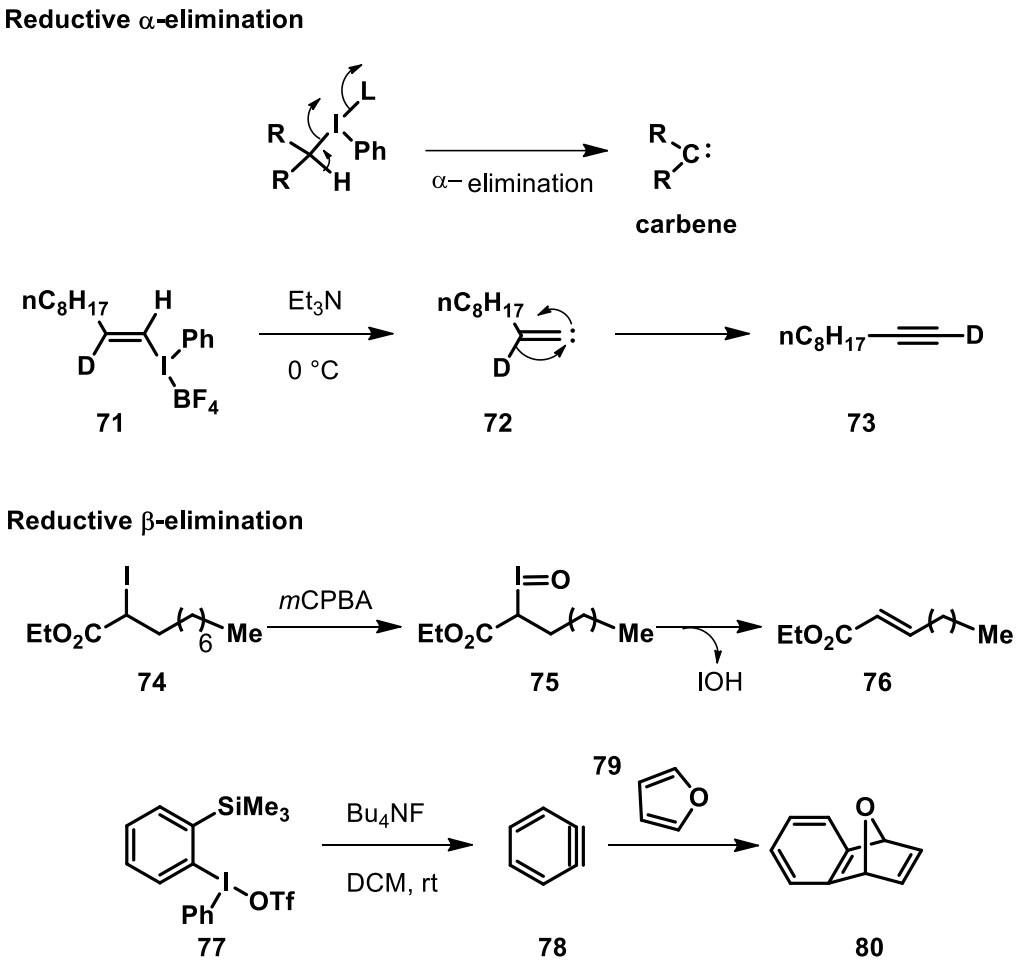


Scheme 1.2iii. λ^3 iodanes ligand exchange with various nucleophiles

iodine atom to normal valence iodine with octet structure, which is the basis for the good leaving group (hypernucleofuge) character of λ^3 iodanes. HIRs (λ^3 iodanes) involve different kinds of reductive elimination processes which include reductive α/β-elimination and reductive elimination with fragmentation/rearrangement/substitution.[39a]

Reductive α-elimination of λ^3 iodanes generates carbene intermediates. For instance, alkenyl λ^3 iodane **71** undergoes reductive α-elimination in the presence of Et_3N to generate terminal alkyne **73** exclusively at 0 °C through the formation of alkylidene carbene intermediate **72** (Scheme 1.2iv).[45] Reductive β-elimination of λ^3 iodanes at different atoms generates different species, β-elimination on carbon atom affords alkenes in the aliphatic system and benzynes in the aromatic system. For example, the oxidation reaction of alkyl iodides **74** bearing electron withdrawing group at the α-carbon atom undergoes elimination in the presence of *m*CPBA to give alkene **76**. This reaction involves reductive β-elimination of hypervalent iodosylalkane **75** (Scheme 1.2iv).[46] Kitamura et al. reported a fluoride-induced reductive β-elimination of *o*-(trimethylsilyl)phenyl-λ^3-iodane **77** to generate benzyne intermediate **78**, which then subsequently involved in Diels-Alder reaction with 1,3-dienes such as furan **79** to afford the cycloadduct **80** in high yields (Scheme 1.2iv).[47]

The reaction of PIDA with stannyl lactol **81** led to the formation of *trans* selective unsaturated lactone **83**. In this reaction, the intermediate **82** undergoes 1,4-fragmentation associated with the reductive elimination of iodobenzene (Scheme 1.2v).[48] Usually, two carbon ligands containing λ^3-iodanes undergo reductive elimination accompanied by the external nucleophilic attack to afford the substituted products. For instance, in the presence of concentrated sulphuric acid, acetophenone **84** reacts with PIDA in acetic acid and acetic anhydride solvent mixture to produce α-acyloxy acetophenone **86**. This reaction is believed to proceed through a α-(phenyl-λ^3-iodanyl) ketone intermediate **85** which subsequently undergoes reductive elimination of iodobenzene associated with substitution (Scheme 1.2v).[49] Primary amide **87** upon reaction with PIFA [$PhI(CF_3COO)_2$] in acetonitrile and water produced the primary amine **90**.



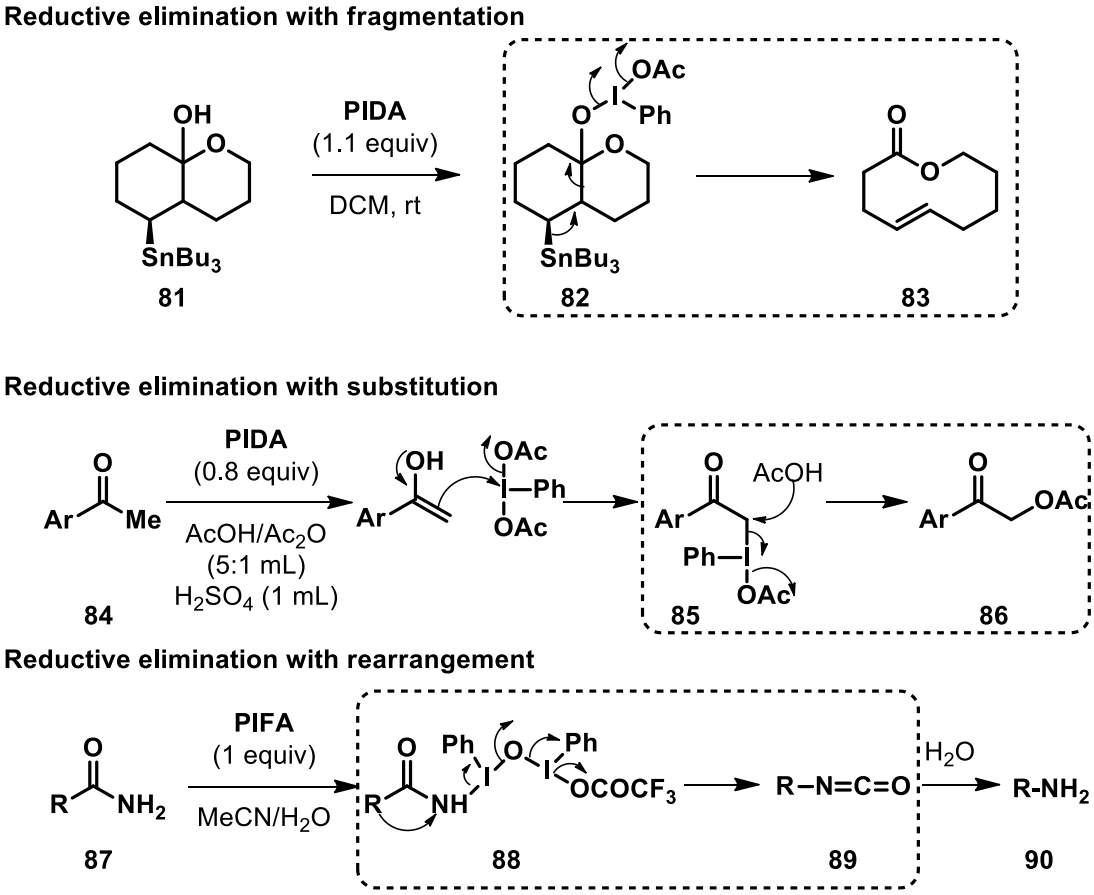
Scheme 1.2iv. Reductive α-/β-eliminations of λ^3-iodanes

Here, the hypervalent intermediate **88** undergoes reductive elimination associated with Hofmann type rearrangement to generate an isocyanate intermediate **89** which in the presence of water affords amine **90** (Scheme 1.2v).[50]

1.2.2C. Pseudorotation

In general, λ^3-HIRs undergo stereomutation (**91**⇄**91'**) due to their configurational instability. Heteroatom ligands L_1 and L_2 in **91** exchange their positions via repeated pseudorotation (Ψ) on iodine(III) to form **91'** (Scheme 1.2vi). During this pseudorotation, equatorial bonds become apical bonds, and apical bonds become equatorial through the formation of the square pyramid structure. Rapid pseudorotation was observed for λ^3 chiral iodane **92** in which the two acetoxy peaks appeared as two distinct singlets at δ

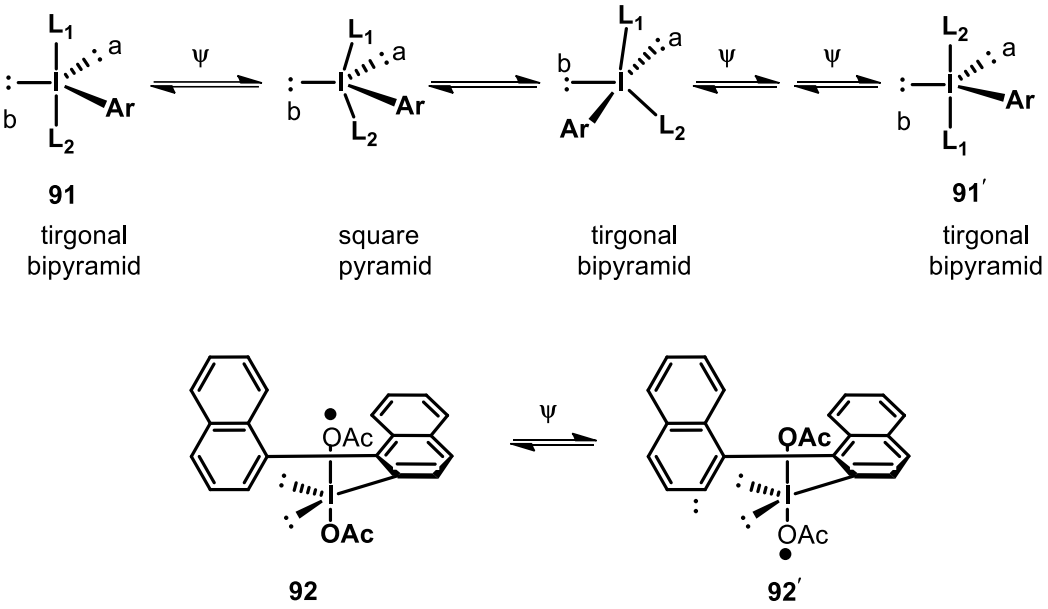
1.52 and 2.0 ppm, respectively in $CDCl_3$ at -10 °C. Whereas at 34 °C, only one singlet peak was observed for the two acetoxy groups at δ 1.73 ppm (Scheme 1.2vi).[51]



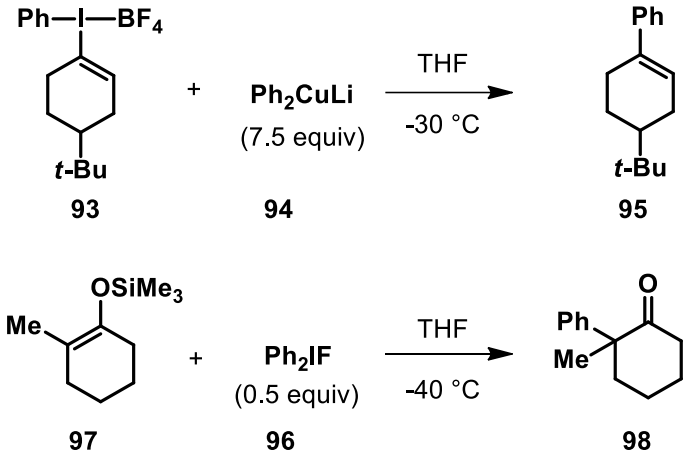
Scheme1.2v. Reductive elimination associated with fragmentation/substitution/ rearrangement

1.2.2D. Ligand coupling

The term ligand coupling in HIRs was first introduced by Prof. Oae to explain the intramolecular coupling of two ligands attached to hypervalent iodine atom.[52] The experimental evidence for this concept is rather less due to fast stereomutation associated with pseudorotation. Alkenyl-λ^3-iodane **93** reacts with diarylcuprate **94** via ligand coupling process to produce *ipso* substituted product **95** (Scheme 1.2vii).[53] Diphenyl(fluoro)-λ^3-iodane **96** upon reaction with silyl enol ether **97** generates α-phenylation product **98** in a regioselective manner by ligand coupling (Scheme 1.2vii).[54]



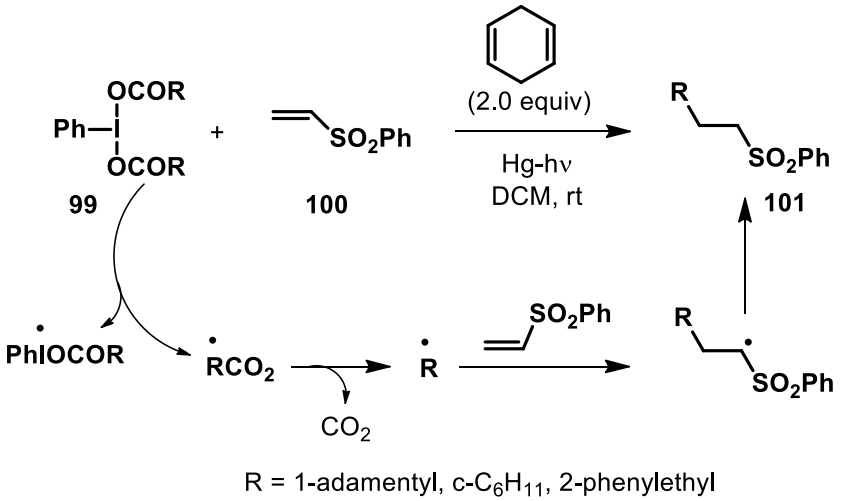
Scheme 1.2vi. Pseudorotation in λ^3 iodanes



Scheme 1.2vii. Ligand coupling reactions of λ^3-iodanes

1.2.2E. Homolytic cleavage

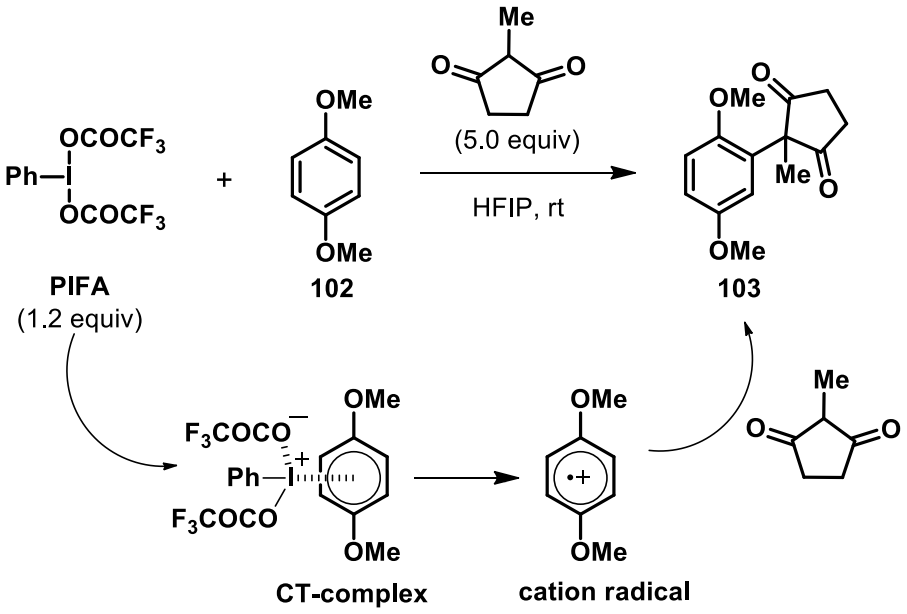
The hypervalent I-O bond in (diacyloxyiodo)arene undergoes homolytic cleavage upon heating or irradiation with mercury lamp to generate acyloxy radical which subsequently decomposes to produce alkyl radical by the loss of carbon dioxide. When an acyloxy-λ^3-iodane **99** treated with vinyl sulfone **100** in the presence of 1,4-cyclohexadiene and high-pressure mercury lamp, the reductive alkylation product **101** was obtained by a radical Michael kind of addition process (Scheme 1.2viii).[55]



Scheme 1.2viii. λ^3-iodanes radical pathway

1.2.2F. Single electron transfer (SET) reactions

Kita et al. observed a direct nucleophilic substitution reaction on *para*-substituted phenol ether **102** in the presence of PIFA in a polar and nonnucleophilic solvent such as 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) to generate the substituted product **103** (Scheme 1.2ix).[56] They have performed a detailed UV-vis and ESR analysis to find SET process from phenol ether **102** to PIFA generating a cation radical intermediate via the formation of charge transfer complex (CT-complex).



Scheme 1.2ix. λ^3-iodanes SET process

1.2.3. Applications of HIRs

HIRs have found enormous synthetic applications in various fields. Separate reviews are available in the literature for different types of HIRs and their applications, which include [hydroxy(tosyloxy)iodo]arenes,[57] iodonium salts,[58] iminoiodanes,[59] iodonium ylides,[60] perfluoro HIRs,[61] benzoiodoxoles,[62] polymer-supported HIRs,[63] and various synthetic applications of trivalent and pentavalent HIRs.[64-73] The representative organic transformations mediated by λ^3-HIRs are discussed in this chapter.

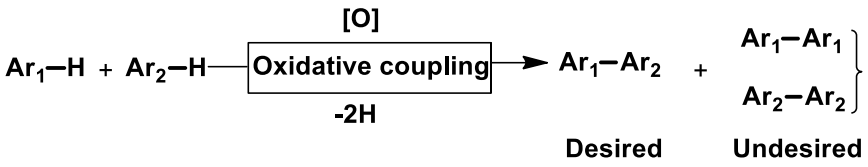
1.2.3A. HIR induced oxidative coupling reactions (new metal-free couplings)

Transition metal-catalyzed cross-coupling reactions for the direct carbon-carbon bond formation is considered as one of the greatest discovery in the twentieth century, and it was rightly recognized with the chemistry Nobel prize in 2010.[74] Despite their emerging applications in various fields, these reactions are associated with some drawbacks[75] which include,

- Transition metals are highly toxic
- Require pre-functionalized starting materials, additives, and co-catalysts
- Very expensive
- Inaccessibility of ligands
- Sensitive to oxygen
- Require stringent reaction conditions
- Difficult to remove trace metal impurities from the final product

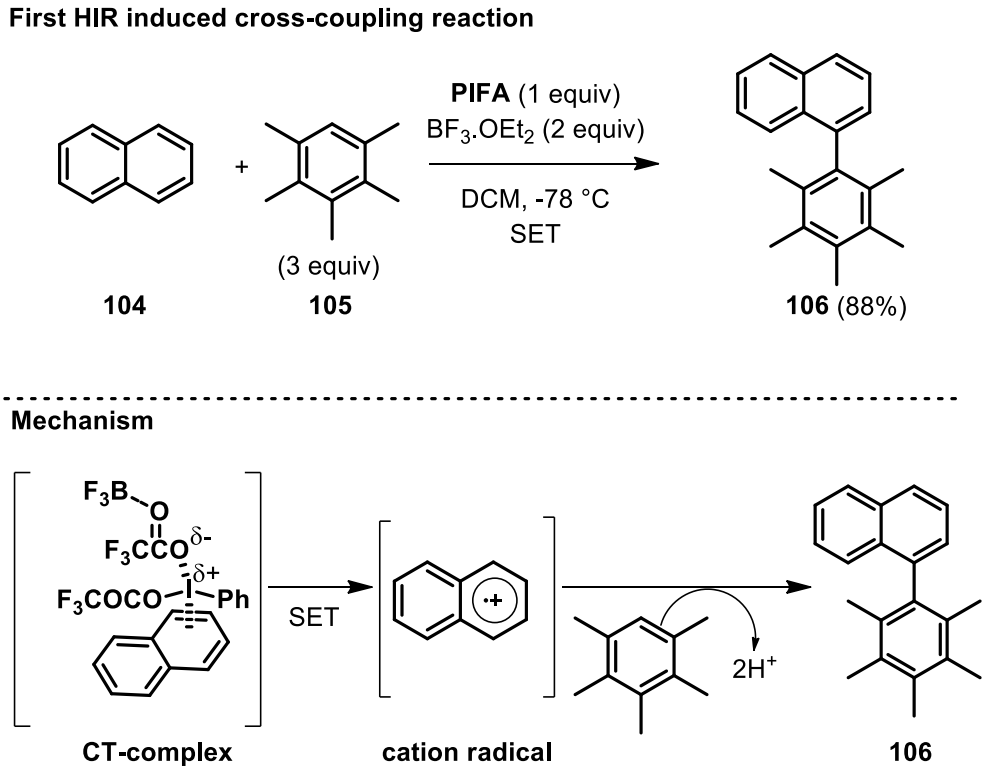
Hence, there is a need for the development of new metal-free cross-coupling reactions under mild conditions. In this context, oxidative cross-coupling between two non-functionalized substrates is considered as an alternate green technology. Especially, HIR mediated cross-coupling reactions received much attention in recent years.[76] In this regard, proper design of oxidation reaction conditions is of utmost importance. Otherwise,

there is every chance of getting undesired homocoupling products along with cross-coupled products (Scheme 1.2x).



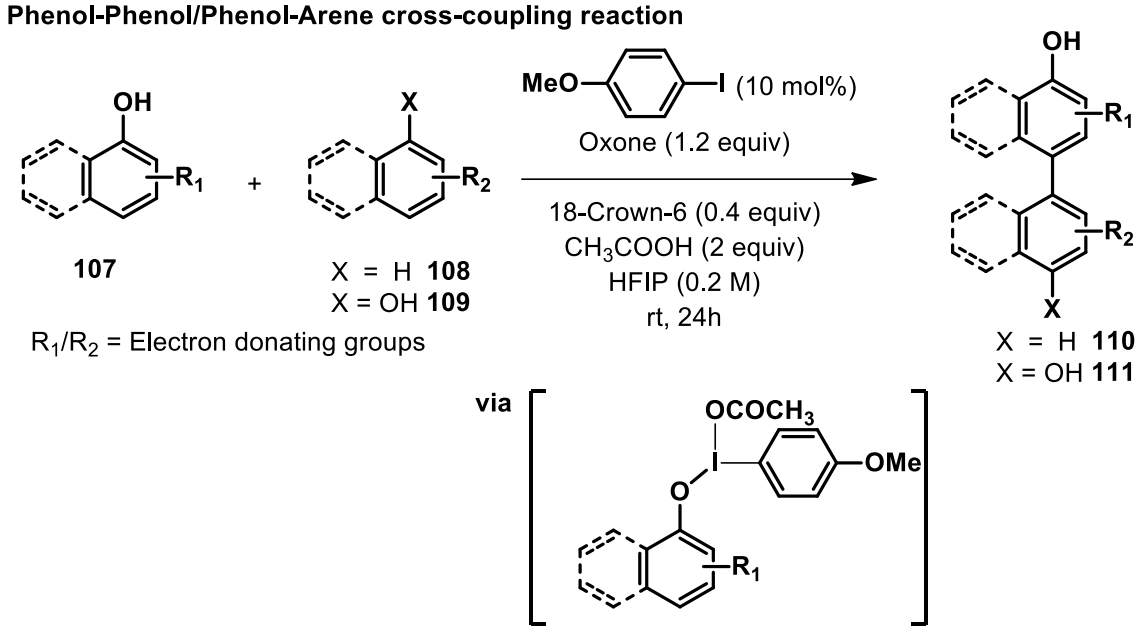
Scheme 1.2x. General oxidative cross-coupling reaction

The first HIR mediated cross-coupling reaction was reported by Kita et al. in the year 2008.[77] They have discovered an elegant cross-coupling reaction between naphthalene **104** and alkylbenzenes **105** mediated by PIFA in the presence of boron trifluoride diethyl etherate ($BF_3.OEt_2$) Lewis acid to afford the cross-coupling product **106**. This reaction involves a radical cation intermediate by a SET process from naphthalene **104** to PIFA through the formation of a charge transfer complex (Scheme 1.2xi).



Scheme 1.2xi. Kita's first iodine(III) mediated cross-coupling reaction

Recently, Prof. Kita group developed an iodobenzene catalyzed phenol-arene (**107**-**108**) and phenol-phenol (**107**-**109**) cross-coupling reactions to synthesize the cross-coupled products **110** and **111** in moderate to good yields (Scheme 1.2xii).[78] In this reaction, the catalytic amount of 4-methoxy iodobenzene generates iodine(III) reagent *in situ* in the presence of oxone, acetic acid and phase transfer catalyst in HFIP solvent.



Scheme 1.2xii. Kita's iodine(III) catalyzed cross-coupling reaction

The concept of HIR induced oxidative cross-coupling reactions were well exploited in several natural products (NP) synthesis, and some of them are listed in figure 1.2D.[76]

1.2.3B. HIRs mediated phenol dearomatization reactions

Generally, phenols are electron rich nucleophilic species which readily participate in electrophilic aromatic substitution reactions. However, HIRs converts nucleophilic phenols to electrophilic species by a dearomatization reaction in the presence of fluoro solvents, and this process is called 'phenol umpolung.[79] Here, fluoro alcohols such as HFIP and TFE (2,2,2-Trifluoroethanol) acts as stabilizing solvents of cationic intermediates produced by the reaction of HIRs.[80] Based on their substitution patterns and

functionalities; phenols can be converted to quinones, quinone methides and other cyclohexadienones (Scheme 1.2xiii).[81]

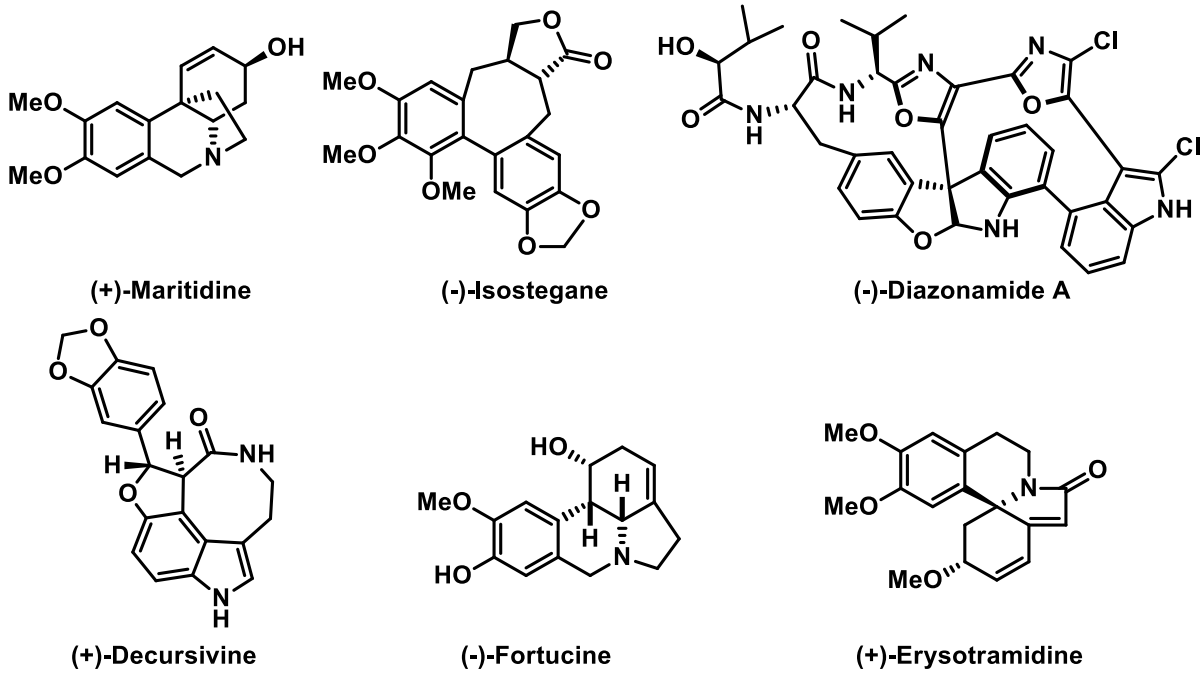
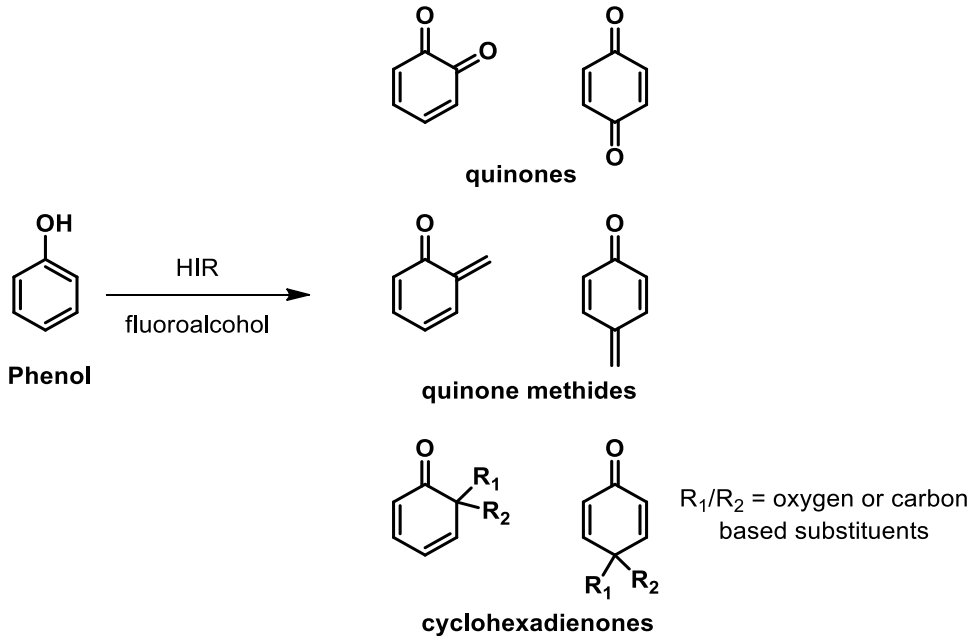


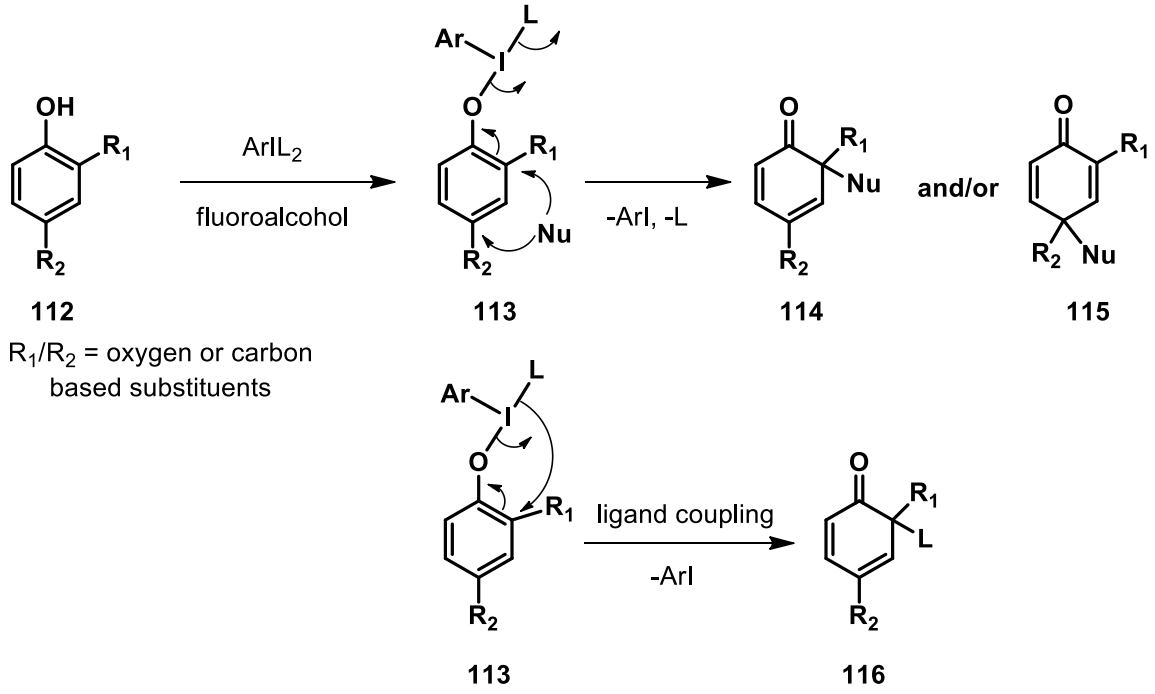
Figure 1.2D. Examples of NPs derived from HIRs cross-coupling strategy

Phenol **112** reacts with $ArIL_2$ (λ^3-iodane) to generate an intermediate **113** by a ligand exchange mechanism which then undergoes nucleophilic attack either at *ortho* or *para* positions depending upon the substituents to yield corresponding cyclohexadienones **114** and **115**. Another possibility is, the intermediate **113** can undergo ligand coupling mechanism to generate cyclohexadienone **116** (Scheme 1.2xiv).[81]

HIR mediated dearomatization of phenols to quinonoids such as quinone, quinone monoketals and quinols and their subsequent applications in organic synthesis are well explored. Recently, Grec et al. reported an organocatalytic Diels-Alder/Michael cascade reaction between 1,4-hydroquinone **117** and dienal **118** to generate tricyclic product **121** with five continuous stereocentres.[82] In this reaction, PIDA converts 1,4-hydroquinone **117** to benzoquinone **119** by oxidative dearomatization, and proline derived catalyst generates a trienamine intermediate **120** from dienal **118** (Scheme 1.2xv).



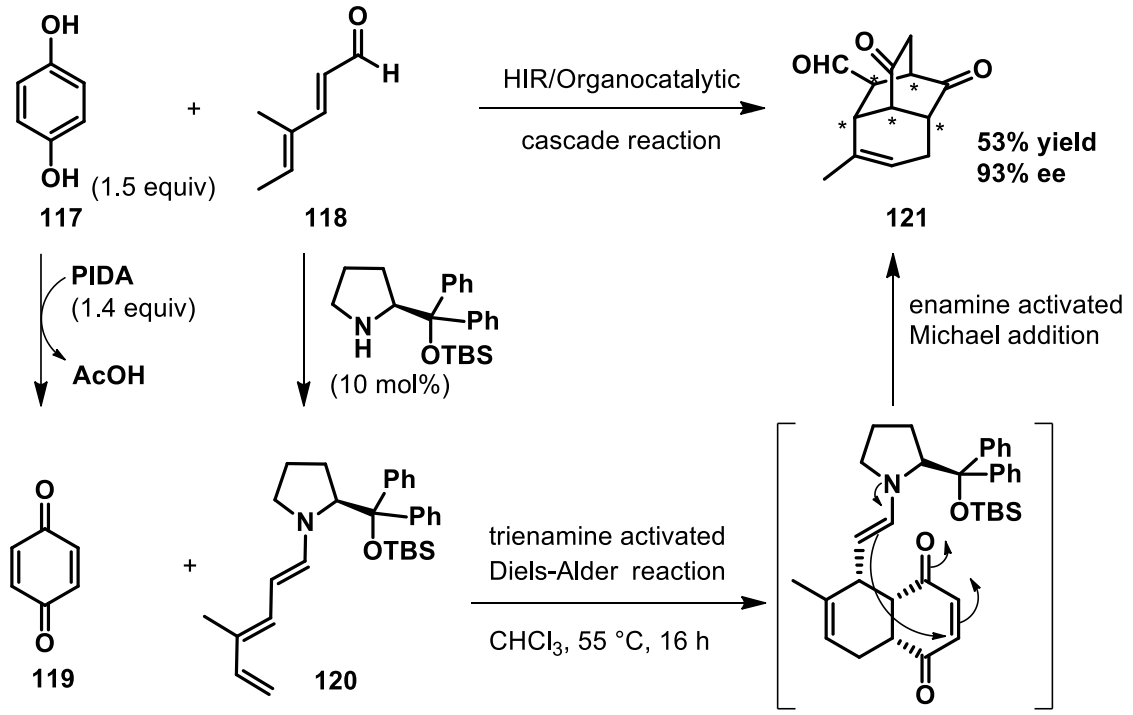
Scheme 1.2xiii. HIR mediated dearomatization of phenols to reactive intermediates



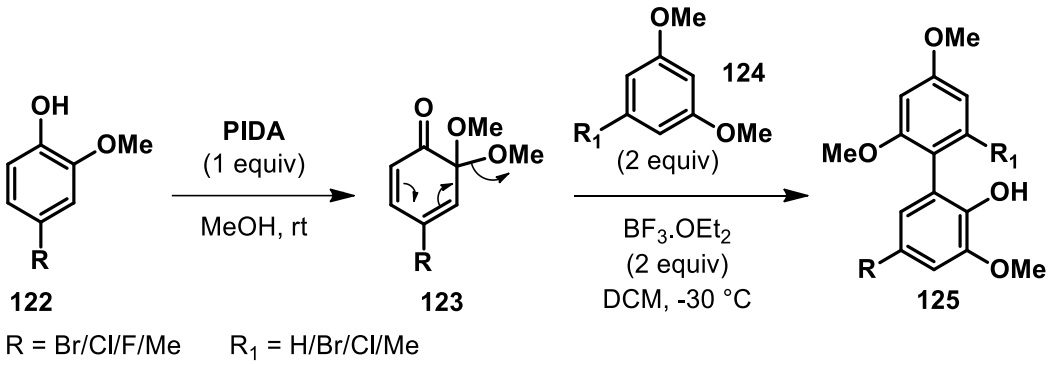
Scheme 1.2xiv. Possible mechanisms for λ^3-iodane mediated dearomatization of phenols

Peddinti et al. successfully utilized the masked *ortho*-benzoquinone intermediate **123** generated by PIDA mediated oxidative dearomatization of substituted 2-methoxyphenol **122** to synthesize oxygenated biaryls **125**.[83] Followed by dearomatization, stoichiometric

amounts of electron rich arenes **124** and $BF_3.OEt_2$ were added in one-pot by changing the solvent from MeOH to DCM (Scheme 1.2xvi).



Scheme 1.2xv. PIDA mediated dearomatization and organocatalyzed cascade reaction



Scheme 1.2xvi. PIDA mediated dearomatization/ SN_2' type substitution sequence

1.2.3C. HIR mediated heterocycles synthesis

Heterocycles represent a broad spectrum of natural products and bioactive molecules. Consequently, the quest for the new synthetic methods to construct diverse heterocyclic scaffolds is always a hot topic. In this regard, λ^3-iodanes such as PIDA, PIFA, iodosobenzene (PhIO), and [hydroxy(tosyloxy)iodo]benzene (Koser's reagent, HTIB)

were extensively utilized in the synthesis of several heterocycles under mild and metal-free conditions.[84]

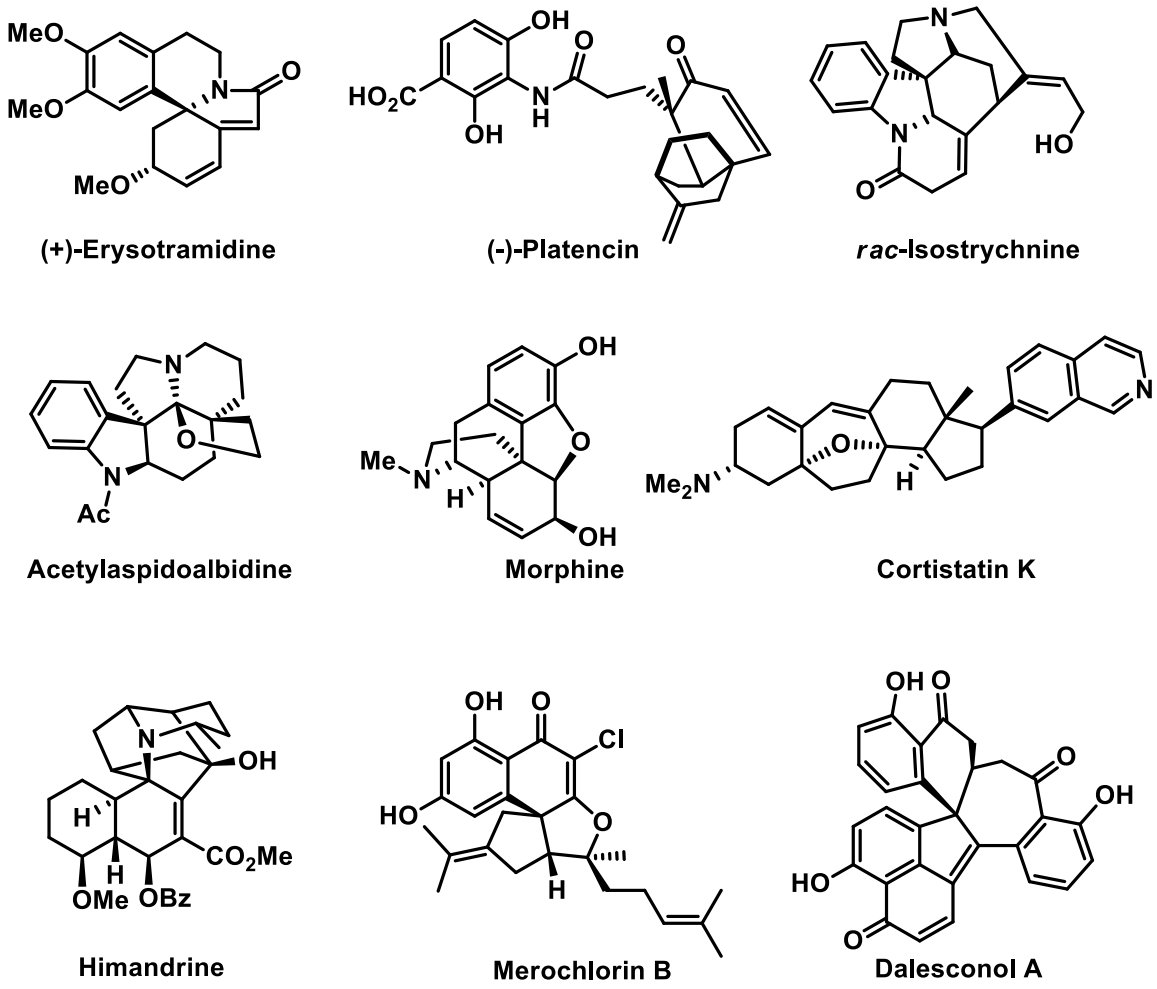
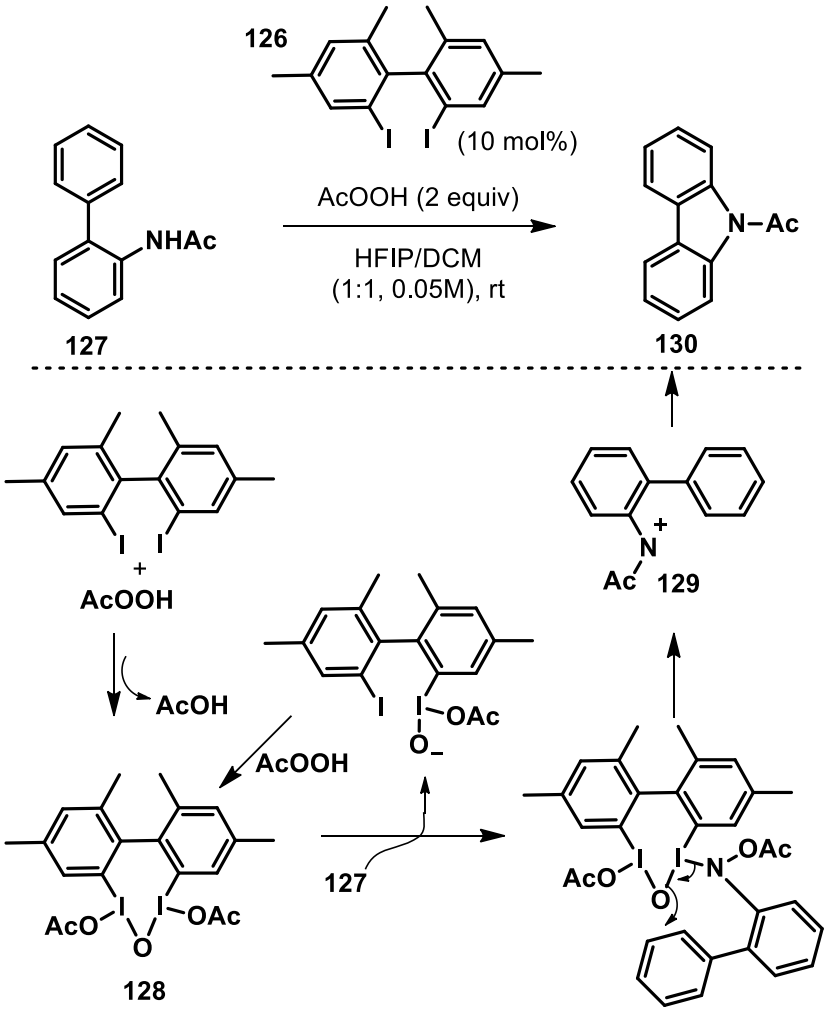


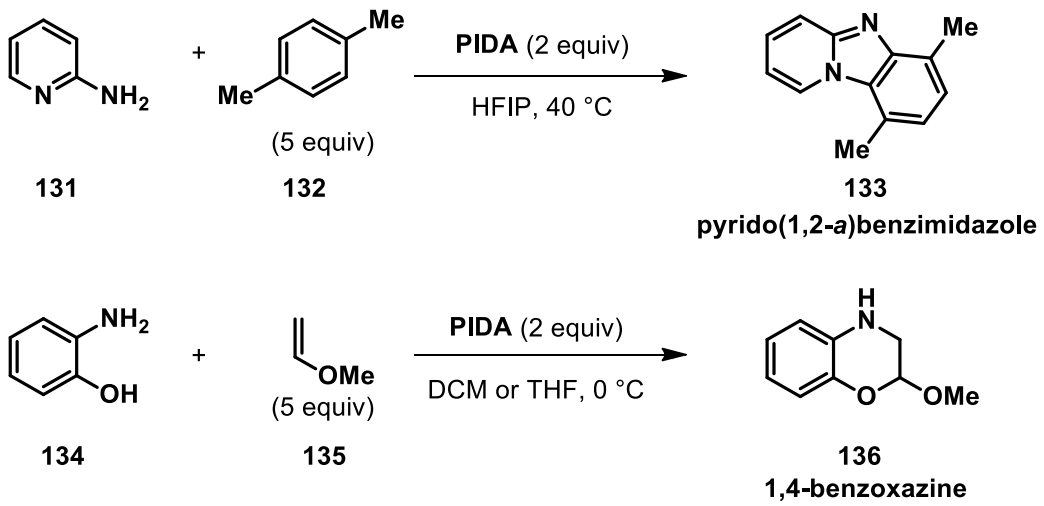
Figure 1.2E. NPs synthesized by using HIR dearomatization approach

For instance, Antonchick et al. reported a 2,2'-diiodoarene **126** catalyzed intramolecular C-H amination reaction of biaryl acetamide **127** for the synthesis of carbazole **130**. They have proposed an ionic mechanism initiated by the formation of oxo-bridged λ^3-iodane **128** from **126** in the presence of peracetic acid. The *in-situ* formed **128** reacts with **127** by a ligand exchange process to generate a nitrenium intermediate **129** which then undergoes electrophilic aromatic substitution to afford desired carbazole **130** (Scheme 1.2xvii).[85]

Apart from the above mentioned intramolecular C-H amination reaction, there are several reports available in the literature for the synthesis of heterocycles by iodine(III) mediated intermolecular C-H amination/C-H oxygenation reactions. For instance, scheme 1.2xviii depicts PIDA mediated intermolecular double C-N bond formation (**131** & **132**) and C-N/C-O bond formation (**134** & 1**35**) reactions for the synthesis of pyrido(1,2-*a*)benzimidazoles **133**[86] and 1,4-benzoxazines **136**,[87] respectively.



Scheme 1.2xvii. Antonchick's iodine(III) mediated intramolecular C-H amination



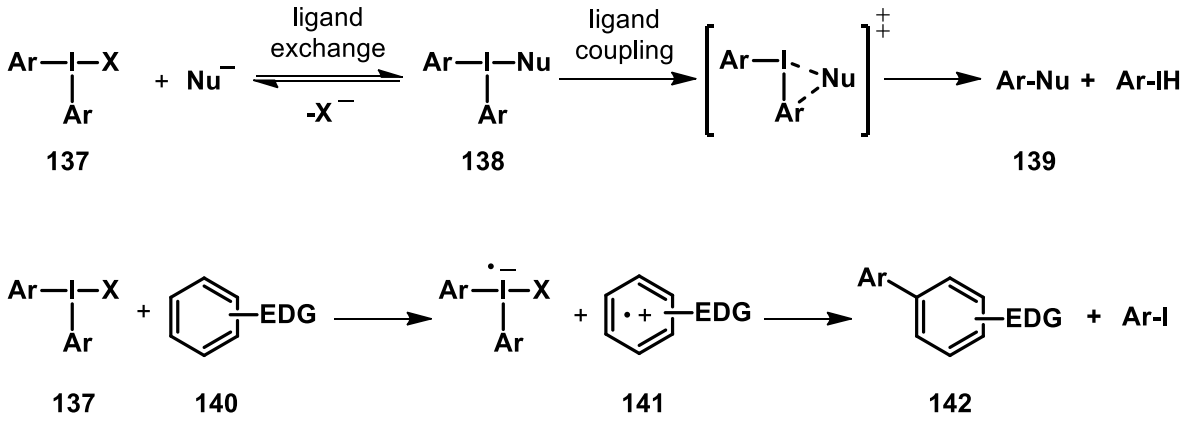
Scheme 1.2xviii. HIR mediated intermolecular carbon-heteroatom bond formation reactions

1.2.3D. HIR mediated electrophilic arylation of nucleophiles

Arylation is one of the most important organic transformations mainly achieved by transition metal catalysis. HIRs, especially diaryliodonium salts **137** (Ar_2IX) were well explored in metal-free arylation of various carbon and heteroatom nucleophiles under mild conditions.[88] X-ray analysis of diaryliodonium salts **137** shows a T-shaped structure which is most common for λ^3-iodanes and the hypervalent 3c-4e bond is shared by a counter ion X and one aryl group. During the reaction of Ar_2IX, one aryl group will be transferred to the nucleophilic site, and another aryl group will be removed as ArI by reductive elimination. Removal of by-product (ArI) in neutral form has several advantages over anionic ligands as by-products in nucleophilic substitution reactions.

General arylation reaction of **137** involves two steps, in which the rapid ligand exchange with external nucleophile at iodine(III) center generates a new T-shaped intermediate **138** either by an associative or dissociative mechanism (Scheme 1.2xix).[89] In the subsequent step, nucleophile and equatorial aryl group undergo ligand coupling by the reductive elimination of ArI to afford the coupled product **139**. Even single electron transfer (SET) mechanisms were also proposed for arylation reactions of **137**.[90] Especially, electron rich

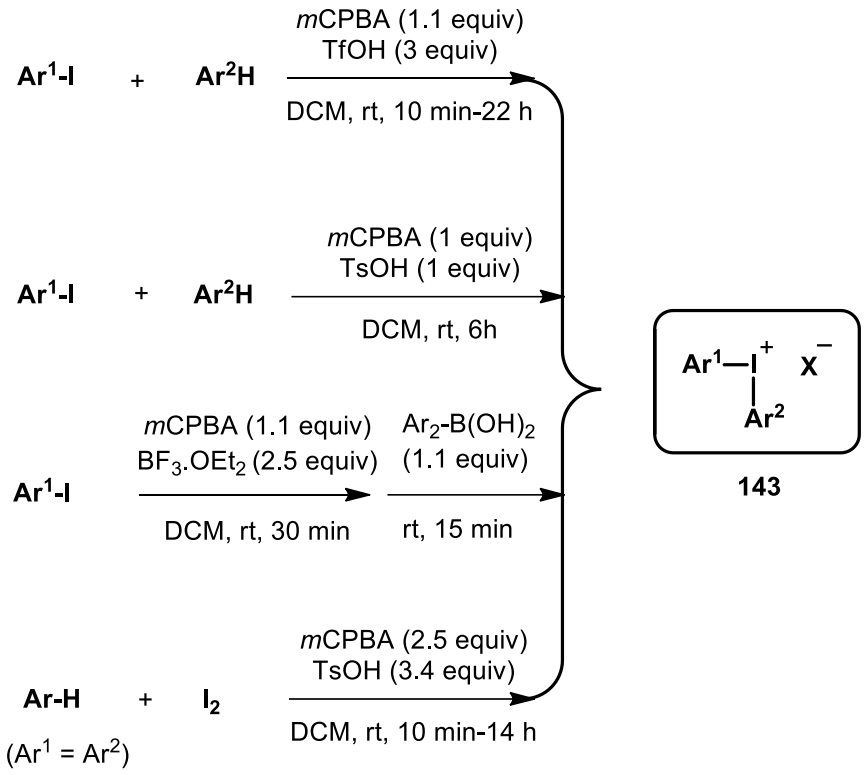
arenes **140** undergo single electron oxidation in the presence of **137** to generate a cation radical **141** which subsequently involves in radical recombination to derive biaryl **142** (Scheme 1.2xix). This SET mechanism is most common in the synthesis of electron rich biaryls by using fluoro alcohols such as HFIP and TFE. In unsymmetrical diaryliodonium salts, electron deficient aryl group is usually transferred to nucleophilic site, but in many reactions, electron rich *ortho*-substituted aryl group transfer is observed due to *ortho* effect.[91]



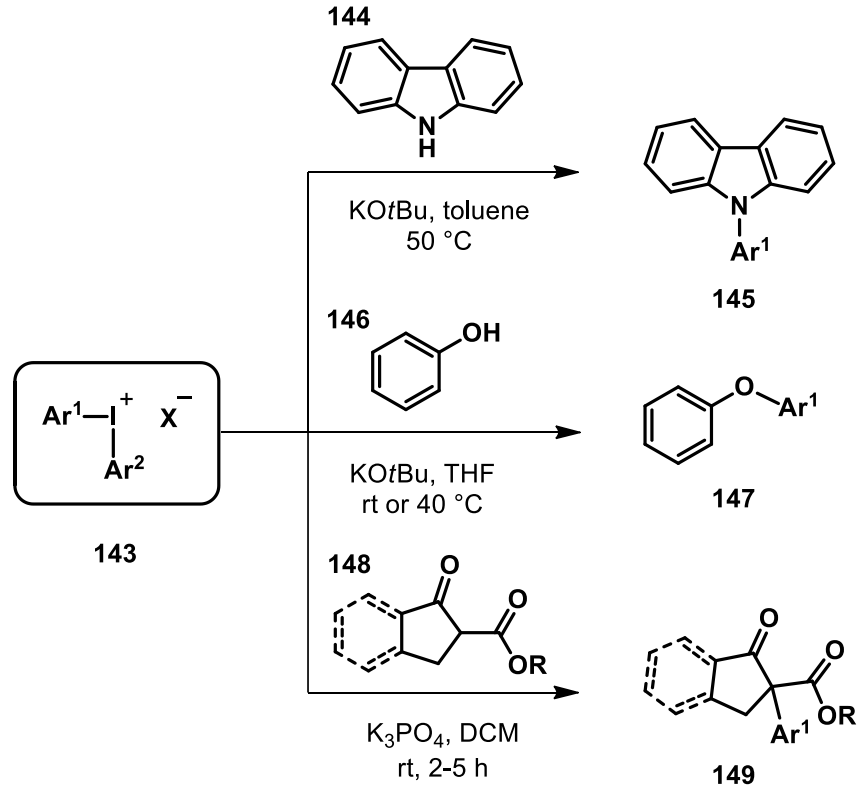
Scheme 1.2xix. General mechanism of electrophilic arylation by diaryliodonium salts

Olofsson et al. developed several one-pot methods for the synthesis of wide range of unsymmetrical di-aryl/hetroaryliodonium salts **143** in short reaction times with excellent yields. In most of the one-pot methods, *m*CPBA was used as an oxidant and DCM as a solvent in the presence of acids such as triflic acid (TfOH), TsOH or $BF_3.OEt_2$ (Scheme 1.2xx).[92]

Arylation of various heteroatom nucleophiles was first developed by Beringer in 1953.[93] Since then; several diaryliodonium salts were synthesized and applied under improved reaction conditions to achieve selective arylation in good to excellent yields. Scheme 1.2.xxi represents electrophilic arylation of the nitrogen (**144**),[94] oxygen (**146**),[95] and carbon (**148**)[96] nucleophiles with diaryliodonium salts **143** leading to the corresponding arylation products **145**, **147**, and **149**, respectively.

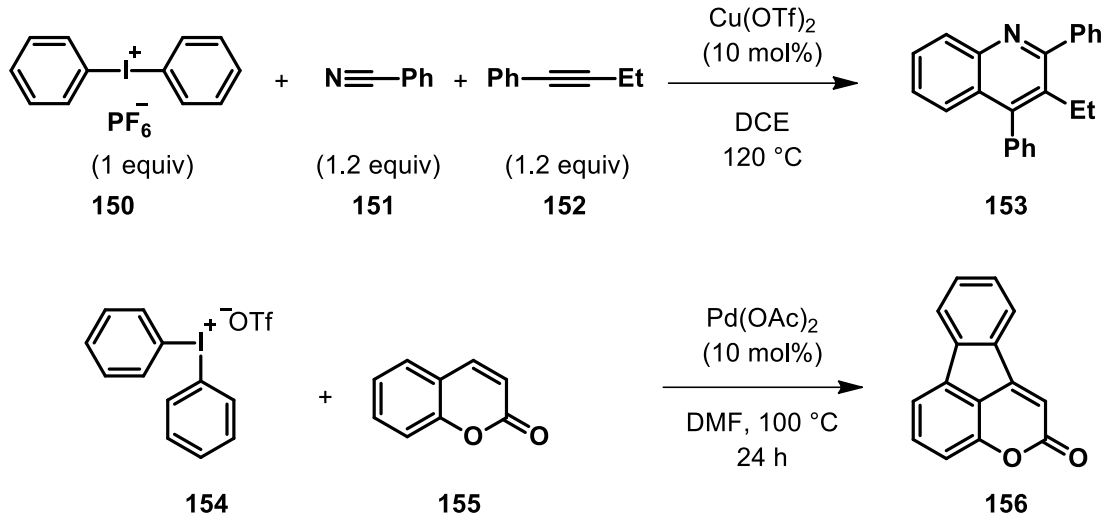


Scheme 1.2xx. Olofsson's synthesis of diaryliodonium salts



Scheme 1.2xxi. Electrophilic arylation of N/O/C-nucleophiles using diaryliodonium salts

Transition metals (TMs), mainly Pd and Cu were also employed in arylation reactions using diaryliodonium salts as arylating agents. Chemoselectivity in TMs catalyzed arylation is different from metal-free arylation reactions. Steric effects play a major role in aryl group transfer, but in the absence of steric factors, mostly electron-rich aryl groups will be transferred with moderate selectivity.[88] For example, Chen et al. reported copper (II) catalyzed [2+2+2] annulation reaction of diaryliodonium salt **150**, nitrile **151** and alkyne **152** for the synthesis of multiply substituted quinolines **153** in moderate to good yields (Scheme 1.2xxii).[97] In this annulation reaction, diaryliodonium salt **150** acts as a C2 building block. Wang et al. reported palladium (II) catalyzed double arylation of coumarins **155** using diphenyliodonium salt **154** for the synthesis of **156** (Scheme 1.2xxii).[98] Authors explained the mechanism in which Pd activates both C-I and vicinal C-H bonds of diphenyliodonium salts.

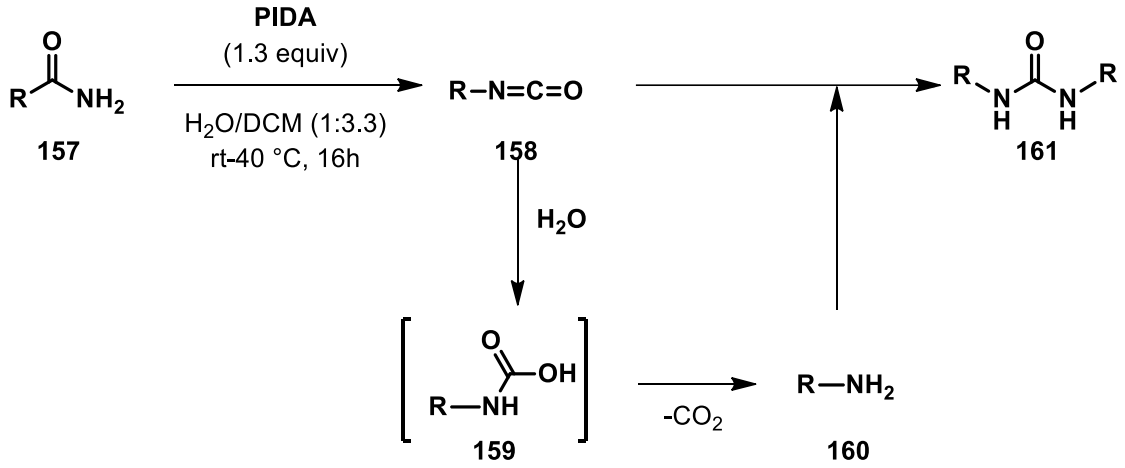


Scheme 1.2xxii. Diaryliodonium salts in cyclization reactions catalyzed by metals

1.2.3E. HIRs induced rearrangement reactions

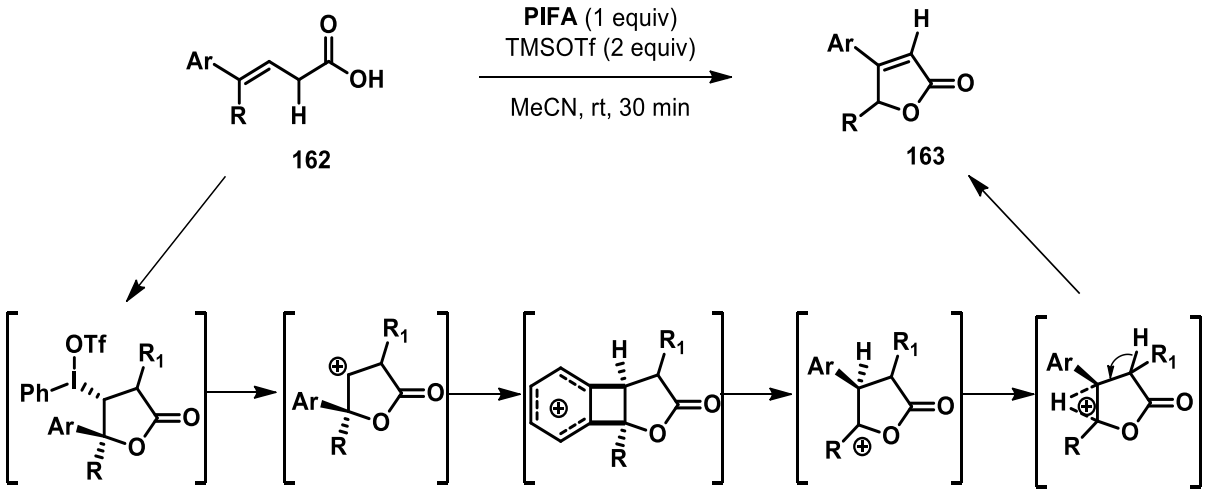
Readily available/accessible HIRs have found applications in some rearrangement reactions to generate highly functionalized compounds.[99] Rearrangements such as Hofmann-Type rearrangement, aryl transposition, and rearrangements associated with phenol dearomatization were well studied using HIRs on different substrates. Kalesse et

al. reported a synthesis of symmetrical urea **161** from primary amides **157** in the presence of PIDA reagent.[100] The reaction proceeds through the formation of an isocyanate intermediate **158** by a Hofmann-Type rearrangement. The intermediate **158** produces carbamic acid intermediate **159** in the presence of water which upon decomposition generates the corresponding amine **160**. Finally, the *in-situ* generated amine **160** reacts with the remaining **158** to afford symmetrical urea **161** (Scheme 1.2xxiii).



Scheme 1.2xxiii. PIDA mediated Hofmann-Type rearrangement

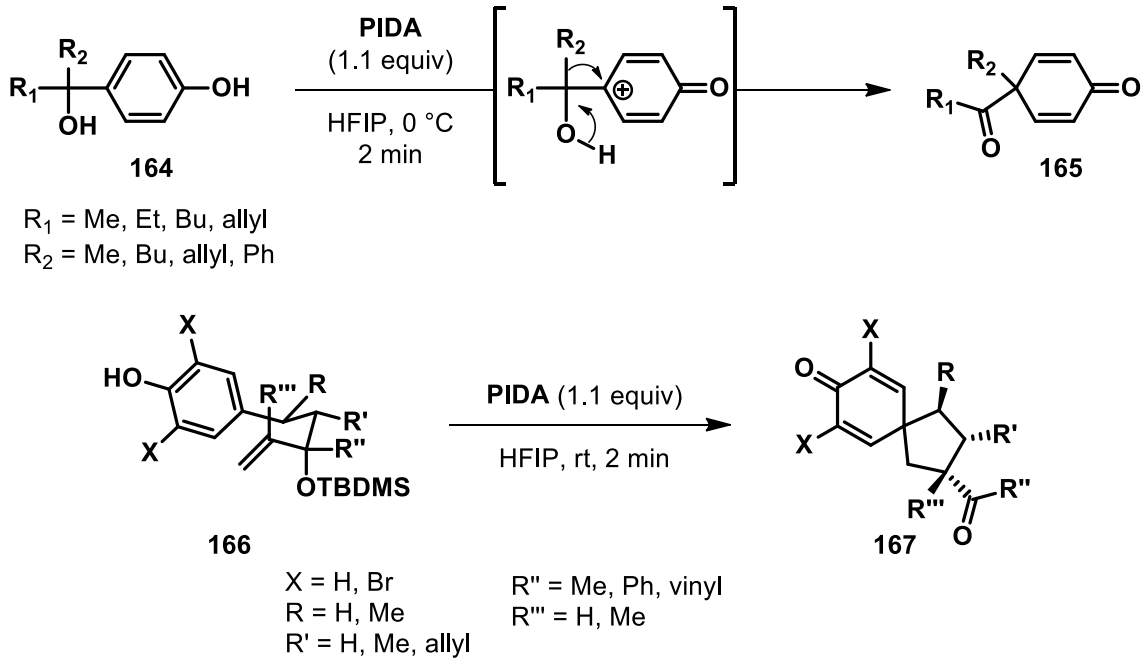
HIRs are also superior reagents to facilitate aryl migration in conjugated molecules in which the reactive cationic intermediates are trapped by an aryl group via Friedel-Crafts-like process, thus leading to a rearranged product.



Scheme 1.2xxiv. PIFA mediated aryl transposition in an unsaturated acid

Wirth et al. observed an unusual transformation of an unsaturated acid **162** to furanone **163** in the presence of PIFA and TMSOTf at room temperature.[101] They have proposed a mechanism which involves the formation of a cationic intermediate and subsequent aryl migration as shown in scheme 1.2xxiv.

HIR mediated rearrangement reactions were also explored in *para*-substituted phenols by oxidative dearomatization mechanism.[99] Electron rich phenols and anilines readily undergo dearomatization to generate highly reactive intermediates in the presence of HIRs. These intermediates can be trapped in an intramolecular fashion to provoke a rearrangement in addition to reaction with external nucleophiles. *Para*-substituted phenols such as **164** and **166** underwent Wagner–Meerwein-type rearrangement/1,2 or 1,3-shift/Prins-pinacol transpositions in the presence of HIR to yield respective rearranged products **165** and **167** (Scheme 1.2xxv).[102]



Scheme 1.2xxv. HIR mediated rearrangements in *para*-substituted phenols

1.2.3F. HIRs as trifluoromethylation agents

The organic compounds containing fluoro and trifluoromethyl substituents found enormous applications in several fields which include medicinal chemistry,

agrochemistry, and material science.[103] For instance, the introduction of trifluoromethyl group, can substantially enhance the activity, lipophilicity, and bioavailability of lead molecule in the drug discovery process. Prof. Togni group synthesized the first trifluoromethyl transfer benziodoxolone **168** and benziodoxole **169** HIRs in 2006, and these reagents are commonly known as Togni's reagents (Figure 1.2F).[104] To date, these reagents are being extensively used in organic synthesis for the electrophilic trifluoromethylation of heteroatom and carbon center nucleophiles as a selective and mild reagents.[105]

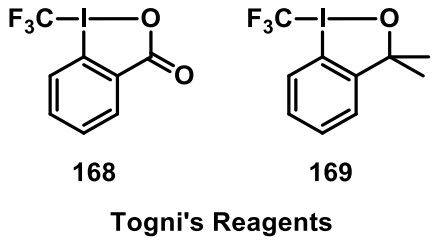
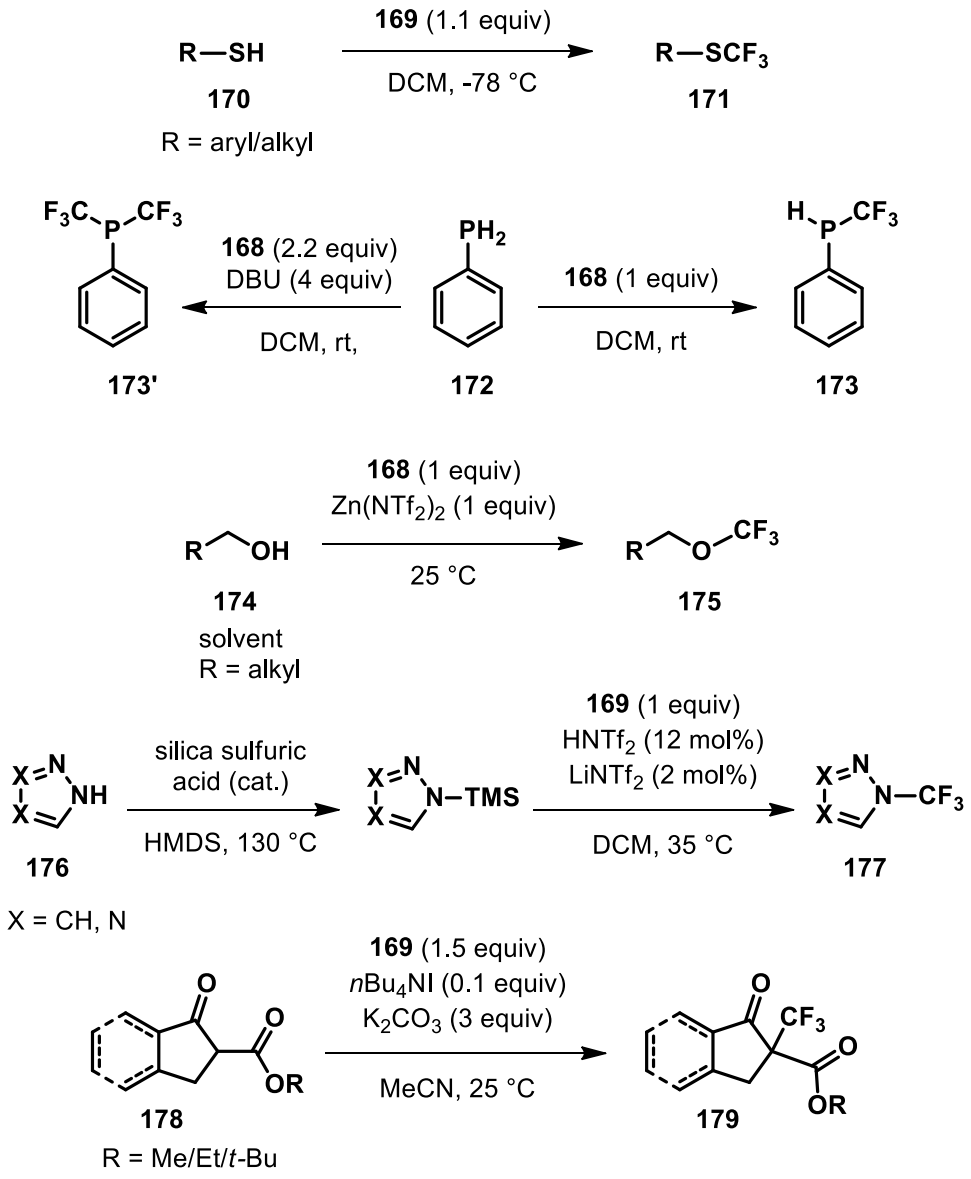


Figure 1.2F. Structures of Togni's reagents

Togni's reagents were well exploited in electrophilic trifluoromethylation of sulfur (**170**), phosphorous (**172**), oxygen (**174**), nitrogen (**176**) and carbon (**178**) nucleophilic centers to access the corresponding trifluoromethylated products **171**, **173**, **175**, **177**, and **179** (Scheme 1.2xxvi).[105]

1.2.3G. HIRs as alkynylation reagents

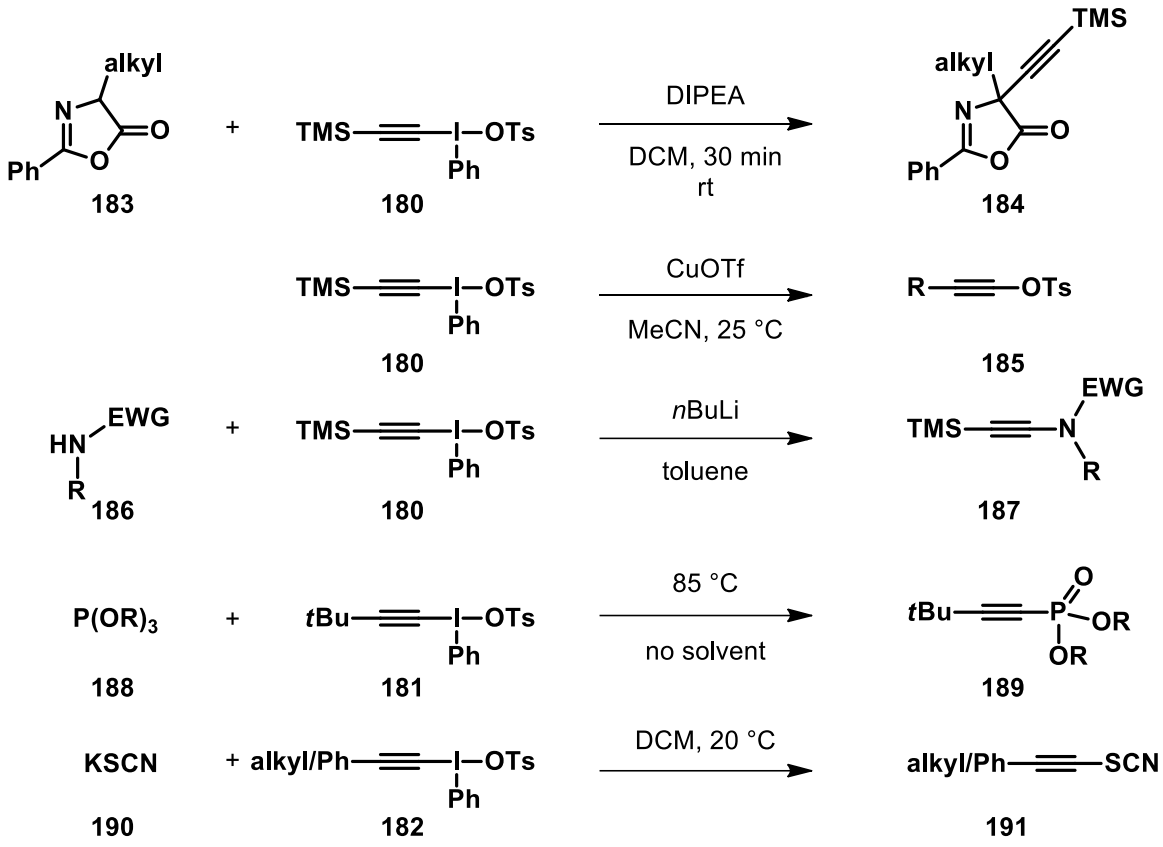
Alkynes are among the most versatile functionality in organic synthesis and found applications in several fields which include chemical biology and material science. Conventionally, alkynes are being introduced into organic molecules as nucleophilic synthons, but HIRs can afford a unique method to generate electrophilic alkyne synthons.[106] Since 1985, various alkynyliodonium salts (eg., **180**, **181** & **182**) were synthesized and explored in electrophilic alkynylation of different soft carbon nucleophiles (**183**) and heteroatom nucleophiles (**186**, **188**, **190**) (Scheme 1.2xxvii).[106]



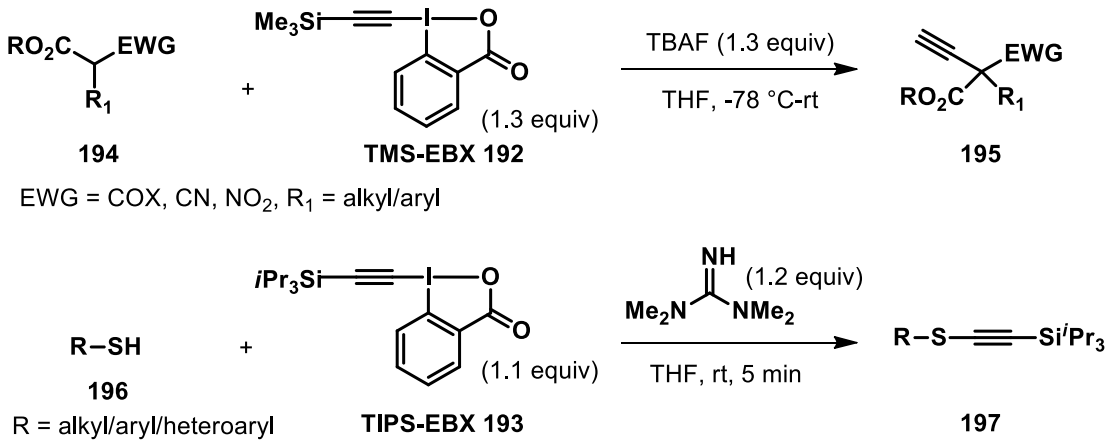
Scheme 1.2xxvi. Trifluoromethylation of heteroatom nucleophiles

Recently, the use of alkynyliodonium salts for the alkynylation reactions was less explored due to their unstable nature. The best way to enhance the stability of HIRs is to incorporate the iodine atom into a cyclic structure fused with the aromatic ring.[107] The first alkynylating cyclic HIR was synthesized by Ochiai et al. in 1991, but their use in organic synthesis has only been explored since 2009.[106] To date, several cyclic HIRs were synthesized and explored in electrophilic alkynylation reactions of various functionalities. In this context, the best known cyclic HIRs are TMS-EBX (**192**) and TIPS-EBX (**193**).

Scheme 1.2xxviii represents alkynylation of carbon (**194**) and sulphur (**196**) nucleophiles with **192/193** under metal-free reaction conditions.[108]



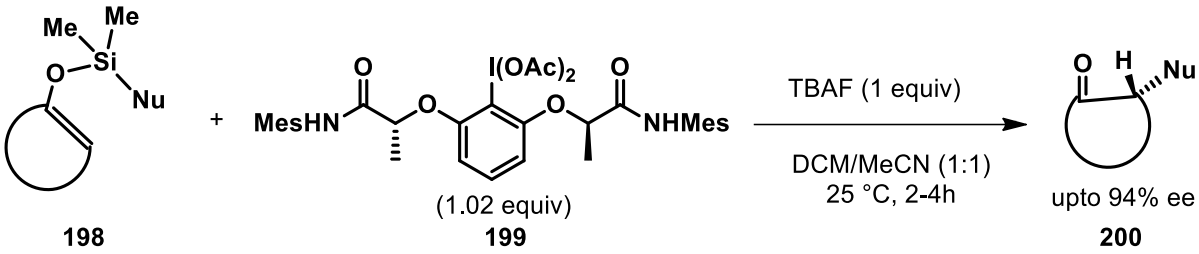
Scheme 1.2xxvii. Alkynyliodonium salts as electrophilic alkynylating agents



Scheme 1.2xxviii. Metal-free alkynylation reactions using cyclic HIRs **192/193**

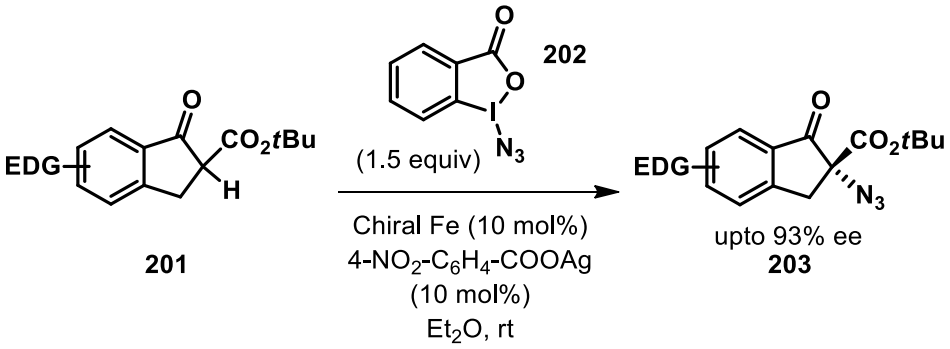
1.2.3H. HIRs in asymmetric synthesis

Over the last decade, the potential of HIRs as reagents or even catalysts in asymmetric synthesis has been well established. Asymmetric reactions can be accessed either by using chiral HIRs or by using achiral HIRs in the presence of chiral ligands.[109] Wirth et al. developed an enantioselective synthesis of α-functionalized carbonyl compounds **200** from silyl enol ethers **198** using lactate based chiral HIR **199** (Scheme 1.2xxix).[110]



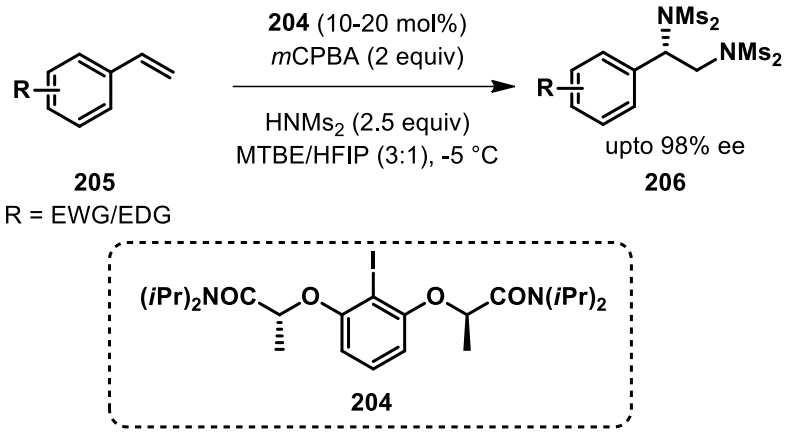
Scheme 1.2xxix. Chiral HIR mediated asymmetric synthesis

HIRs exhibit good compatibility with organocatalysts as well as chiral metal catalysts. Gade et al. reported an enantioselective α-azidation of β-ketoesters **201** by using cyclic HIR **202** as an azide source in the presence of chiral Fe catalyst to afford **203** in good to excellent enantioselectivities (Scheme 1.2xxx).[111]



Scheme 1.2xxx. Combination of HIRs with metals

Very recently, Muniz et al. reported an excellent enantioselective chiral iodine **204** catalyzed diamination of styrenes **205** by *in-situ* generation of HIR to afford the diamination products **206** upto 98% ee (Scheme 1.2xxxi).[112]



Scheme 1.2xxxi. HIR catalyzed asymmetric diamination

Overall, HIRs got much attention across the scientific community during the last few decades and continued to grow at a rapid pace which was clearly seen in an increased number of publications, special issues, cover articles, and conferences.

1.3. DDQ mediated oxidative transformations

The selective oxidation of organic molecules is a continuous challenge in the chemical industry and related fields. Much attention was paid to the development of transition metal catalysts to achieve such reactions. Recently, redox-active organic molecules were also employed in selective oxidative transformations as mild and environmentally benign reagents.[113] In this context, quinones such as DDQ and chloranil are excellent redox-active organic molecules which found applications in various redox processes that include industrial chemicals synthesis, oxidation reactions in organic synthesis and also as an electron carrier, anti-oxidants, and co-factors in biological processes.[113]

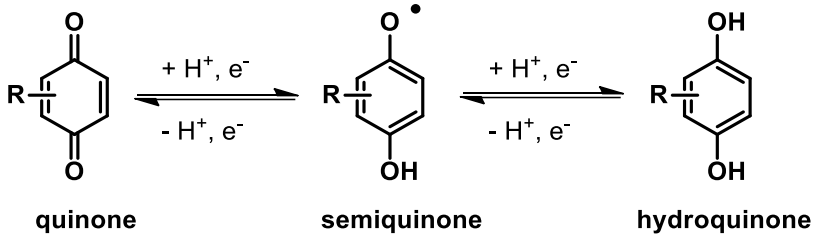


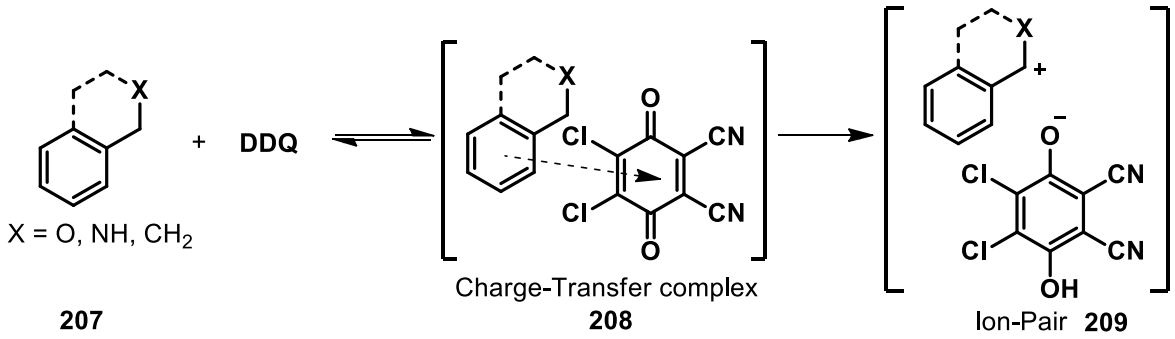
Figure 1.3A. Different oxidation states of quinones

Para-quinones exist in three oxidation states, namely, quinone (fully oxidized), semiquinone (one electron reduced) and hydroquinone (two electrons reduced) (Figure 1.3A).

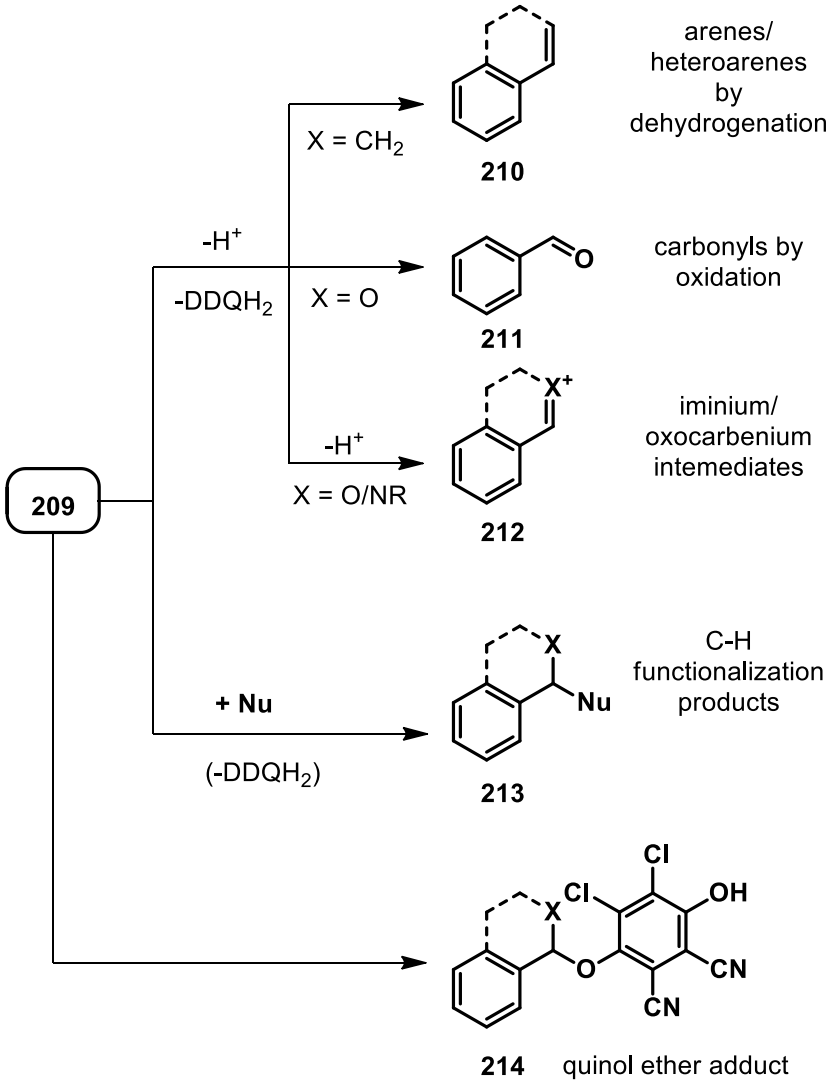
DDQ among the quinones having high reduction potential mainly involves in hydride transfer reactions. DDQ is known for several decades as an effective oxidant in several transformations including protecting-group removal, cross-coupling reactions, cyclizations and biaryl synthesis.[114] DDQ mediated hydride abstraction from a substrate **207** is believed to proceed through the formation of DDQ-substrate 'charge-transfer complex' **208**. In subsequent step, DDQ abstracts hydride ion from **208** resulting in the formation of ion-pair product **209** (Scheme 1.3i). This hydride transfer mechanism is not certain and has been the concept of some controversy. Some reports suggesting that the net hydride transfer is initiated by single electron transfer whereas others support hydrogen atom transfer, however, the direct hydride transfer is favored instead.[113]

The ion-pair **209** undergo a range of chemical reactions as shown in scheme 1.3i. Deprotonation of the substrate **209** by $DDQH^-$ can afford various dehydrogenated products such as arenes/heteroarenes **210**, carbonyl compounds **211**, and oxocarbenium/iminium ions **212**.[115] Alternatively, the intermediate carbocation can undergo nucleophilic addition reactions to generate C-H functionalized substrates **213**,[114b] and finally, the ion pair collapse may lead to quinol ether adduct **214**.[116]

For the last two decades, DDQ has received much attention across the synthetic community as a mild and selective oxidant in several inter- and intramolecular cross dehydrogenative coupling (CDC) reactions. In CDC, the new bond is formed between two non-functionalized carbon-carbon or carbon-hetero atoms under metal or metal-free (oxidants) conditions.[117] Recent progress in DDQ mediated/catalyzed intra/intermolecular bond formation reactions are briefly discussed hereafter.



207 **208** **209**



210 **211** **212** **213** **214**

Scheme 1.3i. DDQ mediated hydride transfer mechanism/subsequent reactions

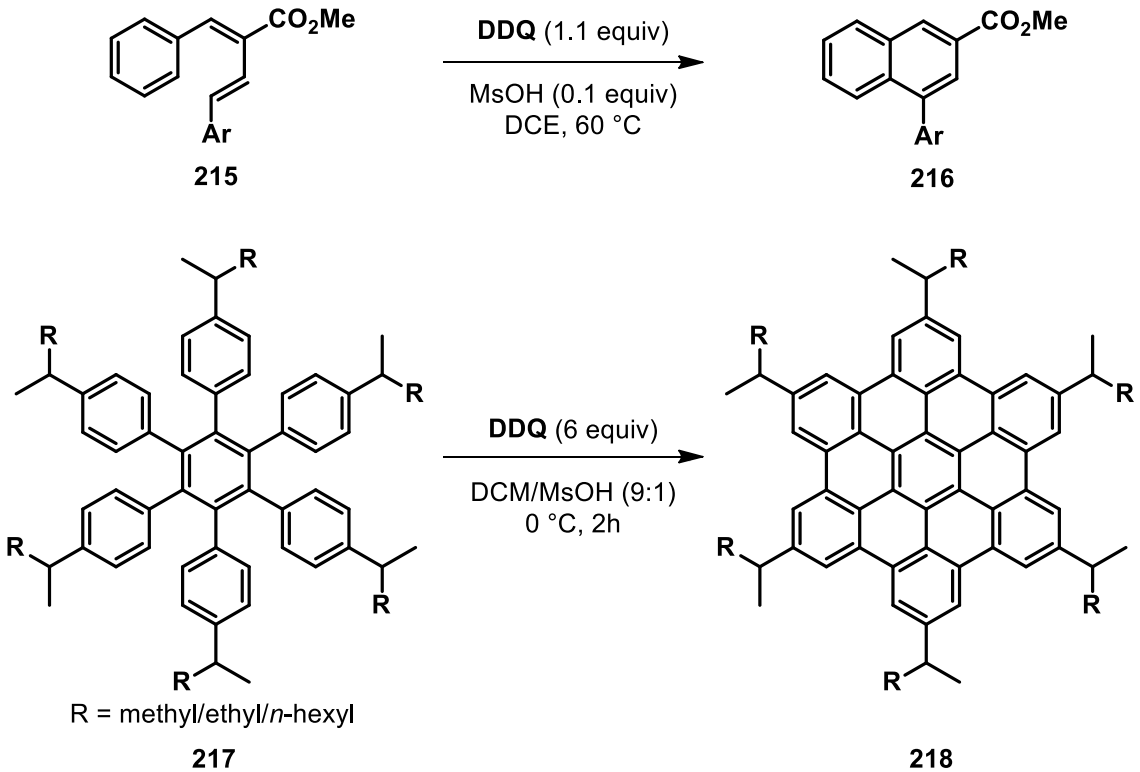
1.3.1. DDQ mediated intramolecular C-C bond formations

DDQ is a mild and readily available oxidant mediating several intramolecular dehydrogenative coupling (IDC) reactions to construct new C-C bonds. Kim et al.

reported an efficient DDQ mediated intramolecular arene-alkene coupling reaction of 1,4-diaryl-1,3-butadienes **215** in the presence of methane sulfonic acid (MsOH) to generate naphthalene derivatives **216** (Scheme 1.3ii).[118] DDQ is considered as one of the best reagents for Scholl reaction, an oldest intramolecular oxidative cyclodehydrogenation reaction to construct planar polyaromatic hydrocarbons (PAHs).[119] Recently, Rathore et al. exploited the Scholl reaction conditions (DDQ/acid) for the synthesis of hexa-*peri*-hexabenzocoronenes **218** from hexakis(4-isoalkylphenyl)benzenes **217** in excellent yields (Scheme 1.3ii).[120]

1.3.2. DDQ mediated intramolecular carbon-heteroatom (C-X) bond formations

Intramolecular oxidative C-H functionalization under metal-free conditions offers a unique alternative to metal-catalyzed reactions to construct various heterocyclic scaffolds which are prevalent in pharmaceuticals, agrochemicals and natural products.



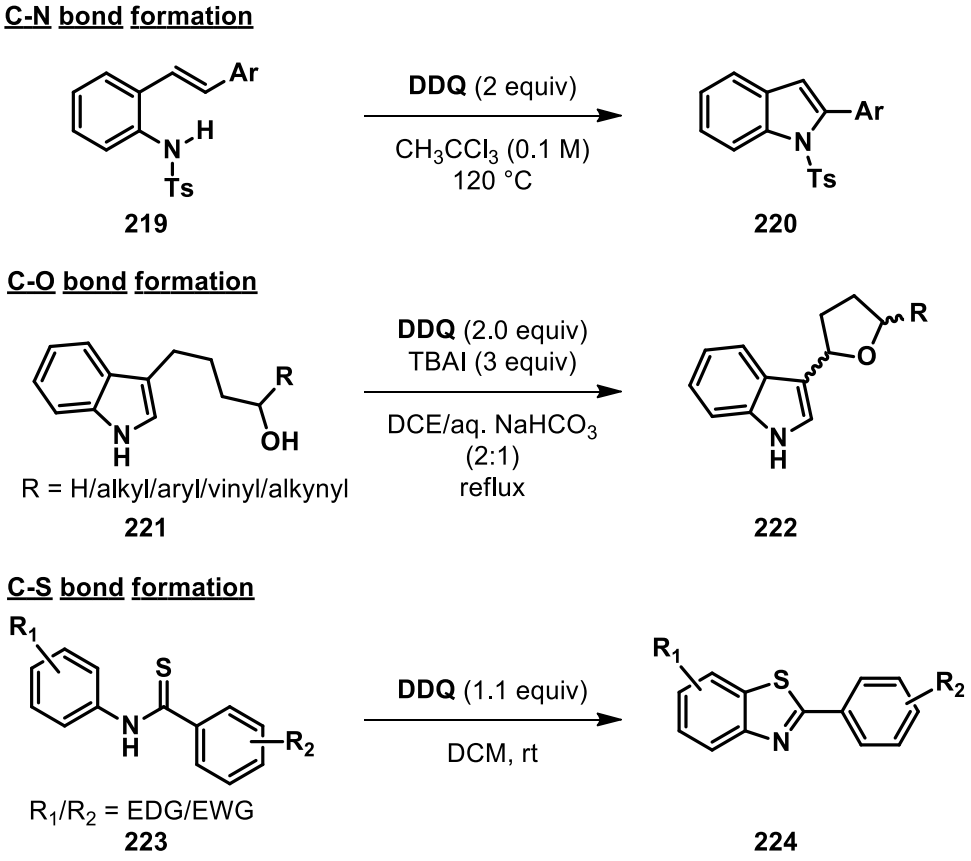
Scheme 1.3ii. DDQ mediated intramolecular C-C bond formation reactions (IDC)

Youn et al. reported an effective DDQ mediated intramolecular C-H amination reaction of N-Ts-2-alkenylanilines **219** to synthesize a diverse range of substituted indoles **220**

(Scheme 1.3iii).[121] Sperry et al. developed a DDQ mediated cycloetherification of indole-3-butanol **221** to access a series of 2-(3′-indolyl)tetrahydrofurans **222** under biphasic oxidation conditions by an intramolecular sp^3 C-H oxygenation reaction (Scheme 1.3iii).[122] Bose et al. reported a practical method for the synthesis of 2-arylbenzothiazoles **224** from thioformanilides **223** via DDQ mediated intramolecular cyclization reaction (Scheme 1.3iii).[123]

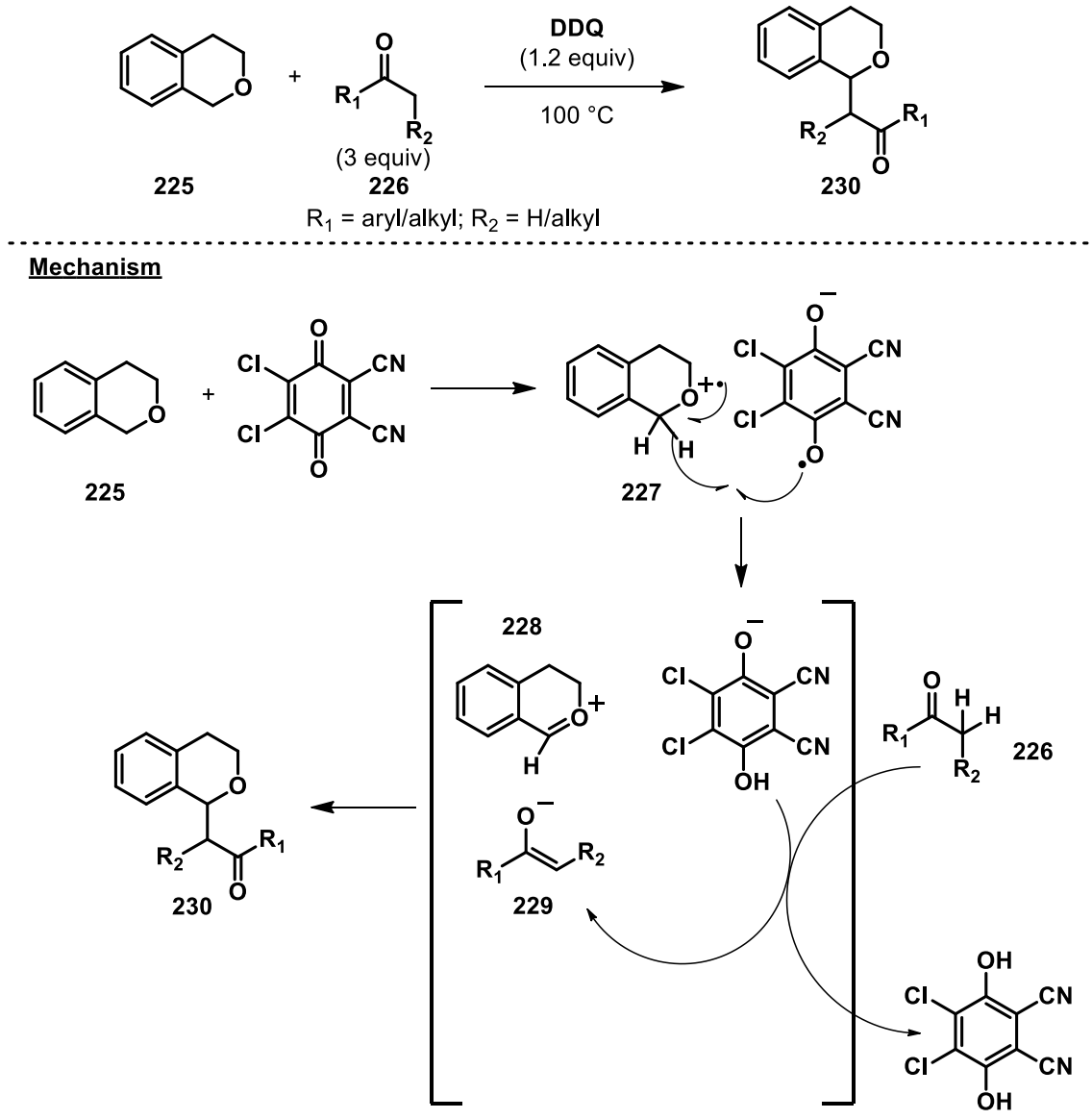
1.3.3. DDQ mediated cross-dehydrogenative couplings (CDC)

Oxidative CDC reactions between two non-functionalized C-H bonds represents the state-of-art in C-C bond formations because it makes synthetic routes shorter and more efficient.[117,124] In 2006, Li et al. developed a first DDQ mediated CDC reaction between benzyl ethers **225** and ketones **226** under solvent-free heating conditions to get the corresponding cross-coupled product **230** in moderate to good yields (Scheme 1.3iv).[114b]



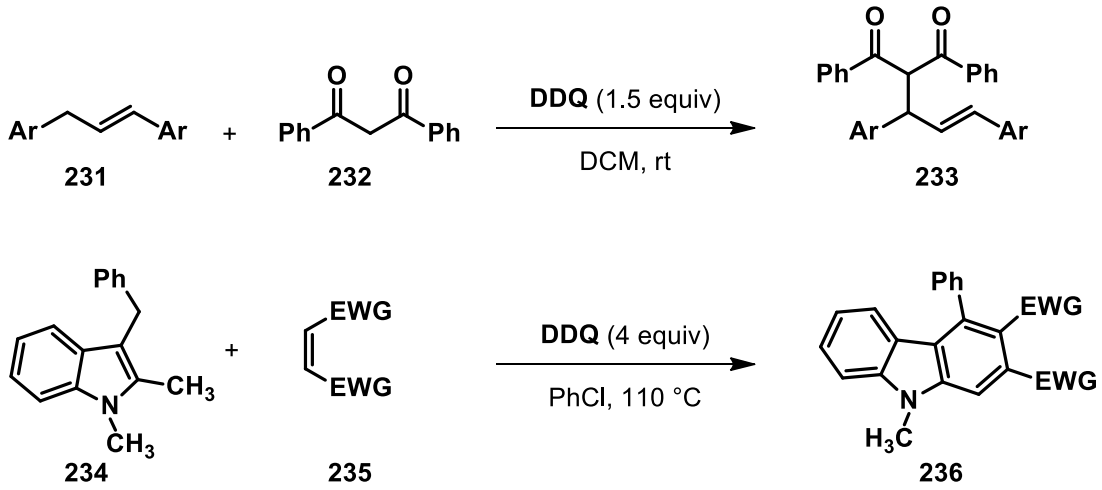
Scheme 1.3iii. DDQ mediated intramolecular C-heteroatom bond formations

They proposed a tentative mechanism which involves SET from benzyl ether **225** to DDQ to produces benzyl ether radical cation **227** and DDQ radical anion. Hydrogen abstraction from radical cation **227** by radical oxygen of DDQ generates benzoxy cation **228**. Then, the resulting DDQ-H anion abstracts a proton from ketone **226** to produce an enolate ion **229** and neutral DDQ-H_2. Finally, nucleophilic attack by enolate anion **229** onto the benzoxy cation **228** affords CDC product **230** (Scheme 1.3iv).



Scheme 1.3iv. Li's first DDQ mediated CDC reaction and proposed mechanism

Other representative CDC reactions include, DDQ mediated cross-coupling between allylic **231** and active methylenic compounds **232** developed by Bao et al. under very mild conditions at room temperature to get the corresponding allylic alkylation products **233** (Scheme 1.3v).[125] Zhang et al. came up with an unprecedented dehydrogenative Diels-Alder reaction between 2-methyl-3-alkyl indoles **234** and dienophiles **235** in the presence of DDQ to synthesize carbazole derivatives **236** (Scheme 1.3v).[126]



Scheme 1.3v. DDQ mediated CDC reactions

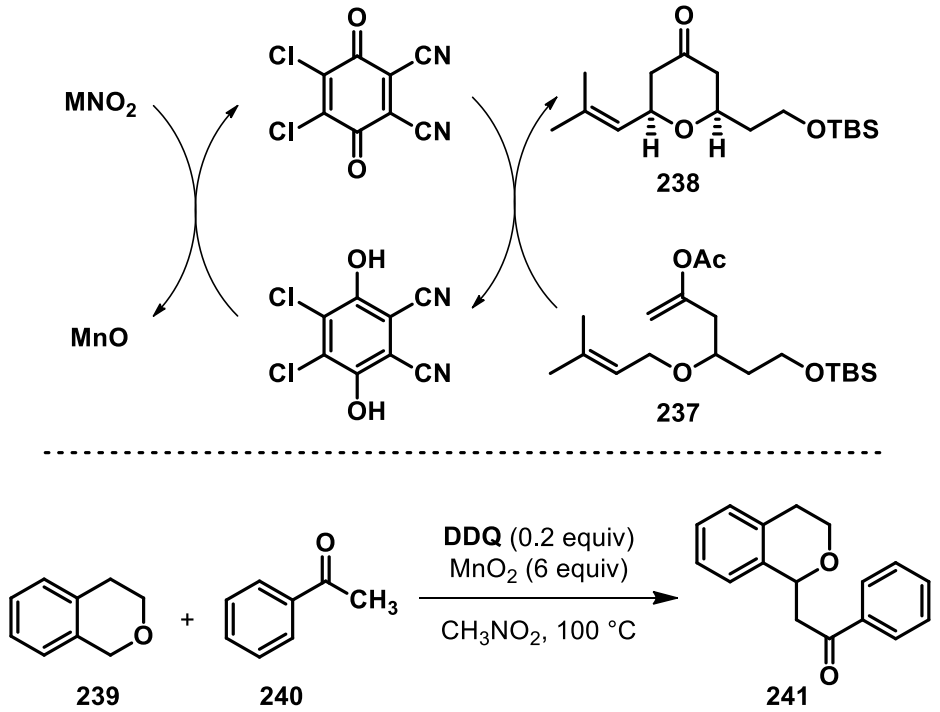
1.3.4. DDQ catalyzed dehydrogenative couplings

Undoubtedly, DDQ is an excellent stoichiometric oxidant in organic synthesis. Despite its versatility, DDQ is associated with some disadvantages,[113] they are

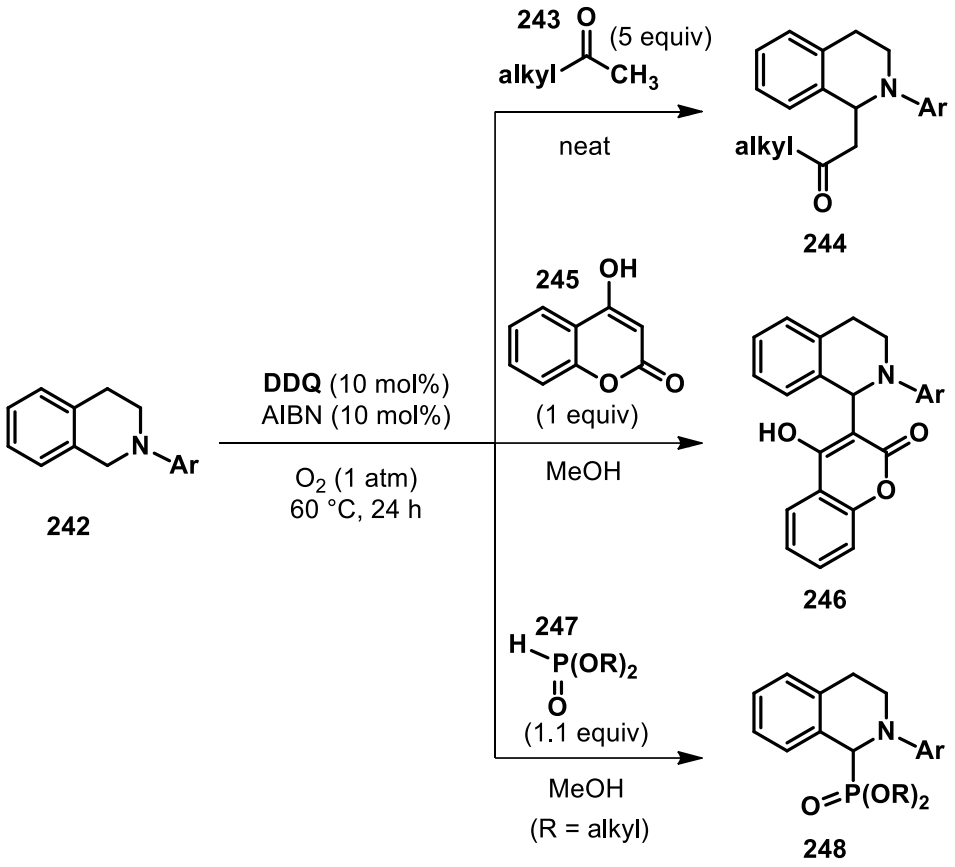
- Relatively high toxicity (LD50 = 82 mg/kg rat)
- Moderately expensive (> $500/mol)
- Hazardous HCN liberation upon reaction with water
- Difficulty in removal of by-product $DDQH_2$

However, DDQ exhibits unique reactivity patterns and replacement with more benign reagent may not always possible. Hence, the best way is to use DDQ as a catalyst by regenerating in the presence more benign oxidants.[127] In this context, Floreancig et al. developed an oxidative IDC reaction of prenyl ether **237** catalyzed by DDQ in the presence of excess amount of MnO_2 as a terminal oxidant to provide tetrahydro pyrone

238 (Scheme 1.3vi).[128] They have further demonstrated the applicability of DDQ/MnO_2 combination for other transformations including deprotection of PMB ether, dehydrogenation of dihdronaphthalene to naphthalene and CDC reaction between acetophenone **239** and isochromans **240** to afford the alkylation product **241** (Scheme 1.3vi). Prabhu et al. exploited the catalytic activity of DDQ (10 mol%) for the C-H activation of N-aryl tetrahydroisoquinoline **242** in a CDC reaction to form new C-C and C-P bonds.[129] The reaction does not require a large quantity of external oxidant, instead, it uses the catalytic amount of AIBN (10 mol%) in the presence of aerobic conditions to regenerate DDQ. They have successfully utilized simple unactivated ketones **243**, 4-hydroxycoumarins **245** and dialkyl phosphites **247** as suitable nucleophiles to access the corresponding CDC products **244**, **246** and **248** (Scheme 1.3vii).



Scheme 1.3vi. DDQ catalyzed IDC and CDC reactions in the presence of excess MnO_2



Scheme 1.3vii. DDQ catalyzed C-C/C-P bond formations by CDC

1.4. Conclusion and present work

Multicomponent reactions (MCRs) offer a unique opportunity to access molecules with enough diversity and complexity. They have been employed as an alternative to conventional two-component reactions and multi-step total synthesis of natural products, lead molecules, and functional materials. In recent years, the synthetic community is paying much attention to improve the efficacy of existing MCRs and also to develop novel MCRs. In this context, we became interested in developing new kind of MCRs by using readily available and common laboratory reagents to synthesize functionalized hetero and carbocycles of biological relevance. Accordingly, we have developed two MCRs under very mild and metal-free conditions to access functionalized 1,2-DHPs and biaryls. The details of the synthetic methods and their applications are comprehensively discussed in chapter 2 and 3, respectively. On the other hand, HIRs and DDQ are mild

and selective oxidants which are known to organic chemists for the last several decades. These oxidants are considered as alternatives to toxic metals in several carbon-carbon and carbon-heteroatom bond formations. Our aim is to develop metal-free methods to synthesize various molecules of biological relevance, and our literature survey revealed that HIRs and DDQ are proper reagents of choice towards this endeavour. In chapter 4, we have discussed new oxidation reactions using these reagents to synthesize a diverse library of molecules which include diindolylketones, cyclohepta[*b*]indoles, indolo[2,3-*b*]quinolines, and 3-alkenyl-oxindoles from readily available diindolylmethane (DIM) substrates.

1.5. References

1. Nicolaou, K. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 131.
2. Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657.
3. Wender, P. A. *Tetrahedron* **2013**, *69*, 7529.
4. Ugi, I.; Dömling, A.; Horl, W. *Endeavour* **1994**, *18*, 115.
5. (a) Brauch, S.; van Berkel, S. S.; Westermann, B. *Chem. Soc. Rev.* **2013**, *42*, 4948. (b) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. (c) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. - Eur. J.* **2000**, *6*, 3321. (d) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969. (e) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234.
6. Strecker, A. *Ann. Chem.* **1850**, *75*, 27.
7. Laurent, A.; Gerhardt, C. F. *Ann. Chem. Phys.* **1838**, *66*, 281.
8. Hantzsch, A. *Justus Liebegs Ann. Chem.* **1882**, *215*, 1.
9. Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474.
10. Biginelli, P. *Chemische Berichte.* **1891**, *24*, 1317.

11. Mannich, C.; Krosche, W. *Arch. Pharm.* **1912**, *250*, 647.

12. Robinson, R. *J. Chem. Soc.* **1917**, *111*, 876.

13. (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (b) Van Berkel, S. S.; Bögels, B. G. M.; Wijdeven, M. A.; Westermann, B.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2012**, *2012*, 3543. (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.

14. Passerini, M.; Simone, L. *Gazz. Chim. Ital.* **1921**, *51*, 126.

15. (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386. (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (c) Akritopoulou-Zanze, I. *Curr. Opin. Chem. Biol.* **2008**, *12*, 324. (d) Biggs Houck, J. E.; Younai, A.; Shaw, J. T. *Curr. Opin. Chem. Biol.* **2010**, *14*, 371.

16. Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583.

17. Weber, L. *Curr. Med. Chem.* **2002**, *9*, 2085.

18. Domling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083.

19. Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439.

20. Sunderhaus, J. D.; Martin, S. F. *Chem. - Eur. J.* **2009**, *15*, 1300.

21. (a) Levi, L.; Muller, T. J. J. *Chem. Soc. Rev.* **2016**, *45*, 2825. (b) De Moliner, F.; Kielland, N.; Lavilla, R.; Vendrell, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 3758.

22. Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234.

23. Dömling, A.; Ugi, I *Angew. Chem., Int. Ed.* **1993**, *32*, 563.

24. Elders, N.; van der Born, D.; Hendrickx, L. J. D.; Timmer, B. J. J.; Krause, A.; Janssen, E.; de Kanter, F. J. J.; Ruijter, E.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 5856.

25. D'Souza, D. M.; Muller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095.

26. (a) Wender, P. A.; Fournogerakis, D. N.; Jeffreys, M. S.; Quiroz, R. V.; Inagaki, F.; Pfaffenbach, M. *Nat. Chem.* **2014**, *6*, 448. (b) Leitch, D. C.; Kayser, L. V.; Han, Z.-

Y.; Siamaki, A. R.; Keyzer, E. N.; Gefen, A.; Arndtsen, B. A. *Nat. Commun.* **2015**, *6*, 7411. (c) Torres, G. M.; Quesnel, J. S.; Bijou, D.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2016**, *138*, 7315.

27. Musher, J. L. *Angew. Chem., Int. Ed.* **1969**, *8*, 54.
28. Gillespie, R. J.; Robinson, E. A. *Inorg. Chem.* **1995**, *34*, 978.
29. Willgerodt, C. *J. Prakt. Chem.* **1886**, *33*, 154.
30. (a) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH Publishers, Inc.: New York, 1992. (b) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; AcademicPress: London, 1997. (c) Moriarty, R. M.; Prakash, O. *Hypervalent Iodine in Organic chemistry: Chemical Transformations*; Wiley-Interscience: 2008.
31. (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (b) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proced. Int.* **1997**, *29*, 409. (c) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271. (d) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (e) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997. (f) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (g) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. (h) Zhdankin, V. V. *Sci. Synth.* **2007**, *31a*, 161.
32. Perkins, C. W.; Martin, J. C.; Arduengo, A. J.; Law, W.; Alegria, A.; Kochi, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 7753.
33. Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299.
34. Musher, J. I. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 65.
35. Martin, J. C. *Science* **1983**, *221*, 509.
36. (a) Landrum, G. A.; Goldberg, N.; Hoffmann, R. *J. Chem. Soc., Dalton Trans.* **1997**, 3605. (b) Ochiai, M.; Sueda, T.; Miyamoto, K.; Kiprof, P.; Zhdankin, V. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 8203.

37. (a) Batchelor, R. J.; Birchall, T.; Sawyer, J. F. *Inorg. Chem.* **1986**, *25*, 1415. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (c) Dess, D. B.; Wilson, S. R.; Martin, J. C. *J. Am. Chem. Soc.* **1993**, *115*, 2488.

38. (a) Hiller, A.; Patt, J. T.; Steinbach, J. *Magn. Reson. Chem.* **2006**, *44*, 955. (b) Richter, H. W.; Cherry, B. R.; Zook, T. D.; Koser, G. F. *J. Am. Chem. Soc.* **1997**, *119*, 9614.

39. (a). Ochiai, M. In *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis;* Wirth, T., Ed.; Springer: New York, 2003. (b) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328.

40. Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, *19*, 244.

41. (a). Pelter,A.; Ward, R. S. *Tetrahedron* **2001**, *57*, 273. (b) Stang, P. J.; Boehshar, M.; Wingert, H.; Kitamura, T. *J. Am. Chem. Soc.* **1988**, *110*, 3272.

42. (a). Hadjiarapoglou, L.; Spyroudis, S.; Varvoglis, A. *Synthesis* **1983**, *1983*, 207. (b) Rabah, G. A.; Koser, G. F. *Tetrahedron Lett.* **1996**, *37*, 6453.

43. Kita, Y.; Okuno, T.; Tohma, H.; Akai, S. *Tetrahedron Lett.* **1994**, *35*, 2717.

44. (a). Koser, G. F.; Wettach, R. H.; Smith, C. S. *J. Org. Chem.* **1980**, *45*, 1543. (b) Williamson, B. L.; Stang, P. J.; Arif, A. M. *J. Am. Chem. Soc.* **1993**, *115*, 2590.

45. Ochiai, M.; Takaoka, Y.; Nagao, Y. *J. Am. Chem. Soc.* **1988**, *110*, 6565.

46. Reich, H. J.; Peake, S. L. *J. Am. Chem. Soc.* **1978**, *100*, 4888.

47. Kitamura, T.; Yamane, M.; Inoue, K.; Todaka, M.; Fukatsu, N.; Meng, Z.; Fujiwara, Y.*J. Am. Chem. Soc.* **1999**, *121*, 11674.

48. Ochiai, M.; Iwaki, S.; Ukita, T.; Nagao, Y. *Chem. Lett.* **1987**, 133.

49. Mizukami, F.; Ando, M.; Tanaka, T.; Imamura, J. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 335.

50. Loudon, G. M.; Radhakrishna, A. S.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem.* **1984**, *49*, 4272.

51. Ochiai, M.; Takaoka, Y.; Masaki, Y.; Nagao, Y.; Shiro, M. *J. Am. Chem. Soc.* **1990**, *112*, 5677.

52. Oae, S.; Uchida, Y. *Acc. Chem. Res.* **1991**, *24*, 202.

53. Ochiai, M.; Sumi, K.; Takaoka, Y.; Kunishima, M.; Nagao, Y.; Shiro, M.; Fujita, E. *Tetrahedron* **1988**, *44*, 4095.

54. Chen, K.; Koser, G. F. *J. Org. Chem.* **1991**, *56*, 5764.

55. Togo, H.; Katohgi, M. *Synlett* **2001**, 565.

56. Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684.

57. Koser, G. F. *Aldrichimica Acta* **2001**, *34*, 89.

58. (a). Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052. (b) Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165.

59. Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571.

60. (a). Muller, P. *Acc. Chem. Res.* **2004**, *37*, 243. (b) Malamidou-Xenikaki, E.; Spyroudis, S. *Synlett* **2008**, *2008*, 2725.

61. Frohn, H.-J.; Hirschberg, M. E.; Wenda, A.; Bardin, V. V. *J. Fluorine Chem.* **2008**, *129*, 459.

62. Brand, J. P.; Gonzalez, D. F.; Nicolai, S.; Waser, J. *Chem. Commun.* **2011**, *47*, 102.

63. Togo, H.; Sakuratani, K. *Synlett* **2002**, 1966.

64. (a). Moriarty, R. M.; Prakash, O. *Org. React.* **2001**, *57*, 327. (b). Quideau, S.; Pouysegu, L.; Deffieux, D. *Synlett* **2008**, *2008*, 467.

65. Moreno, I.; Tellitu, I.; Herrero, M. T.; SanMartin, R.; Dominguez, E. *Curr. Org. Chem.* **2002**, *6*, 1433.

66. Singh, F. V.; Wirth, T. *Synthesis* **2013**, *45*, 2499.

67. Silva, L. F., Jr. *Molecules* **2006**, *11*, 421.

68. Dohi, T.; Kita, Y. *ChemCatChem* **2014**, *6*, 76.

69. Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924.

70. Liang, H.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 11849.

71. (a) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed*. **2006**, *45*, 4402. (b) Singh, F. V.; Wirth, T. *Chem. - Asian J.* **2014**, *9*, 950.

72. Ladziata, U.; Zhdankin, V. V. *Arkivoc* **2006**, *ix*, 26.

73. Wang, X.; Studer, A. *Acc. Chem. Res.* **2017**, *50*, 1712.

74. Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus,V. *Angew. Chem., Int. Ed.* **2012**, *51*,5062.

75. Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219.

76. Dohi, T.; Kita, Y. *Top. Curr. Chem.* **2016**, *373*, 1.

77. Dohi, T.; Ito, M.; Morimoto, K.; Iwata, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 1301.

78. Morimoto, K.; Sakamoto, K.; Ohshika, T.; Dohi, T.; Kita, Y. *Angew. Chem., Int. Ed.* **2016**, *55*, 3652.

79. Quideau, S.; Pouysegu, L.; Deffieux, D. *Synlett* **2008**, *2008*, 467.

80. Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775.

81. Quideau, S.; Pouysegu, L.; Peixoto, P. A.; Deffieux, D. *Top Curr Chem.* **2016**, *373*, 25.

82. Portalier, F.; Bourdreux, F.; Marrot, J.; Moreau, X.; Coeffard, V.; Greck, C. *Org. Lett.* **2013**, *15*, 5642.

83. Parumala, S. K. R.; Peddinti, R. K. *Org. Lett.* **2013**, *15*, 3546.

84. Murarka, S.; Antonchick, A. P. *Top. Curr. Chem.* **2015**, *373*, 75.

85. Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 8605.

86. Manna, S.; Matcha, K.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 8163.

87. Bodipati, N.; Peddinti, R. K. *Org. Biomol. Chem.* **2012**, *10*, 1958.

88. Olofsson, B. *Top. Curr. Chem.* **2016**, *373*, 135.

89. Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052.

90. Kita, Y.; Dohi, T. *Chem. Rec.* **2015**, *15*, 886.

91. Wang, B.; Graskemper, J. W.; Qin, L.; DiMagno, S. G. *Angew. Chem., Int. Ed.* **2010**, *49*, 4079.

92. (a) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610. (b) Bielawski, M.; Olofsson, B. *Chem. Commun.* **2007**, *2007*, 2521. (c) Olofsson, B.; Zhu, M.; Jalalian, N. *Synlett* **2008**, *2008*, 592. (d) Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602.

93. Beringer, F. M.; Brierley, A.; Drexler, M.; Gindler, E. M.; Lumpkin, C. C. *J. Am. Chem. Soc.* **1953**, *75*, 2708.

94. Guo, F.; Wang, L.; Wang, P.; Yu, J.; Han, J. *Asian J. Org. Chem.* **2012**, *1*, 218.

95. Jalalian, N.; Ishikawa, E. E.; Silva, L. F.; Olofsson, B. *Org. Lett.* **2011**, *13*, 1552.

96. Matsuzaki, K.; Okuyama, K.; Tokunaga, E.; Shiro, M.; Shibata, N. *Chemistry Open* **2014**, *3*, 233.

97. Wang, Y.; Chen, C.; Peng, J.; Li, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 5323.

98. Wu, X.; Yang, Y.; Han, J.; Wang, L. *Org. Lett.* **2015**, *17*, 5654.

99. Maertens, G.; Canesi, S. *Top. Curr. Chem.* **2015**, *373*, 223.

100. Kalesse, M.; Landsberg, D. *Synlett* **2010**, *2010*, 1104.

101. Singh, J.; Rehbein, F. V.; Wirth, T. *ChemistryOpen* **2012**, *1*, 245.

102. (a) Guerard, K. C.;´ Chapelle, C.; Giroux, M.-A.; Sabot, C.; Beaulieu, M.-A.; Achache, N.; Canesi, S. *Org. Lett.* **2009**, *11*, 4756. (b) Beaulieu, M.-A.; Sabot, C.; Achache, N.; Guerard, K. C.; Canesi, S.´ *Chem. - Eur. J.* **2010**, *16*, 11224.

103. Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Ace Ça, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422.

104. Eisenberger, P.; Gischig, S.; Togni, A. *Chem. - Eur. J.* **2006**, *12*, 2579.

105. Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650.

106. Waser, J. *Top. Curr. Chem.* **2015**, *373*, 187.

107. Brand, J. P.; Gonzales, D. F.; Nicolai, S.; Waser, J. *Chem. Commun.* **2011**, *47*, 102.

108. (a) Gonzalez, D. F.; Brand, J. P.; Waser, J.´ *Chem. - Eur. J.* **2010**, *16*, 9457. (b) Frei, R.; Waser, J. *J. Am. Chem. Soc.* **2013**, *135*, 9620.

109. Kumar, R.; Wirth, T. *Top. Curr. Chem.* **2015**, *373*, 243.

110. Mizar, P.; Wirth, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 5993.

111. Deng, Q.-H.; Bleith, T.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2013**, *135*, 5356.

112. Muñiz, K.; Barreiro, L.; Romero, R. M.; Martínez, C. *J. Am. Chem. Soc.* **2017**, *139*, 4354.

113. Wendlandt, A. E.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2015**, *54*, 14638.

114. (a) Cheng, D.; Bao, W. *J. Org. Chem.* **2008**, *73*, 6881. (b) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242. (c) Liu, L.; Floreancig, P. E. *Org. Lett.* **2010**, *12*, 4686. (d). Navale, T. S.; Thakur, K.; Rathore, R. *Org. Lett.* **2011**, *13*, 1634.

115. (a) Hilt, G.; Danz, M. *Synthesis* **2008**, 2257. (b) Auvinet, A.-L.; Harrity, J. P. A.; Hilt, G. *J. Org. Chem.* **2010**, *75*, 3893. (c) Manning, J. R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2008**, *130*, 8602. (d) Peng, K.; Chen, F.; She, X.; Yang, C.; Cui, Y.;

Pan, X. *Tetrahedron Lett.* **2005**, *46*, 1217. (e) Rahim, M. A.; Matsumura, S.; Toshima, K. *Tetrahedron Lett.* **2005**, *46*, 7307.

116. Batista, V. S.; Crabtree, R. H.; Konezny, S. J.; Luca, O. R.; Praetorius, J. M. *New J. Chem.* **2012**, *36*, 1141.
117. Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.
118. Kim, K. H.; Lim, C. H.; Lim, J. W.; Kim, J. N. *Adv. Synth. Catal.* **2014**, *356*, 697.
119. Scholl, R.; Mansfeld, J. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1734.
120. Zhai, L.; Shukla, R.; Rathore, R. *Org. Lett.* **2009**, *11*, 3474.
121. Jang, Y. H.; Youn, S. W. *Org. Lett.* **2014**, *16*, 3720.
122. Gillard, R. M.; Sperry, J. *J. Org. Chem.* **2015**, *80*, 2900.
123. Bose, D. S.; Idrees, M. *Tetrahedron Lett.* **2007**, *48*, 669.
124. (a). Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (b). Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068.
125. Cheng, D.; Bao, W. *Adv. Synth. Catal.* **2008**, *350*, 1263.
126. Zhou, L.; Xu, B.; Zhang, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 9092.
127. Qin, Y.; Zhu, L.; Luo, S. *Chem. Rev.* **2017**, *117*, 9433.
128. Liu, L.; Floreancig, P. E. *Org. Lett.* **2010**, *12*, 4686.
129. Alagiri, K.; Devadig, P.; Prabhu, K. R. *Chem. - Eur. J.* **2012**, *18*, 5160.

Chapter-2

A Three-Component Synthesis of 1,2-Dihydropyridines

2.1. Abstract

This chapter involves synthesis of functionalized 1,2-dihydropyridines (1,2-DHPs) by a facile one-pot three-component reaction (3CR). This reaction comprises of an unexplored dienaminodioate (**2**) and readily available aromatic aldehydes (**3**) and amines (**4**) in the presence of a stoichiometric amount of trifluoroacetic acid (TFA) in acetonitrile solvent (Figure 2.1A). All the reactions were conducted at room temperature in an expedient manner generating the products in good to excellent yields. This metal-free condensation reaction exhibited broad aromatic substrate scope.

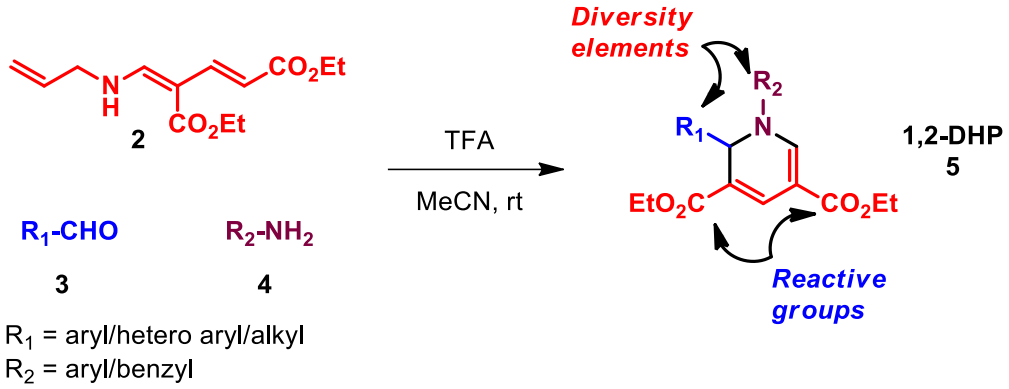


Figure 2.1A. Synthesis of 1,2-DHP by a cascade 3CR approach

2.2. Introduction

Dihydropyridines serve as important intermediates in the synthesis of pyridine derivatives and fascinated both synthetic and medicinal chemists for the last several decades.[1] Hantzsch reported the first synthesis of dihydropyridine (DHP) in 1882.[2] During his attempted synthesis of pyridine derivatives; he discovered a 1,4-dihydropyridine (1,4-DHP) intermediate which is the basis for dihydropyridine chemistry. Theoretically, five isomeric DHP structures **6-10** are possible (Figure 2.2A), but most of the known DHPs

are either the 1,2-DHP **6** or the 1,4-DHP **7**, due to imine tautomerizing to stable enamines.[1a]

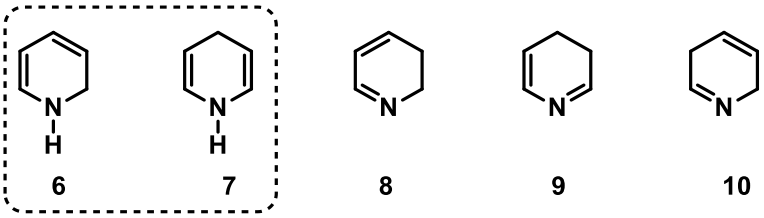


Figure 2.2A. Possible isomeric structures of DHP

2.2.1. Importance of dihydropyridines

2.2.1A. 1,4-DHP

Since the discovery of 1,4-DHP by Hantzsch, this heterocyclic motif received much attention across the scientific community and exhibited a broad spectrum of biological activities. The resurgence of interest in this molecule is due to its close resemblance to the reduced form of nicotinamide adenine dinucleotide (NADH), which is an oxidoreductase co-enzyme in biological systems.[1d] 1,4-DHPs are well-known calcium channel modulating agents in the treatment of cardiovascular diseases (eg., Nifedipine, Amlodipine, Lacidipine, Felodipine, Nimodipine and Isradipine) (Figure 2.2B), and also explored as anticancer, antimycobacterial and anticonvulsant agents.[3]

2.2.1B. 1,2-DHP

1,2-DHP is a relatively unexplored motif in medicinal chemistry. Very recently, Wang et al. investigated the neuroprotective effect of 2-substituted 1,2-DHP, and indeed it has exhibited good neuroprotective effect by mitochondrial pathway.[4] 1,2-DHP is considered as an important intermediate in the synthesis of pyridines, piperidines, and pyridones.[5] For instance, Charette et al. reported the conversion of 1,2-DHP intermediate **11** to the corresponding pyridine **12** and piperidine **13** under oxidation and reduction conditions, respectively (Scheme 2.2.1).[5a-c]

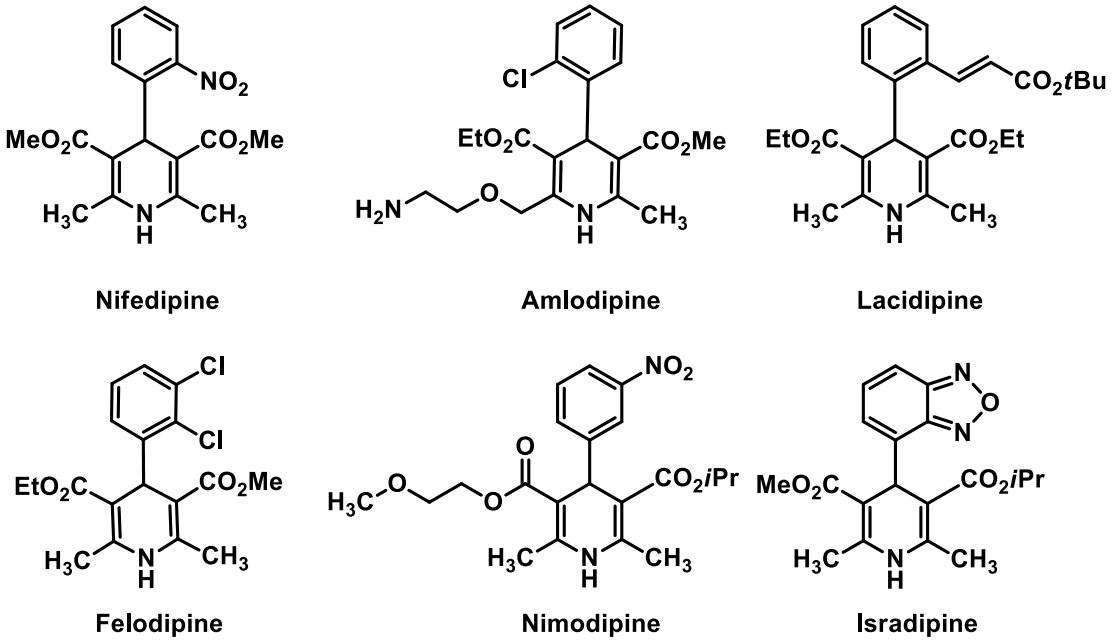
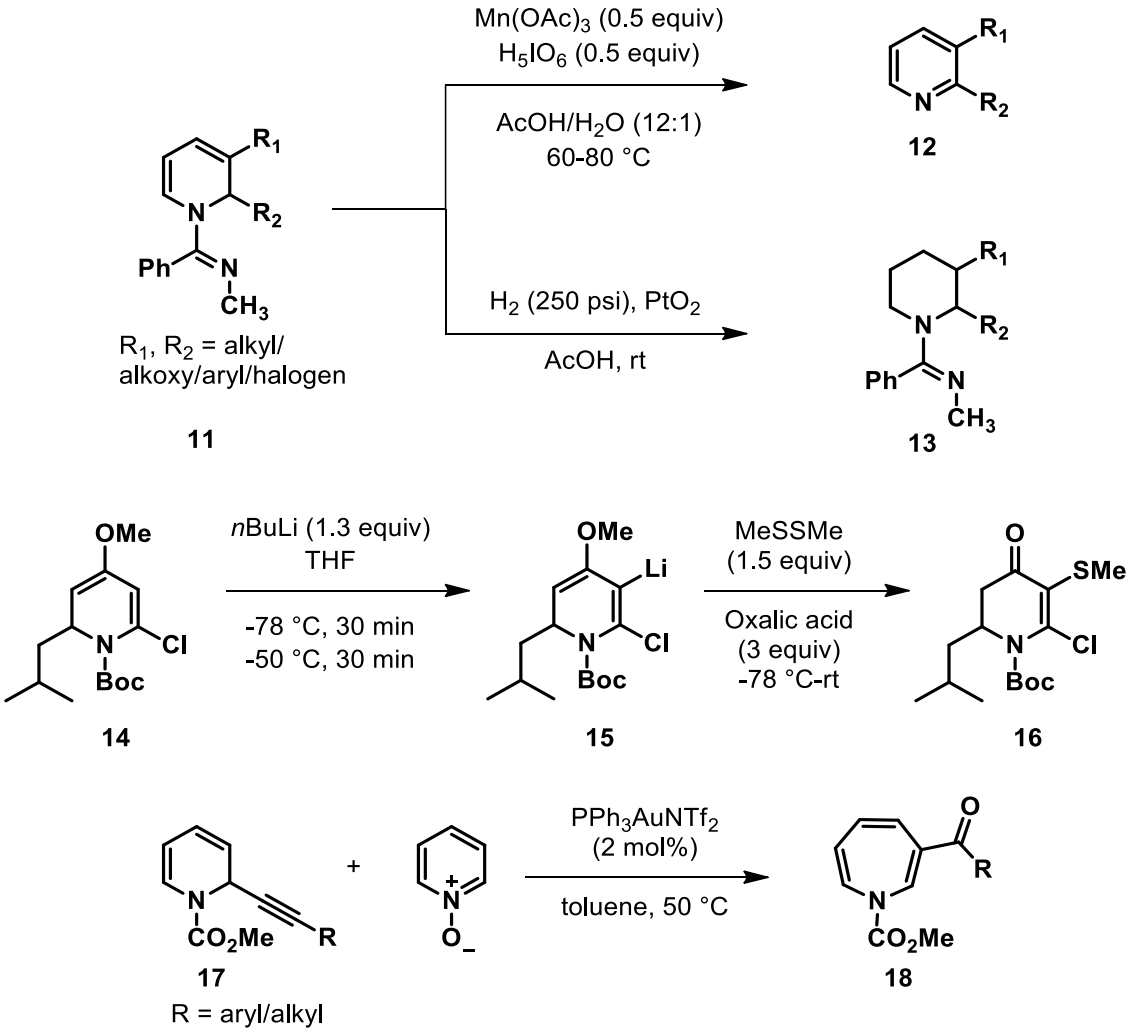


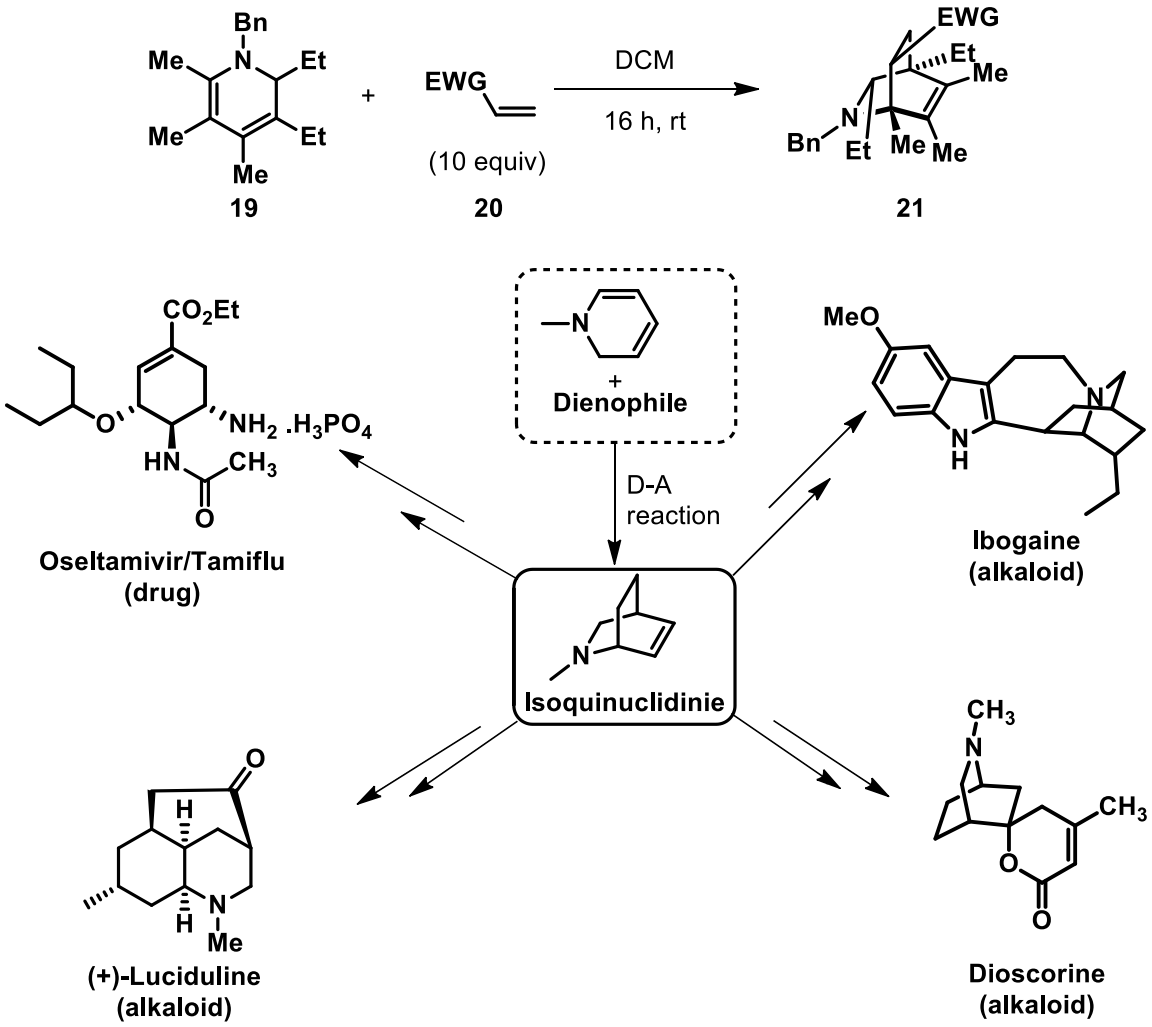
Figure 2.2B. Calcium channel modulating 1,4-DHP drugs available in the market



Scheme 2.2.1. Transformation of 1,2-DHP to pyridine, piperidine, pyridone and azepines

Comins et al. applied the direct lithiation/electrophilic substitution strategy on N-Boc protected 1,2-DHP **14** to access the corresponding dihydropyridone **16** via intermediate **15** (Scheme 2.2.1).[5e]

Recently, Li et al. transformed 2-alkynyl substituted 1,2-DHP **17** to functionalized azepines **18** by gold catalyzed oxidative ring expansion reaction in the presence of pyridine N-oxide oxidant (Scheme 2.2.1).[5f] 1,2-DHPs have also found a wide range of applications in the Diels-Alder (D-A) reaction as diene components. Especially, in the synthesis of isoquinuclidine structural motif,[6] which is a key intermediate in the synthesis of some alkaloids, namely tetrahydroisoquinoline, Iboga, Cantharanthus, Dioscorin and anti-influenza drug Oseltamivir phosphate (Scheme 2.2.2).[7]



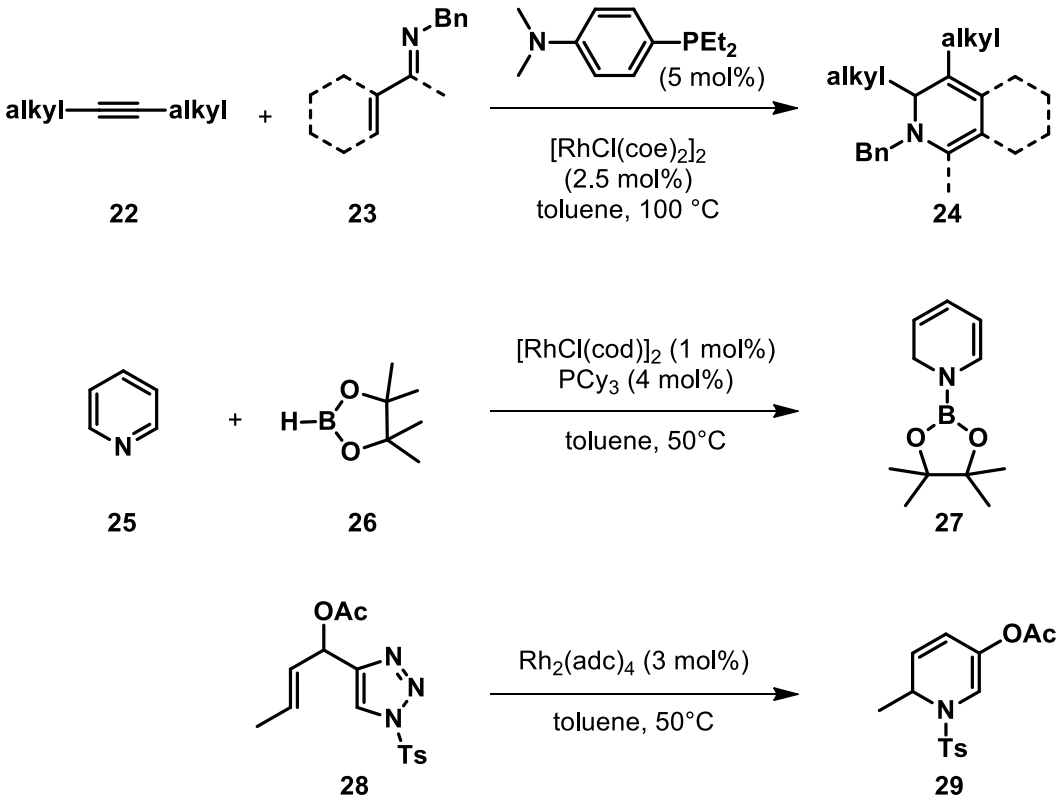
Scheme 2.2.2. 1,2-DHP in D-A synthesis of isoquinuclidine and its utility

For instance, Ellman et al. developed a stereo and regioselective Diels-Alder reaction between 1,2-DHP **19** and dienophile **20** under mild conditions to synthesize fully substituted isoquinuclidine **21** (Scheme 2.2.2).[6a]

2.2.2. Synthetic routes to 1,2-DHP

2.2.2A. Metal-catalyzed synthesis of 1,2-DHP

Rhodium-catalyzed C-H activation and subsequent cyclization reactions were well explored in the synthesis of 1,2-DHP. For example, Ellman et al. reported a rhodium catalyzed cascade C-H alkenylation and electrocyclization reaction between alkyne **22** and α,β-unsaturated N-benzyl imine **23** to synthesize 1,2-DHP **24** in the presence of a special phosphine ligand (Scheme 2.2.3).[8a] A similar kind of reaction was reported in the presence of low valent cobalt catalysts.[8b] Suginome et al. performed a rhodium catalyzed hydroboration of pyridines **25** with pinacolboranes **26** at 50 °C. They have isolated the desired N-boryl 1,2-DHP **27** in high yields with regioselectivity (Scheme 2.2.3).[8c]

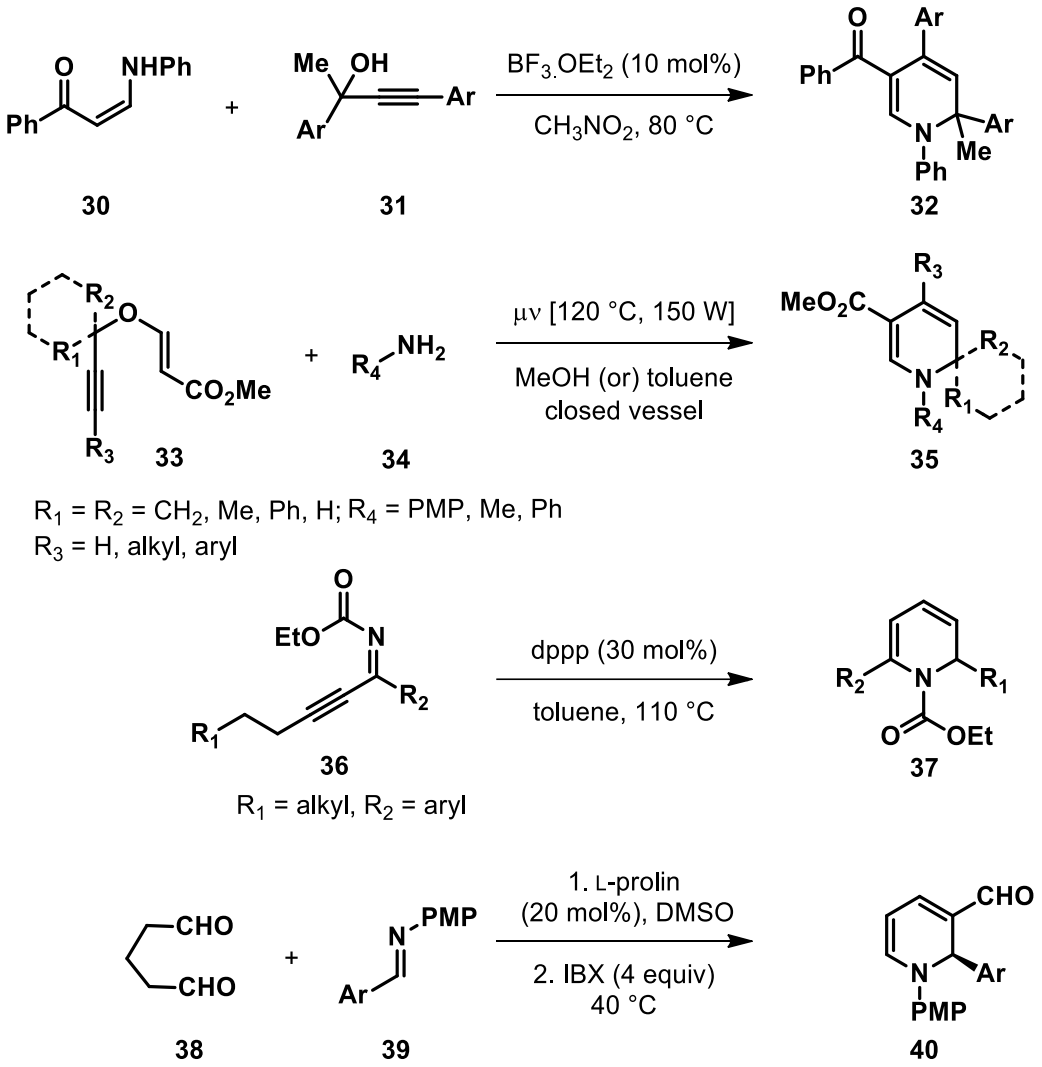


Scheme 2.2.3. Rhodium-catalyzed synthesis of 1,2-DHP

Very recently, Li et al. observed a rhodium catalyzed tandem α-imino rhodium carbene, 1,2-migration of an acetoxy group and six electron electrocyclic ring closure reaction of 4-(1-acetoxyallyl)-1-sulfonyl-1,2,3-triazole **28** to access the corresponding 1,2-DHP **29** in moderate to good yields. (Scheme 2.2.3).[8d]

2.2.2B. Metal-free synthesis of 1,2-DHP

There are few efficient transition metal-free reactions that exist in the literature for the synthesis of 1,2-DHPs under mild reaction conditions. For example, Li et al. developed a Lewis acid catalyzed cyclization of enaminones **30** with propargylic alcohols **31** to generate multisubstituted 1,2-DHPs **32** (Scheme 2.2.4).[9a] This regioselective reaction needed a catalytic amount of $BF_3.OEt_2$ to provide **32** in good to excellent yields and the proposed mechanism involves an allenyl/propargylic cation intermediate. Tejedor et al. reported a general and practical protocol for the synthesis of 1,2-DHP **35** with mono, di and spiro substitution at sp^3 carbon.[9b] It is a microwave assisted domino reaction between propargyl vinyl ethers **33** and aliphatic or aromatic amines **34** in toluene or methanol solvent (Scheme 2.2.4). Trost et al. devised a phosphine catalyzed redox cycloisomerization approach for the synthesis of 2,6-disubstituted 1,2-DHP **37**.[9c] In this reaction, the starting substrate propargylidenecarbamate **36** undergoes a one-pot alkyne isomerization and electrocyclization sequence to afford 1,2-DHP **37** in good yields (Scheme 2.2.4). Further, they have extended this methodology for the synthesis of histamine H3 receptor agonists. Kumar et al. developed an enantioselective synthesis of 1,2-DHP **40** from glutaraldehyde **38** and N-PMP protected imine **39** by a proline-catalyzed [4+2] cycloaddition reaction (Scheme 2.2.4).[9d] The mechanism involves amino catalytic direct Mannich reaction/cyclization followed by IBX mediated selective oxidation to afford 1,2-DHP **40** in high yields and enantioselectivities.

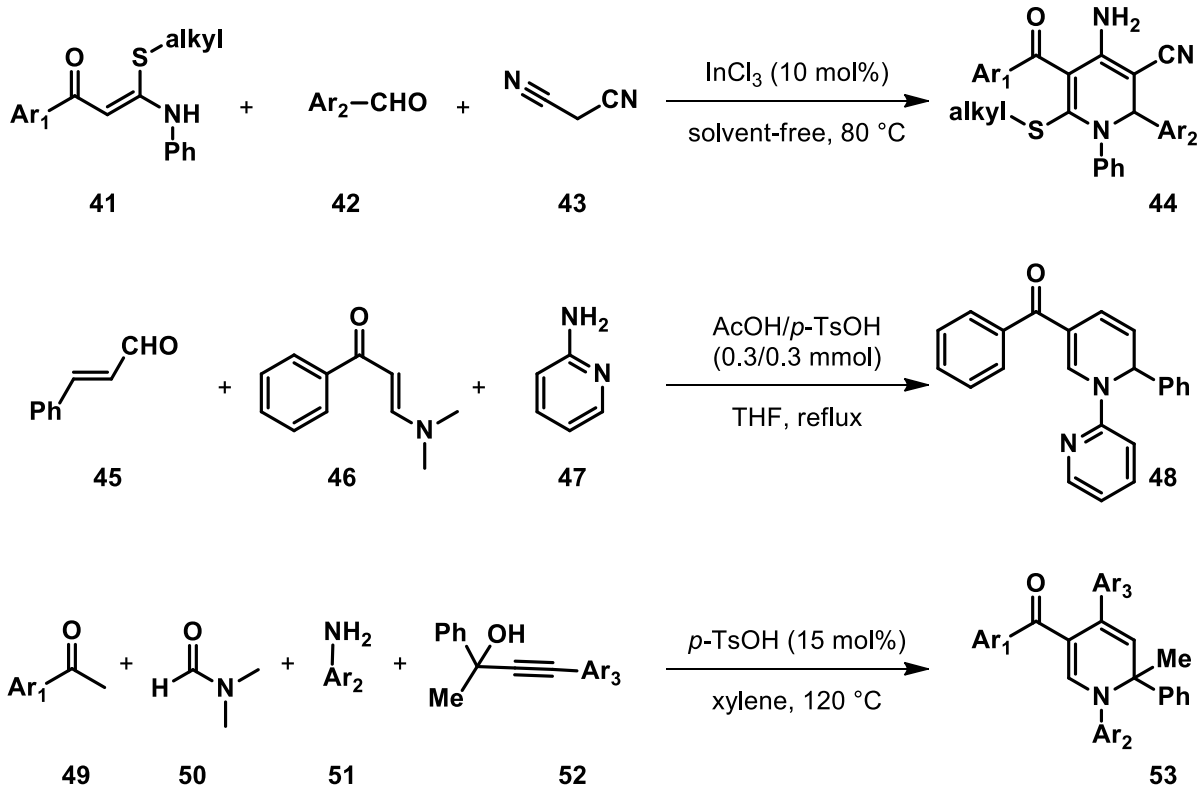


Scheme 2.2.4. Metal-free reports for the synthesis of 1,2-DHP

2.2.2C. Multicomponent synthesis of 1,2-DHP

As described in the introductory chapter, multicomponent synthesis is the best way to construct any molecular scaffold with more diversity and complexity associated with time and resource economical process. Considerably, very few reports are available in the literature for the synthesis of 1,2-DHPs by MCR approach. Singh et al. reported a Lewis acid catalyzed highly convergent and regioselective three component coupling of α-oxoketene-*N*,*S*-arylaminoacetals **41**, aldehydes **42**, and malononitrile **43** to synthesize 4-amino-1,2-dihydropyridines **44** (Scheme 2.2.5).[10a]

The reaction involves $InCl_3$ catalyzed cascade Knoevenagel condensation/Michael addition/cyclization sequence leading to the formation of three consecutive new bonds and one ring. Wen et al. described a simple *p*-TsOH/AcOH catalyzed three-component assembly of enals **45**, N,N-disubstituted enaminones **46**, and 2-aminopyridines **47** to access the corresponding 1,2-DHP **48** in a regioselective manner (Scheme 2.2.5).[10b] This reaction exhibited broad substrate scope and provided the products in moderate to good yields. Very recently, Wang et al. devised a metal-free *p*-TsOH catalyzed four-component reaction (4CR) of aromatic ketones **49**, DMF **50**, amine **51** and propargylic alcohols **52** to construct the functionalized 1,2-DHP **53** in moderate to good yields (Scheme 2.2.5).[10c] This reaction utilizes DMF **50** as a one carbon synthon in the formation of **53**.



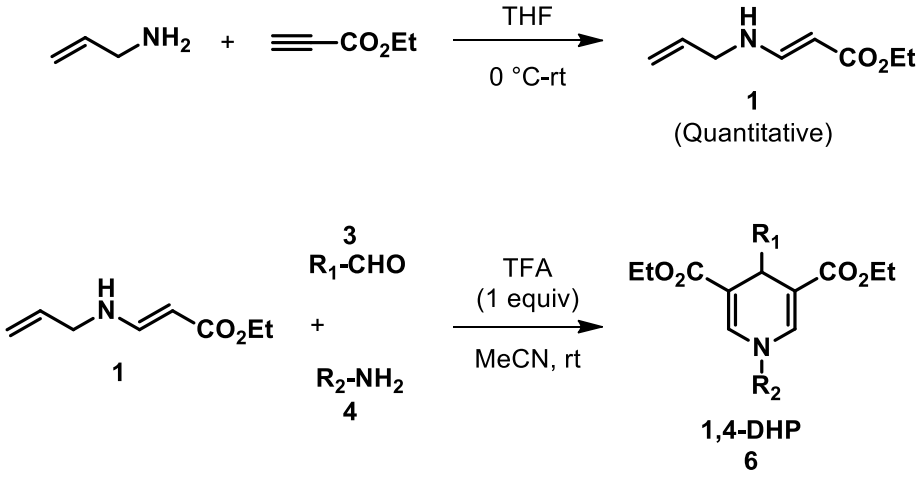
Scheme 2.2.5. MCR approach for the synthesis of 1,2-DHP

Overall, most of the reported metal and metal-free reactions for the synthesis of 1,2-DHPs are associated with some disadvantages which include harsh reaction conditions, usage of

toxic and costly metals, requirement of multistep derived substrates, long reaction times and moisture sensitive conditions. Hence, there is a need for the development of new metal-free and user friendly reactions for the synthesis of this valuable and yet unexplored molecular scaffold. The MCR approach described in scheme 2.2.5 for 1,2-DHP synthesis are the recent reports and our present 3CR approach was published prior to these reports.

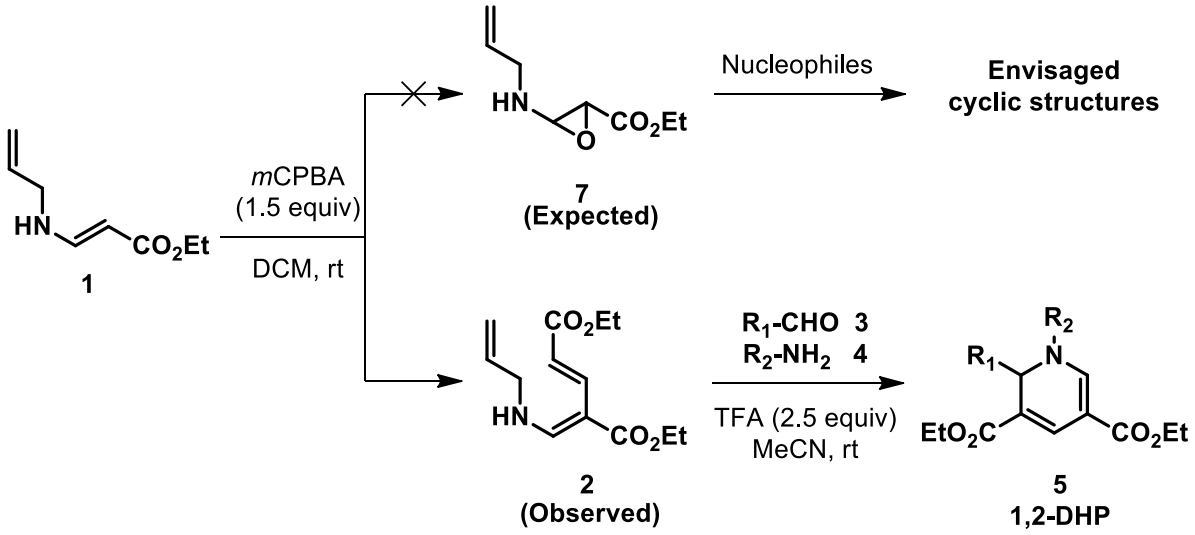
2.3. Results and discussions

The goal of our laboratory in synthetic methodology is to utilize readily available/accessible substrates to generate new structural motifs of biological relevance under mild and metal-free reaction conditions. Accordingly, we developed a new metal-free three-component reaction (3CR) for the synthesis of dihydropyridines in this chapter. We made our initial attempt by reacting enaminoate **1** derived from allylamine and ethyl propiolate with aldehyde **3** and amine **4** in the presence of trifluoroacetic acid (TFA), which led to the formation of 1,4-DHP structural motif **6** in very low yields (Scheme 2.3.1). Literature search revealed that the analogues of enaminoate **1** have already been utilized in acid catalyzed/mediated synthesis of 1,4-DHP derivatives.[11]



Scheme 2.3.1. Synthesis of enaminoate **1** and 1,4-DHP **6**

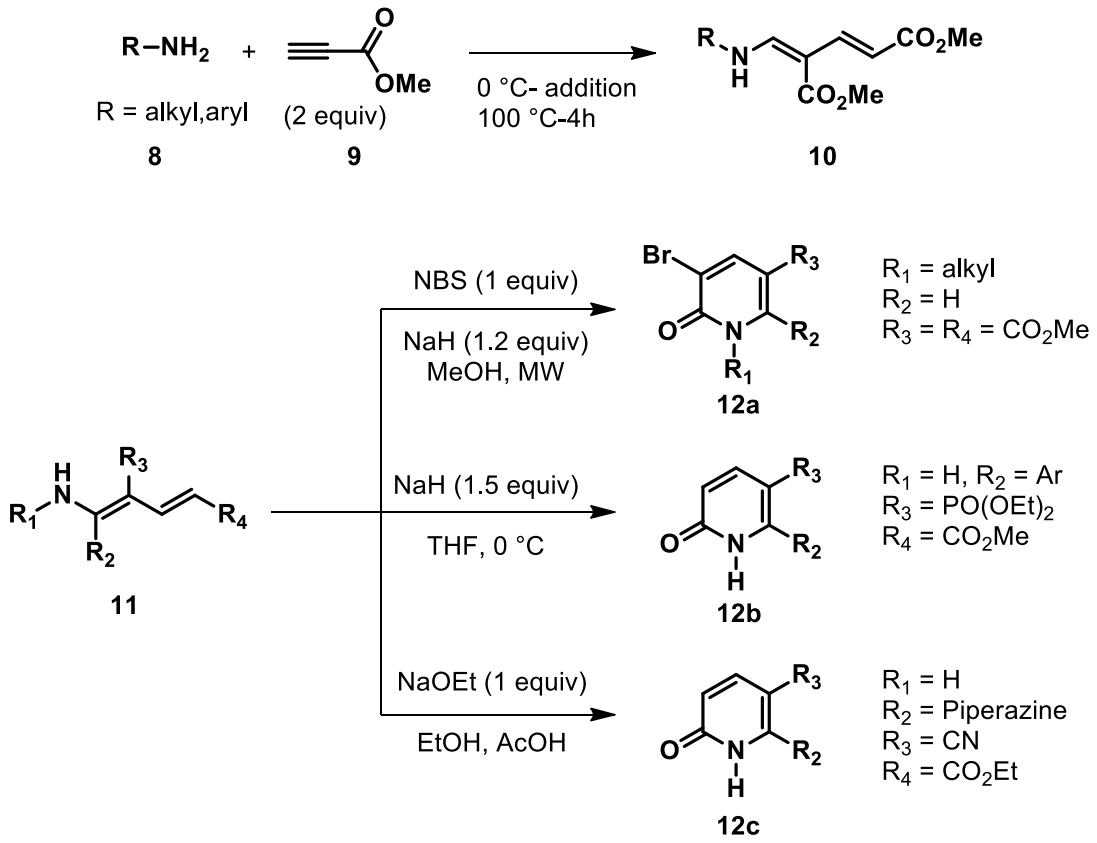
These reports prompted us to explore the utility of **1** in different directions. Accordingly, we attempted a *m*CPBA mediated oxidation reaction to synthesize the corresponding epoxide **7** which we thought could be open up with specific nucleophiles to access the envisaged cyclic structures (Scheme 2.3.2). Unfortunately, we didn't observe the formation of desired epoxide **7**, instead we isolated a dienaminodioate **2** in 18% yield (Scheme 2.3.2). Based on our previous synthesis of 1,4-DHP **6** (Scheme 2.3.1), we envisaged 1,2-DHP **5** formation from dienaminodioate **2** under similar reaction conditions. As expected, the reaction of **2** with aldehyde **3** and amine **4** generated the desired 1,2-DHP **5** in a clean three-component (3CR) approach (Scheme 2.3.2).



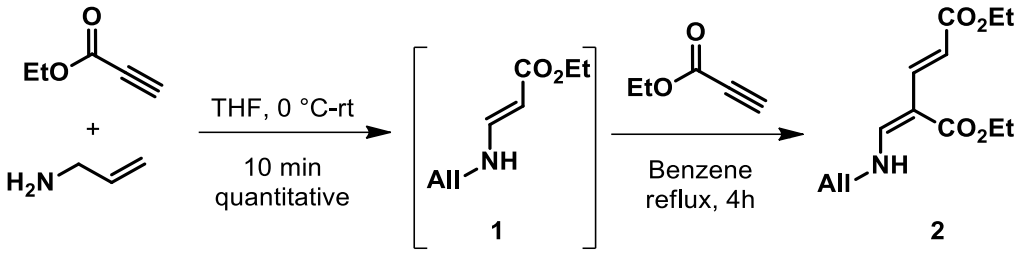
Scheme 2.3.2. Serendipitous observation of **2** and its utilization in the synthesis of 1,2-DHP **5**

In 1967, Bottomley achieved the first synthesis of compound **2** methyl ester analogue **10** from the corresponding amine **8** and methyl propiolate **9** by a Michael kind of addition reaction (Scheme 2.3.3).[12] Since then, differently substituted compound **2** analogues such as **11** was synthesized and their utility was mainly restricted to the formation of 2-pyridone derivatives **12** under base mediated intramolecular cyclizations (Scheme 2.3.3).[13] This relatively unexplored and easily accessible nature of compound **2** inspired

us to check its efficacy as a suitable substrate for the synthesis of functionalized carbo- and heterocycles. Accordingly, we have achieved a highly efficient synthesis of 1,2-DHP under metal-free reaction conditions. As our initial *m*CPBA reaction generated the compound **2** in a very low yield, we adopted a reported two-step procedure as shown in scheme 2.3.4.[14] It is a one-pot sequential reaction of ethyl propiolate with allylamine which generated enaminoate **1** in a quantitative yield. Subsequent solvent evaporation and addition of one more equivalent of ethyl propiolate in benzene solvent under reflux conditions afforded compound **2**.



Scheme 2.3.3. Bottomley synthesis of **10** and Base mediated cyclization to 2-pyridones



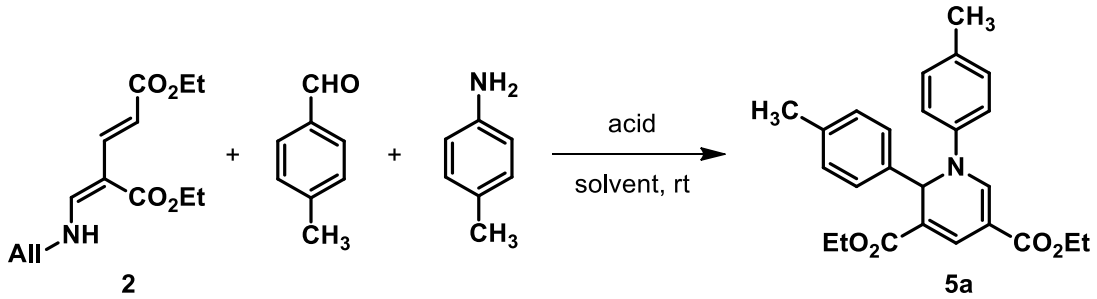
Scheme 2.3.4. Adopted one-pot two-step method for the synthesis of compound **2**

Initially, we tried to investigate the reaction with an aromatic imine derived *in situ* from 4-methyl benzaldehyde and *p*-toluidine as model substrates in a one-pot cascade reaction with **2** in the presence of catalytic amount of trifluoroacetic acid (TFA). As expected, this reaction afforded a yellow colored spot on TLC in trace amount which after isolation was characterized as 1,2-DHP **5a** using NMR and HR-ESI-MS techniques (Table 2.3.1). The ^{1}H NMR analysis of **5a** shows two discernible singlets for olefinic protons at δ 7.70 and 8.05 ppm. A characteristic splitting pattern of ethyl group of both the esters and presence of both the phenyl groups, which was evident from the integration, established the structure of **5a**. Encouraged by this result, we proceeded to optimize the reaction conditions for this 3CR to afford 1,2-DHP using different acids (Table 2.3.1). Initial attempt with TFA (25 mol%) using CH_3CN as the solvent provided 1,2-DHP **5a** in an impressive 92% yield (entry 1) at room temperature. To avoid longer reaction time we increased TFA concentration to the stoichiometric amount (1 equiv) which led to complete formation of product in just 45 minutes with 95% yield (entry 2). The increase in number of equivalents of TFA to 1.5 or 2.5 led to no considerable change in time or yield of the product (entries 3-4). By keeping the TFA concentration as one equiv and changing the solvent to polar protic solvent EtOH led to a considerable decrease in the product yield with prolonged time (entry 5). Other moderately polar aprotic solvents namely, DCM and THF also gave the desired product in considerable yield but with slow kinetics (entries 6-7). To ascertain the generality of the acid, investigation of other

common Brønsted and Lewis acids which include *p*-TsOH, 4M HCl, $BF_3.OEt_2$, TMSOTf, and $FeCl_3$ in stoichiometric amounts (entries 8-12) led to drastic reduction in the yield of 1,2-DHP with longer reaction times. Interestingly, usage of 1 equiv of acetic acid and trichloroacetic acid (entries 13–14) showed the influence of pKa over the outcome of the reaction with respect to yield and time. Based on the above investigations, we have chosen one equiv of TFA and CH_3CN solvent as the optimized conditions for one-pot cascade synthesis of 1,2-DHP (entry 2). To determine the mildness of our approach, all reactions were conducted without distillation of solvents and in the absence of inert atmosphere.

Having the optimized condition in hand, we explored the generality of this multicomponent reaction. In our first attempt, we fixed the amine component *p*-toluidine and varied the aldehydes (Table 2.3.2). Aromatic aldehydes, in general, gave good yields of 1,2-DHP in less than 2 h. As shown in table 2, functional group tolerance was clearly evident under this reaction conditions. However, aldehydes containing electron withdrawing groups comparatively gave the desired products in excellent yields (**5e**, **5f**). Heteroaromatic aldehydes, however, took longer reaction time with the desired 1,2-DHPs as major products along with other impurities.

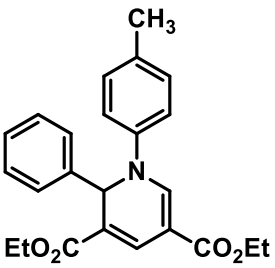
Table 2.3.1. Optimization of reaction conditions for synthesis of 1,2-DHP **5a**[a]



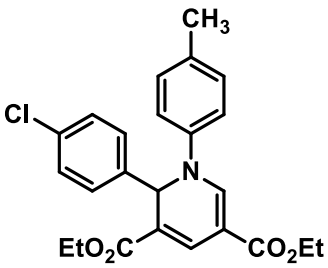
entry	acid	solvent[b]	time	yield[c]
1	TFA	CH_3CN	4 h	92%
2	TFA	CH_3CN	45 min	95%
3	TFA	CH_3CN	45 min	95%
4	TFA	CH_3CN	45 min	94%
5	TFA	EtOH	4 h	61%
6	TFA	CH_2Cl_2	45 min	84%
7	TFA	THF	4 h	93%
8	*p*-TsOH	CH_3CN	8 h	27%
9	4M HCl in Dioxane	CH_3CN	7 h	30%
10	$BF_3.Et_2O$	CH_3CN	1.5 h	68%
11	TMSOTf	CH_3CN	8 h	12%
12	$FeCl_3$	CH_3CN	11 h	38%
13	AcOH	CH_3CN	24 h	61%
14	TCA	CH_3CN	1.4 h	82%

[a] Unless mentioned, all reactions were carried out with 1.2 equiv of both aldehyde and amine, and 1 equiv of acid except for entries 1 and 3-4 where 0.25, 1.5, and 2.5 equivalents were used, respectively. [b] Solvents were used without distillation. [c] Isolated yields. TFA = trifluoroacetic acid, TMSOTf = trimethylsilyl triflate, *p*-TsOH = *p*-toluenesulfonic acid. TCA = trichloroacetic acid.

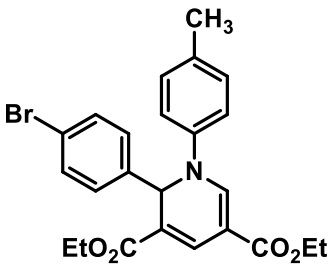
Table 2.3.2. 3CR synthesis of 1,2-DHP **5** by variation of aldehyde component



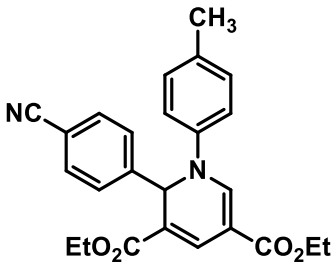
5b (87%)



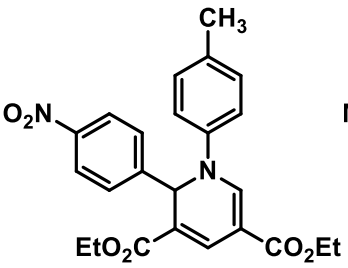
5c (75%)



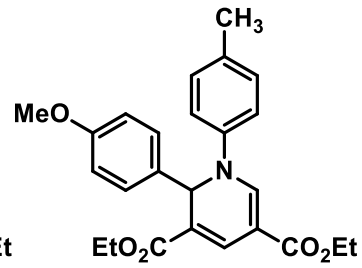
5d (74%)



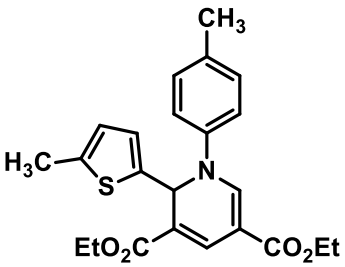
5e (91%)



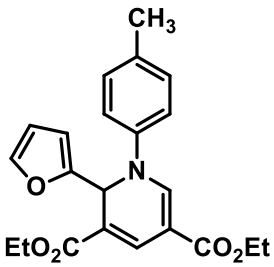
5f (96%)



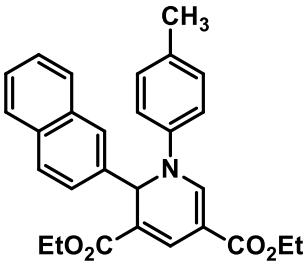
5g (77%)



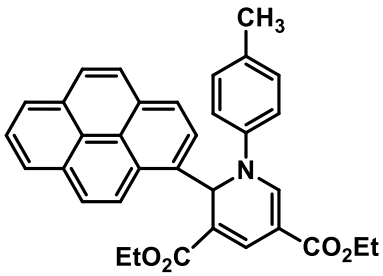
5h (75%)



5i (75%)



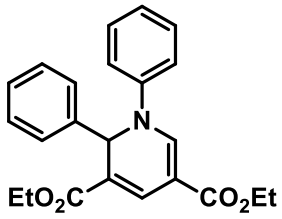
5j (84%)



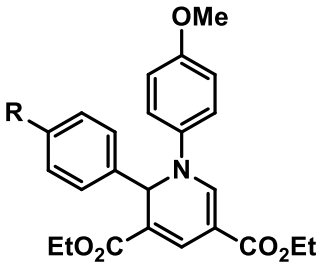
5k (79%)

Polycyclic aromatic aldehydes showed similar behaviour towards reactivity as simple aromatic aldehydes without offering any steric hindrance in the formation of 1,2-DHPs. The substrate scope was further investigated by variation of amines along with a few representative aldehydes for the formation of 1,2-DHP **5'** (Table 2.3.3).

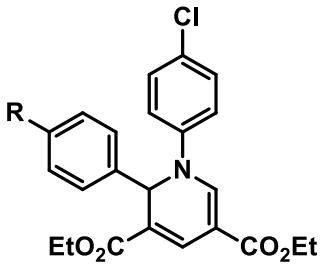
Table 2.3.3. 3CR synthesis of 1,2-DHP **5'** by variation of aldehydes and amines



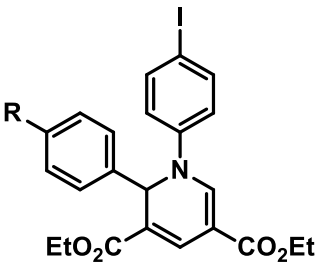
5a′ (98%)



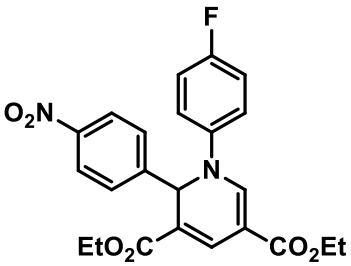
R =
OMe**----5b′** (97%)
NO_2**-----5c′** (93%)
CN**------5d′** (80%)
Cl**-------5e′** (95%)



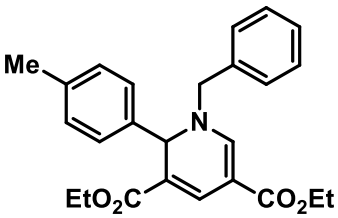
R =
OMe**------5f′** (97%)
NO_2**------5g′** (98%)
CN**-------5h′** (75%)



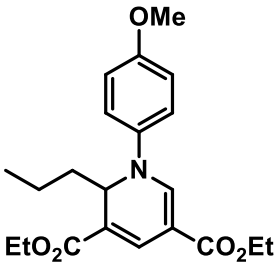
R =
OMe**------5i′** (65%)
CN**-------5j′** (71%)
Cl**-------5k′** (70%)



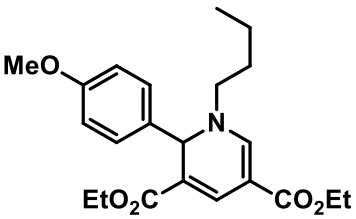
5l′ (91%)



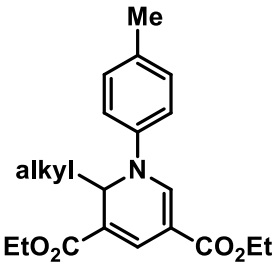
R_1 = Me, R_2 = H**-----5m′** (94%)
R_1 = Me, R_2 = F**------5n′** (42%)
R_1 = NO_2, R_2 = H **---5o′** (69%)
R_1 = NO_2, R_2 = F**----5p′** (89%)



5q′ (22%)



5r′ (trace)

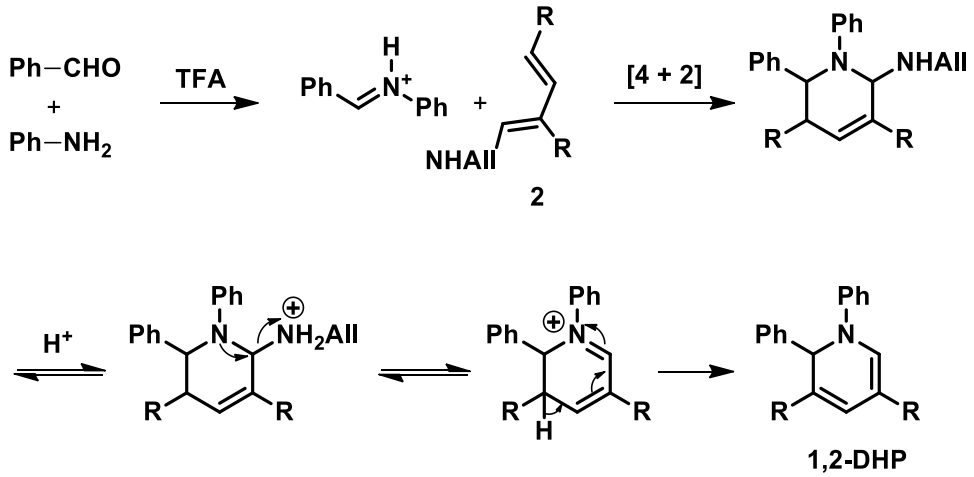


5s′ (trace)

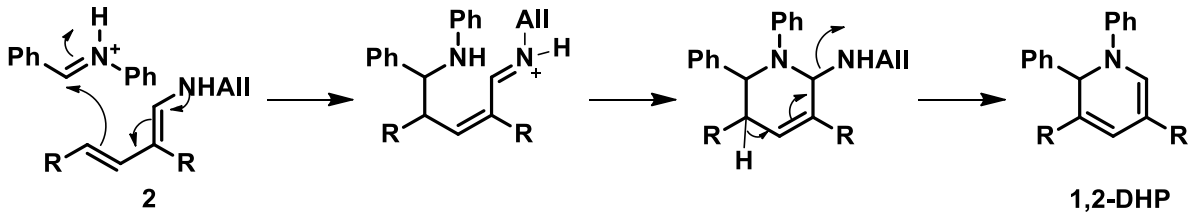
Whereas, simple butylamine, and other aldehydes including cyclohexanecarboxaldehyde, citral, β-cyclocitral and heptanal failed to produce a clean transformation as we observed traces of product along with complex mixture of spots on TLC.

The results were as expected with impressive yields showing functional group tolerance with both electron releasing and withdrawing substituents in the *para* position. Even benzylic amines offered decent yields for this transformation which prompted us to try aliphatic aldehyde such as butyraldehyde, but we observed the product formation in a

lower yield under the reaction conditions (**5q'**). The mechanistic rationale behind the primary event during the cascade sequence could be realized as a hetero Diels–Alder cycloaddition of *in situ* generated imine and compound **2** as proposed by Palacios et al. in their 1,2-DHP synthesis,[15] followed by elimination of allylamine in the presence of an acid and rearrangement to afford 1,2-DHP (Scheme 2.3.5). Other possible pathway is stepwise annulation followed by cyclization and allyl amine elimination to generate 1.2-DHP (Scheme 2.3.6).



Scheme 2.3.5. Proposed hetero Diels-Alder mechanism for 1,2-DHP formation



Scheme 2.3.6. Proposed step-wise annulation for 1,2-DHP formation

2.4. Conclusion

In summary, we have developed a one-pot cascade reaction of *in situ* generated imine with dienaminodioate **2** for the formation of 1,2-dihydropyridines. A broad aromatic substrate scope with various aromatic, heteroaromatic aldehydes, and anilines, benzylic

amines with impressive yields, demonstrates synthetic utility in diversification of 1,2-DHPs to produce pharmaceutically important libraries. The advantages associated with this transformation over the current methods of 1,2-DHP synthesis include conditions that are metal-free, one-pot, room temperature, usage of undistilled solvents and expeditious in excellent yields.

2.5. Experimental section

2.5.1. General Experimental Methods. Acetonitrile (CH_3CN) and THF solvents were used directly without distillation; ethanol was distilled over magnesium powder. All reactions were carried out in open air atmosphere. Silica gel G-60 F_{254} aluminium TLC plates were used to monitor the reactions with short wavelength ultraviolet light and/or by iodine staining to visualize the spots. Flash column chromatography was performed on silica gel 230-400 mesh. ^{1}H, and ^{13}C NMR spectra were recorded at 500, and 125 MHz, respectively. Chemical shifts are given in ppm using solvent residual peak of chloroform δ 7.26 ppm as reference, and coupling constants in Hz. HR-ESI-MS analysis was recorded using electrospray ionization with ions given in m/z.

2.5.2. General procedure for the synthesis of (2E,4E)-diethyl 4-((allylamino)methylene)-pent-2-enedioate (2)

To a solution of allylamine (382 µL, 5.09 mmol) in THF was added ethyl propiolate (520 µL, 5.09 mmol) slowly at 0 °C and warmed to room temperature. After 10 min, the reaction mixture was concentrated and the resulting enaminoate **1** was dissolved in benzene (5 mL). To the reaction mixture additional equiv of ethyl propiolate (520 µL, 5.09 mmol) was added and stirred under reflux for 4 h at 100 °C. The reaction mixture was then concentrated and purified by flash column chromatography (10:1 hexane/EtOAc) affording dienaminodioate **2** (669 mg, 52%) as a light yellow oily product.

2.5.3. General procedure for the synthesis of 1,2-DHP

To a solution of **2** in CH_3CN was added pertinent aldehyde (1.2 equiv), amine (1.2 equiv), and TFA (1.0 equiv) in a sequence at room temperature. The reaction mixture usually develops a bright yellow color within 15 min which is an indication of the formation of 1,2-DHP. After complete consumption of **2**, as observed on TLC, the reaction mixture was quenched with saturated $NaHCO_3$, extracted with ethyl acetate, dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash column chromatography to afford 1,2-DHP derivative.

2.5.4. Spectral details of products

(2E,4E)-diethyl 4-((allylamino)methylene)pent-2-enedioate (2). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.0 Hz, $–CO_2CH_2CH_3$), 1.35 (t, 3H, *J* = 7.0 Hz, $–CO_2CH_2CH_3$), 3.89 (app t, 2H, *J* = 5.5 Hz, $–CH_2–CH$), 4.18 (q, 2H, *J* = 7.0 Hz, $–CO_2CH_2CH_3$), 4.25 (q, 2H, *J* = 7.0 Hz, $–CO_2CH_2CH_3$), 5.24 (m, 2H, $–CH=CH_2$), 5.86 (ddt, 1H, *J* = 5.5, 10.5, 16.0 Hz, $–CH=CH_2$), 6.03 (d, 1H, *J* = 15.5 Hz, $CH=CHCO_2Et$), 7.19 (d, 1H, *J* = 13.5 Hz, C=CH), 7.39 (d, 1H, *J* = 15.5 Hz, $-CH=CHCO_2Et$), 8.94 (brs, 1H, NH). 13C NMR ($CDCl_3$) δ 14.4, 14.4, 51.1, 59.6, 59.8, 95.3, 108.2, 117.9, 133.4, 143.2, 156.9, 168.8, 169.1. HR-ESI-MS $[M+Na]^+$ $C_{13}H_{19}NO_4Na$ calcd for m/z 276.12118, found 276.12000.

Diethyl 1,2-di-*p*-tolyl-1,2-dihydropyridine-3,5-dicarboxylate (5a).

Yellow colored amorphous solid (56.5 mg, 95%). R_f 0.39 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.0 Hz), 1.32 (t, 3H, *J* = 7.0 Hz), 2.30 (s, 3H), 2.31 (s, 3H), 4.18 (m, 2H), 4.25 (q, 2H, *J* = 7.0 Hz), 6.07 (s, 1H), 7.03 (d, 2H, *J* = 8.0 Hz), 7.08 (d, 2H, *J* = 8.0 Hz), 7.09 (d, 2H, *J* = 8.5 Hz), 7.27 (d, 2H, *J* = 7.5 Hz), 7.70 (s, 1H), 8.05 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 20.8, 21.1, 59.9, 60.4, 61.2, 102.5, 114.1, 121.1, 125.9, 129.3, 130.0, 130.6, 136.2, 137.8, 138.7, 142.1, 145.2, 165.9, 165.9. HR-ESI-MS $[M+Na]^+$ $C_{25}H_{27}NO_4Na$ calcd for m/z 428.18378, found 428.18415.

Figure 2.5A. ^{1}H and ^{13}C-NMR of dienaminodioate 2

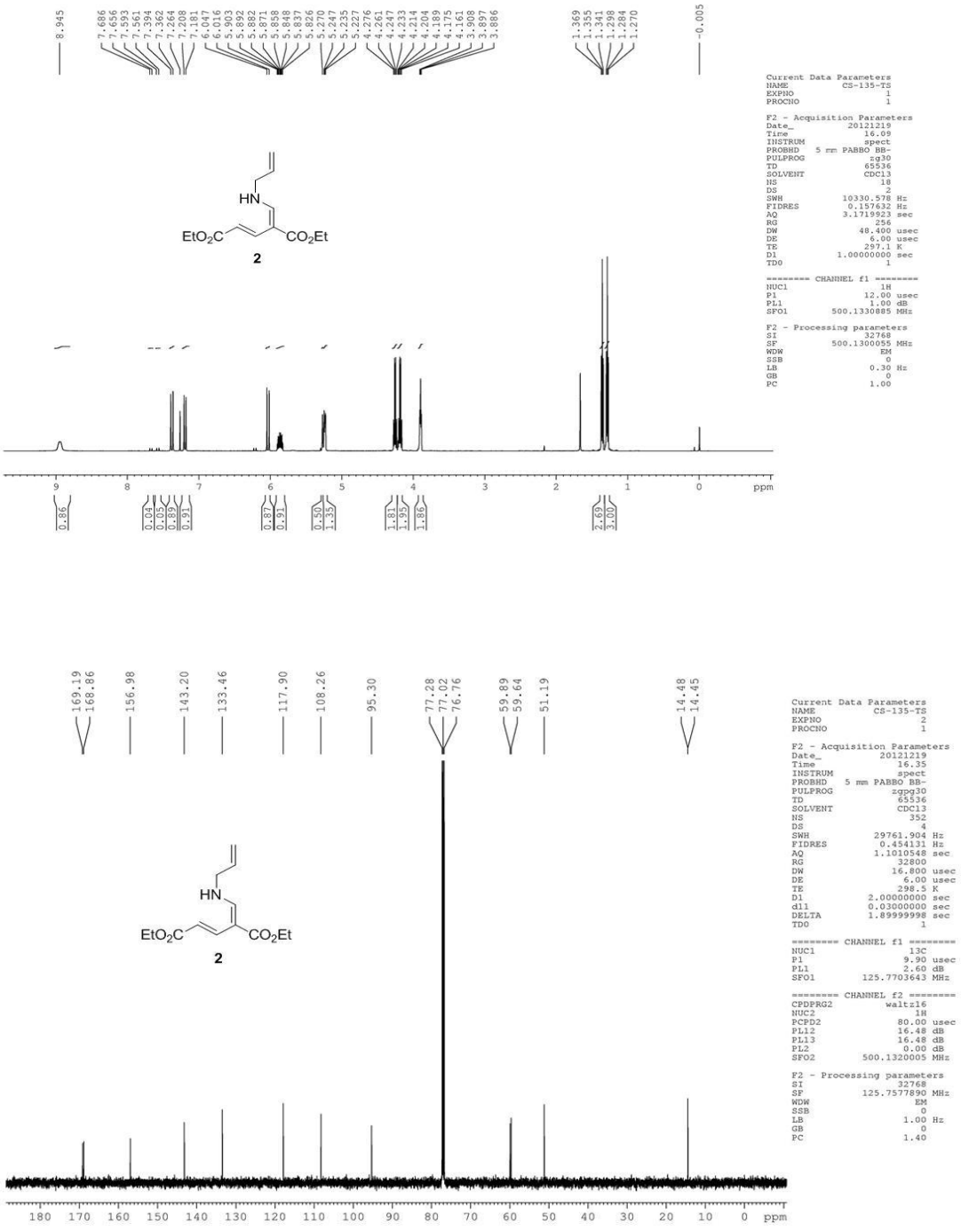
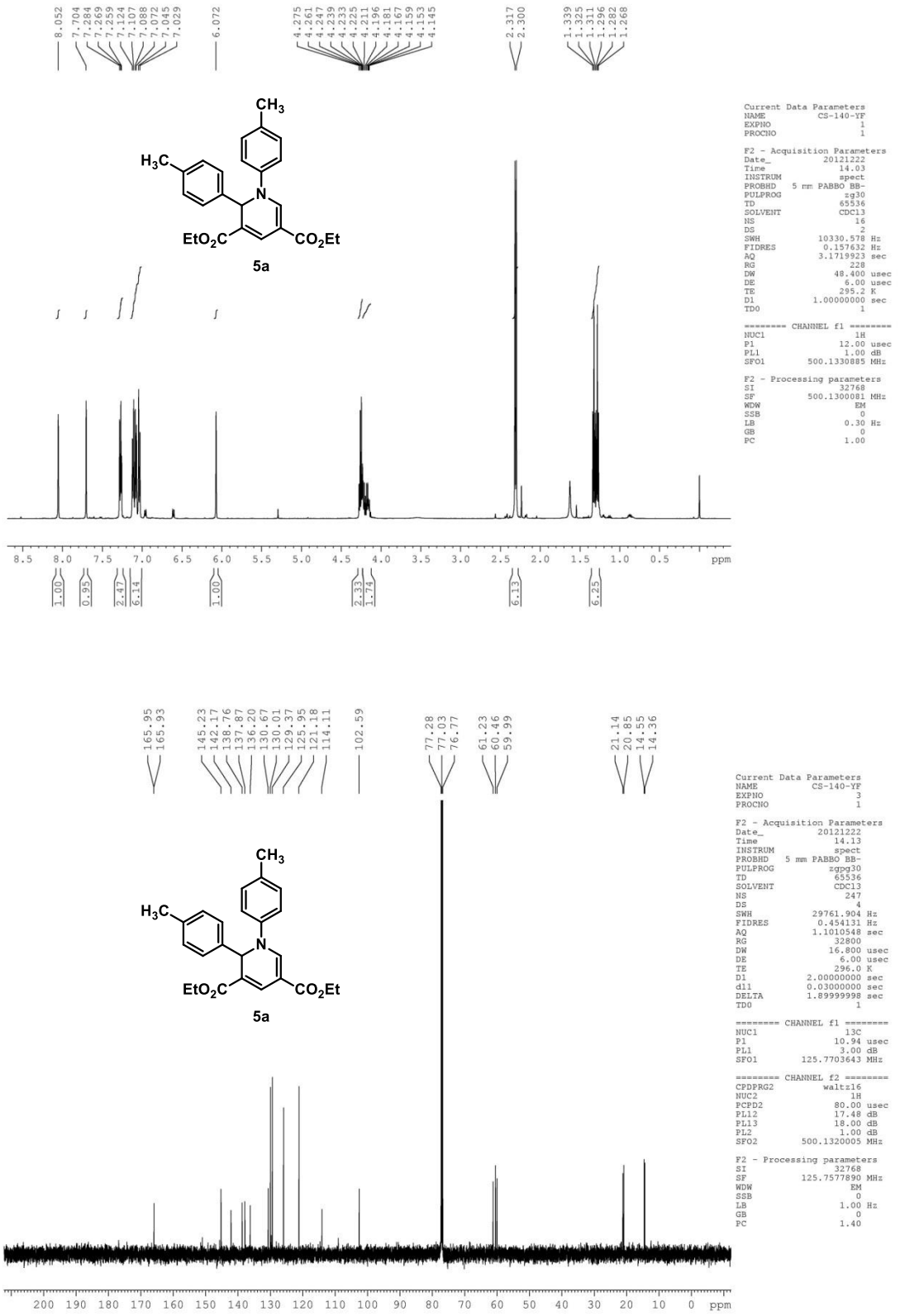


Figure 2.5B. ^{1}H and ^{13}C-NMR of 1,2-DHP 5a



Diethyl 2-phenyl-1-(*p*-tolyl)-1,2-dihydropyridine-3,5-dicarboxylate (5b).

Yellow colored amorphous solid (66 mg, 87%). R_f 0.26 (hexane/EtOAc 9:1). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.5 Hz), 1.32 (t, 3H, *J* = 7.0 Hz), 2.31 (s, 1H), 4.19 (m, 2H), 4.25 (q, 2H, *J* = 8.0 Hz), 6.11 (s, 1H), 7.03 (d, 2H, *J* = 8. 0 Hz), 7.11 (d, 2H, *J* = 8.0 Hz), 7.26 (m, 3H), 7.39 (d, 2H, *J* = 7.0 Hz), 7.71 (s, 1H), 8.06 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 20.8, 60.0, 60.5, 60.4, 102.7, 113.9, 121.1, 126.0, 128.1, 128.7, 130.0, 130.8, 136.2, 141.5, 142.1, 145.2, 165.9. HR-ESI-MS $[M+Na]^+$ $C_{24}H_{25}NO_4Na$ calcd for m/z 414.16813, found 414.16833.

Diethyl 2-(4-chlorophenyl)-1-(*p*-tolyl)-1,2-dihydropyridine-3,5-dicarboxylate (5c).

Yellow colored amorphous solid (65.5 mg, 75%). R_f 0.31 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.0 Hz), 2.32 (s, 3H), 4.18 (m, 2H), 4.26 (q, 2H, *J* = 7.0 Hz), 6.08 (s, 1H), 7 (d, 2H, *J* = 8.0 Hz), 7.13 (d, 2H, *J* = 8.5 Hz), 7.24 (d, 2H, *J* = 8.5 Hz), 7.32 (d, 2H, *J* = 8.5 Hz), 7.71 (s, 1H), 8.03 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 20.8, 60.1, 60.6, 61.0, 102.6, 113.7, 115.2, 121.2, 127.5, 128.8, 130.1, 131.0, 133.9, 136.5, 140.0, 141.9, 145.2, 165.7; ESI-HRMS $[M+Na]^+$ $C_{24}H_{24}NO_4ClNa$ calcd for m/z 448.12916, found 448.12940.

Diethyl 2-(4-bromophenyl)-1-(*p*-tolyl)-1,2-dihydropyridine-3,5-dicarboxylate (5d).

Yellow colored amorphous solid (85 mg, 74%). R_f 0.38 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.0 Hz), 1.32 (t, 3H, *J* = 7.5 Hz), 2.33 (s, 3H), 4.18 (m, 2H), 4.26 (q, 2H, *J* = 7.0 Hz), 6.07 (s, 1H), 7.0 (d, 2H, *J* = 8.0 Hz), 7.13 (d, 2H, *J* = 8.0 Hz), 7.26 (d, 2H, *J* = 8.0 Hz), 7.40 (d, 2H, *J* = 8.5 Hz), 7.71 (s, 1H), 8.03 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 20.8, 60.1, 60.6, 61.0, 102.6, 113.5, 121.2, 122.1, 127.8, 130.1, 131.0, 131.8, 136.5, 140.5, 141.8, 145.2, 165.7. HR-ESI-MS $[M+Na]^+$ $C_{24}H_{24}NO_4BrNa$ calcd for m/z 492.07864, found 492.07893.

Diethyl 2-(4-cyanophenyl)-1-(*p*-tolyl)-1,2-dihydropyridine-3,5-dicarboxylate (5e).

Yellow colored amorphous solid (64 mg, 91%). R_f 0.31 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.0 Hz), 2.33 (s, 3H), 4.2 (m, 2H), 4.26 (q, 2H, *J* = 7.0 Hz), 6.18 (s, 1H), 6.98 (d, 2H, *J* = 8.0 Hz), 7.14 (d, 2H, *J* = 8.0 Hz), 7.50 (d, 2H, *J* = 8.0 Hz), 7.58 (d, 2H, *J* = 8.0 Hz), 7.73 (s, 1H), 8.07 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 20.8, 60.2, 60.8, 61.0, 103.1, 112.0, 112.9, 129.9, 126.7, 130.2, 131.5, 132.6, 136.7, 141.5, 145.0, 146.1, 165.5, 165.6. HR-ESI-MS $[M+Na]^+$ $C_{25}H_{24}N_2O_4Na$ calcd for m/z 439.16338, found 439.16368.

Diethyl 2-(4-nitrophenyl)-1-(*p*-tolyl)-1,2-dihydropyridine-3,5-dicarboxylate (5f).

Yellow colored amorphous solid (108 mg, 96%). R_f 0.41 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.0 Hz), 2.33 (s, 3H), 4.23 (m, 4H), 6.24 (s, 1H), 6.99 (d, 2H, *J* = 8.0 Hz), 7.14 (d, 2H, *J* = 8.0 Hz), 7.57 (d, 2H, *J* = 8.5 Hz), 7.75 (s, 1H), 8.08 (s, 1H), 8.15 (d, 2H, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 20.8, 60.2, 60.8, 60.9, 103.1, 112.9, 120.9, 124.1, 127.0, 130.3, 131.6, 136.8, 141.5, 145.1, 147.7, 148.0, 165.6. HR-ESI-MS $[M+Na]^+$ $C_{24}H_{24}N_2O_6Na$ calcd for m/z 459.15321, found 459.15351.

Diethyl 2-(4-methoxyphenyl)-1-(*p*-tolyl)-1,2-dihydropyridine-3,5-dicarboxylate (5g).

Yellow colored amorphous solid (68 mg, 77%). R_f 0.25 (hexane/EtOAc 9:1). ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, *J* = 7.5 Hz), 1.32 (t, 3H, *J* = 7.0 Hz), 2.31 (s, 3H), 3.76 (s, 3H), 4.18 (m, 2H), 4.25 (q, 2H, *J* = 7.0 Hz), 6.03 (s, 1H), 6.79 (d, 2H, *J* = 8.5 Hz), 7.03 (d, 2H, *J* = 8.5 Hz), 7.11 (d, 2H , *J* = 8.0 Hz), 7.31 (d, 2H, *J* = 8.5 Hz), 7.71 (s, 1H), 8.02 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 20.8, 55.2, 59.9, 60.4, 61.1, 102.1, 113.9, 114.2, 121.4, 127.4, 130.0, 130.5, 134.1, 136.2, 142.2, 145.3, 159.4, 165.8, 165.9. HR-ESI-MS $[M+Na]^+$ $C_{25}H_{27}NO_5Na$ calcd for m/z 444.17869, found 444.17937.

Diethyl2-(5-methylthiophen-2-yl)-1-(*p*-tolyl)-1,2-dihydropyridine-3,5-dicarboxylate (5h).

Yellow colored amorphous solid (70 mg, 75%). R_f 0.44 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.3 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.0 Hz), 2.34 (s, 3H), 2.38 (s, 3H), 4.2 (m, 4H), 6.25 (s, 1H), 6.51 (d, 1H, *J* = 3.0 Hz), 6.73 (d, 1H, *J* = 3.5 Hz), 7.15 (m, 4H), 7.73 (s, 1H), 7.94 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 15.3, 20.8, 57.4, 60.0, 60.5, 103.3, 113.8, 121.0, 124.5, 124.6, 130.0, 130.6, 136.2, 139.6, 141.3, 141.8, 144.1, 165.4, 165.7. HR-ESI-MS $[M+Na]^+$ $C_{23}H_{25}NO_4SNa$ calcd for m/z 434.14020, found 434.13889.

Diethyl 2-(furan-2-yl)-1-(*p*-tolyl)-1,2-dihydropyridine-3,5-dicarboxylate (5i).

Yellow colored amorphous solid (57 mg, 75%). R_f 0.28 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.0 Hz), 1.32 (t, 3H, *J* = 7.5 Hz), 2.35 (s, 3H), 4.19 (m, 2H), 4.25 (q, 2H, *J* = 8.5 Hz), 6.18 (s, 1H), 6.22 (d, 1H, *J* = 3.5 Hz), 6.27 (t, 1H, *J* = 3.0 Hz), 7.19 (d, 2H, *J* = 8.0 Hz), 7.25 (t, 2H, *J* = 6.5 Hz), 7.35 (s, 1H), 7.84 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 20.8, 54.8, 60.0, 60.5, 103.9, 108.4, 110.4, 110.8, 121.2, 130.0, 132.0, 136.1, 141.9, 142.5, 143.8, 152.7, 165.2, 165.8. HR-ESI-MS $[M+Na]^+$ $C_{22}H_{23}NO_5Na$ calcd for m/z 404.14739, found 404.14680.

Diethyl 2-(naphthalen-2-yl)-1-(*p*-tolyl)-1,2-dihydropyridine-3,5-dicarboxylate (5j).

Yellow colored amorphous solid (88 mg, 84%). R_f 0.3 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.0 Hz), 2.30 (s, 3H), 4.24 (m, 4H), 6.28 (s, 1H),7.07 (m, 4H), 7.44 (m, 2H), 7.58 (d, 2H, *J* = 8.5 Hz), 7.53 (s, 1H), 7.78 (m, 4H), 8.13 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 20.8, 60.0, 60.5, 61.7, 102.6, 113.8, 121.3, 124.7, 126.1, 126.1, 127.6, 128.3, 128.8, 130.0, 130.9, 133.1, 136.3, 138.9, 142.1, 145.4, 165.9. HR-ESI-MS $[M+Na]^+$ $C_{28}H_{27}NO_4Na$ calcd for m/z 464.18378, found 464.18420.

Diethyl 2-(pyren-1-yl)-1-(*p*-tolyl)-1,2-dihydropyridine-3,5-dicarboxylate (5k).

Yellow colored amorphous solid (75 mg, 79%). R_f 0.4 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3H, *J* = 7.0 Hz), 1.38 (t, 3H, *J* = 7.0 Hz), 2.16 (s, 3H), 3.99 (m, 2H),

4.33 (q, 2H, *J* = 7.0 Hz), 6.92 (m, 4H), 7.15 (s, 1H), 7.25 (s, 1H), 7.91 (s, 1H), 8.08 (m, 9H), 8.49 (d, 1H, *J* = 8.5 Hz), 8.55 (d, 1H, *J* = 9.5 Hz). ^{13}C NMR ($CDCl_3$) δ 14.1, 14.2, 14.6, 20.7, 22.6, 31.5, 58.5, 60.0, 60.3, 100.2, 115.4, 122.9, 123.0, 124.3, 124.7, 125.0, 125.5, 125.9, 125.9, 126.3, 126.7, 127.3, 127.6, 128.2, 130.0, 130.6, 131.1, 131.3, 131.4, 136.6, 136.8, 142.4, 147.2, 165.7, 166.1. HR-ESI-MS $[M+Na]^+$ $C_{34}H_{29}NO_4Na$ calcd for m/z 538.19942, found 538.19849.

Diethyl 1,2-diphenyl-1,2-dihydropyridine-3,5-dicarboxylate (5a').

Yellow colored amorphous solid (45.5 mg, 98%). R_f 0.4 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.0 Hz), 4.19 (m, 2H), 4.26 (q, 2H, *J* = 7.0 Hz), 6.15 (s, 1H), 7.15 (m, 3H), 7.30 (m, 4H), 7.40 (d, 2H, *J* = 7.0 Hz), 7.71 (s, 1H), 8.10 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 60.1, 60.5, 61.2, 103.4, 114.4, 119.1, 121.0, 125.9, 126.2, 128.1, 128.7, 129.5, 129.6, 130.6, 141.4, 144.4, 144.9, 165.8, 165.8. HR-ESI-MS $[M+Na]^+$ $C_{23}H_{23}NO_4Na$ calcd for m/z 400.15248, found 400.15152.

Diethyl 1,2-di-*p*-methoxyphenyl-1,2-dihydropyridine-3,5-dicarboxylate (5b').

Yellow colored amorphous solid (75 mg, 97%). R_f 0.25 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.26 (3H, *J* = 7.0 Hz), 1.32 (t, 3H, *J* = 7.0 Hz), 3.76 (s, 3H), 3.78 (s, 3H), 4.16 (m, 2H), 4.25 (q, 2H, *J* = 7.0 Hz), 5.95 (s, 1H) , 6.81 (m, 4H), 7.05 (d, 2H, *J* = 9.0 Hz), 7.30 (d, 2H, *J* = 9.0 Hz), 7.72 (s, 1H), 7.93 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 55.1, 55.5, 59.9, 60.3, 61.8, 101.4, 113.4, 113.9, 114.5, 123.5, 127.6, 130.6, 134.2, 138.0, 145.9, 158.1, 159.4, 165.8, 165.9. HR-ESI-MS $[M+Na]^+$ $C_{25}H_{27}NO_6Na$ calcd for m/z 460.17361, found 460.17382.

Diethyl 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1,2-dihydropyridine-3,5-dicarboxylate (5c').

Yellow colored amorphous solid (105 mg, 93%). R_f 0.2 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.5 Hz), 3.79 (s, 3H), 4.19 (m, 2H),

4.26 (q, 2H, *J* = 7.0 Hz), 6.18 (s, 1H), 6.85 (d, 2H, *J* = 9.0 Hz), 7.01 (d, 2H, *J* =8.5 Hz), 7.57 (d, 2H, *J* = 8.5 Hz), 7.75 (s, 1H), 8.00 (s, 1H), 8.15 (d, 2H, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 26.9, 55.5, 60.2, 60.7, 61.6, 102.4, 112.5, 114.8, 123.0, 124.1, 127.1, 131.7, 137.3, 145.6, 147.7, 148.0, 158.4, 165.5, 165.6. HR-ESI-MS $[M+Na]^+$ $C_{24}H_{24}N_2O_7Na$ calcd for m/z 475.14812, found 475.14697.

Diethyl 2-(4-cyanoyphenyl)-1-(4-methoxyphenyl)-1,2-dihydropyridine-3,5-dicarboxylate (5d').

Yellow colored amorphous solid (57 mg, 80%). R_f 0.27 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.0 Hz), 3.79 (s, 3H), 4.20 (m, 2H), 4.26 (q, 2H, *J* = 7.0 Hz), 6.12 (s, 1H), 6.85 (d, 2H, *J* = 9.0 Hz), 7.00 (d, 2H, *J* = 9.0 Hz), 7.51 (d, 2H, *J* = 8.5 Hz), 7.59 (d, 2H, *J* = 8.0 Hz), 7.74 (s, 1H), 7.99 (s, 1H). ^{13}C NMR (CDCl3) δ 14.3, 14.5, 55.5, 60.2, 60.7, 61.7, 102.4, 112.0, 112.5, 114.8, 118.5, 123.0, 126.9, 131.5, 132.6, 137.4, 145.6, 146.2, 158.3, 165.5, 165.6. HR-ESI-MS $[M+Na]^+$ $C_{25}H_{24}N_2O_5Na$ calcd for m/z 455.15829, found 455.15799.

Diethyl2-(4-chloroyphenyl)-1-(4-methoxyphenyl)-1,2-dihydropyridine-3,5-dicarboxylate (5e').

Yellow colored amorphous solid (79.5 mg, 95%). R_f 0.5 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ1.27 (t, 3H, *J* = 7.0 Hz), 1.32 (t, 3H, *J* = 7.0 Hz), 3.74 (s, 3H), 4.18 (m, 2H), 4.25 (q, 2H, *J* = 7.0 Hz), 6.01 (s, 1H), 6.84 (d, 2H, *J* = 8.5 Hz), 7.03 (d, 2H, *J* = 9.0 Hz), 7.25 (d, 2H, *J* = 8.5 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 7.73 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 55.5, 60.0, 60.5, 61.6, 101.8, 113.2, 114.6, 123.3, 127.6, 128.9, 131.0, 134.0, 137.7, 140.1, 145.8, 158.2, 165.7, 165.8. HR-ESI-MS $[M+Na]^+$ $C_{24}H_{24}NO_5ClNa$ calcd for m/z 464.12407, found 464.12363.

Diethyl 1-(4-chloroyphenyl)-2-(4-methoxyphenyl)-1,2-dihydropyridine-3,5-dicarboxylate (5f').

Yellow colored amorphous solid (56 mg, 97%). R_f 0.4 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3H, *J* = 7.0 Hz), 1.26 (t, 3H, *J* = 7.0 Hz), 3.69 (s, 3H), 4.11 (m, 2H), 4.19 (q, 2H, *J* = 7.0 Hz), 5.93 (s, 1H), 6.73 (d, 2H, *J* = 8.5 Hz), 7.01 (d, 2H, *J* = 8.5 Hz), 7.21 (m, 4H), 7.61 (s, 1H), 7.91 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 13.3, 13.5, 54.2, 59.1, 59.5, 59.9, 102.3, 113.1, 114.2, 121.4, 126.3, 128.5, 129.0, 130.7, 132.5, 142.0, 143.3, 158.5, 164.7. HR-ESI-MS $[M+Na]^+$ $C_{24}H_{24}NO_5ClNa$ calcd for m/z 464.12407, found 464.12449.

Diethyl 1-(4-chloroyphenyl)-2-(4-nitrophenyl)-1,2-dihydropyridine-3,5-dicarboxy-late (5g').

Yellow colored amorphous solid (92 mg, 98%). R_f 0.4 (hexane/EtOAc 4/1). ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J* = 7), 1.34 (t, 3H, *J* = 7), 4.22 (m, 2H), 4.28 (q, 2H, *J* = 6.5), 6.22 (s, 1H), 7.04 (d, 2H, *J* = 9.0 Hz), 7.32 (d, 2H, *J* = 8.5 Hz), 7.57 (d, 2H, *J* = 8.5 Hz), 7.73 (s, 1H), 8.06 (s, 1H), 8.16 (d, 2H, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 60.4, 60.6, 61.0, 104.4, 113.9, 121.9, 124.2, 126.8, 129.9, 131.2, 132.2, 142.4, 144.0, 147.4, 147.8, 165.2, 165.4. HR-ESI-MS $[M+Na]^+$ $C_{23}H_{21}ClN_2O_6Na$ calcd for m/z 479.09858, found 479.09860.

Diethyl 1-(4-chloroyphenyl)-2-(4-cyanophenyl)-1,2-dihydropyridine-3,5-dicarboxy-late (5h').

Yellow colored amorphous solid (63.5 mg, 75%). R_f 0.33(hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J* = 7.0 Hz), 1.34 (t, 3H, *J* = 7.0 Hz), 4.21 (m, 2H), 4.27 (q, 2H, *J* = 7.5 Hz), 6.16 (s, 1H), 7.03 (d, 2H, *J* = 8.5 Hz), 7.32 (d, 2H, *J* = 8.5 Hz), 7.50 (d, 2H, *J* = 8.5 Hz), 7.60 (d, 2H, *J* = 8.5 Hz), 7.71 (s, 1H), 8.04 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 55.0, 60.8, 60.9, 103.9, 104.2, 104.4, 112.3, 113.4, 114.0, 118.6, 121.9, 126.6, 129.8, 131.1, 132.8, 144.0, 145.6, 156.1, 165.7. HR-ESI-MS $[M-H]^-$ $C_{24}H_{20}N_2O_4Cl$ calcd for m/z 435.11116, found 435.11227.

Diethyl 1-(4-iodophenyl)-2-(4-methoxyphenyl)-1,2-dihydropyridine-3,5-dicarboxylate (5i').

Yellow colored amorphous solid (67 mg, 65%). R_f 0.25 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.0 Hz), 3.76 (s, 3H), 4.20 (m, 2H), 4.26 (q, 2H, *J* = 7.0 Hz), 6.01 (s, 1H), 6.80 (d, 2H, *J* = 8.5 Hz), 6.9 (d, 2H, *J* = 8.5 Hz), 7.29 (d, 2H, *J* = 8.5 Hz), 7.63 (d, 2H, *J* = 8.5 Hz), 7.68 (s, 1H), 7.99 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 55.2, 60.2, 60.6, 60.6, 90.1, 103.7, 114.1, 115.5, 122.7, 127.2, 130.0, 133.5, 138.5, 144.0, 144.1, 159.5, 165.7. HR-ESI-MS $[M+Na]^+$ $C_{24}H_{24}NO_5INa$ calcd for m/z 556.05969, found 556.06038.

Diethyl 2-(4-cyanophenyl)-1-(4-iodophenyl)-1,2-dihydropyridine-3,5-dicarboxylate (5j').

Yellow colored amorphous solid (87.5 mg, 71%). R_f 0.31 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.5 Hz), 4.22 (m, 2H), 4.27 (q, 2H, *J* = 7.0 Hz), 6.16 (s, 1H), 6.85 (d, 2H, *J* = 8.5 Hz), 7.50 (d, 2H, *J* = 8.5 Hz), 7.59 (d, 2H, *J* = 8.0 Hz), 7.66 (d, 2H, *J* = 8.5 Hz), 7.70 (s, 1H), 8.04 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 60.4, 60.5, 60.9, 90.5, 104.6, 112.3, 114.2, 118.4, 122.3, 126.6, 131.1, 132.7, 138.7, 143.5, 143.7, 145.6, 152.0, 165.2, 165.4. HR-ESI-MS $[M-H]^-$ $C_{24}H_{20}N_2O_4I$ calcd for m/z 527.04678, found 527.04767.

Diethyl 2-(4-chlorophenyl)-1-(4-iodophenyl)-1,2-dihydropyridine-3,5-dicarboxylate (5k').

Yellow colored amorphous solid (91 mg, 70%). R_f 0.43 (hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 1.21 (t, 3H, *J* = 7.5), 1.26 (t, 3H, *J* = 7), 4.14 (m, 2H), 4.19 (q, 2H, *J* = 7.5), 5.99 (s, 1H), 6.81 (d, 2H, *J* = 8.5), 7.18 (d, 2H, *J* = 8.5), 7.24 (d, 2H, *J* = 8.5), 7.56 (d, 2H, *J* = 8.5), 7.61 (s, 1H), 7.94 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 60.3, 60.4, 60.8, 90.4,

104.12, 114.9, 122.5, 127.3, 129.0, 130.5, 134.2, 138.6, 139.4, 143.8, 143.9, 165.5. HR-ESI-MS $[M+Na]^+$ $C_{23}H_{21}NO_4IClNa$ calcd for m/z 560.01015, found 560.00995.

Diethyl 1-(4-fluorophenyl)-2-(4-nitrophenyl)-1,2-dihydropyridine-3,5-dicarboxylate (5l').

Yellow colored amorphous solid (73 mg, 91%). R_f 0.33 (hexane/EtOAc 4:1). ^1H NMR ($CDCl_3$) δ 1.30 (t, 3H, *J* = 7.5 Hz), 1.34 (t, 3H, *J* = 7.0 Hz), 4.21 (m, 2H), 4.28 (q, 2H, *J* = 7.0 Hz), 6.19 (s, 1H), 7.06 (m, 4H), 7.58 (d, 2H, *J* = 8.5 Hz), 7.74 (s, 1H), 8.02 (s, 1H), 8.16 (d, 2H, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 60.3, 60.9, 61.2, 103.6, 113.3, 116.6, 116.8, 123.0, 123.1, 124.2, 127.0, 131.4, 144.9, 147.6, 147.8, 165.3, 165.4. HR-ESI-MS $[M-H]^-$ $C_{23}H_{20}N_2O_6F$ calcd for m/z 439.13054, found 439.13017.

Diethyl 1-benzyl-2-(*p*-tolyl)-1,2-dihydropyridine-3,5-dicarboxylate (5m').

Yellow colored amorphous solid (47 mg, 94%). R_f 0.41 (hexane/EtOAc 4:1). ^1H NMR ($CDCl_3$) δ 1.16 (t, 3H, *J* = 7.0 Hz), 1.31 (t, 3H, *J* = 7.0 Hz), 2.33 (s, 3H), 4.13 (m, 2H), 4.23 (q, 2H, *J* = 7.0 Hz), 4.32 (q, 2H, J = 6.5 Hz), 5.38 (s, 1H), 7.13 (d, 2H, *J* = 8.0 Hz), 7.23 (d, 2H, *J* = 7.0 Hz), 7.29 (d, 2H, *J* = 9.0 Hz), 7.37 (m, 3H), 7.7 (d, 2H, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 14.1, 14.2, 14.6, 21.2, 22.6, 29.6, 29.7, 30.7, 31.9, 57.9, 59.6, 59.9, 60.0, 96.7, 100.0, 113.0, 127.5, 127.9, 128.5, 129.1, 129.3, 131.8, 134.3, 138.2, 138.4, 150.0, 165.7, 166.1. HR-ESI-MS $[M+Na]^+$ $C_{25}H_{27}NO_4Na$ calcd for m/z 428.18378, found 428.18398.

Diethyl 1-(4-fluorobenzyl)-2-(*p*-tolyl)-1,2-dihydropyridine-3,5-dicarboxylate (5n').

Yellow colored amorphous solid (41 mg, 42%). R_f 0.41 (hexane/EtOAc 4:1). ^1H NMR ($CDCl_3$,) δ 1.17 (t, 3H, *J* = 7.0 Hz), 1.32 (t, 3H, *J* = 7.0 Hz), 2.33 (s, 3H), 4.04 (m, 2H), 4.23 (q, 2H, *J* = 7.5 Hz), 4.29 (s, 2H), 5.35 (s, 1H), 7.07 (t, 2H, *J* = 8.5 Hz), 7.12 (d, 2H, *J* = 8.0 Hz), 7.19 (m, 2H), 7.27 (m, 2H), 7.69 (d, 2H, *J* = 4.0 Hz). ^{13}C NMR (CDCl3) δ 14.2, 14.5, 21.1, 57.2, 59.7, 59.8, 60.0, 97.0, 113.1, 116.0, 116.2, 129.3, 129.6, 129.7,

129.8, 130.0, 131.6, 138.0, 138.4, 149.7, 165.6, 166.0. HR-ESI-MS $[M+Na]^+$ $C_{25}H_{26}NO_4FNa$ calcd for m/z 446.17436, found 446.17450.

Diethyl 1-benzyl-2-(4-nitrophenyl)-1,2-dihydropyridine-3,5-dicarboxylate (5o').

Yellow colored amorphous solid (49 mg, 69%). R_f 0.25 (hexane/EtOAc 4:1). ^1H NMR ($CDCl_3$) δ 1.19 (t, 3H, *J* = 7.5 Hz), 1.33 (t, 3H, *J* = 7.0 Hz), 4.06 (m, 2H), 4.25 (q, 3H, *J* = 7.0 Hz), 4.43 (, 1H,), 5.57 (s, 1H), 7.20 (d, 2H, *J* = 7.0 Hz), 7.37 (m, 3H), 7.57 (d, 2H, *J* = 8.5 Hz), 7.73 (s, 1H), 7.81 (s, 1H), 8.17 (d, 2H, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ 14.2, 14.5, 58.6, 59.6, 59.9, 60.4, 97.5, 124.0, 127.8, 128.3, 128.9, 129.3, 132.5, 147.5, 150.0, 165.3. HR-ESI-MS $[M-H]^-$ $C_{24}H_{23}N_2O_6$ calcd for m/z 435.15561, found 435.15686.

Diethyl 1-(4-fluorobenzyl)-2-(4-nitrophenyl)-1,2-dihydropyridine-3,5-dicarboxylate (5p').

Yellow colored amorphous solid (61 mg, 89%). R_f 0.4 (hexane/EtOAc 4:1). ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.0 Hz), 4.07 (m, 2H), 4.25 (m, 2H), 4.26 (m, 1H), 4.40 (d, 1H, *J* = 15.0 Hz), 5.53 (s, 1H), 7.08 (t, 2H, *J* = 8.5 Hz), 7.19 (t, 2H, *J* = 8.0 Hz), 7.57 (d, 2H, *J* = 8.5 Hz), 7.72 (s, 1H), 7.95 (s, 1H), 8.18 (d, 2H, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$) δ 14.2, 14.5, 57.8, 59.4, 60.0, 60.5, 97.2, 112.3, 116.2, 116.4, 124.0, 128.2, 129.6, 129.7, 132.4, 147.3, 147.9, 149.8, 165.3, 165.6. ESI-HRMS $[M+H]^+$ $C_{24}H_{24}FN_2O_6$ calcd for m/z 455.16184, found 455.16132.

Diethyl 1-(4-methoxyphenyl)-2-propyl-1,2-dihydropyridine-3,5-dicarboxylate (5q').

Yellow colored amorphous solid (25 mg, 22%). R_f 0.38 (hexane/EtOAc 4:1). ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, *J* = 7.5 Hz), 1.31 (m, 10H), 3.82 (s, 3H), 4.21 (m, 4H), 5.13 (m, 1H), 6.94 (d, 2H, *J* = 8.5 Hz), 7.20 (d, 2H, *J* = 9.0 Hz), 7.70 (s, 1H), 7.78 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.1, 14.4, 14.5, 17.6, 35.7, 55.6, 57.8, 59.9, 60.3, 102.9, 112.1, 114.8, 122.5, 131.9, 137.8, 144.9, 157.8, 166.1, 166.1. HR-ESI-MS $[M+Na]^+$ $C_{21}H_{27}NO_5Na$ calcd for m/z 396.17869, found 396.17921.

2.6. References

1. (a) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1. (b) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223. (c) Singh, S. K.; Sharma, V. K. *Curr. Org. Chem.* **2014**, *18*, 1159. (d) Sharma, V. K.; Singh, S. K. *RSC Adv.* **2017**, *7*, 2682.
2. Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.
3. (a) Edraki, N.; Mehdipour, A. R.; Khoshneviszadeh, M.; Miri, R. *Drug Discovery Today* **2009**, *14*, 1058. (b) Safak, C.; Simsek, R. *Mini-Rev. Med. Chem.* **2006**, *6*, 747.
4. Wang, D.; Hu, S.; Zhang, J.; Li, D.; Liu, X.; Li, Y. *Mol. Med. Rep.* **2017**, *16*, 1133.
5. (a) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. B. *Org. Lett.* **2004**, *6*, 3517. (b) Sales, M.; Charette, A. B. *Org. Lett.* **2005**, *7*, 5773. (c) Pelletier, G.; Constantineau-Forget, L.; Charette, A. B. *Chem. Commun.* **2014**, *50*, 6883. (d) Duttwyler, S.; Chen, S.; Lu, C.; Mercado, B. Q.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 3877. (e) Young, D.W.; Comins, D. L. *Org. Lett.* **2005**, *7*, 566. (f) Chen, M.; Chen, Y.; Sun, N.; Zhao, J.; Liu, Y.; Li, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 1200.
6. (a) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2013**, *15*, 444. (b) Krow, G. R.; Huang, Q.; Szczepanski, S. W.; Hausheer, F. H.; Carroll, P. J. *J. Org. Chem.* **2007**, *72*, 3458. (c) Nakano, H.; Osone, K.; Takeshita, M.; Kwon, E.; Seki, C.; Matsuyama, H.; Takano, N.; Kohari, Y. *Chem. Commun.* **2010**, *46*, 4827. (d) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5734.
7. (a) Faruk Khan, M. O.; Levi, M. S.; Clark, C. R.; Ablordeppey, S. Y.; Law, S.-L.; Wilson, N. H.; Borne, R. F. *Stud. Nat. Prod. Chem.* **2008**, *34*, 753. (b) Comins, D. L.; Brooks, C. A.; Al-awar, R. S.; Goehring, R. R. *Org. Lett.* **1999**, *1*, 229. (c) Jana, G. K.; Sinha, S. *Tetrahedron* **2012**, *68*, 7155. (d) Sundberg, R. J.; Hong, J.; Smith, S. Q.; Sabat, M. *Tetrahedron* **1998**, *54*, 6259.

8. (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645. (b) Fallon, B. J.; Derat, E.; Amatore, M.; Aubert, C.; Petit, M. *ACS Catal.* **2015**, *5*, 7493. (c) Oshima, K.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2012**, *134*, 3699. (d) Dai, H.; Yu, S.; Cheng, W.; Xu, Z.; Li, C-Y. *Chem. Commun.* **2017**, *53*, 6417.
9. (a) Shao, Y.; Zhu, K.; Qin, Z.; Li, E.; Li, Y. *J. Org. Chem.* **2013**, *78*, 5731. (b) Tejedor, D.; Cotos, L.; Mendez-Abt, G.; Garcia-Tellado, F. *J. Org. Chem.* **2014**, *79*, 10655. (c) Trost, B. M.; Biannic, B. *Org. Lett.* **2015**, *17*, 1433. (d) Ramaraju, P.; Mir, N. A.; Singh, D.; Gupta, V. K.; Kant, R.; Kumar, I. *Org. Lett.* **2015**, *17*, 5582.
10. (a) Koley, S.; Chowdhury, S.; Chanda, T.; Ramulu, B. J.; Samai, S.; Motisa, L.; Singh, M. S. *Tetrahedron* **2015**, *71*, 301. (b) Cao, S.; Xin, L.; Liu, Y.; Wan, J.-P.; Wen, C. *RSC Adv.* **2015**, *5*, 27372. (c) Xie, Y.; Ye, S.; Chen, W.; Hu, Y.; Li, D.; Wang, L. *Asian J. Org. Chem.* **2017**, *6*, 746.
11. (a) Sato, Y.; Ichihashi, M.; Okumura, K. *Chem. Pharm. Bull.* **1992**, *40*, 912. (b) Ogawa, A. K.; Willoughby, C. A.; Bergeron, R.; Ellsworth, K. P.; Geissler, W. M.; Myers, R. W.; Yao, J.; Harris, G.; Chapman, K. T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3405. (c) Sirijindalert, T.; Hansuthirakul, K.; Rashatasakhon, P.; Sukwattanasinitt, M.; Ajavakom, A. *Tetrahedron* **2010**, *66*, 5161.
12. Bottomley, W. *Tetrahedron Lett.* **1967**, *21*, 1997.
13. (a) Adams, J.; Hardin, A.; Vounatsos, F. *J. Org. Chem.* **2006**, *71*, 9895. (b) Cocco, M. T.; Congiu, C.; Maccioni, A.; Onnis, V. *Synthesis* **1992**, 371. (c) Palacios, F.; Garcia, J.; Ochoa de Retana, A.; Oyarzabal, J. *Heterocycles* **1995**, *41*, 1915.
14. Anghelide, N.; Draghici, C.; Raileanu, D. *Tetrahedron* **1974**, *30*, 623.
15. Palacios, F.; Herran, E.; Rubiales, G. *J. Org. Chem.* **1999**, *64*, 6239.

Chapter 3

A cascade synthesis of biaryl-2-carbaldehydes

3.1 Abstract

This chapter reveals a novel synthetic route to highly functionalized biaryl-2-carbaldehydes under metal-free reaction conditions. The reaction utilizes easily accessible acyclic substrates dienaminodioate (**1**) derived from ethyl propiolate, cinnamaldehyde (**2**) and allylamine (**3**) to afford biaryls (**5**) via cascade annulation approach (Figure 3.1A). Based on the detailed mechanistic studies, we proposed a Diels-Alder pathway which proceeds through the formation of trienamine intermediate **4** in the presence of trifluoroacetic acid at room temperature. The reaction exhibited broad substrate scope by generating polyfunctional biaryls in moderate to good yields. Synthetic applications of the resulting biaryl-2-carbaldehyde have been demonstrated by conversion into an array of diverse molecules with biological and materials chemistry relevance. The present work offers a complementary route to the existing metal mediated cross-coupling methods for the preparation of biaryls.

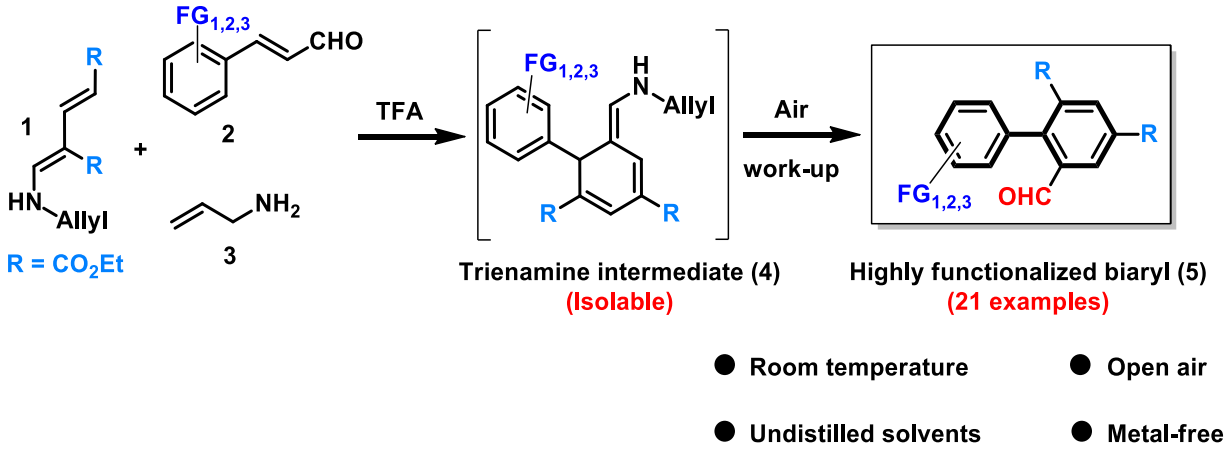


Figure 3.1A. Cascade synthesis of biaryl-2-carbaldehyde

3.2. Introduction

Biaryl motifs are key structural components in a myriad of exotic carbon frameworks which include a variety of natural products,[1] pharmaceuticals,[2] advanced materials,[3] chiral ligands,[4] and agrochemicals.[5] Some of the representative molecules possessing biaryl motif are highlighted in figure 3.2A.

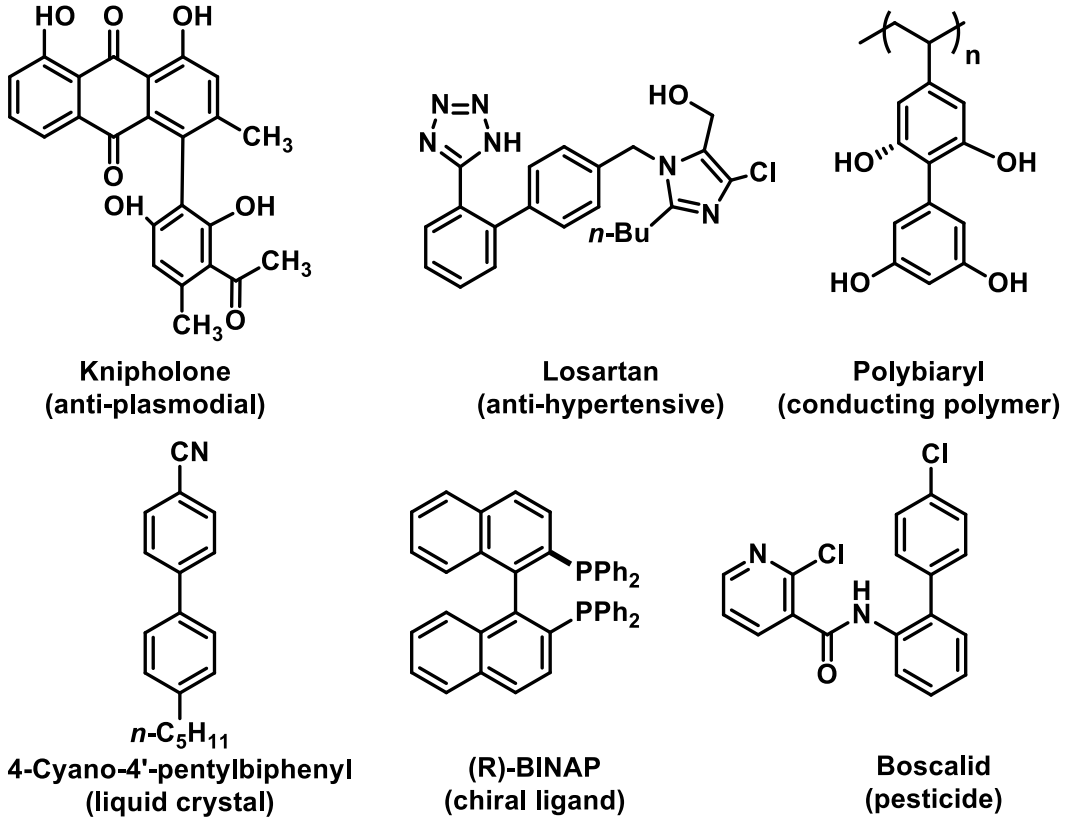
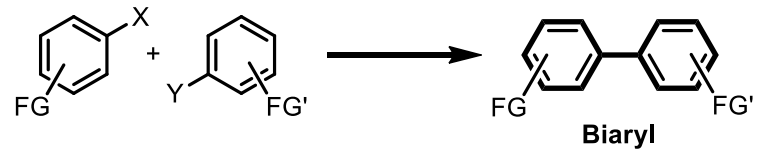


Figure 3.2A. Representative biaryl structural motifs

Since the inception of biaryl synthesis in the presence of copper by Ullman,[6] several synthetic strategies were developed with improved reaction conditions and yields. Breakthrough in this direction was the discovery of transition metal catalyzed cross-coupling reactions involving aryl halide and aryl organometallic reagents.[7] In particular, palladium-catalyzed cross-coupling strategies such as Kharasch, Suzuki-Miyaura, Hiyama, Kumada, Negishi, and Stille couplings have been the front runners (Figure 3.2B).[8] These conventional techniques for biaryl synthesis require an inevitable pre-activation of aromatic substrates. As an alternative to pre-activation, cross-coupling by

direct arylation of simple arenes have begun to appear which replaces organometallic species.[9] Apart from these strategies, several other coupling reactions which include metal-free cross-coupling,[10] decarboxylative coupling,[11] and HIR mediated oxidative couplings[12] have recently drawn the attention of synthetic community (Figure 3.2B).



Cross-coupling strategies:

a) Conventional metal catalyzed
X = Metal Y = Halogen

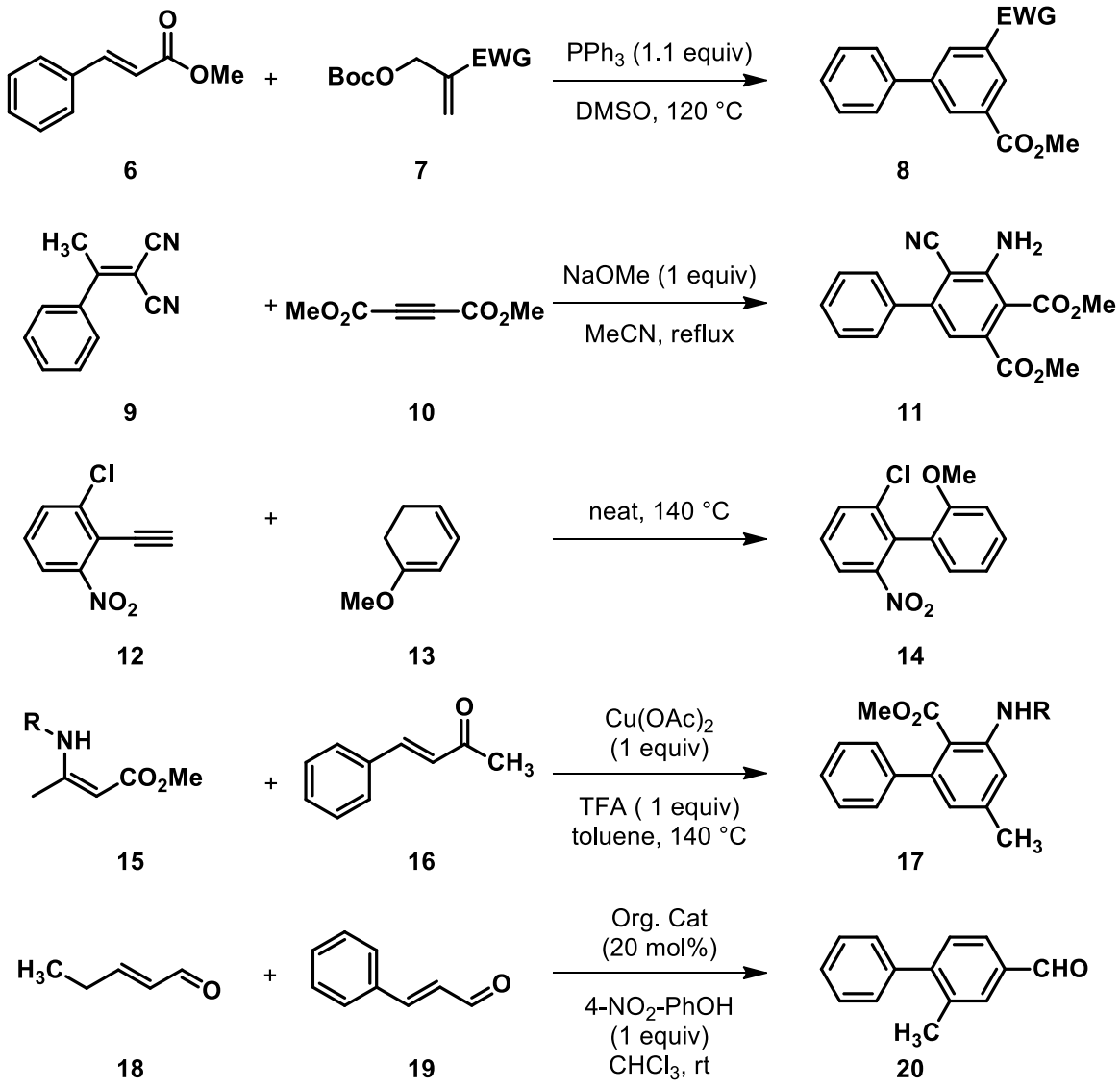
b) Direct arylation
X = H Y = Halogen

c) Decarboxylative coupling
X = COOH Y = Halogen

d) Oxidative coupling
X = H Y = H

Figure 3.2B. Major cross-coupling strategies available for biaryl synthesis

The biaryl synthesis was also achieved using acyclic substrates annulation strategy as an alternative to cross-coupling reactions, which provides biaryls with diverse functionalities. Few notable contributions towards this approach involve strategies such as domino benzannulation[13] of β,δ-unsaturated α-ketoester **6** and Morita-Baylis-Hillman (MBH) carbonate **7** mediated by phosphine,[13a] cyclocondensation[14] utilizing substrates such as vinyl malononitriles **9**, dialkyl acetylenedicarboxylates **10** in presence of base,[14a] Diels-Alder reaction[15] using substituted acetylenes **12** and dienes **13**,[15c] [3+3] cycloaddition[16] of enaminoate **15** with enone **16**,[16a] and organocatalytic dimerization of enal substrates **18** and **19** (Scheme 3.2.1).[17]

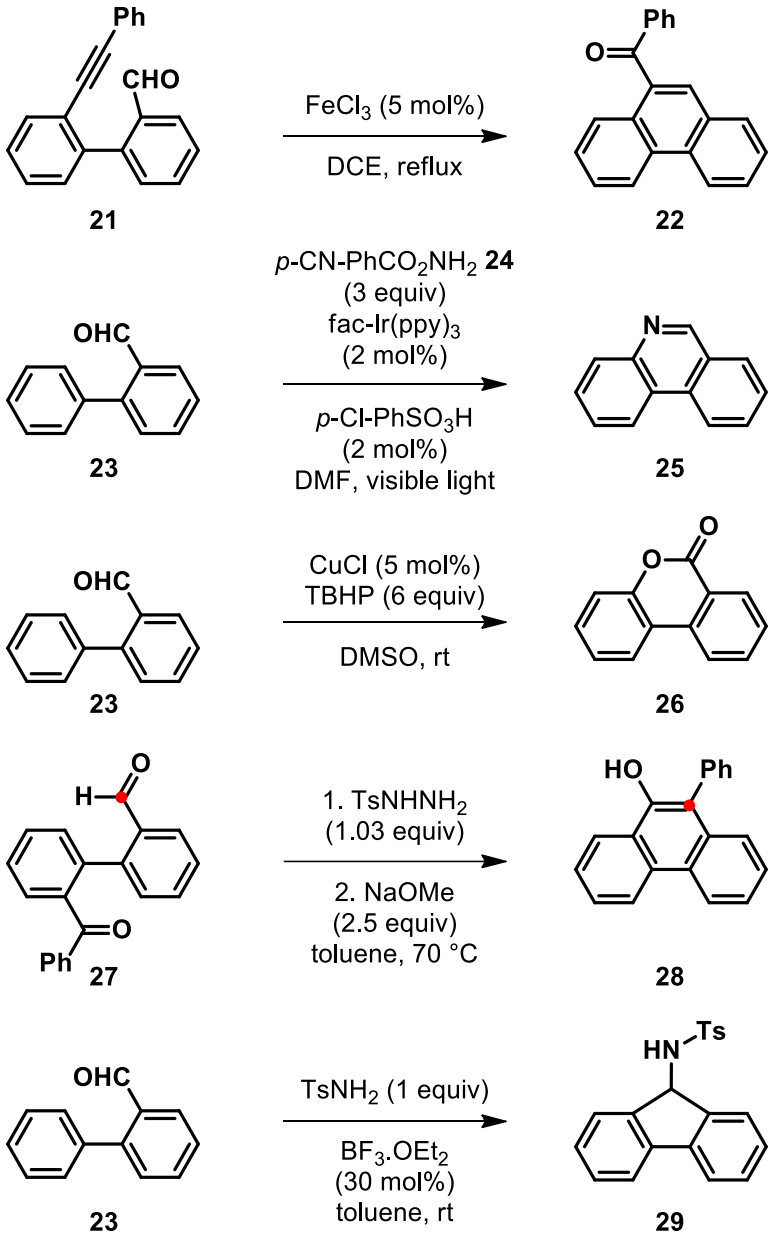


Scheme 3.2.1. Representative cyclization approaches for biaryl synthesis

Given the importance of biaryl motif in a multitude of applications, there has been a continued methodological attention to complement the existing methods for operational simplicity, functional group tolerance, avoiding metals or strong oxidizing reagents, usage of simple starting materials and one-pot conditions. A synthetic technique that generates polyfunctional system under such mild conditions is highly desirable for industrial applications.

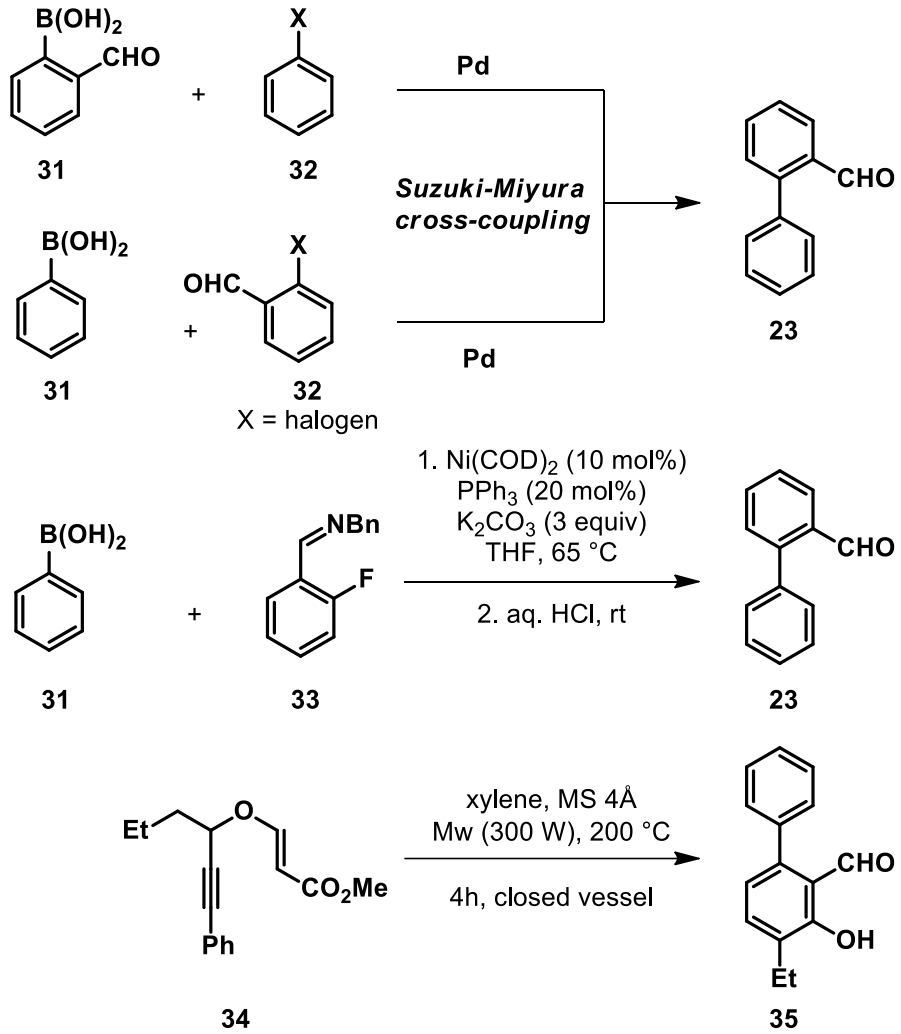
On the other hand, biaryl-2-carbaldehyde which is topic of the present chapter is a key starting material in the construction of several pharmaceutically relevant scaffolds.

For instance, Jana et al. reported an efficient Fe(III) catalyzed intramolecular coupling of biaryl-2-carbaldehyde **21** for the synthesis of functionalized phenanthrenes **22** (Scheme 3.2.2).[18a] Yu et al. developed a visible light mediated one-pot synthesis of phenanthridine **25** from biaryl-2-carbaldehyde **23**. The reaction utilizes *O*-(4-Cyanobenzoyl)-hydroxylamine **24** as the nitrogen source to *O*-acyl oximes generated *in situ* from **23** catalyzed by Brønsted acid (Scheme 3.2.2).[18b]



Scheme 3.2.2. Representative transformations of biaryl-2-carbaldehydes

Ray et al. described copper catalyzed intramolecular aryl C–H oxidative lactonization of biaryl-2-carbaldehyde **23** to access dibenzopyranone **26** in the presence of TBHP oxidant at room temperature (Scheme 3.2.2).[18c] Wang et al. successfully transformed biaryl-2-carbaldehyde **27** to the corresponding phenanthrols **28** under base mediated intramolecular cyclization conditions (Scheme 3.2.2).[18d] The reaction is recognized as catalyst-free intramolecular formal diazo carbon insertion of *N*-tosylhydrazones generated from **27** and tosylhydrazene into keto C-C bonds.



Scheme 3.2.3. Representative methods for biaryl-2-carbaldehyde synthesis

Lu et al. reported a $BF_3.OEt_2$ catalyzed one-pot synthesis of N-tosyl-9-aminofluorenes **30** from biaryl-2-carbaldehyde **23** (Scheme 3.2.2).[18e] The reaction proceeds through the

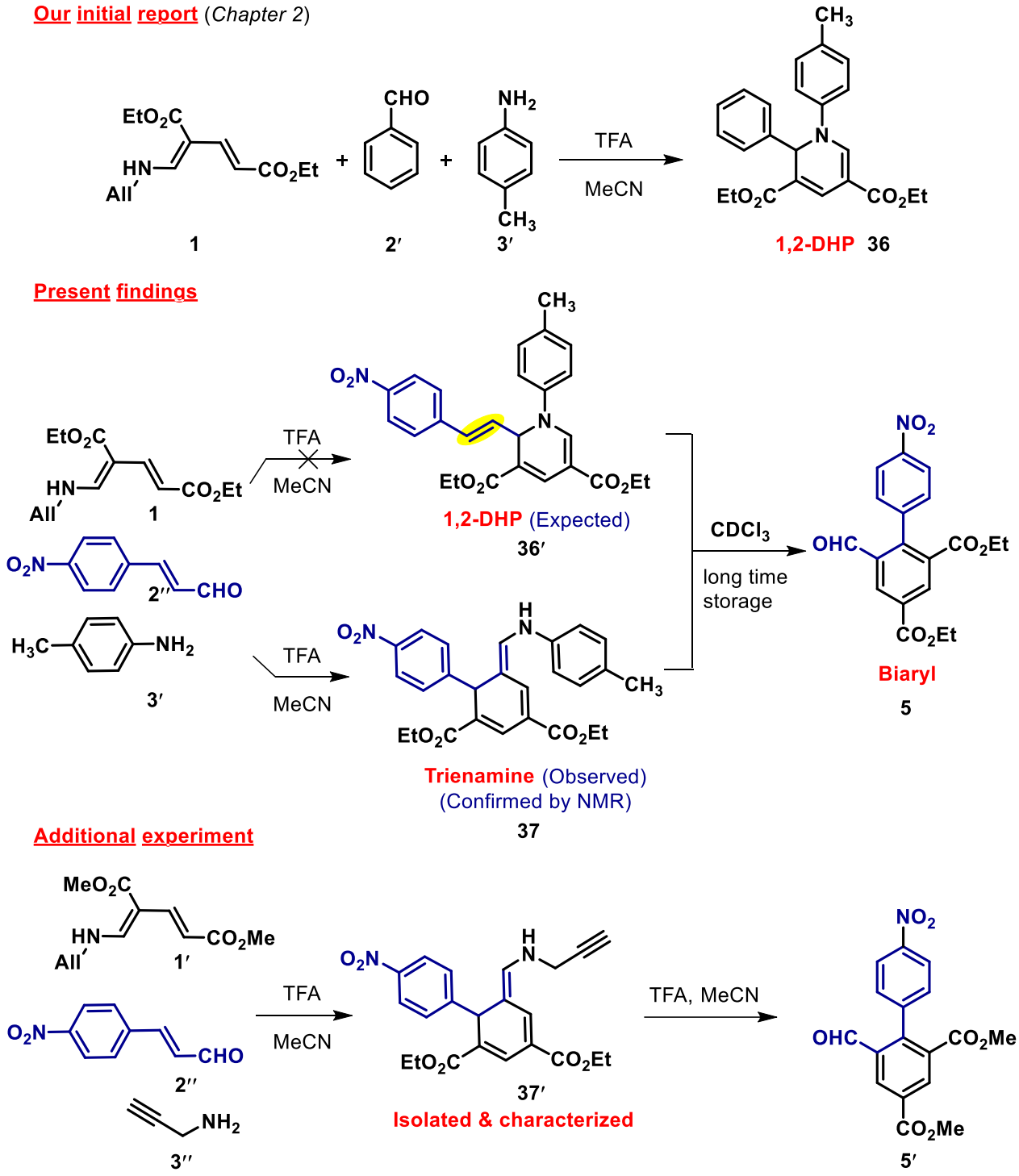
formation of an *in situ* generated N-tosylbenzaldimines via an aza-Friedel–Crafts reaction.

Despite its profound importance, the dominant method of choice for biaryl-2-carbaldehyde synthesis has been limited to Suzuki-Miyaura reaction of boronic acids **31** and halides **32** (Scheme 3.2.3),[19] along with few other nickel catalyzed cross-coupling reactions between **31** and **33** (3.2.3).[20] However, Tejedor et al. reported synthesis of biaryl-2-carbaldehyde **35** under microwave conditions at 200 ºC by rearrangement of propargyl vinyl ethers **34** (3.2.3).[21]

By and large, biaryl-2-carbaldehyde is an important precursor to access a wide range of molecular scaffolds, but the currently available methods limit its use as a more potential candidate in various fields. Especially, metal-free reactions which can provide polysubstituted biaryl-2-carbaldehydes are very scarce. Hence, our present metal-free cascade reaction under mild conditions offers a complementary route to currently available methods for the synthesis of biaryl-2-carbaldehydes.

3.3. Results and discussions

In chapter 2, we have presented a one-pot cascade multicomponent reaction (MCR) for synthesis of 1,2-dihydropyridine (1,2-DHP) **36** from dienaminodioate **1** and an *in situ* generated imine with a broad substrate scope utilizing different aromatic aldehydes **2'** and amines **3'** with good yields, in presence of trifluoroacetic acid (TFA) (Scheme 3.3.1).[22] The reaction could be easily monitored visually by yellow colouration of the reaction mixture which is an indication of 1,2-DHP formation. During this attempt, we have also utilized *p*-nitrocinnamaldehyde **2''** as the aldehyde component with *p*-toluidine **3'** which was presumed to produce the 1,2-DHP **36'** containing a styryl side-chain. Surprisingly, the 1,2-DHP **36'** in $CDCl_3$ underwent slow rearrangement to a new non-polar product which was characterized by NMR as a biaryl **5** (Scheme 3.3.1).



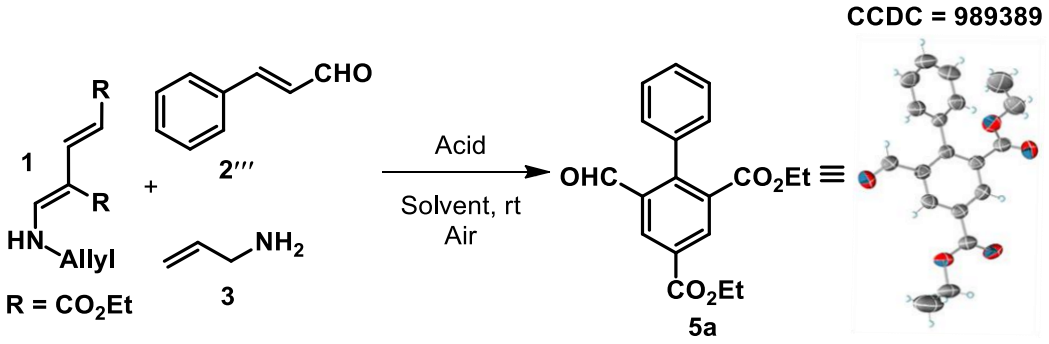
Scheme 3.3.1. Formation of trienamine and conversion to biaryl under same TFA conditions

A detailed characterization by 2D-NMR studies revealed the identity of the presumed 1,2-DHP from *p*-nitrocinnamaldehyde as trienamine **37**. To further confirm the formation of trienamine with simplified NMR spectra, an annulation reaction was performed with

dienaminodioate **1'**, *p*-nitrocinnamaldehyde **2''** and propargylamine **3''** which afforded trienamine **37'** which was isolated and treated with trifluoroacetic acid under open air which provided the expected biaryl **5'** (Scheme 3.3.1).

This serendipitous result motivated us to pursue a synthetic method for biaryls under metal-free and mild conditions in a one-pot operation. We have performed the optimization reactions using dienaminodioate **1**, simple cinnamaldehyde **2'''** and allylamine **3**. Trienamine formation was immediate and predominant, but the desired biaryl **5a** was formed in a trace amount despite an increase in the concentration of TFA (entry 1, Table 3.3.1). The structure of biaryl **5a** was further supported by a single crystal XRD analysis. Interestingly, a change of solvent to DCM afforded biaryl **5a** in 25% yield (entry 2). Attempts using solvents such as MeOH, THF and toluene led to no considerable improvement in the yields (entries 3-5). However, when MeCN was used along with DCM/$CHCl_3$ as a co-solvent and by increasing the concentration of TFA/**2'''**/**3** to three equivalents with respect to one equivalent of dienaminodioate **1,** the reaction afforded biaryl **5a** with a 60% yield (entries 6-7). There was no biaryl formation when the reaction was attempted either in the absence of TFA or allylamine **3** (entry 8-9). Attempts with other acids such as $FeCl_3$, trichloroacetic acid, and acetic acid had no significant improvement in the yield of biaryl **5a** (entries 10-12); and there was no biaryl formation in the presence of $BF_3.Et_2O$ or *p*-TsOH (entries 13-14).

Table.3.3.1. Optimization of reaction conditions

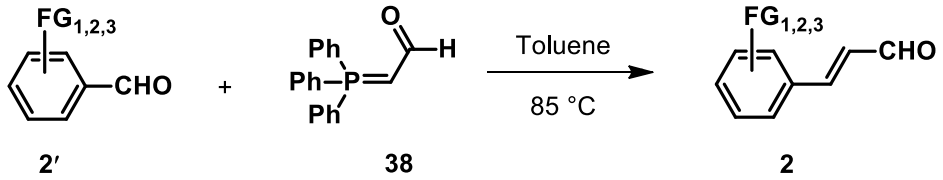


entry	**acid (equiv)**	**ratio[a] 2':3**	**solvent[b]**	**time (h)**	**yield[c] (%)**
1	TFA (5)	1.2:1.2	MeCN	2.0	Trace
2	TFA (1)	1.2:1.2	DCM	on	25
3	TFA (3)	2:2	MeOH	on	27
4	TFA (3)	2:2	THF	on	26
5	TFA (3)	2:2	Toluene	on	32
6[d]	**TFA (3)**	**3:3**	**MeCN/DCM**	**4.30**	**60**
7[e]	**TFA (3)**	**3:3**	**MeCN/$CHCl_3$**	**4.30**	**60**
8[d]	-	3:3	MeCN/DCM	60	n.d.
9[d]	TFA (3)	3:0	MeCN/DCM	1.0	n.d.
10	$FeCl_3$ (3)	3:3	MeCN	7.25	44
11[d]	TCA (3)	3:3	MeCN/DCM	> 96	21
12[f]	AcOH	1.2:1.2	MeCN	on	47
13	$BF_3.OEt_2$ (3)	3:3	MeCN	on	n.d.
14	*p*-TsOH (3)	3:3	MeCN	on	n.d.
15[d]	TFA (1)	1:1	MeCN/DCM	on	29
16	TFA (3)	3:3	DMF	on	25
17[d]	TFA (3)	2:2	MeCN/Toluene	on	44
18[d]	TFA (2)	1.5:2	MeCN/DCM	on	31
19[d]	TFA (3)	1.5:3	MeCN/DCM	on	46
20[e]	TFA (3)	3:3	MeCN/DCE	on	43

[a] Equivalents of **2'** and **3**, respectively. [b] Undistilled solvents. [c] Isolated yields. [d] MeCN–DCM (1:2). [e] MeCN–$CHCl_3$ (DCE) (1:1). [f] AcOH–MeCN (0.25:2.5 mL). on = overnight, n.d. = not detected.

Further optimization studies by variation of the substrate molar ratio and solvents could not improve the yield of biaryl significantly (entries 15-20), which led us to consider a substrate molar ratio of 1:3:3:3 for **1**/**2'''**/**3**/**TFA** in MeCN–$CHCl_3$ (DCM) (1:1) (0.1 M of compound **1**, 3 mL) as the optimized condition to test the generality of the reaction. The substrate scope was demonstrated by screening various substituted cinnamaldehydes **2**

under the optimized conditions, which were synthesized in one step by Wittig reaction[23] between commercially available (triphenylphosphoranylidene)acetaldehyde **38** and pertinent aromatic aldehydes **2'** (Scheme 3.3.2).



2′ 38 2

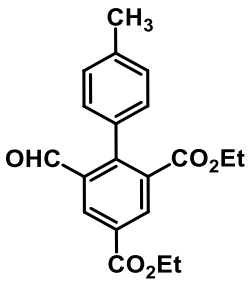
Scheme 3.3.2. General Wittig reaction for the synthesis of cinnamaldehydes

Cinnamaldehydes with diverse mono-, di-, and tri- substitutions that confer varied electronic properties to the phenyl ring were applied towards the optimized methodology (Table 3.3.2). Simple cinnamaldehydes with *para*-substitutions such as methyl, methoxy, chloro, bromo, cyano, and nitro reacted smoothly, as expected, to afford biaryls **5b**, **5c**, **5d**, **5e**, **5f**, and **5g** respectively, in good yields. These results clearly show that this methodology tolerates both electron donating and withdrawing substituents. Interestingly, with *p*-formyl cinnamaldehyde, the biaryl product **5h** was produced in 56% yield without any formation of 1,2-DHP by the competing involvement of *para*-formyl group as expected from our previous experience. Reaction with *o*-bromo and *o*-ethynyl cinnamaldehydes also afforded the corresponding biaryls **5i** and **5j**, which clearly indicates that ortho substitutions are not detrimental for biaryl formation. Moving on to cinnamaldehydes with di-substitutions held at various positions, biaryls **5k-n** were produced in reasonably good yields. Biaryls **5m-n** with halogen substitutions clearly offers a viable alternative to the existing traditional Pd catalyzed cross-coupling methodologies to surmount the chemoselectivity obstacle in multi-halogen substituted substrates. Furthermore, **5i-5j** and **5l-5n** marks entry into the tri and tetra ortho-substituted class of biaryls. An elegant display of polyfunctional biaryl was demonstrated by the formation of multifaceted **5o** with tri-substitutions in each phenyl unit, which can

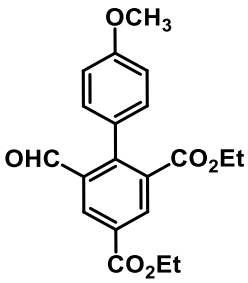
be moulded further into demanding structures which otherwise are conceived in a multi-step manner. To the best of our knowledge, **5o** represents the first diverse biaryl structure derived by a one-pot strategy. The generality of this method was extended towards substituted heteroaromatic unsaturated aldehydes which afforded biaryls **5p-q** in moderate yields, which further vindicates the generality of this method towards the successful synthesis of hetero biaryls. Cinnamaldehydes derived from substituted salicylaldehydes are advantageous in a way that the resulting biaryls spontaneously undergoes cyclization to produce benzopyrones **5r-5s** in good yields. It is worth mentioning that the present method of one-pot benzopyrone synthesis serves as an alternative to such synthesis reported by utilizing expensive metal catalysts and pre-functionalized starting materials.[24] A four-component reaction towards the existing method was envisaged to add more dimensions to the methodology. As a result, with substituted salicylaldehydes in a solvent system comprising MeOH/MeCN (1:1) the reaction afforded a tricyclic product with the successful incorporation of methanol in the product **5t**. Similarly, replacing MeOH to *n*-butanol afforded the expected tricyclic product **5u** in a good yield.

We have proposed a mechanism which proceeds via Diels-Alder reaction through MacMillan's iminium activation[25] of aldehyde. The resulting adduct **B** undergoes rearrangement to a more stable trienamine intermediate by a loss of proton. Aromatization to intermediate **D** can be facilitated by air oxidation and subsequent workup affords biaryl (Scheme 3.3.3). The oxidation step was further confirmed by treating the isolated trienamine intermediate with DDQ/DCM which produced a facile conversion to biaryl. The double bond geometry of cinnamaldehyde starting material offers no threat to the biaryl formation as attempts were even made with cis-trans mixture.

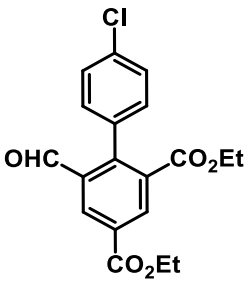
Table 3.3.2. Scope of biaryl synthesis[x]



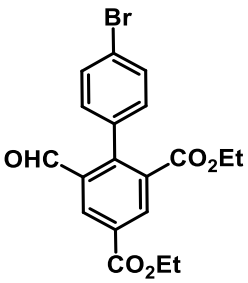
5b (60%)[a]



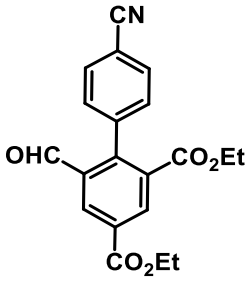
5c (55%)[a]



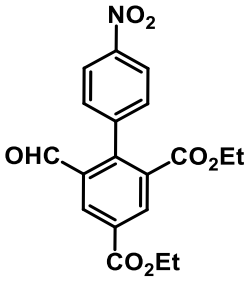
5d (63%)[a]



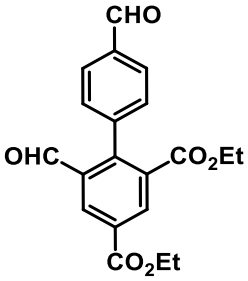
5e (84%)[a]



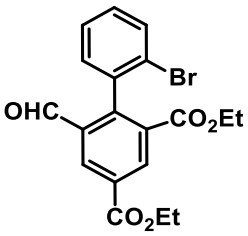
5f (86%)[a]



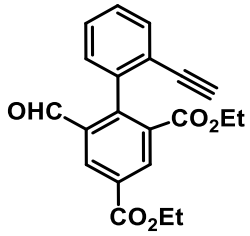
5g (50%)[a]



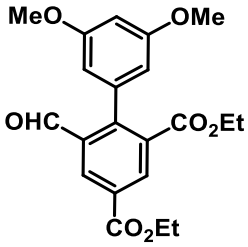
5h (56%)[a]



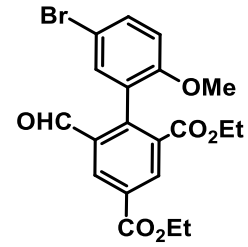
5i (74%)[a]



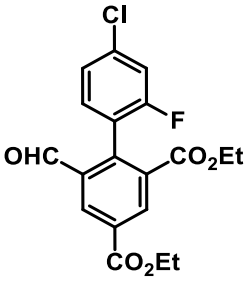
5j (69%)[b]



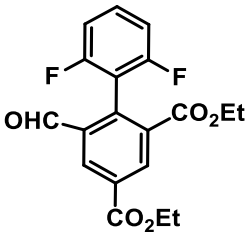
5k (67%)[a]



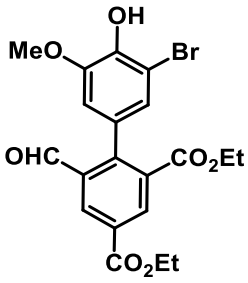
5l (85%)[a]



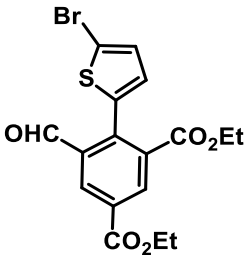
5m (68%)[b]



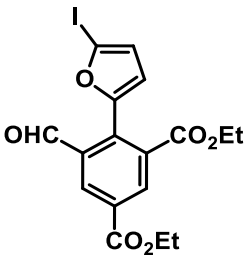
5n (68%)[a]



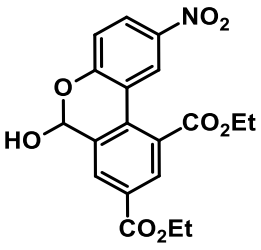
5o (38%)[b]



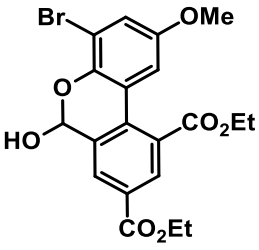
5p (49%)[b]



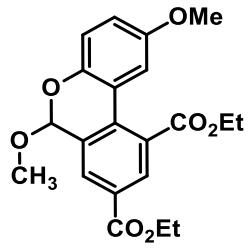
5q (55%)[a]



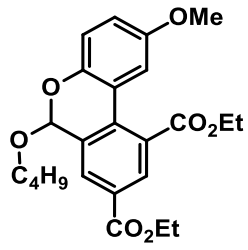
5r (68%)[a]



5s (77%)[b]

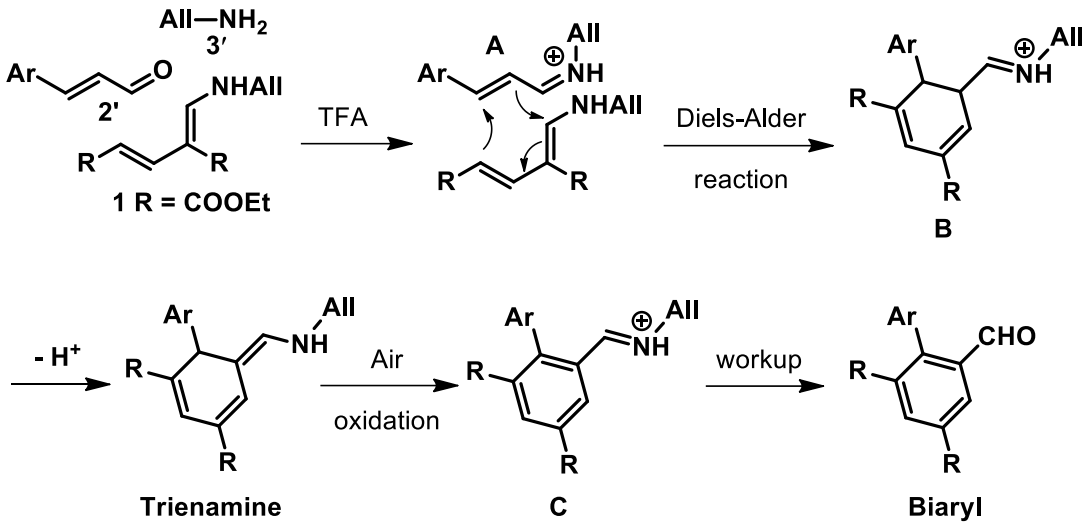


5t (60%)[c]



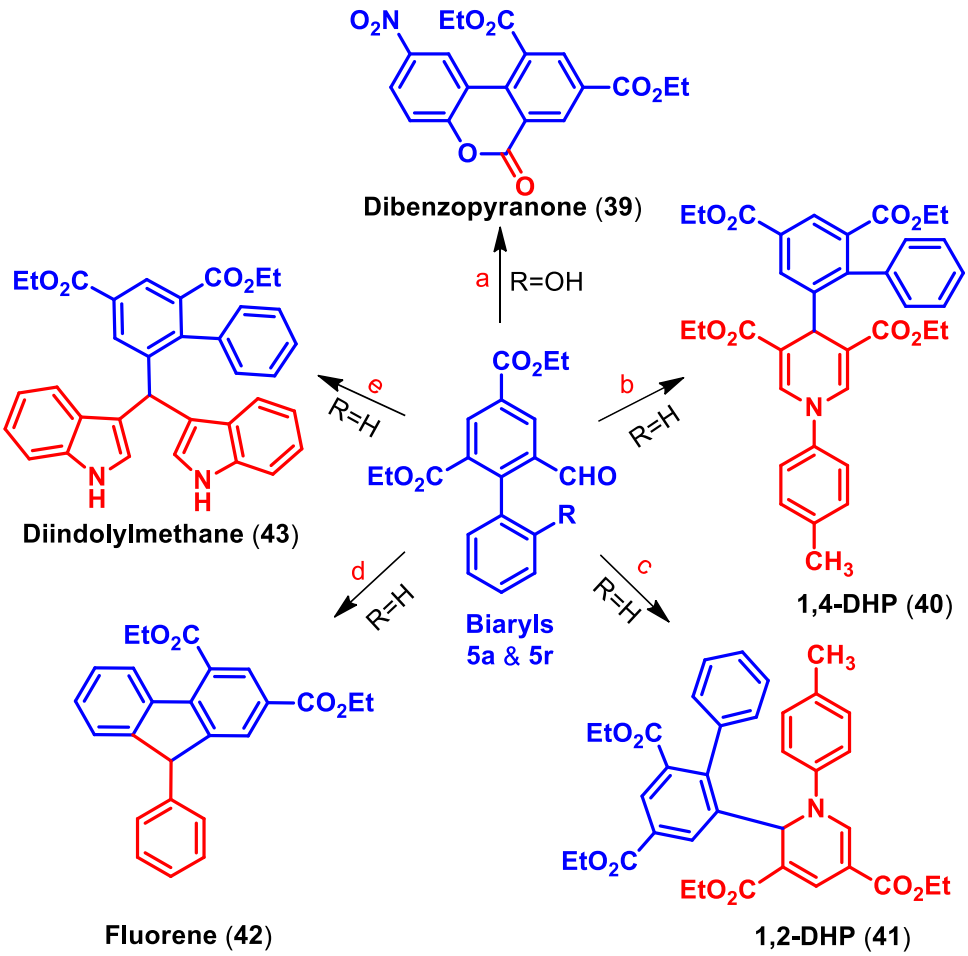
5u (66%)[c]

[x]Unless otherwise mentioned, all reactions were conducted using 3:3:3 ratios of **2**:**3**:**TFA** at room temperature in open air atmosphere. [a]MeCN/$CHCl_3$ (1:1), [b]MeCN/DCM (1:2), [c]MeCN/MeOH and MeCN/BuOH (1:1).



Scheme 3.3.3. Proposed Diels-Alder mechanism for biaryl formation

To justify the paramount importance of 2-carbaldehyde functionality in biaryls, a series of transformations were carried out on biaryls **5r** and **5a** to afford dibenzopyranone **39**, 1,4-DHP **40**, 1,2-DHP **41**, fluorene **42**, and diindolylmethane (DIM) **43** (Scheme 3.3.4). A number of natural products contain benzopyranone as a core feature and its synthesis from biaryl-2-ol involves palladium-catalyzed CO insertion via C-H activation.[26] Dibenzopyranone **39** was synthesized from biaryl **5r** in a quantitative yield by Dess-Martin periodinane oxidation. As described in the introductory part of chapter-2, both 1,4-DHP and 1,2-DHP are valuable scaffolds.[27] Our present synthesis of 1,4-DHP **40** and 1,2-DHP **41** in one-step from biaryl **5a**, unequivocally, demonstrates a new entry into the repertoire of aryl scaffolds. Fluorenes which gained prominence in the form of conjugated polymers in display applications with exceptional electro-optical properties are synthesized by metal-catalyzed annulations.[28]



Scheme 3.3.4. Synthetic transformations of biaryl to various scaffolds

Reaction conditions: (a) **5r** (1.0 equiv), Dess–Martin periodinane (3.0 equiv), DCM, rt; (b) **5a** (1.0 equiv), ethyl 3-(allylamino)acrylate (2.0 equiv), *p*-toluidine (1.0 equiv), TFA (1.0 equiv), MeCN, rt; (c) **1** (1.0 equiv), **5a** (1.2 equiv), *p*-toluidine (1.2 equiv), TFA (1.0 equiv), MeCN, rt; (d) (i) **5a** (1.0 equiv), PhMgBr (5.0 equiv), THF, 0 °C (ii) *p*-TsOH (cat.), toluene, reflux; (e) **5a** (1.0 equiv), indole (2.0 equiv), *p*-TsOH (cat.), ethanol, reflux.

Fluorene **42** was synthesized in two steps in a quantitative yield from biaryl **5a** by Grignard addition followed by Friedel-Crafts alkylation. DIMs are known to exhibit a broad range of important biological activities against various diseases especially in cancer inhibition.[29] DIM **43** was synthesized from biaryl **5a** in one step from indole in the presence of a catalytic amount of *p*-TsOH. The present work for the synthesis of biaryls

under mild conditions, in consequence, presents an efficient alternative to synthesize such diverse array of molecules from biaryl-2-carbaldehydes.

3.4. Conclusion

In summary, we have developed a one-pot method for currently inaccessible biaryls utilizing dienaminodioate and cinnamaldehyde derivatives. The simplicity of this transformation involves avoiding metal catalysts, using undistilled solvents under open conditions to afford polyfunctional biaryl products. A high functional group tolerance as exhibited by the synthesized compounds demonstrates the viability of this method for synthesis of privileged scaffolds. The 2-carbaldehyde, 4,6-carboxylate appendages along with halogen substituents serves as versatile functionalities to furnish complex molecular architectures which otherwise requires multi-step synthetic endeavours. This method offers a complementary route to the existing cross-coupling methods for the preparation of biaryls with polyfunctional groups. We have also demonstrated the utility of biaryl-2-carbaldehyde by transformation into molecules which are of significance in biology and materials chemistry.

3.5. Experimental section

3.5.1. General experimental methods

All the solvents were used without distillation, and all biaryl syntheses were carried out at room temperature under inert-free aerobic atmosphere. Silica gel G-60 F_{254} aluminium TLC plates were used to monitor the reactions with short wavelength ultraviolet light to visualize the spots. Flash column chromatography was performed on silica gel 230-400 mesh. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively. Chemical shifts are given in ppm using the solvent residual peak of chloroform δ 7.26 ppm as a reference, and coupling constants in Hz. HR-ESI-MS analysis was recorded using electrospray ionization with ions given in m/z.

3.5.2. General procedure for the synthesis of cinnamaldehydes: Cinnamaldehydes were synthesized by following a known procedure employing Wittig reaction. To a 50 mL round bottom flask equipped with a magnetic bar were added toluene (10 mL), pertinent aromatic aldehyde (1.5 mmol), (triphenylphosphoranylidene)acetaldehyde (Wittig reagent) (500 mg, 1 mmol) and the resulting mixture was stirred at 85 °C for overnight. After complete consumption of the Wittig reagent as indicated by TLC, the reaction mixture was concentrated and subjected to flash column chromatography. The product was eluted with DCM/hexane solvent system to afford the desired cinnamaldehyde.

3.5.3. Procedure for synthesis of biaryl 5: To a solution of dienaminodioate **1** (31 mg, 1.0 equiv) in $CHCl_3$/MeCN (1:1) were added cinnamaldehyde **2** (46.20 µL, 3.0 equiv), allyl amine **3** (27.5 µL, 3.0 equiv) and TFA (28.0 µL, 3.0 equiv) in a sequential manner at room temperature. After immediate addition of TFA, the reaction mixture appears intense red in colour indicating the formation of trienamine. After complete consumption of compound **1** as visualized on TLC, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with DCM (1x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated and the crude mixture was subjected to flash column chromatography by eluting with DCM/hexane solvent system to afford the desired biaryl **5a** (24 mg, 60%). This general procedure was followed for the synthesis of the remaining biaryls.

3.5.4. Synthetic procedures for compounds 39-43

Synthesis of Diethyl-2-nitro-6-oxo-6H-benzo[*c*]chromene-8,10-dicarboxylate (**39**): To a solution of benzopyrone **5r** (14 mg, 1.0 equiv) in DCM (1.5 mL) was added Dess-Martin periodinane (DMP) (46 mg, 3.0 equiv) at room temperature. After complete consumption of **5r** as indicated on TLC, the reaction mixture was quenched with

saturated aqueous $NaHCO_3$ (6 mL) and extracted with DCM (10 mL × 2). The organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by flash column chromatography (DCM/hexane 1:1) to afford the desired dibenzopyranone **39** (14 mg) in a quantitative yield.

Synthesis of Diethyl-4-(4,6-bis(ethoxycarbonyl)biphenyl-2-yl)-1-*p*-tolyl-1,4-dihydro-pyridine-3,5-dicarboxylate (**40**): To a solution of biaryl-2-carbaldehyde **5a** (24 mg, 1.0 equiv) in MeCN (1.5 mL) were added ethyl 3-(allylamino)acrylate (23 mg, 2.0 equiv), *p*-toluidine (8 mg, 1.0 equiv) and TFA (5.68 µL, 1.0 equiv) in a sequential manner at room temperature. After complete consumption of biaryl **5a** as indicated on TLC, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (10 mL × 2). The organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by flash column chromatography (hexane/DCM 2:1) to produce the desired 1,4-DHP **40** (19 mg, 42%).

Synthesis of Diethyl-2-(4,6-bis(ethoxycarbonyl)biphenyl-2-yl)-1-*p*-tolyl-1,2-dihydro-pyridine-3,5-dicarboxylate (**41**): To a solution of biaryl-2-carbaldehyde **5a** (24.3 mg, 1.2 equiv) in MeCN (2 mL) were added dienaminodiester **1** (15.7 mg, 1.0 equiv), *p*-toluidine (8 mg, 1.2 equiv) and TFA (5 µL, 1.0 equiv) in a sequential order at room temperature under aerobic atmosphere. After complete consumption of dienaminodiester **1** as observed on TLC, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (8 mL) and extracted with EtOAc (15 mL × 2). The organic layer was dried over anhydrous Na_2SO_4, concentrated, and the crude mixture was subjected to flash column chromatography (hexane/DCM/EtOAc 4:2:0.2) to afford the desired 1,2-DHP **41** (19 mg, 50%).

Synthesis of Diethyl-9-phenyl-9*H*-fluorene-2,4-dicarboxylate (**42**): To a solution of biaryl-2-carbaldehyde **5a** (11 mg, 1.0 equiv) in THF (1 mL) was added phenylmagnesium

bromide (3M in ether, 56.2 µL, 5.0 equiv) at 0 °C under argon atmosphere. The reaction was allowed to attain room temperature slowly, and after complete consumption of biaryl **5a** as indicated on TLC, the reaction mixture was quenched with water (15 mL), 1M HCl (5 mL), and then extracted with EtOAc (10 mL × 2). The solvent was evaporated and the crude residue was directly treated with a catalytic amount of *p*-TsOH in toluene (1.5 mL) under reflux conditions. After complete consumption of starting material as indicated on TLC, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (10 mL × 2). The organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by flash column chromatography (hexane/DCM 4:1.5) to afford the desired fluorene **42** (13.6 mg) in a quantitative yield.

Synthesis of Diethyl-6-(di(1*H*-indol-3-yl)methyl)biphenyl-2,4-dicarboxylate (**43**): Catalytic amount of *p*-TsOH was added to a stirred solution of biaryl-2-carbaldehyde **4** (23.1 mg, 1.0 equiv) and indole (16.5 mg, 2.0 equiv) in ethanol solvent. The reaction mixture was kept at reflux temperature and stirred for overnight. After complete consumption of biaryl **5a** as indicated on TLC, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (10 mL × 2). The organic layer was dried over anhydrous Na_2SO_4, concentrated, and the crude mixture was subjected to flash column chromatography (hexane/DCM/EtOAc 4:2:1) to afford the desired BIM **43** (30.0 mg, 79%).

3.5.5. Spectral details of trienamines, biaryls, and compounds 39-43

Diethyl 2-(4-nitrostyryl)-1-*p*-tolyl-1,2-dihyropyridine-3,5-dicarboxylate (37):

^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, *J* = 7.0 Hz), 1.37 (t, 3H, *J* = 7.0 Hz), 2.28 (s, 3H), 4.16 (m, 2H), 4.30 (q, 2H, *J* = 7.0 Hz), 5.11 (s, 1H), 6.55 (d, 1H, *J* = 13.5 Hz), 6.74 (d, 2H, *J* = 8.0 Hz), 7.08 (d, 2H, *J* = 8.0 Hz), 7.23 (d, 1H, *J* = 13.5 Hz), 7.57 (s, 1H), 7.61 (d, 2H, *J* = 8.5 Hz), 7.72 (s, 1H), 8.14 (d, 2H, *J* = 8.5 Hz), ^{13}C NMR ($CDCl_3$) δ 13.8, 14.2, 14.3, 14.4,

20.6, 21.0, 29.6, 40.7, 60.5, 60.6, 61.6, 61.8, 112.9, 114.9, 115.7, 120.8, 123.3, 123.6, 124.1, 128.5, 129.8, 130.2, 130.3, 132.5, 132.9, 133.5, 135.7, 136.9, 139.5, 143.3, 147.0, 150.3,155.0, 165.7, 166.4, HR-ESI-MS $[M+Na]^+$ $C_{26}H_{26}N_2O_6Na$ calcd for m/z 485.1688, found 485.1698.

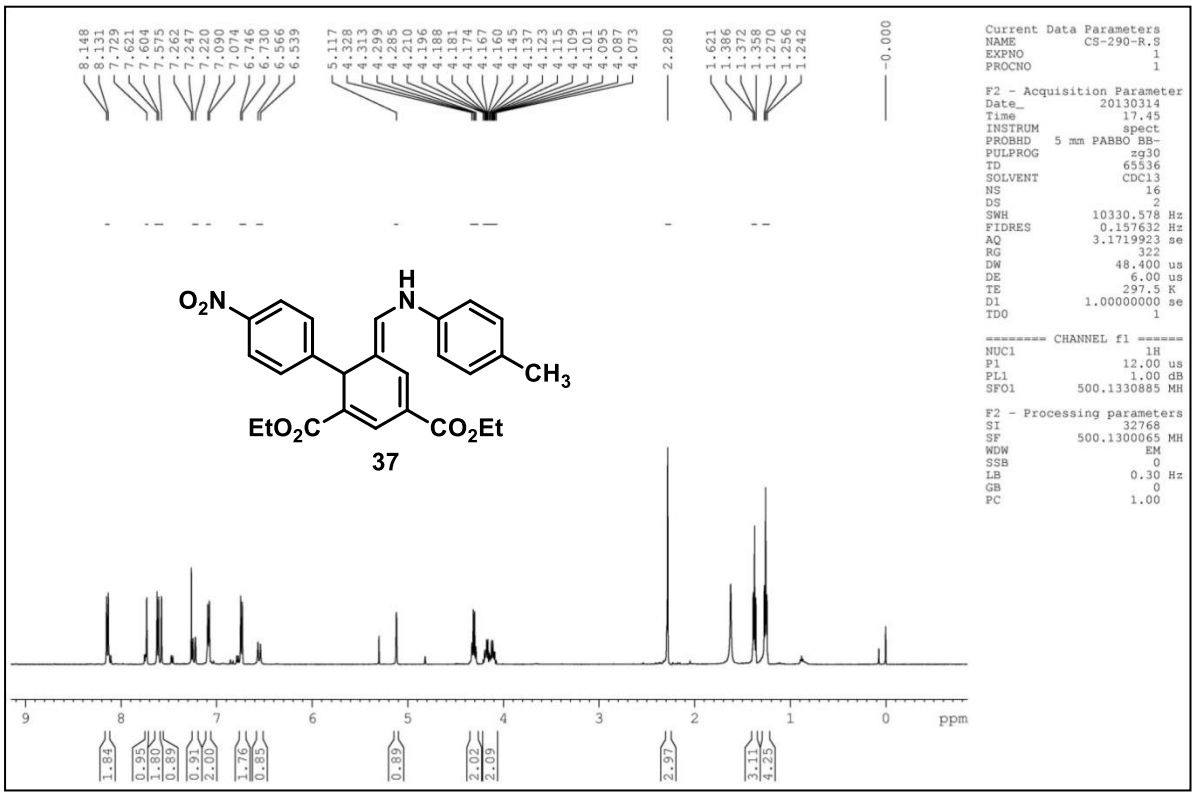
Dimethyl 6-(4-nitrophenyl)-5-((prop-2-ynylamino)methylene)cyclohexa-1,3-diene-1,3-dicar-boxylate (37'): ^1H NMR ($CDCl_3$) δ 2.35 (app t, 1H), 3.67 (s, 3H), 3.81 (s, 3H), 3.90 (m, 2H), 4.78 (m, 1H), 4.93 (s, 1H), 6.82 (d, 1H, *J* = 13.5 Hz), 7.50 (s, 1H), 7.52 (d, 2H, *J* = 9.0 Hz), 7.68 (s, 1H), 8.09 (d, 2H, *J* = 8.5 Hz), ^{13}C NMR ($CDCl_3$) δ 37.5, 40.5, 51.6, 74.1, 77.9, 111.2, 113.2, 122.6, 123.9, 128.5, 132.8, 144.2, 146.9, 147.2, 150.3, 166.2, 166.9.

Dimethyl 6-formyl-4'-nitrobiphenyl-2,4-dicarboxylate (**5'**):

^1H NMR ($CDCl_3$) δ 3.71 (s, 3H), 4.02 (s, 3H), 7.47 (d, 2H, *J* = 8.5 Hz), 8.34 (d, 2H, *J* = 8.5 Hz), 8.80 (d, 1H, *J* = 1.5 Hz), 8.84 (d, 1H, *J* = 1.5 Hz), 9.71 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 52.6, 52.9, 123.2, 123.3, 130.1, 131.2, 132.0, 132.2, 135.0, 135.8, 142.4, 146.7, 147.9, 164.8, 165.5, 189.1.

Diethyl 6-formyl-biphenyl-2,4-dicarboxylate (5a): Yield: 24.0 mg, 60%. ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, 3H, *J* = 7.0 Hz), 1.44 (t, 3H, *J* = 7.0 Hz), 4.07 (q, 2H, *J* = 7.0 Hz), 4.45 (q, 2H, *J* = 7.0 Hz), 7.28 (m, 2H), 7.46 (m, 3H), 8.68 (d, 1H, *J* = 2.0 Hz), 8.74 (d, 1H, *J* = 1.5 Hz), 9.77 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.3, 61.5, 61.7, 128.1, 128.5, 129.3, 130.4, 130.9, 133.8, 134.9, 135.0, 135.2, 148.6, 164.8, 166.7, 190.8. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{20}H_{22}O_6Na$ calcd for m/z 381.1314, found 381.1318.

Figure 3.5A. ^{1}H and ^{13}C-NMR images of 37



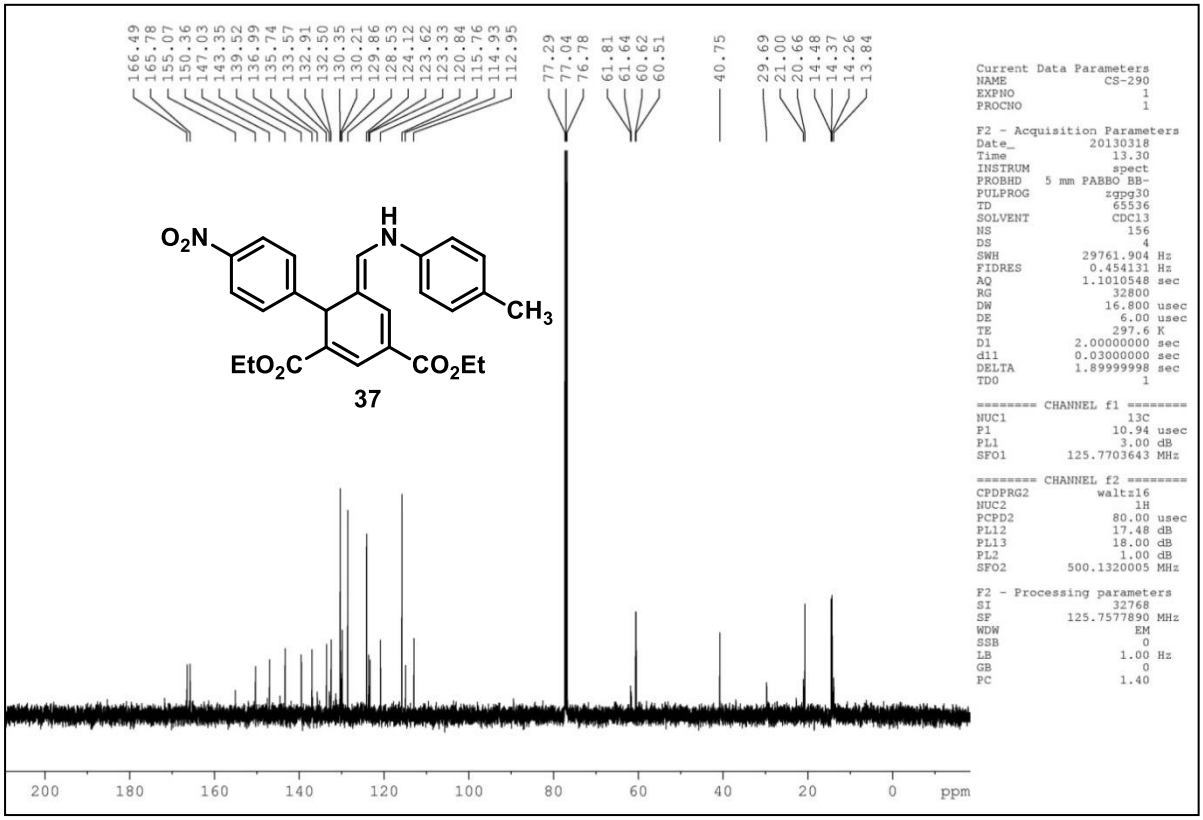


Figure 3.5B. Key COSY correlation of 37

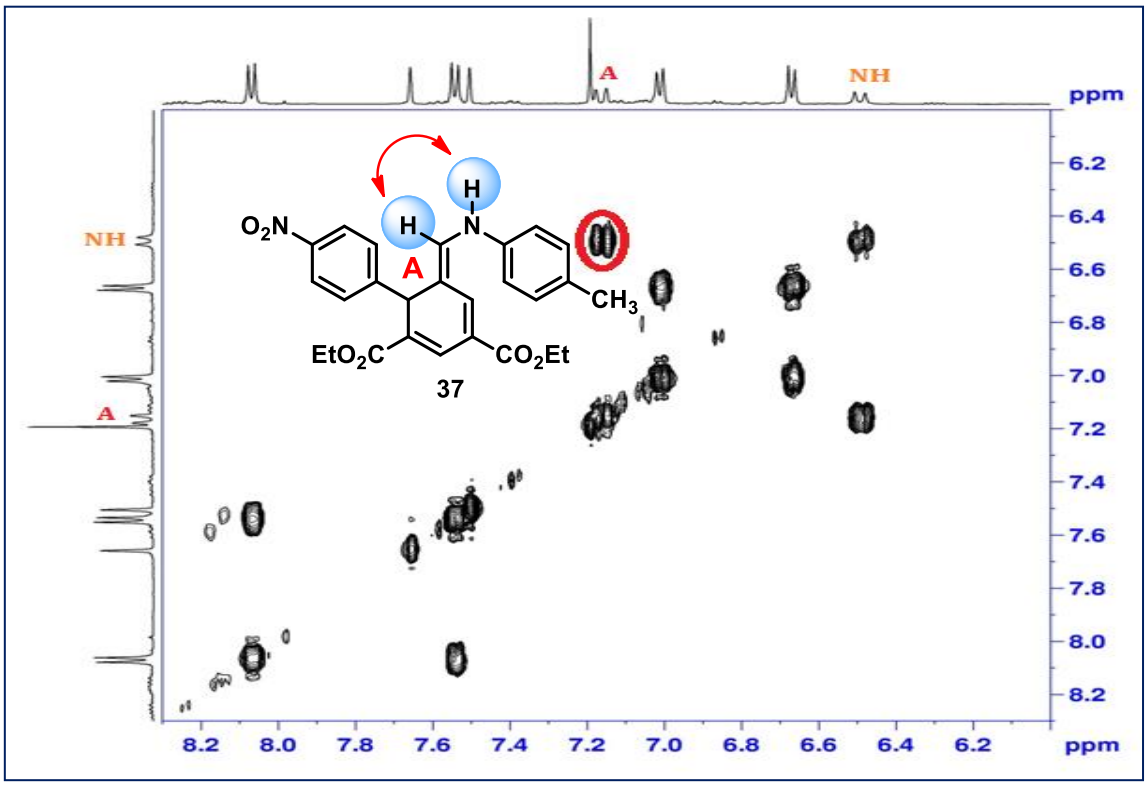


Figure 3.5C. Key HMQC correlations of 37

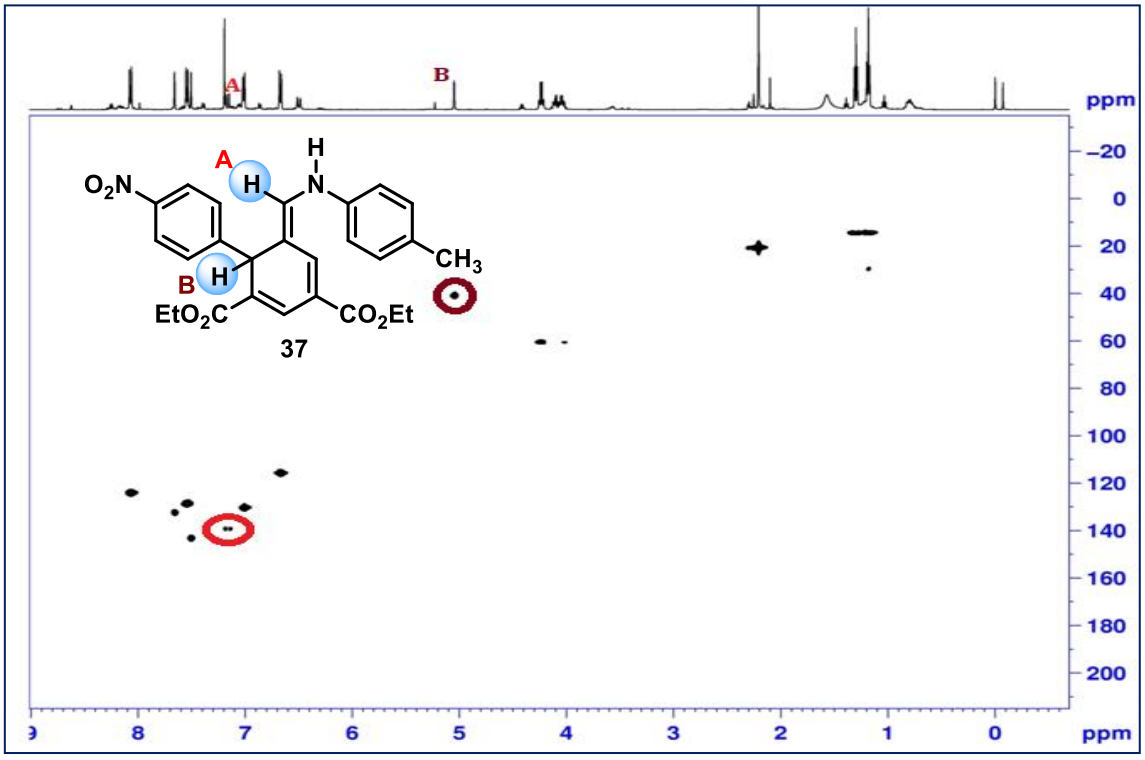


Figure 3.5D. '-NH' exchange experiment for 37 by adding a drop of D_2O

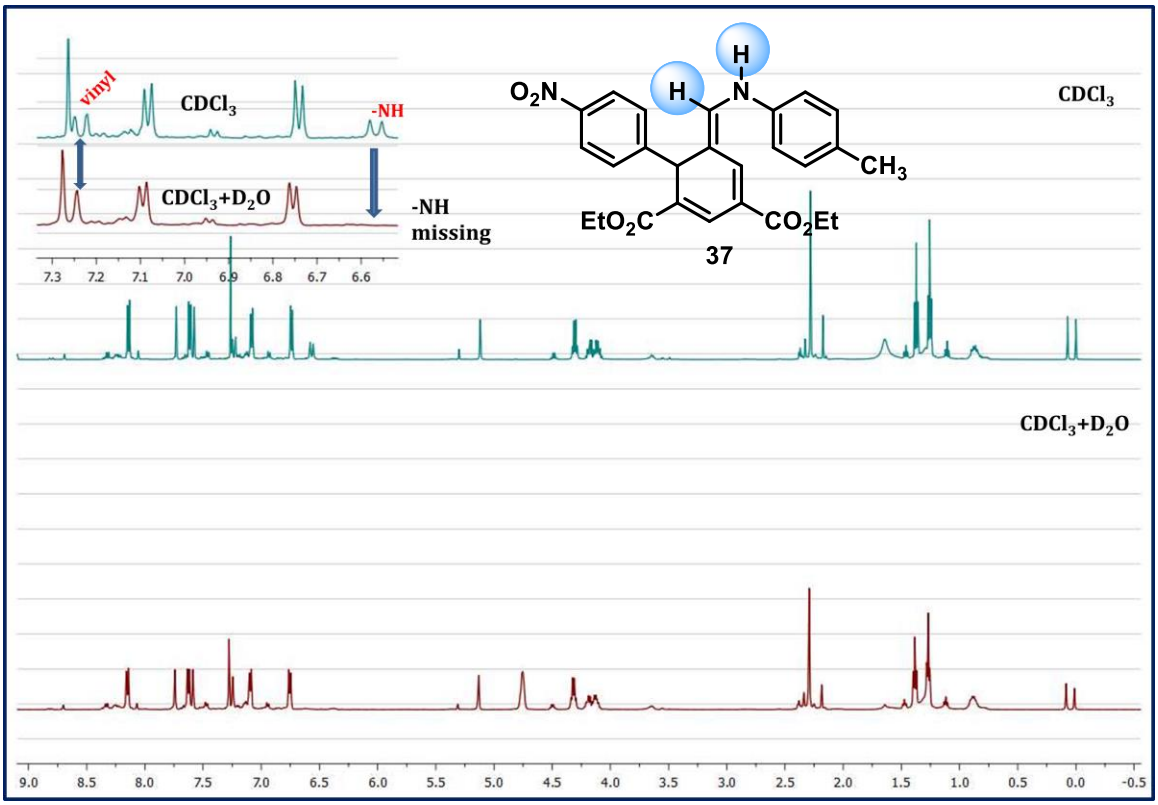
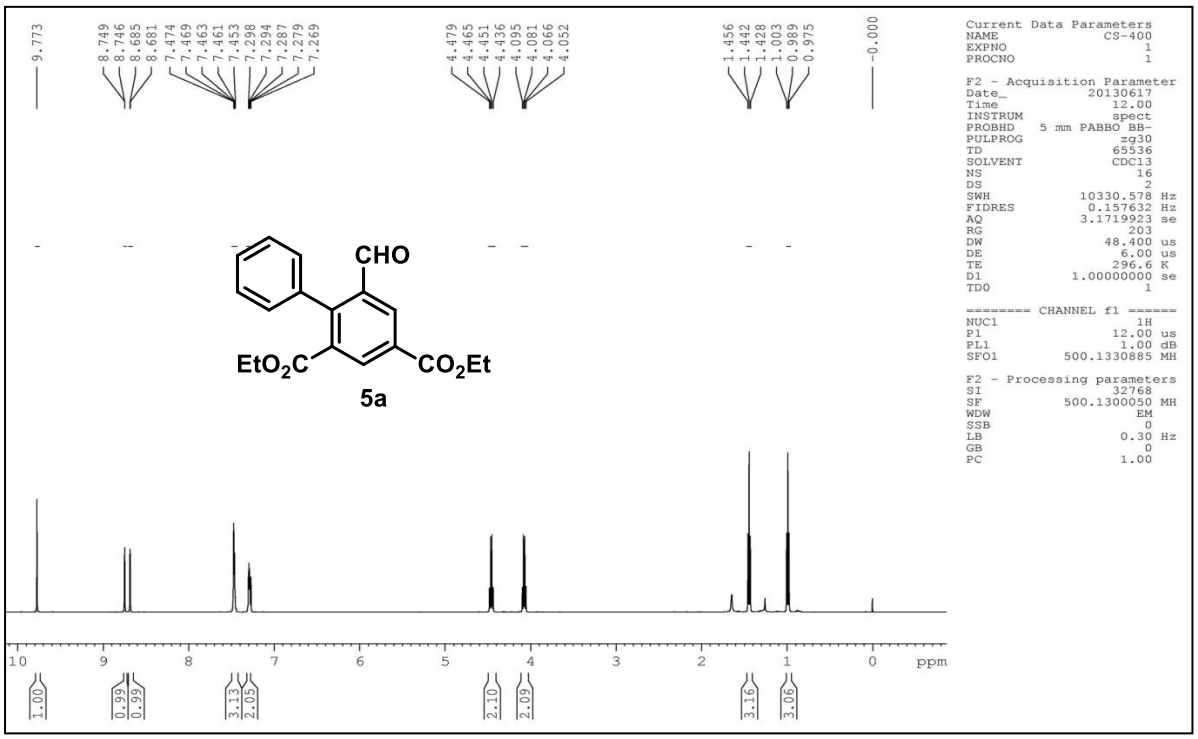


Figure 3.5E. ^{1}H and ^{13}C-NMR of 5a



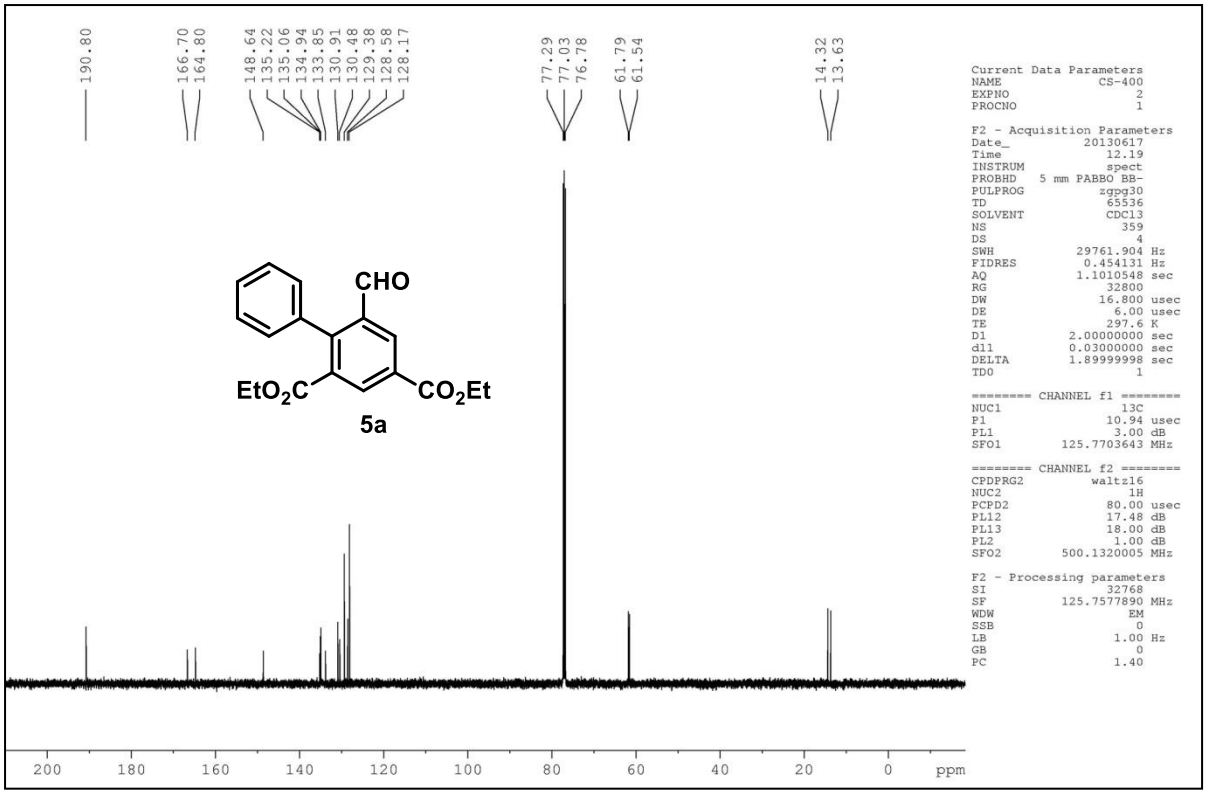


Figure 3.5F. Key HMBC correlation of 5a

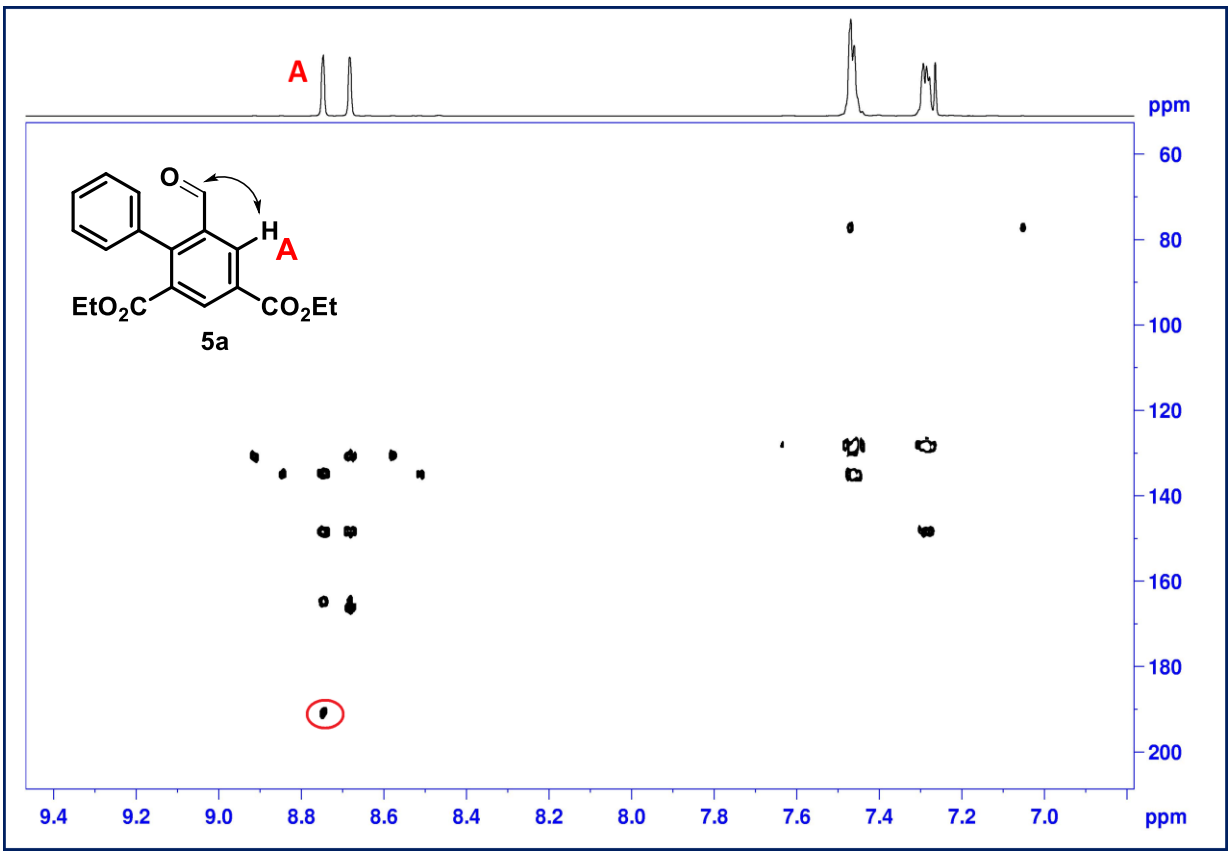
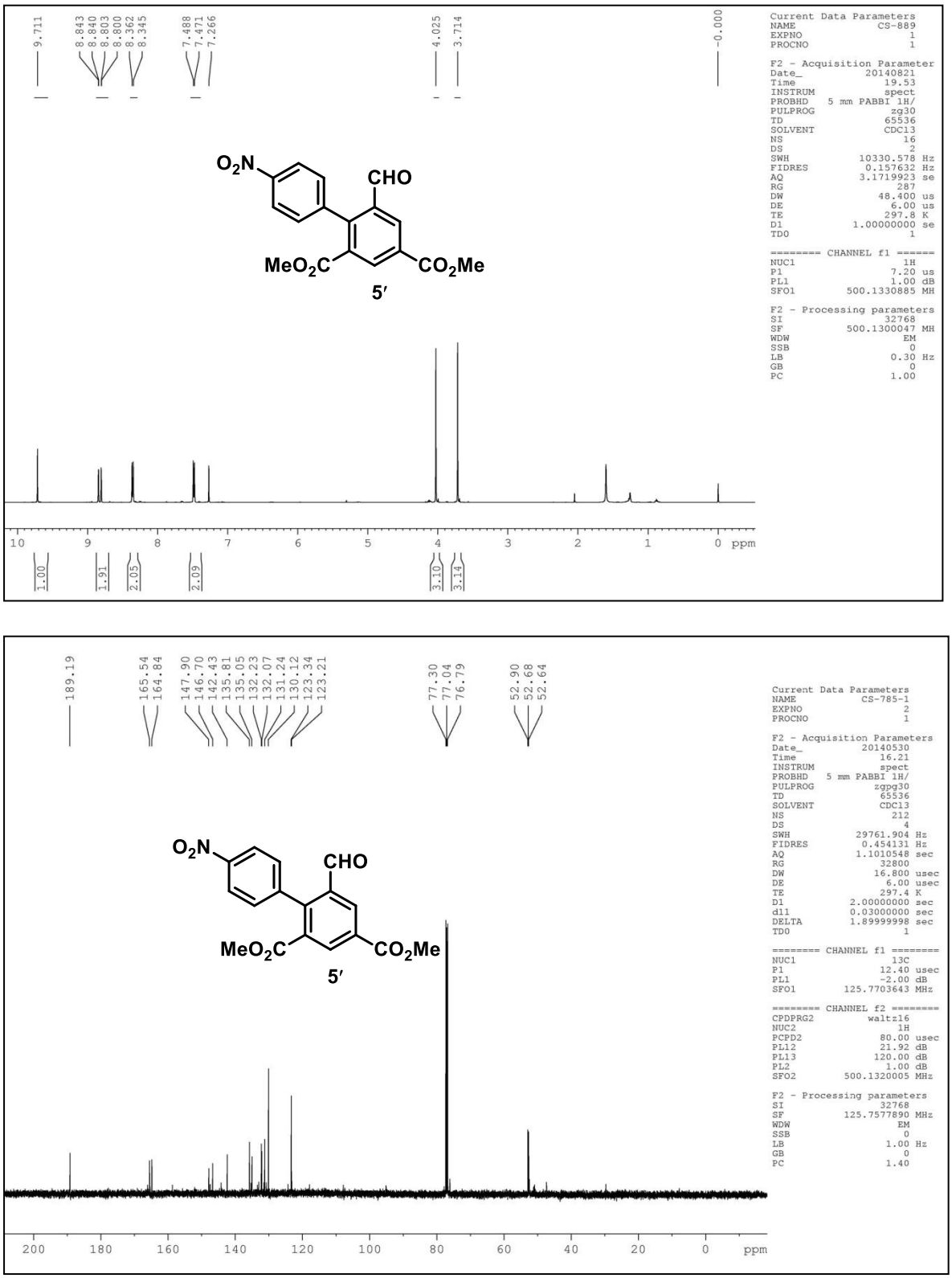


Figure 3.5G. ^{1}H and ^{13}C-NMR of 5'



Diethyl 6-formyl-4'-methylbiphenyl-2,4-dicarboxylate (5b): Yield: 40.0 mg, 60%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (t, 3H, *J* = 7.0 Hz), 1.43 (t, 3H, *J* = 7.0 Hz), 2.43 (s, 3H),

4.10 (q, 2H, *J* = 7.0 Hz), 4.44 (m, 2H), 7.16 (d, 2H, *J* = 8.0 Hz), 7.27 (bs, 2H), 8.65 (d, 1H, *J* = 2.0 Hz), 8.72 (d, 1H, *J* = 1.5 Hz), 9.78 (s,1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.3, 21.2, 29.6, 61.5, 61.7, 128.8, 129.3, 130.2, 130.8, 132.0, 133.9, 134.7, 135.1, 138.5, 148.8, 164.8, 166.7, 190.9. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{21}H_{24}O_6Na$ calcd for m/z 395.1470, found 395.1471.

Diethyl 6-formyl-4'-methoxybiphenyl-2,4-dicarboxylate (5c): Yield: 32.8 mg, 55%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (t, 3H, *J* = 7.0 Hz), 1.43 (t, 3H, *J* = 7.0 Hz), 3.87 (s, 3H), 4.12 (q, 2H, *J* = 7.0 Hz), 4.44 (q, 2H, *J* = 7.0 Hz), 6.98 (d, 2H, *J* = 8.5 Hz), 7.19 (d, 2H, *J* = 9.0 Hz), 8.63 (d, 1H, *J* = 1.5 Hz), 8.71 (d, 1H, *J* = 2.0 Hz), 9.80 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.3, 55.3, 61.5, 61.7, 113.6, 127.1, 130.1, 130.7, 130.8, 134.1, 134.7, 135.3, 148.3, 159.9, 164.8, 166.9, 191.0. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{21}H_{24}O_7Na$ calcd for m/z 411.1419, found 411.1422.

Diethyl 6-formyl-4'-chlorobiphenyl-2,4-dicarboxylate (5d): Yield: 29 mg, 63%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (t, 3H, *J* = 7.0 Hz), 1.44 (t, 3H, *J* = 7.0 Hz), 4.12 (q, 2H, *J* = 7.0 Hz), 4.46 (q, 2H, *J* = 7.0 Hz), 7.24 (d, 2H, *J* = 8.5 Hz), 7.46 (d, 2H, *J* = 8.5 Hz), 8.70 (d, 1H, *J* = 1.5 Hz), 8.74 (d, 1H, *J* = 2.0 Hz), 9.76 (s, 1H).^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 14.3, 61.7, 61.8, 128.4, 130.6, 130.8, 131.2, 133.5, 133.7, 134.8, 135.1, 135.2, 147.3, 164.6, 166.2, 190.2. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{20}H_{21}ClO_6Na$ calcd for m/z 415.0924, found 415.0929.

Diethyl 6-formyl-4'-bromobiphenyl-2,4-dicarboxylate (5e): Yield: 88.5 mg, 84%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (t, 3H, *J* = 7.0 Hz), 1.44 (t, 3H, *J* = 7.0 Hz), 4.11 (q, 2H, *J* = 7.0 Hz), 4.46 (q, 2H, *J* = 7.0 Hz), 7.16 (d, 2H, *J* = 8.5 Hz), 7.60 (d, 2H, *J* = 8.5 Hz), 8.71 (s, 1H), 8.74 (d, 1H, *J* = 2.0 Hz), 9.76 (s, 1H).^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 14.3, 61.7, 61.8, 123.0, 130.8, 130.9, 131.2, 131.3, 133.4, 134.2, 135.0, 135.2, 147.3,

164.6, 166.2, 190.2. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{20}H_{21}BrO_6Na$ calcd for m/z 459.0419, found 459.0417.

Diethyl 6-formyl-4'-cyanobiphenyl-2,4-dicarboxylate (5e): Yield: 38.6 mg, 86%. ^1H NMR (500 MHz, $CDCl_3$) δ 1.08 (t, 3H, *J* = 7.0 Hz), 1.45 (t, 3H, *J* = 7.0 Hz), 4.13 (q, 2H, *J* = 7.0 Hz), 4.48 (q, 2H, *J* = 7.0 Hz), 7.43 (d, 2H, *J* = 8.0 Hz), 7.78 (d, 2H, *J* = 8.0 Hz), 8.77 (d, 1H, *J* = 1.5 Hz), 8.79 (d, 1H, *J* = 2.0 Hz), 9.70 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 14.2, 61.8, 62.0, 112.5, 118.2, 130.0, 131.4, 131.8, 132.7, 134.8, 135.6, 140.6, 146.5, 164.4, 165.5, 189.4. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{21}H_{21}NO_6Na$ calcd for m/z 406.1266, found 406.1271.

Diethyl 6-formyl-4'-nitrobiphenyl-2,4-dicarboxylate (5g): Yield: 25.0 mg, 50%. ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, 3H, *J* = 7.0 Hz), 1.46 (t, 3H, *J* = 7.0 Hz), 4.14 (q, 2H, *J* = 7.0 Hz), 4.47 (q, 2H, *J* = 7.0 Hz), 7.48 (d, 2H, *J* = 8.5 Hz), 8.34 (d, 2H, *J* = 8.5 Hz), 8.78 (s, 1H), 8.81 (s, 1H), 9.72 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.2, 61.9, 62.0, 123.3, 130.2, 131.6, 132.0, 132.6, 134.9, 135.7, 142.6, 146.2, 147.8, 164.4, 165.3, 189.3. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{20}H_{21}NO_8Na$ calcd for m/z 426.1164, found 426.1171.

Diethyl 4',6-diformylbiphenyl-2,4-dicarboxylate (5h): Yield: 20.6 mg, 56%. ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, 3H, *J* = 7.0 Hz), 1.45 (t, 3H, *J* = 7.0 Hz), 4.11 (q, 2H, *J* = 7.0 Hz), 4.47 (q, 2H, *J* = 7.0 Hz), 7.48 (d, 2H, *J* = 8.0 Hz), 8.01 (d, 1H, *J* = 8.5 Hz), 8.78 (s, 2H), 9.73 (s, 1H), 10.12 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 14.3, 61.7, 61.9, 129.3, 130.0, 131.2, 131.5, 132.9, 134.9, 135.5, 136.1, 141.9, 147.3, 164.5, 165.8, 189.8, 191.4. HR-ESI-MS $[M+2MeOH+Na]^+C_{22}H_{26}O_8Na$ calcd for m/z 441.1525, found 441.1520.

Diethyl 6-formyl-2'-bromobiphenyl-2,4-dicarboxylate (5i): Yield: 47.4 mg, 74%. ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, 3H, *J* = 7.0 Hz), 1.44 (t, 3H, *J* = 7.0 Hz), 4.11 (m,

2H), 4.47 (q, 2H, *J* = 7.0 Hz), 7.23 (dd, 1H, *J* =7.5, 1.0 Hz), 7.34 (m, 1H), 7.42 (m, 1H), 7.69 (dd, 1H, *J* = 8.0, 0.5 Hz), 8.80 (d, 1H, *J* = 1.5 Hz), 8.86 (d, 1H, *J* = 2.0 Hz), 9.66 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.3, 61.5, 61.8, 123.3, 127.1, 130.0, 130.6, 131.1, 131.5, 132.4, 132.6, 134.9, 135.9, 136.8, 147.3, 164.6, 165.3, 190.0. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{20}H_{21}BrO_6Na$ calcd for m/z 459.0419, found 459.0426.

Diethyl 6-formyl-2'-ethynylbiphenyl-2,4-dicarboxylate (5j): Yield: 30.7 mg, 69%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (t, 3H, *J* = 7.0 Hz), 1.45 (t, 3H, *J* = 7.0 Hz), 2.94 (s, 1H), 4.11 (q, 2H, *J* = 7.0 Hz), 4.46 (q, 2H, *J* = 7.0 Hz), 7.25 (m, 1H), 7.46 (m, 2H), 7.64 (m, 2H), 8.80 (s, 1H), 8.83 (s, 1H), 9.70 (s, 1H).^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.3, 61.4, 61.7, 81.3, 82.1, 122.1, 128.4, 128.5, 129.4, 130.8, 131.2, 132.5, 133.1, 135.2, 135.6, 138.7, 147.4, 164.8, 165.8, 190.2. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{22}H_{22}O_6Na$ calcd for m/z 405.1314, found 405.1310.

Diethyl 6-formyl-3',5'-dimethoxybiphenyl-2,4-dicarboxylate (5k): Yield: 50.0 mg, 67%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (t, 3H, *J* = 7.0 Hz), 1.43 (t, 3H, *J* = 7.0 Hz), 3.80 (s, 6H), 4.13 (q, 2H, *J* = 7.0 Hz), 4.44 (q, 2H, *J* = 7.0 Hz), 6.42 (d, 2H, *J* = 2.0 Hz), 6.54 (d, 1H, *J* = 2.0 Hz), 8.64 (d, 1H, *J* = 2.0 Hz), 8.72 (d, 1H, *J* = 1.5 Hz), 9.81 (s,1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 14.3, 55.4, 61.5, 61.7, 100.3, 105.5, 107.9, 130.4, 130.6, 133.6, 134.7, 134.9, 137.0, 148.3, 160.5, 164.7, 166.6, 190.8. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{22}H_{26}O_8Na$ calcd for m/z 441.1525, found 441.1520.

Diethyl 6-formyl-5'-bromo-2'-methoxybiphenyl-2,4-dicarboxylate (5l): Yield: 60.2 mg, 85%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (t, 3H, *J* = 7.0 Hz), 1.43 (t, 3H, *J* = 7.0 Hz), 3.71 (s, 3H), 4.15 (m, 2H), 4.46 (q, 2H, *J* = 7.0 Hz), 6.86 (d, 1H,*J* = 9.0 Hz), 7.24 (d, 1H, *J* = 2.0 Hz), 7.55 (dd, 1H, *J* = 2.0, 9.0 Hz), 8.75 (s, 2H), 9.73 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.3, 55.8, 61.5, 61.7, 112.1, 112.8, 126.3, 130.8, 131.0, 132.9,

133.0, 133.5, 135.0, 135.5, 143.8, 155.7, 164.7, 166.0, 190.5. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{21}H_{23}BrO_7Na$ calcd for m/z 489.0524, found 489.0535.

Diethyl 6-formyl-4'-chloro-2'-fluorobiphenyl-2,4-dicarboxylate (5m): Yield: 21.2 mg, 68%. ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, 3H, *J* = 7.0 Hz), 1.45 (t, 3H, *J* = 7.0 Hz), 4.18 (q, 2H, *J* = 7.0 Hz), 4.46 (q, 2H, *J* = 7.0 Hz), 7.15 (t, 1H, *J* = 7.0 Hz), 7.26 (m, 2H), 8.78 (d, 1H, *J* = 2.0 Hz), 8.83 (d, 1H, *J* = 2.0 Hz), 9.79 (d, 1H, *J* = 1.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 14.3, 61.8, 61.9, 116.2, 116.4, 124.5, 131.5, 131.7, 131.9, 133.2, 135.3, 135.8, 141.2, 160.3, 164.5, 165.4, 189.3. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{20}H_{20}ClFO_6Na$ calcd for m/z 433.0830, found 433.0831.

Diethyl 6-formyl-2',6'-difluorobiphenyl-2,4-dicarboxylate (5n): Yield: 53 mg, 68%. ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, 3H, *J* = 7.0 Hz), 1.45 (t, 3H, *J* = 7.0 Hz), 4.21 (q, 2H, *J* = 7.0 Hz), 4.47 (q, 2H, *J* = 7.0 Hz), 7.04 (m, 2H), 7.47 (m, 1H), 8.83 (d, 1H, *J* = 2.0 Hz), 8.93 (d, 1H, *J* = 2.0 Hz), 9.83 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 14.3, 30.9, 61.7, 61.9, 111.1-111.3, 112.6, 130.9, 131.0, 131.1, 131.8, 132.2, 133.1, 135.4, 136.0, 136.2, 158.7, 160.7, 164.5, 165.0, 189.5. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{20}H_{20}F_2O_6Na$ calcd for m/z 417.1125, found 417.1114.

Diethyl 6-formyl-3'-bromo-4'-hydroxy-5'-methoxybiphenyl-2,4-dicarboxylate (5o): Yield: 19 mg, 38%. ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, 3H, *J* = 7.0 Hz), 1.44 (t, 3H, *J* = 7.0 Hz), 3.89 (s, 3H), 4.16 (q, 2H, *J* = 7.0 Hz), 4.46 (q, 2H, *J* = 7.0 Hz), 6.12 (brs, 1H), 6.73 (s, 1H), 7.04 (s, 1H), 7.26 (s, 1H), 8.64 (s, 1H), 8.71 (s, 1H), 9.83 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.2, 56.5, 61.7, 108.2, 111.3, 125.6, 127.5, 130.6, 130.9, 134.0, 134.8, 135.2, 143.5, 146.7, 164.6, 166.4, 190.5. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{21}H_{23}BrO_8Na$ calcd for m/z 505.0474, found 505.0470.

Diethyl 4-(5-bromothiophene-2-yl)-5-formylisophthalate (5p): Yield: 54 mg, 49%. ^1H NMR (500 MHz, $CDCl_3$) δ 1.19 (t, 3H, *J* = 7.0 Hz), 1.43 (t, 3H, *J* = 7.0 Hz), 4.23 (q, 2H,

J = 7.0 Hz), 4.46 (q, 2H, *J* = 7.0 Hz), 6.83 (d, 1H, *J* = 3.5 Hz), 7.11 (d, 1H, *J* = 3.0 Hz), 8.65 (s, 1H), 8.71 (s, 1H), 9.98 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.2, 61.9, 114.7, 130.0, 130.2, 130.9, 131.6, 134.8, 134.9, 136.3, 139.4, 164.4, 166.0, 189.8. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{18}H_{19}BrO_6SNa$ calcd for m/z 464.9983, found 464.9978.

Diethyl 4-(5-iodofuran-2-yl)-5-formylisophthalate (5q): Yield: 38.0 mg, 55%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, 3H, *J* = 7.0 Hz), 1.43 (t, 3H, *J* = 7.0 Hz), 4.28 (q, 2H, *J* = 7.0 Hz), 4.44 (q, 2H, *J* = 7.0 Hz), 6.52 (d, 1H, *J* = 3.5 Hz), 6.76 (d, 1H, *J* = 3.0 Hz), 8.63 (d, 1H, *J* = 1.5 Hz), 8.71 (d, 1H, *J* = 1.5 Hz), 10.06 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 14.2, 24.6, 36.6, 61.9, 62.1, 90.5, 116.9, 122.2, 131.2, 131.4, 134.0, 134.6, 134.9, 135.0, 151.4, 162.4, 166.5, 189.9. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{18}H_{19}IO_7Na$ calcd for m/z 497.0073, found 497.0072.

Diethyl 6-hydroxy-2-nitro-6H-benzo[c]chromene-8,10-dicarboxylate (5r): Yield: 36.6 mg, 68%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, 3H, *J* = 7.0 Hz), 1.43 (t, 3H, *J* = 7.0 Hz), 3.85 (d, 1H, *J* = 5.0 Hz), 4.44 (m, 3H), 4.55 (m, 1H), 6.52 (d, 1H, *J* = 4.5 Hz), 7.28 (s, 1H), 8.20 (d, 1H, *J* = 1.0 Hz), 8.25 (dd, 1H, *J* = 9.0, 2.5 Hz), 8.34 (d, 1H, *J* = 1.5 Hz), 8.52 (d, 1H, *J* = 2.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.2, 61.8, 62.7, 93.1, 119.8, 119.9, 120.7, 123.2, 126.0, 128.6, 129.2, 130.4, 130.6, 131.5, 133.5, 142.4, 156.8, 164.7, 168.7. HR-ESI-MS $[M+Na]^+$ $C_{19}H_{17}NO_8Na$ calcd for m/z 410.0851, found 410.0848.

Diethyl 4-bromo-6-hydroxy-2-methoxy-6H-benzo[c]chromene-8,10-dicarboxylate (5s): Yield: 18.4 mg, 77%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, 3H, *J* = 7.0 Hz), 1.41 (t, 3H, *J* = 7.0 Hz), 3.49 (bs, 1H),3.93 (s, 3H), 4.41 (m, 4H), 6.48 (s, 1H), 7.08 (s, 1H), 7.26 (s, 1H), 8.17 (d, 1H, *J* = 1.5 Hz), 8.28 (d, 1H, *J* = 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.2, 30.9, 56.4, 61.6, 62.3, 92.8, 114.0, 116.1, 121.6, 121.9, 129.1, 129.9, 130.3,

131.2, 133.9, 140.2, 150.7, 164.9, 169.2. HR-ESI-MS $[M+Na]^+$ $C_{20}H_{19}BrO_7Na$ calcd for m/z 473.0211, found 473.0206.

Diethyl 2,6-dimethoxy-6H-benzo[c]chromene-8,10-dicarboxylate (5t):Yield: 20 mg, 60%. ^1H NMR (500 MHz, $CDCl_3$) δ 1.32 (t, 3H, *J* = 7.0 Hz), 1.42 (t, 3H, *J* = 7.0 Hz), 3.52 (s, 3H), 3.78 (s, 3H), 4.40 (m, 4H), 5.88 (s, 1H), 6.94 (dd, 1H, *J* = 9.0, 3.5 Hz), 7.07 (d, 1H, *J* = 3.0 Hz), 7.12 (d, 1H, *J* = 9.0 Hz), 8.10 (d, 1H, *J* = 1.5 Hz), 8.25 (d, 1H, *J* = 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.3, 30.9, 55.7, 61.4, 62.0, 98.7, 111.9, 117.2, 119.3, 120.6, 129.2, 129.3, 130.0, 131.1, 131.5, 133.4, 145.3, 154.5, 165.1, 169.5. HR-ESI-MS $[M+Na]^+$ $C_{21}H_{22}O_7Na$ calcd for m/z 409.1263, found 409.1260.

Diethyl 6-butoxy-2-methoxy-6H-benzo[c]chromene-8,10-dicarboxylate (5u): Yield: 15.2 mg, 66%. ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (t, 3H, *J* = 7.0 Hz), 1.25 (m, 3H), 1.32 (t, 3H, *J* = 7.0 Hz), 1.42 (t, 3H, *J* = 7.0 Hz), 1.51 (m, 2H), 3.70 (m, 1H), 3.78 (s, 3H), 3.84 (m, 1H), 4.42 (m, 4H), 5.96 (s, 1H), 6.92 (dd, 1H, *J* = 9.0, 3.0 Hz), 7.06 (m, 2H), 8.08 (d, 1H, *J* = 1.5 Hz), 8.23 (d, 1H, *J* = 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.3, 19.1, 22.6, 29.6, 31.3, 55.7, 61.4, 61.9, 68.5, 97.7, 111.8, 117.1, 119.3, 120.6, 129.1, 129.2, 130.0, 130.9, 131.6, 133.7, 145.6, 154.3, 165.2, 169.6. HR-ESI-MS $[M+Na]^+$ $C_{24}H_{28}O_7Na$ calcd for m/z 451.1732, found 451.1732.

Diethyl-2-nitro-6-oxo-6H-benzo[*c*]chromene-8,10-dicarboxylate (39): ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 (m, 6H), 4.49 (q, 2H, *J* = 7.0 Hz), 4.63 (q, 2H, *J* = 7.0 Hz), 7.56 (d, 1H, *J* = 9.0 Hz), 8.42 (dd, 1H, *J* = 9.0, 2.0 Hz), 8.61 (s, 1H), 8.83 (d, 1H, *J* = 2.0 Hz), 9.17 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.1, 62.3, 63.4, 116.6, 119.3, 119.8, 122.8, 123.2, 126.6, 131.3, 131.9, 133.8, 136.0, 143.9, 155.3, 158.5, 163.8, 168.2. HR-ESI-MS $[M+MeOH+Na]^+$ $C_{20}H_{19}NO_9Na$ calcd for m/z440.0957, found 440.0962.

Diethyl-4-(4,6-bis(ethoxycarbonyl)biphenyl-2-yl)-1-*p*-tolyl-1,4-dihydropyridine-3,5-dicar-boxylate (40): ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, *J* = 7.0 Hz), 1.15 (t, 6H,

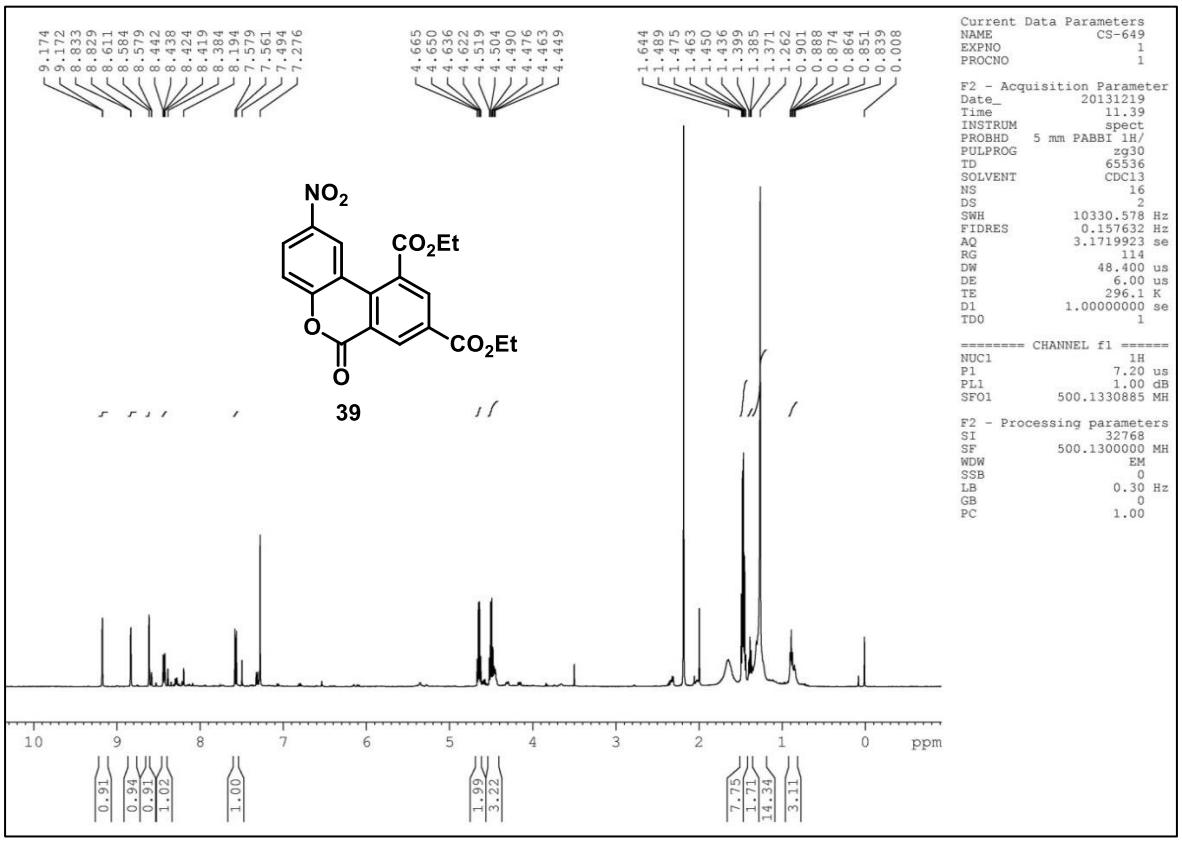
J = 7.0 Hz), 1.39 (t, 3H, *J* = 7.0 Hz), 2.38 (s, 3H), 3.89 (q, 2H, *J* = 7.0 Hz), 4.05 (m, 4H), 4.39 (q, 2H, *J* = 7.0 Hz), 5.24 (s, 1H), 7.03 (d, 2H, *J* = 8.5 Hz), 7.22 (d, 2H, *J* = 8.5 Hz), 7.29 (s, 1H), 7.32 (t, 2H, *J* = 7.5 Hz), 7.36 (s, 2H), 7.45 (d, 2H, *J* = 7.5 Hz), 8.19 (s, 1H), 8.32 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.2, 14.3, 20.8, 29.6, 60.1, 61.0, 61.1, 110.2, 120.7, 126.8, 127.2, 128.1, 129.0, 130.1, 130.3, 134.9, 136.2, 136.9, 138.2, 140.4, 144.7, 165.8, 166.6, 168.8. HR-ESI-MS $[M+Na]^+$ $C_{36}H_{37}NO_8Na$ calcd for m/z 634.2416, found 634.2425.

Diethyl-2-(4,6-bis(ethoxycarbonyl)biphenyl-2-yl)-1-*p*-tolyl-1,2-dihydropyridine-3,5-dicarboxylate (41): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77 (t, 3H, *J* = 7.0 Hz), 1.31 (m, 6H), 1.39 (t, 3H, *J* = 7.0 Hz), 2.31 (s, 3H), 3.80 (m, 2H), 4.20 (m, 4H), 4.40 (q, 2H, *J* = 7.0 Hz), 5.76 (d, 1H, *J* = 7.5 Hz), 6.25 (s, 1H), 6.47 (d, 2H, *J* = 8.0 Hz), 6.80 (t, 1H, *J* = 7.5 Hz), 6.88 (d, 2H, *J* = 8.0 Hz), 7.20 (t, 1H, *J* = 7.5 Hz), 7.35 (t, 1H, *J* = 7.5 Hz), 7.47 (s, 1H), 7.80 (d, 1H, *J* = 7.5 Hz), 7.98 (s, 1H), 8.27 (d, 1H, *J* = 1.5 Hz), 8.61 (d, 1H, *J* = 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 13.6, 14.3, 14.5, 22.6, 58.2, 59.8, 60.3, 61.0, 61.1, 115.4, 125.1, 126.9, 127.1, 127.2, 128.9, 129.5, 130.0, 130.1, 130.2, 130.7, 133.7, 133.8, 136.9, 137.3, 140.1, 141.3, 143.3, 165.4, 165.5, 165.7, 168.4. HR-ESI-MS $[M+Na]^+$ $C_{36}H_{37}NO_8Na$ calcd for m/z 634.2416, found 634.2421.

Diethyl-9-phenyl-9*H*-fluorene-2,4-dicarboxylate (42): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (t, 3H, *J* = 7.0 Hz), 1.49 (t, 3H, *J* = 7.0 Hz), 4.30 (m, 2H), 4.55 (q, 2H, *J* = 7.0 Hz), 5.06 (s, 1H), 7.06 (d, 2H, *J* = 6.5 Hz), 7.25 (m, 3H), 7.31 (m, 2H), 7.40 (m, 1H), 8.04 (s, 1H), 8.42 (d, 1H, *J* = 7.5 Hz), 8.46 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 54.1, 61.3, 61.6, 125.2, 125.5, 126.8, 127.2, 127.5, 128.4, 128.6, 128.9, 129.1, 130.7, 138.4, 140.3, 144.1, 149.8, 149.9, 165.9, 167.7. HR-ESI-MS $[M+1]^+$ $C_{25}H_{23}O_4$calcd for m/z 387.1596, found 387.1587.

Diethyl-6-(di(1*H*-indol-3-yl)methyl)biphenyl-2,4-dicarboxylate(43): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, *J* = 7.0 Hz), 1.36 (t, 3H, *J* = 7.0 Hz), 4.00 (q, 2H, *J* = 7.0 Hz), 4.36 (q, 2H, *J* = 7.0 Hz), 5.68 (s, 1H), 6.35 (s, 2H), 6.93 (t, 2H, *J* = 7.0 Hz), 7.06 (d, 2H, *J* = 8.0 Hz), 7.13 (m, 4H), 7.24 (m, 5H), 8.00 (s, 2H), 8.16 (d, 1H, *J* = 1.5 Hz), 8.31 (d, 1H, *J* = 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.2, 36.3, 61.1, 61.5, 111.1, 118.9, 119.5, 121.7, 124.2, 126.5, 127.5, 127.8, 128.1, 128.5, 129.2, 132.6, 133.3, 136.7, 138.6, 144.0, 145.1, 166.5, 168.4. HR-ESI-MS $[M+Na]^+$ $C_{35}H_{30}O_4N_2Na$ calcd for m/z 565.2103, found 565.2104.

Figure 3.5H. ^{1}H and ^{13}C-NMR of 39



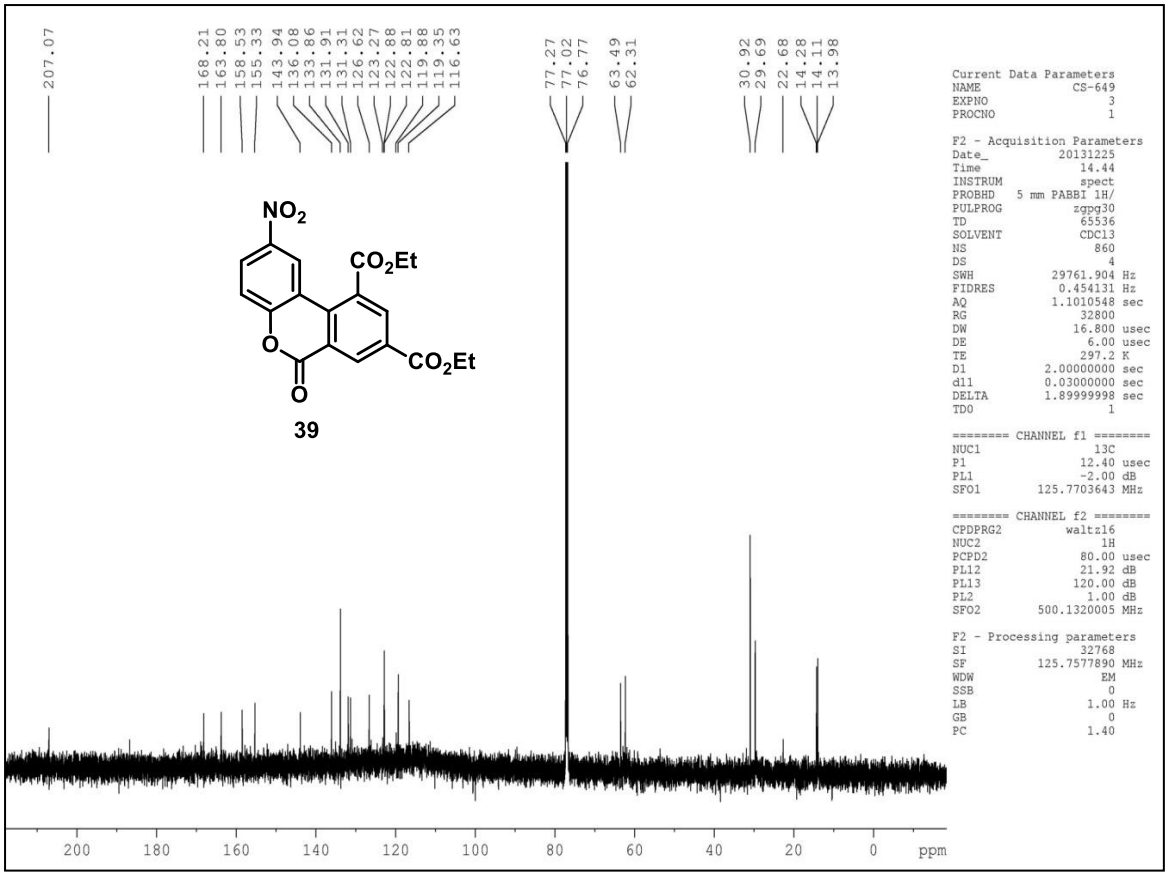
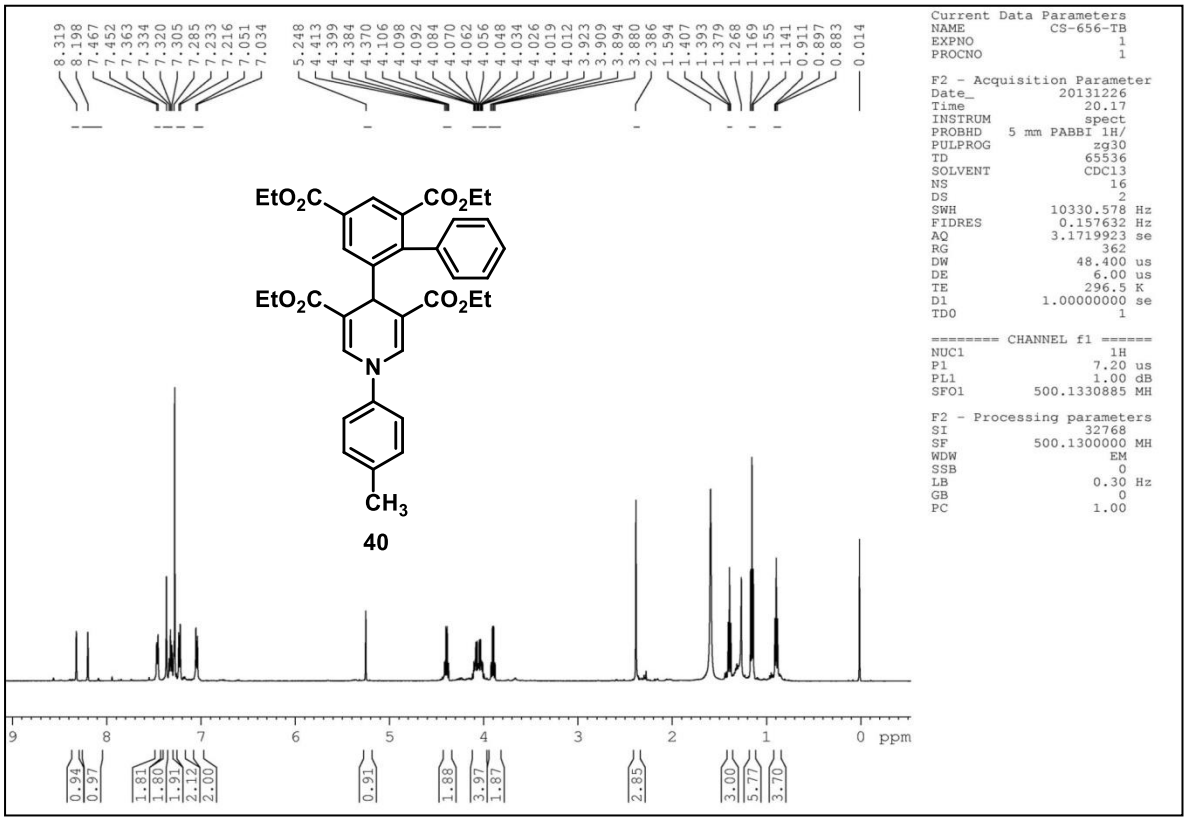


Figure 3.5I. ^{1}H and ^{13}C-NMR of 40



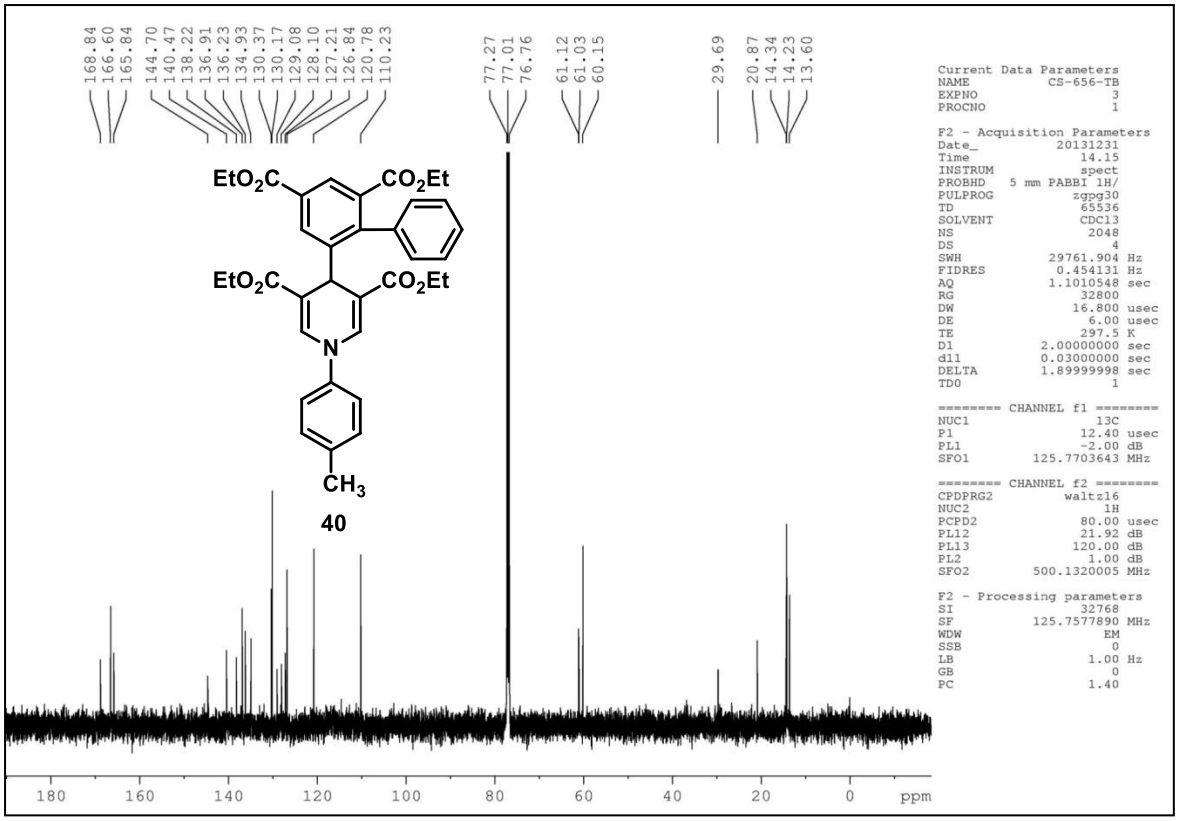
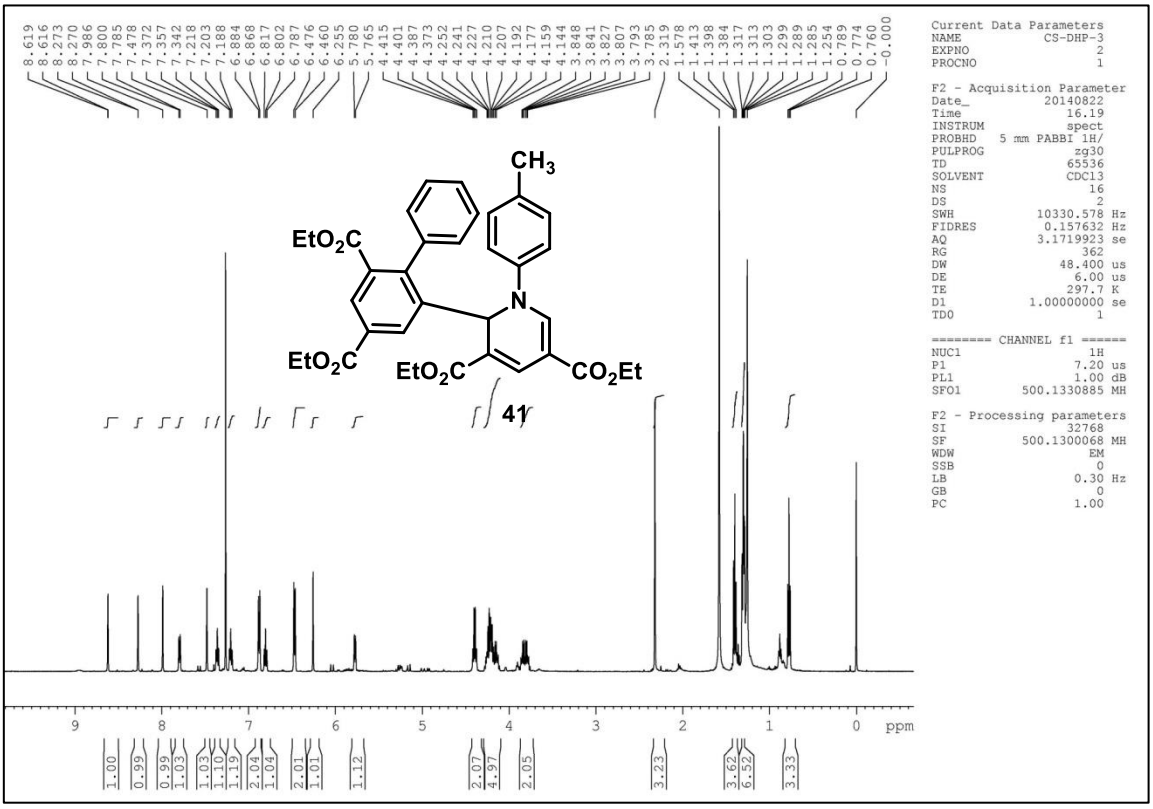


Figure 3.5J. ^{1}H and ^{13}C-NMR of 41



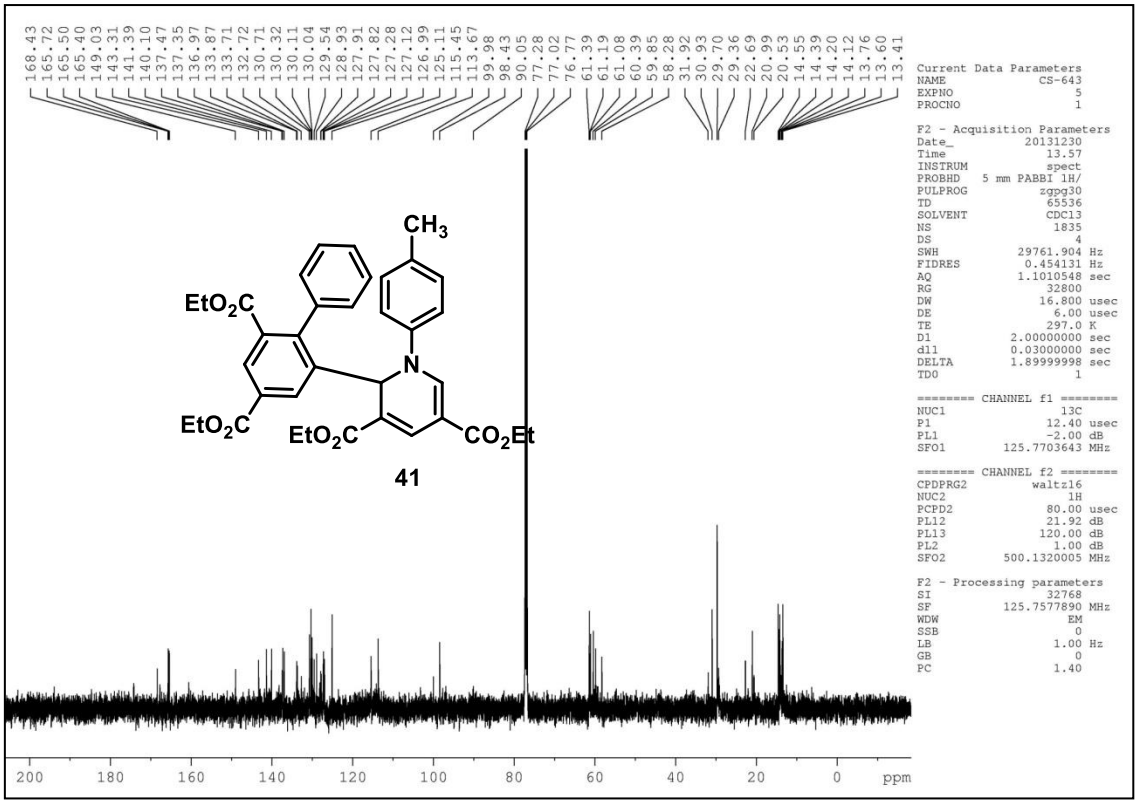
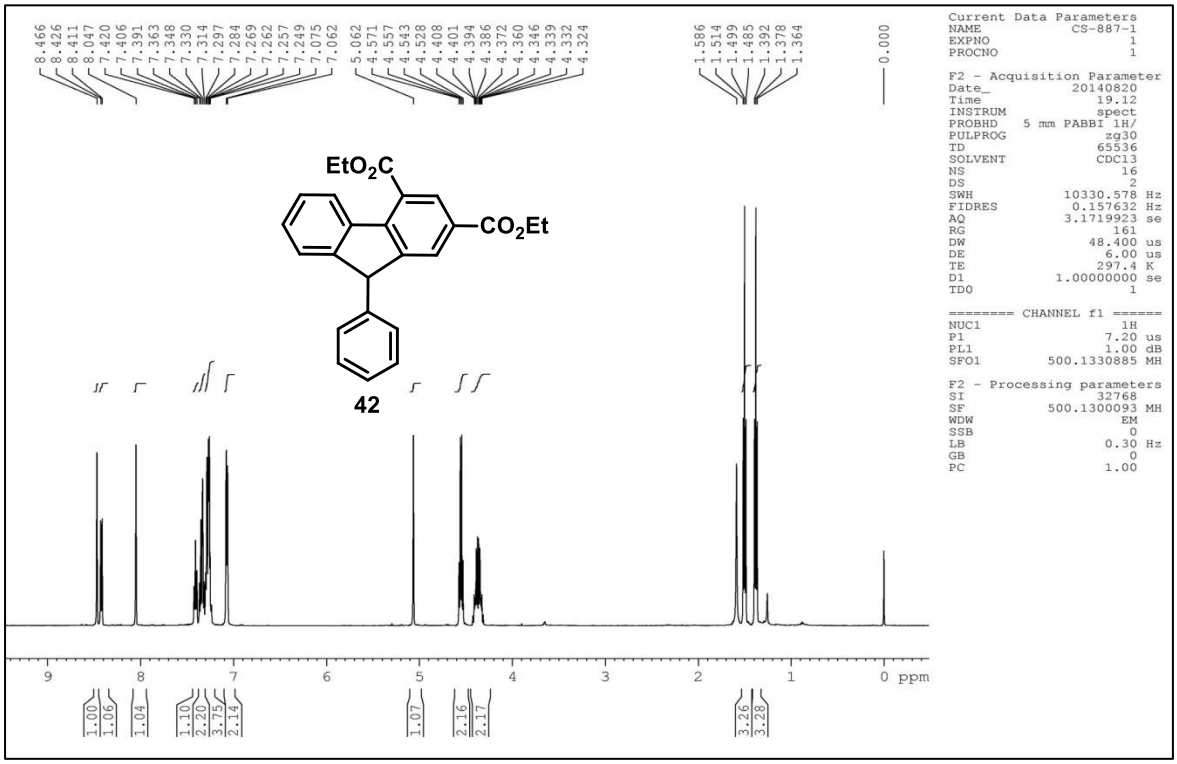


Figure 3.5K. ^{1}H and ^{13}C-NMR of 42



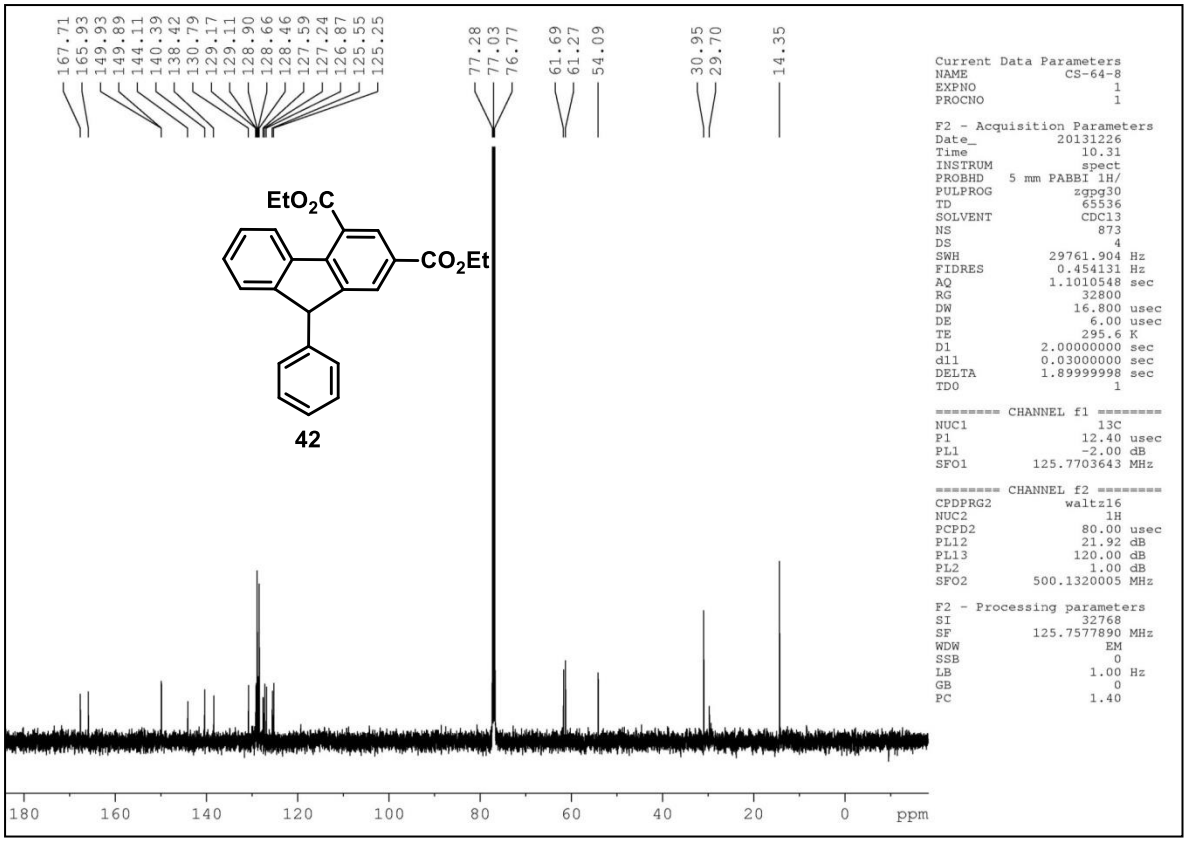
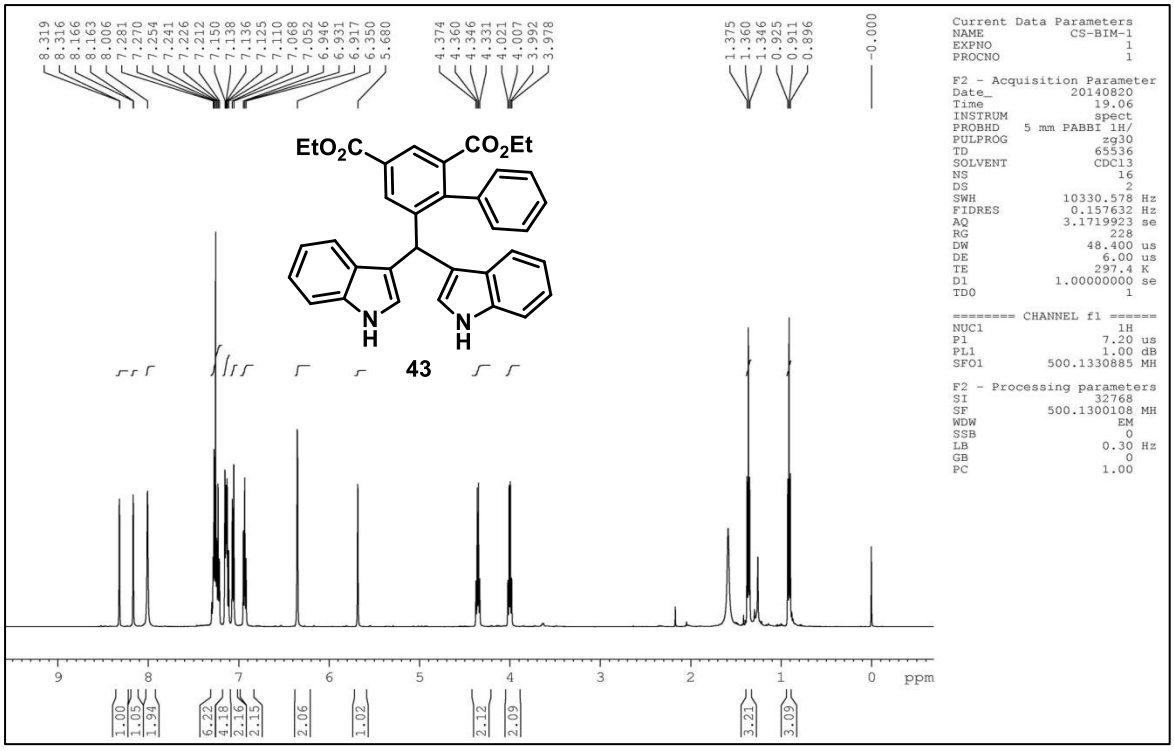
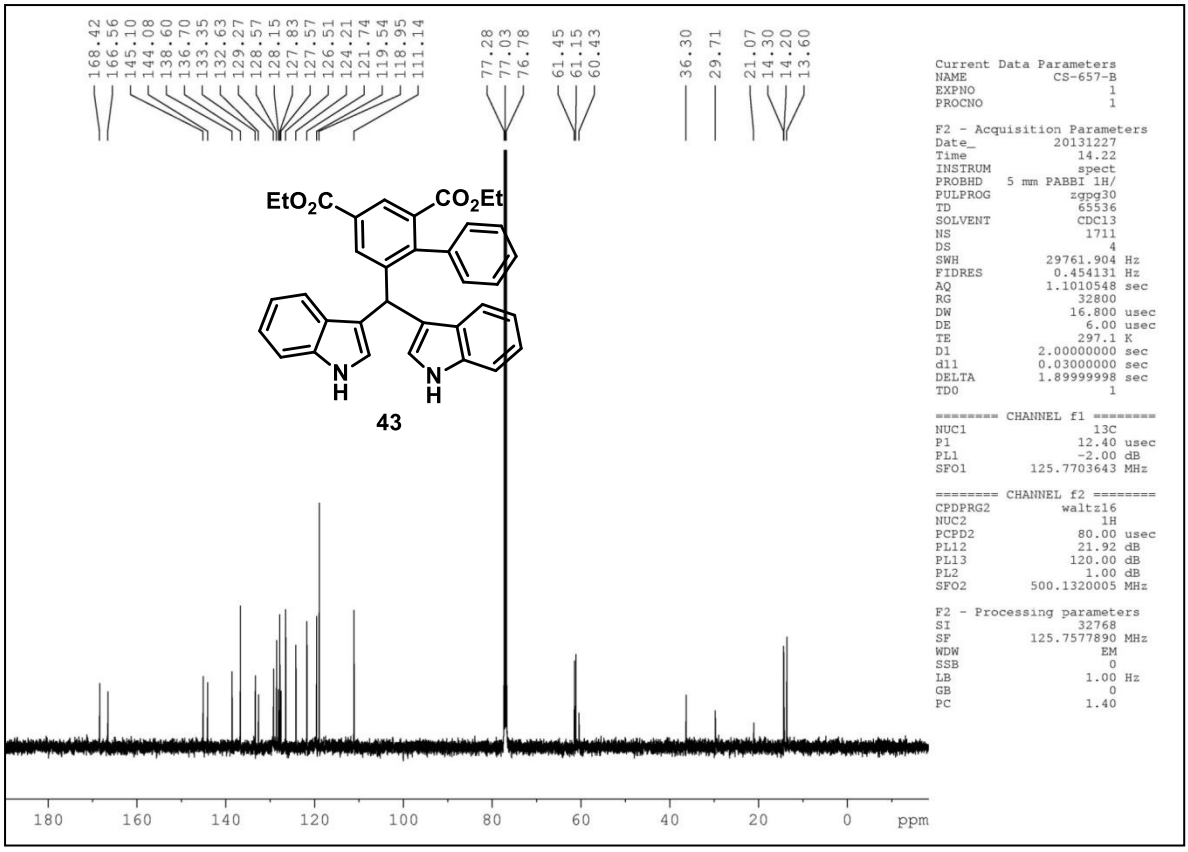


Figure 3.5L. ^{1}H and ^{13}C-NMR of 43





3.6. References

1. Bringmann, G.; Menche, D.; Bezabih, M.; Abegaz, B.M.; Kaminsky, R. *Planta Med.* **1999**, *65*, 757.
2. Goa, K. L.; Wagstaff, A. J. *Drugs* **1996**, *51*, 820.
3. (a) Nagamani, C.; Guo, J.; Thayumanavan, S. *J. Polym. Sci., Part A: Polym. Chem*. **2012**, *50*, 1187. (b) Gray, G. W. *Liq. Cryst*. **1998**, *24*, 5.
4. Noyori, R.; Takaya, H. *Acc. Chem. Res*. **1990**, *23*, 345.
5. Matheron, M. E.; Porchas, M. *Plant Dis*. **2004**, *88*, 665.
6. Ullmann, F.; Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174.
7. (a) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002,** *102*, 1359. (b) Saito, S.; Yamamoto, Y. *Chem. Rev*. **2000**, 100, 2901.
8. (a) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (b) Seechurn, C. C. C. J.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed*. **2012**, *51*, 5062.
9. For reviews, see: (a) Campeau, L. -C.; Fagnou, K. *Chem. Commun*. **2006**, 1253. (b) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev*. **2009**, *38*, 2447. (c) Daugulis, O.;

Do, H. -Q.; Shabashov, D. *Acc. Chem. Res*. **2009**, *42*, 1074. (d) Alberico, A.; Scott, M. E.; Lautens, M. *Chem. Rev*. **2007**, *107*, 174.

10. (a) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 5660. (b) Sun, C. L.; Li, H.; Yu, D. -G.; Yu, M.; Zhou, X.; Lu, X. -Y.; Huang, K.; Zheng, S. -F.; Li, B. -J.;. Shi, Z. -J. *Nat. Chem*. **2010**, *2*, 1044. (c) Gao, H.; Ess, D. H.; Yousufuddin, M.; Kürti, L. *J. Am. Chem. Soc.* **2013**, *135*, 7086. (d) Diemer, V.; Begaud, M.; Leroux, F. R.; Colobert, F. *Eur. J. Org. Chem*. **2011**, 341. (e) Dichiarante, V.; Fagnoni, M.; Albini, A. *Angew. Chem.* **2007**, *119*, 6615.
11. (a) Gooßen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (b) Rodríguez, N.; Goossen, L. J. *Chem. Soc. Rev*. **2011**, *40*, 5030.
12. (a) Parumala, S. K. R.; Peddinti, R. K. *Org. Lett.* **2013**, *15*, 3546. (b) Jacquemot, G.; Ménard, M. -A.; L'Homme, C.; Canesi, S. *Chem. Sci*. **2013**, *4*, 1287. (c) Dohi, T.; Kita, Y. *Top. Curr. Chem.* **2016**, *373*, 1. (d) Morimoto, K.; Sakamoto, K.; Ohshika, T.; Dohi, T.; Kita, Y. *Angew. Chem., Int. Ed.* **2016**, *55*, 3652.
13. (a) Xie, P.; Huang, Y.; Chen, R. *Chem. Eur. J*. **2012**, *18*, 7362. (b) Diallo, A.; Zhao, Y. -L.; Wang, H.; Li, S. -S.; Ren, C. -Q.; Liu, Q. *Org. Lett.* **2012**, *14*, 5776. (c) Zheng, J.; Huang, Y.; Li, Z. *Org. Lett.* **2013**, *15*, 5064.
14. (a) Esmaeili, A. A.; Moradi, A.; Mohammadi, H. K. *Tetrahedron* **2010**, *66*, 3575. (b) Xue, D.; Li, J.; Zhang, Z. -T.; Deng, J. -G. *J. Org. Chem.* **2007**, *72*, 5443. (c) Sharma, A.; Pandey, J.; Tripathi, R. P. *Tetrahedron Lett*. **2009**, *50*, 1812.
15. (a) Ashburn, B. O.; Carter, R. G. *Angew. Chem., Int. Ed*. **2006**, *45*, 6737. (b) Minuti, L.; Temperini, A.; Ballerini, E. *J. Org. Chem*. **2012**, *77*, 7923. (c) Ashburn, B. O.; Carter, R. G.; Zakharov, L. N. *J. Org. Chem*. **2008**, *73*, 7305.
16. (a) Li, L.; Zhao, M. -N.; Ren, Z. -H.; Li, J. -L.; Guan, Z. -H. *Org. Lett.* **2012**, *14*, 3506. (b) Shu, Z. -C.; Zhu, J. -B.; Liao, S.; Sun, X. -L.; Tang, Y. *Tetrahedron* **2013**, *69*, 284. (c) Specowius, V.; Kelzhanova, N.; Abilov, Z. A.; Langer, P. *Monatsh. Chem*. **2012**, *143*, 1151.
17. Song, X.; Zhang, X.; Zhang, S.; Li, H.; Wang, W. *Chem. Eur. J*. **2012**, *18*, 9770.
18. (a) Bera, K.; Sarkar, S.; Jalal, S.; Jana, U. *J. Org. Chem*. **2012**, *77*, 8780. (b) An, X.-D.; Yu, S. *Org. Lett.* **2015**, *17*, 2692. (c) Singha, R.; Dhara, S.; Ghosh, M.; Ray, J. K. *RSC Adv.* **2015**, *5*, 8801. (d) Xia, Y.; Qu, P.; Liu, Z.; Ge, R.; Xiao, Q.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed*. **2013**, *52*, 2543. (e) Yu, X.; Lu, X. *Adv. Synth. Catal.* **2011**, *353*, 569.

19. (a) Zhou, Y.; Wang, S.; Wu, W.; Li, Q.; He, Y.; Zhuang, Y.; Li, L.; Pang, J.; Zhou, Z.; Qiu. L. *Org. Lett.* **2013**, *15*, 5508. (b) Sindelar, M.; Lutz, T. A.; Petrera, M.; Wanner, K. T. *J. Med. Chem*. **2013**, *56*, 1323.
20. (a) Motti, E.; Della Ca', N.; Xu, D.; Piersimoni, A.; Bedogni, E.; Zhou, Z. -M.; Catellani, M. *Org. Lett.* **2012**, *14*, 5792. (b) Dogan, Ö., Gürbüz, N., Özdemir, I., and Çetinkaya, B. *Heteroat. Chem.* **2008**, *19*, 569. (c) Sun, A. D.; Love, J. A. *Org. Lett.* **2011**, *13*, 2750.
21. Tejedor, D.; Mendez-Abt, C.; Cotos, L.; Ramirez, M. A.; Garcia-Tellado, F. *Chem. Eur. J*. **2011**, *17*, 3318.
22. Challa, C.; John, M.; Lankalapalli, R. S. *Tetrahedron Lett*. **2013**, *54*, 3810.
23. Kulhnek, J.; Bures, S.; Pytela, O.; Mikysek, T.; Ludvk, J. *Chem. Asian J*. **2011**, *6*, 1604.
24. Das, A.; Chang, H. - K.; Yang, C. - H.; Liu, R. - S. *Org. Lett*. **2008**, *10*, 4061.
25. Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta*, **2006**, *39*, 79.
26. Lee, T. - H.; Jayakumar, J.; Cheng, C. - H.; Chuang, S. - H. *Chem. Commun.* **2013**, *49*, 11797.
27. Sharma, V. K.; Singh, S. K. *RSC Adv.* **2017**, *7*, 2682.
28. (a) Liu, T. -P.; Xing, C. -H.; Hu, Q. -S. *Angew. Chem., Int. Ed*. **2010**, *49*, 2909. (b) Gorin, D. J.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736.
29. Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Chem. Rev.* **2010**, *110*, 2250.

Chapter-4a

PIDA mediated multiple carbon-carbon and carbon-hydrogen bond activations in Diindolylmethanes (DIMs)

4a.1. Abstract

This chapter describes a novel phenyliodine diacetate (PIDA) [$PhI(OAc)_2$] mediated oxidative transformation of unstrained phenol substituted 3,3'-diindolylmethanes (DIPMs) (**1**) to 2,3'-diindolylketones (**2**) under mild and metal-free reaction conditions (Figure 4a.1A). The reaction is characterized as the first hypervalent iodine (HIR) mediated multiple C-C and C-H bond activations with associated unusual rearrangement. The detailed density functional theory (DFT) calculations and control experiments revealed that the reaction proceeds through a new "charge-switching" mechanism by synergistic involvement of the two indole units with overall low activation energy. Further, the "charge-switching" concept was successfully employed in synthesis of cyclohepta[*b*]indole (**3**) core motif from the biaryl appended DIBM (**1'**) in a one-pot two-step operation via spirodienone intermediate (Figure 4a.1B).

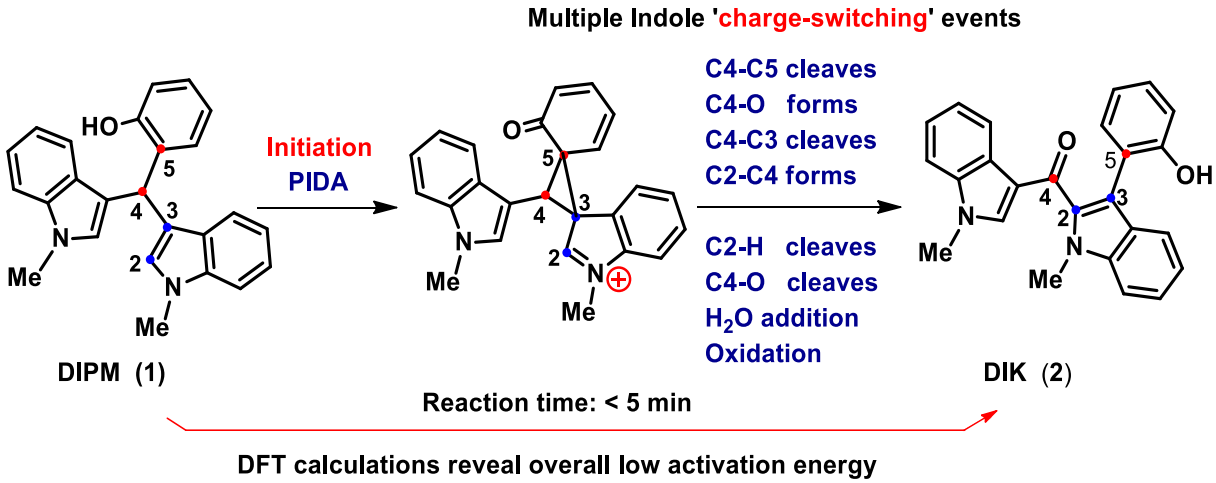


Figure 4a.1A. PIDA mediated indole "charge-switching" reaction in DIPM

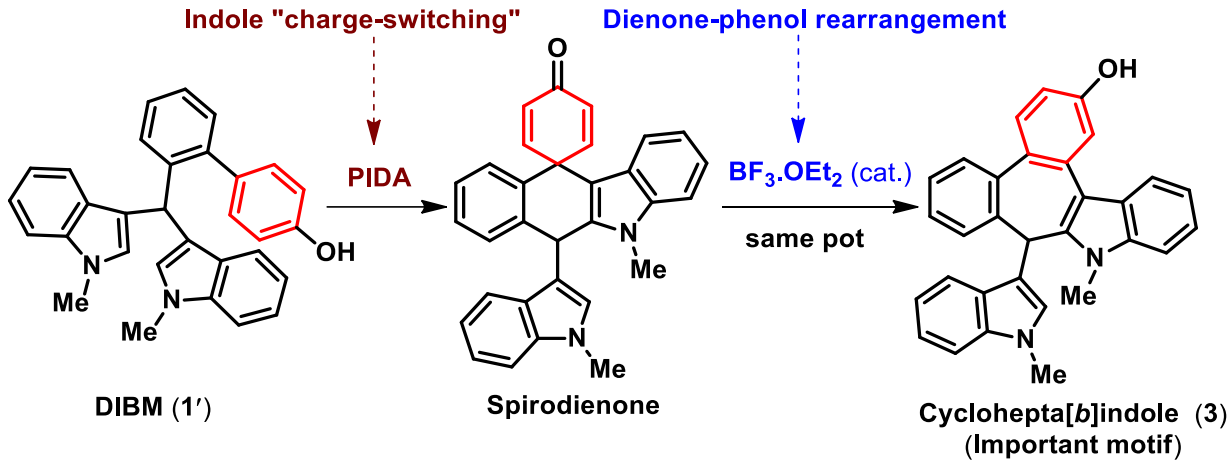
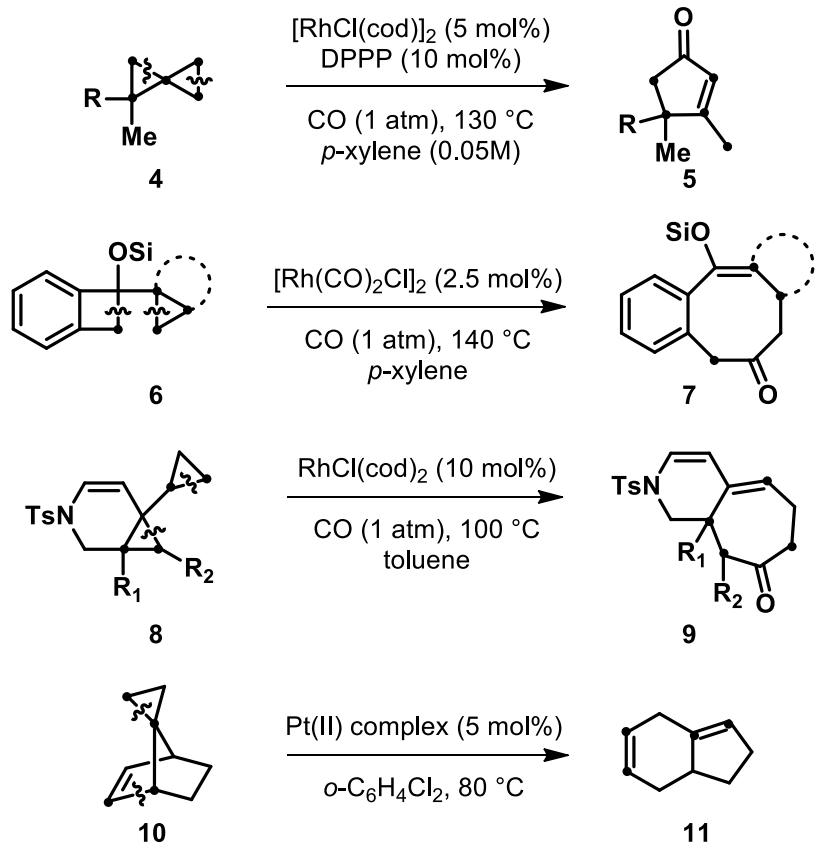


Figure 4a.1B. Extension of "charge-switching" concept for cyclohepta[*b*]indole synthesis

4a.2. Introduction

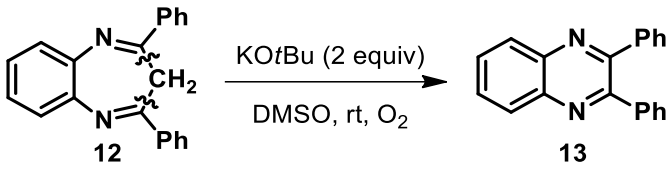
Carbon-Carbon (C-C) single bond has its ubiquitous presence in the majority of organic compounds as the simplest functional group in organic chemistry. Activation of the fundamental C-C single bond is considered as one of the most demanding areas of contemporary synthetic chemistry. Direct functionalization of the ubiquitous C-C single bonds offers a huge economic advantage to chemical industries. However, development of synthetic methodologies involving C-C single bond cleavage is challenging due to thermodynamic and kinetic factors such as high bond energies and constrained directionality of C-C σ orbitals, respectively.[1] Even in biological systems, oxygenative C-C bond cleavage reactions are limited to β-dicarbonyl substrates catalyzed by metalloenzyme such as Dke1, a non-heme Fe^{+2} dependant enzyme comprising three histidine facial triad at the active site of the enzyme.[2] In synthetic chemistry, transition metal-based catalytic systems play a pivotal role in promoting C-C bond cleavage reactions *via* three major routes *viz*. oxidative addition, β-carbon elimination, and retro-allylation.[3] To date, most of such reactions were reported for strained substrates,[4] and substrates which offer strong chelation assistance.[5] Reports of unstrained C-C single bond cleavage reactions associated with C-Csp, C-Csp2, C-Csp3 were also mostly supported by

transition metal catalysis.[6] Reports on multiple C-C single bond cleavage reactions are scarce, and the reported ones are driven by release of strain under metal-catalyzed conditions (Scheme 4a.2.1).[7-10] For instance, Rhodium (I) catalyzed carbonylation reaction of spiropentane **4** afforded cyclopentenone **5** involving two C-C bond cleavage steps (Scheme 4a.2.1).[7] Synthesis of challenging eight- and seven-membered carbocyclic rings (**7/9**) was accomplished by Rh (I) catalyzed carbonylative cycloaddition of cyclopropyl-benzocyclobutenes **6** and biscyclopropanes **8**, respectively (Scheme 4a.2.1).[8-9] Rearrangement of a spirocyclopropane hydrocarbon **10** to pentahydroindene **11** was achieved by double C-C single bond cleavage using platinum (II) complex (Scheme 4a.2.1).[10]



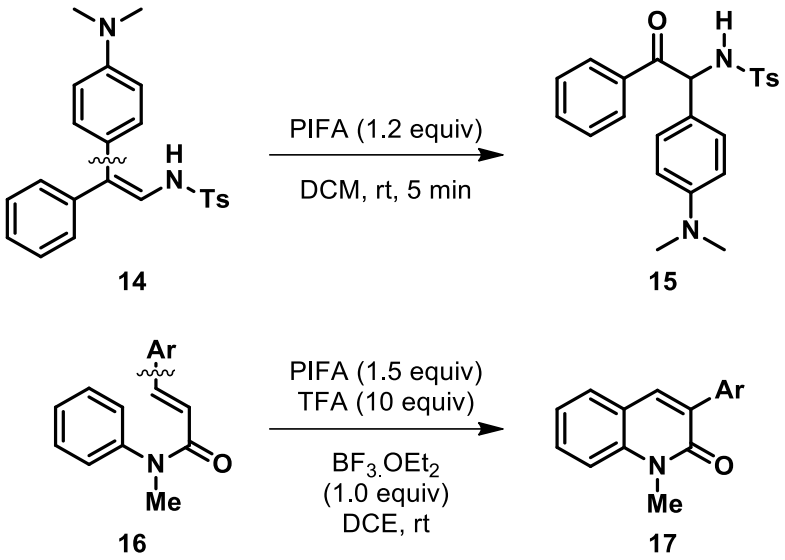
Scheme 4a.2.1. Transition metal catalyzed multiple C-C bond cleavages in strained system

Developing a metal-free method for C-C single bond cleavage of an unactivated and unstrained organic system is one of the most arduous tasks in synthetic chemistry. Hitherto, cleavage of C-C single bonds which are directly attached to carbonyl (CO) groups or adjacent to heteroatoms have been reported under metal-free conditions.[11-13] Multiple C-C single bond cleavage reactions involving strain free systems under metal-free conditions is yet to be explored in chemistry. A study that falls somewhat close to this description is the extrusion of -CH_2 group from benzo[*b*][1,4]diazepine **12** to access quinoxaline **13** reported by Shen et al. wherein strain in the 7-membered ring and close proximity of two C_{sp2} atoms drive the extrusion process (Scheme 4a.2.2).[14]



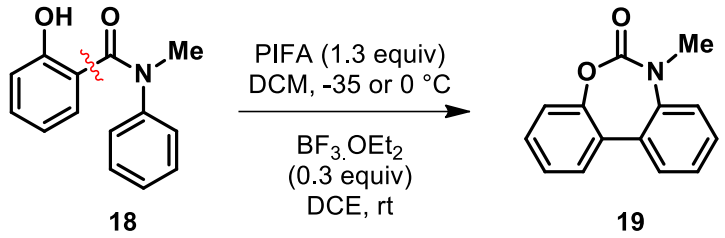
Scheme 4a.2.2. Metal-free double C-C single bond cleavage

PIDA and related environmentally benign hypervalent iodine reagents (HIRs) are known for their good electrophilicity and excellent leaving group character which render them with reactivity pattern similar to the transition metal-catalyzed reactions.[15] The chemistry and synthetic applications of commercially available HIRs are extensively discussed in the introductory chapter. In the context of present work, some of the representative HIR mediated C-C single bond cleavage reactions will be discussed in this chapter. HIR mediated C-C single bond cleavage related to 1,2-aryl group migrations were prevalent in substituted alkenes.[16] For example, substrates such as **14** and **16** underwent one C-C single bond cleavage associated with 1,2-aryl migration in the presence of PIFA to afford the corresponding rearranged products **15** and **17** (Scheme 4a.2.3).



Scheme 4a.2.3. HIR mediated one C-C bond cleavage in substituted alkenes

As discussed in the introductory chapter, phenolic substrates readily undergo oxidative dearomatization which can result in a migratory cleavage of C-C single bonds. Especially, rearrangements were the prerogative of *para*-substituted phenols by *ipso*-substitution.[17] This class of reactions were well documented in chapter-1 under HIR mediated rearrangements section. However, HIR mediated oxidative dearomatization of *para*-substituted phenol was explained by the initial formation of phenoxyiodine intermediate which generates the phenoxenium ion to afford spirodienone.[18] *Ortho*-substituted phenols were less explored in dearomatization induced C-C single bond cleavage/rearrangements in the presence of HIR. One such example depicts a PIFA/BF_3.Et_2O-mediated spirocyclization of an ortho-substituted phenol **18** with a concomitant C_{sp2}-C_{sp3} single bond cleavage and lactonization to afford dibenzoxazepinones **19** in moderate yields (Scheme 4a.2.4).[19] Nevertheless, the intermediates derived from dearomatization of *ortho*-substituted phenols were utilized as valuable building blocks for the synthesis of complex natural products.[20]



18 19

Scheme 4a.2.4. C-C cleavage associated with aryl-aryl coupling in *ortho*-substituted phenol

On the other hand, diindolylmethane (DIM)/bis(indolyl)methane (BIM) renowned for its anticancer properties is a metabolic product of Indole-3-carbinol (I3C), a glucosinolate conjugate in various cruciferous vegetables.[21] Formation of DIM under the physiological conditions is considered as a prerequisite for the I3C induced anti-carcinogenesis.[22] The basic skeleton of DIM consisting of two indole units bridged by single carbon atom at the 3 and 3' positions, and are frequently isolated from marine and terrestrial sources (Figure 4a.2A).[23] DIMs and their analogues have found a wide range of biological activities, especially in cancer chemotherapy.[24]

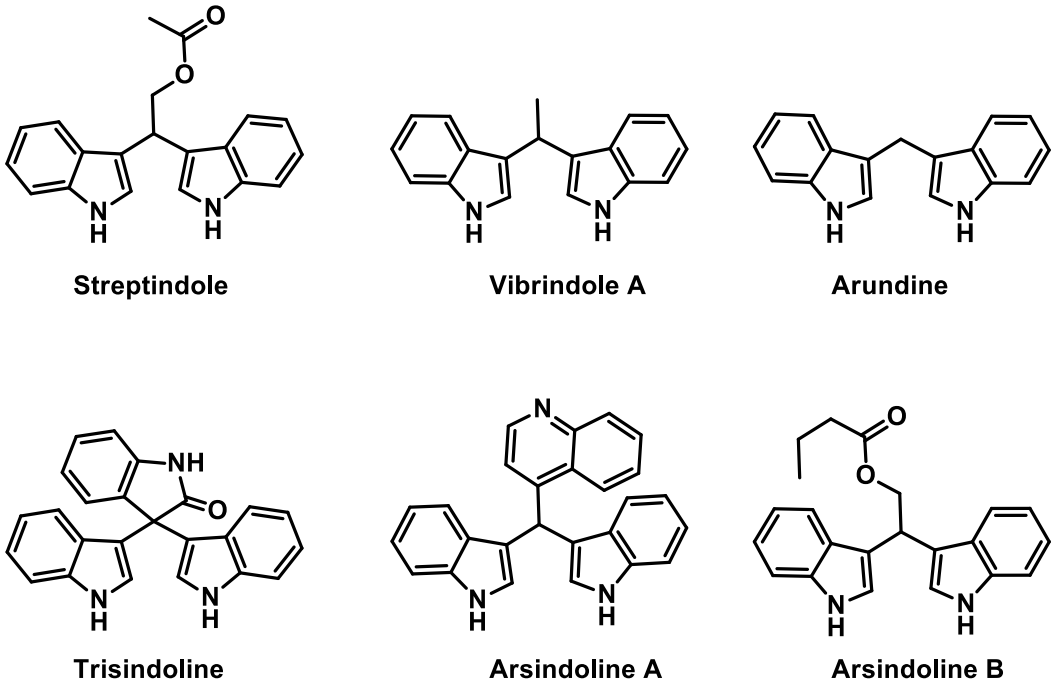
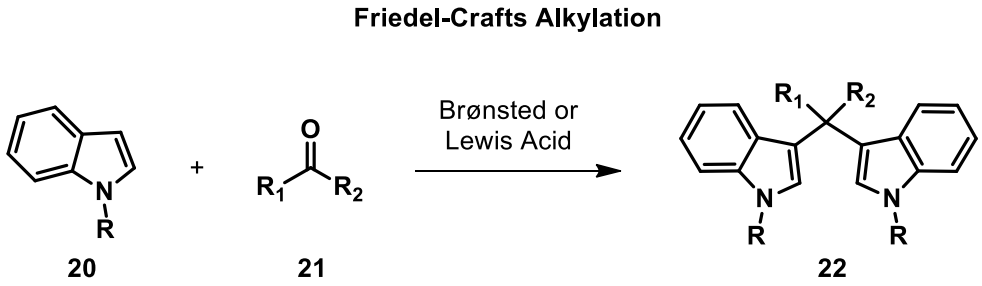


Figure 4a.2A. Examples of naturally occurring DIMs

Consequently, several methods are available in the literature to access this core and the most commonly employed method is Friedel-Crafts alkylation reaction between indole **20** and carbonyl compounds **21** in the presence of Brønsted or Lewis acid (Scheme 4a.2.5.).[24]

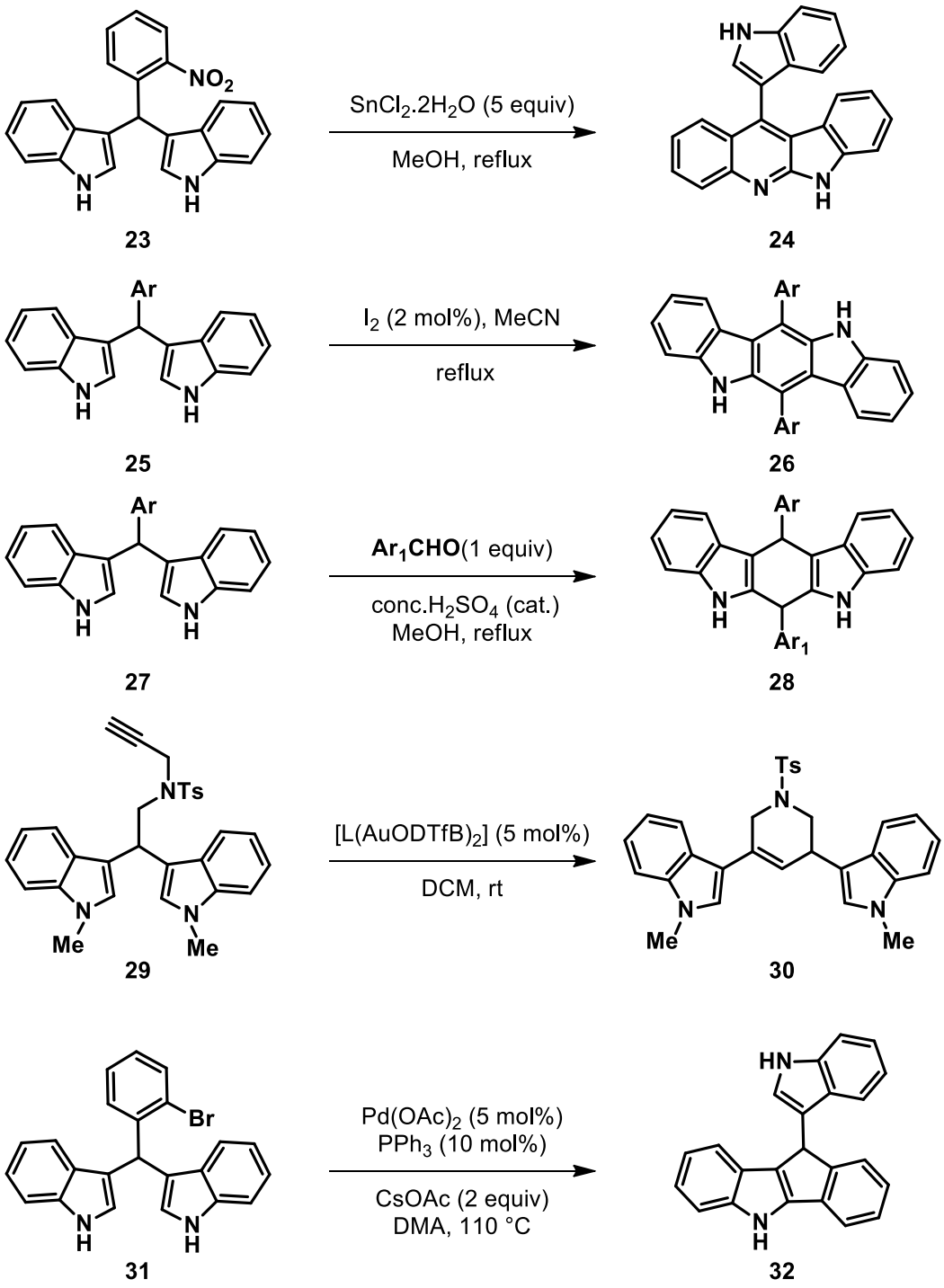


Scheme 4a.2.5. Common synthetic route for DIMs synthesis

Despite their ease of synthesis, DIMs are relatively unexplored substrates in organic synthesis. DIMs are mainly used as substrates for the synthesis of 6*H*-indolo[2,3-*b*]quinolines **24**, indolo[3,2-*b*]carbazoles **26**, tetrahydroindolocarbazoles **28**, and bisindole alkaloid analogues **30** & **32** from the corresponding DIMs **23**, **25**, **27**, **29**, and **31**, respectively (Scheme 4a.2.6).[25]

On the whole, metal-free C-C single bond cleavage reports are scarce and even metal-catalyzed multiple C-C single bond cleavage reports are limited to strain releasing substrates. In the present study, we have readily transformed an easily accessible and unexplored DIPM **1** with ortho-substituted phenol to 2,3'-diindolylketone (DIK) **2** in the presence of PIDA. The reaction characterized by multiple bond cleavages, formations, rearrangements, and functionalizations may be rated as one of the most unprecedented reactions in organic chemistry and even a comparable reaction in biology under metal-free condition is hard to locate. Density functional theory calculations reveal cationic 'charge-switching' between the two indole units by synergy with associated aromatization-dearomatization steps, thus, facilitating low activation free energy for the

entire reaction and the exothermic energy profile resembles a biological enzymatic reaction.

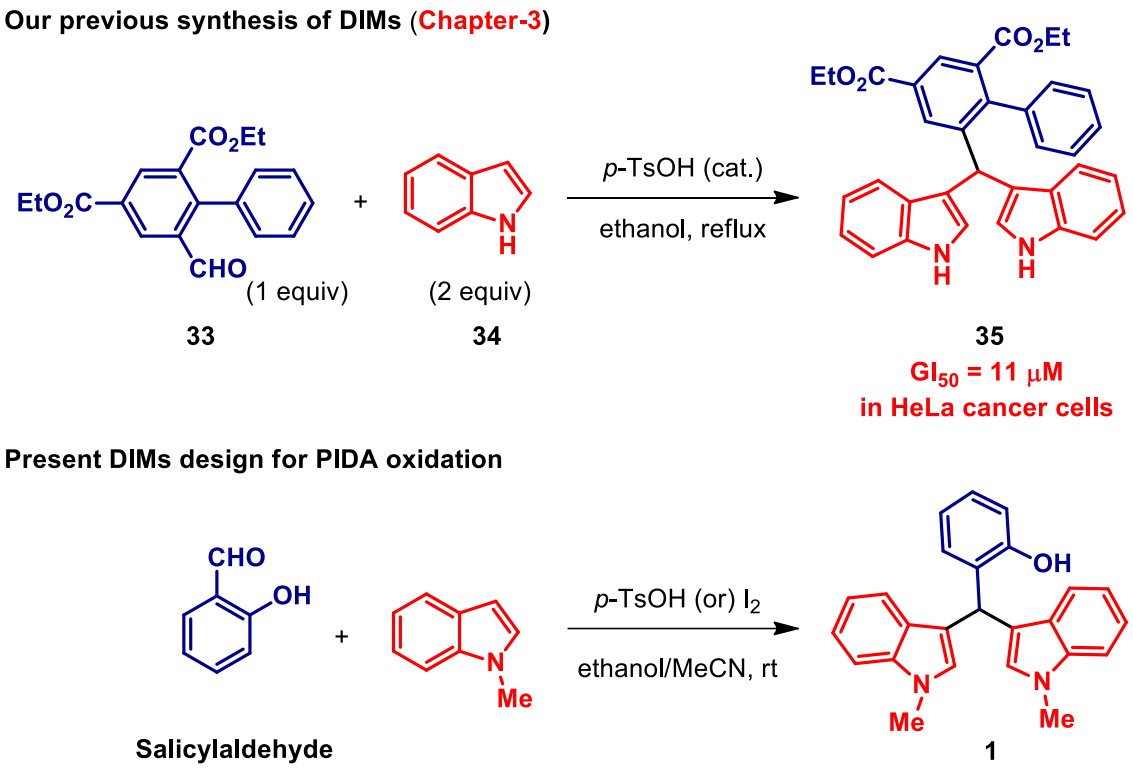


Scheme 4a.2.6. Synthetic methodologies using DIMs substrates

4a.3. Results and discussions

4a.3.1. Synthesis of 2,3'-diindolylketones

In chapter-3, we made a successful attempt in synthesizing biaryl appended diindolylmethane (DIM) **35** by utilizing biaryl-2-carbaldehyde **33** and indole **34** in the presence of catalytic *p*-TsOH (Scheme 4a.3.1).[26] Our group further synthesized a small library of biaryl appended DIMs **35** by the variation of differently substituted biaryls **33** and exploited their anti-cancer activity against HeLa cells.[27] Indeed, some of the DIMs exhibited caspase-dependent apoptosis in HeLa cells and was found to be non-toxic to H9C2 normal cells. The ease of DIMs synthesis and its biological activities prompted us to investigate its synthetic utility as a promising substrate for PIDA mediated oxidative transformations. Accordingly, we have designed a phenol substituted DIPM **1** where the prerequisite of a phenolic moiety in PIDA mediated oxidative transformation was met by choosing salicylaldehyde (Scheme 4a.3.1).



Scheme 4a.3.1. Our previous synthesis of DIM **22** and present design of DIPM **1**

Our initial attempt of treating DIPM **1** prepared by a facile condensation of salicylaldehyde and *N*-methylindole, with PIDA (1.5 equiv) in DCM was unsuccessful (entry 1, Table 4a.3.1). However, changing the solvent from DCM to HFIP/DCM (1:1) along with 2 equiv of PIDA afforded a major product as observed on TLC which was isolated and characterized by 1D- and 2D-NMR spectroscopy to discover the formation of a rearranged product diindolylketone **2a** in 67% yield (entry 2). The structure of compound **2a** was further unambiguously confirmed by single crystal X-ray analysis of a 4-nitrobenzoate derivative of **2a** (**2a'**, Figure 4a.3A).

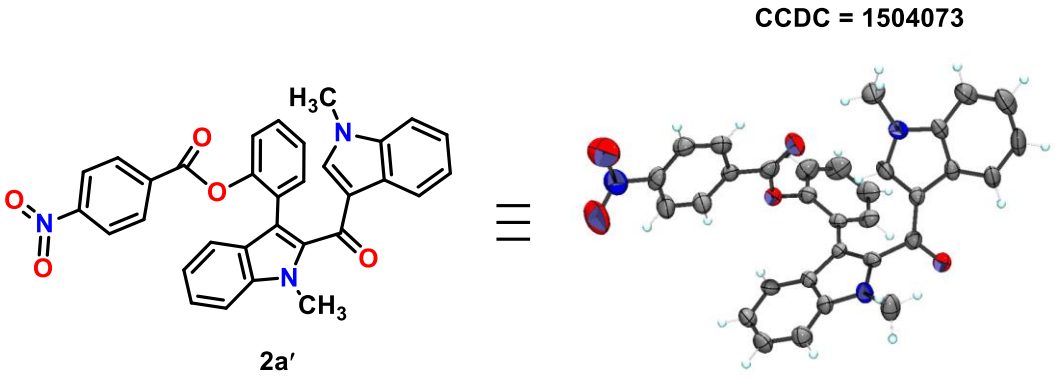
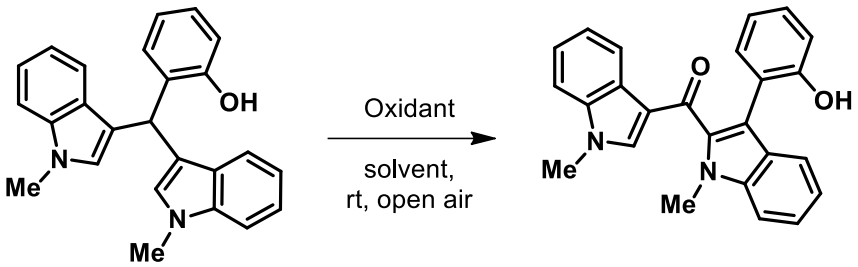


Figure 4a.3A. Ortep drawing of **2a'**

There was no improvement in the yield of compound **2a** while using HFIP or TFE in the presence of PIDA (entries 3-4). Utilization of other hypervalent iodine reagents *viz.* PIFA and $PhI(OPiv)_2$ afforded product **2a** in 35% and 46% yields, respectively (entries 5-6); whereas Koser's reagent failed to generate the desired product (entry 7). Attempts of *in situ* generation of HIR using Oxone®/PhI, $K_2S_2O_8$/PhI and *m*CPBA/PhI combinations were unsuccessful (entries 8-10). Further extensive optimization studies by variation of oxidants, solvent combinations/ratios, and stoichiometry could not improve the yield of product **2a** (entries 11-26), which led us to consider a solvent combination of HFIP/DCM (1:1) (0.05 M of DIPM **1**, 3 mL) along with 2 equiv of PIDA as the optimized condition to demonstrate the substrate scope.

Table 4a.3.1. Optimization of reaction conditions[a]



DIPM **1** DIK **2a**

S.No.	Oxidant (equiv)/ Additive (equiv)	Solvent [conc. in M]	Yield of **2a**[b]
1	PIDA (1.5)	DCM	n.d
2	**PIDA (2)**	**HFIP/DCM (1:1)**	**67**
3	PIDA (2)	HFIP (0.07)	38
4	PIDA (2)	TFE (0.07)	38
5	PIFA (2)	HFIP/DCM (1:1)	35
6	$PhI(OPiv)_2$ (2)	HFIP/DCM (1:1)	46
7	PhI(OH)OTs (2)	HFIP/DCM (1:4)	n.d.
8	Oxone® (3)/PhI (0.5)	HFIP/MeOH/H_2O[c]	n.d.
9	$K_2S_2O_8$ (4)/PhI (0.5)	TFE/DCM (1:1)	n.d.
10	*m*CPBA (3)/PhI (0.5)	DCM	n.d.
11	PIDA (2)	HFIP/MeOH/H_2O[c]	51
12	PIDA (2)	DMF [0.05]	n.d.
13	PIDA (2)	HFIP/DCE (1:1) [0.07]	50
14	PIDA (2)	HFIP/$CHCl_3$ (1:1) [0.07]	57
15	PIDA (0.25)	HFIP/DCM (1:1) [0.07]	10
16	PIDA (0.5)	HFIP/DCM (1:1)[0.07]	18
17	PIDA (1.0)	HFIP/DCM (1:1) [0.05]	40

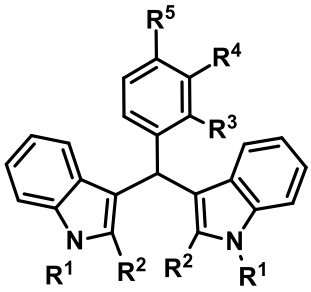
18	PIDA (1.5)	HFIP/DCM (1:1) [0.05]	54
19	PIDA (2.5)	HFIP/DCM (1:1) [0.07]	52
20	PIDA (3.5)	HFIP/DCM (1:1) [0.07]	24
21	PIDA (2)	HFIP/DCM (1:2) [0.07]	57
22	PIDA (2)/H_2SO_4 (5)	EtOAc [0.05]	n.d.
23	CAN (3)	DMF [0.05]	n.d.
24	NIS (3)	DCM [0.05]	n.d.
25	NBS (3)	DCM [0.05]	n.d.
26	IBX (2)	DMF [0.05]	n.d.

[a]All reactions were conducted using 0.05-0.15 mmol of DIPM **1** (0.07-0.05 M) at room temperature in the open air; [b] Yields are chromatography isolated and are given in percentages (%); [c]HFIP/MeOH/H_2O solvent ratio is 1:1:0.1; n.d. = not detected.

The reaction was successful only while using DIPM prepared from *N*-methylindole but failed to produce the corresponding rearrangement for DIPM obtained from 1*H*-indole (Table 4a.3.2, entry 1), which prompted us to investigate the substituent requirements of DIPM in this transformation. Accordingly, a detailed substrate requirement study was performed to find other compatible DIPM substrates. The absence of ortho-hydroxy phenyl substitution in DIPM **1** or presence of *ortho* -OMe group, did not yield the desired product in the presence of PIDA (entries 2-3). Similarly, DIPMs with *meta*- or *para*-hydroxy phenyl substitutions (entries 4-5) could not produce the desirable outcome which clearly shows the significance of *ortho*-hydroxy phenyl substitution in the present transformation. DIPM bearing ortho-hydroxy phenyl substitution prepared from 2-methylindole was also not a suitable substrate (entry 6, where R_2 = Me). Further, an

electron-withdrawing carbamate protection (entry 7) was also not suitable for the product formation. From these observations, we found that the presence of *ortho*-hydroxyl group and N-alkyl indoles in DIPM are necessary for this transformation.

Table 4a.3.2. Substrate requirement study[a]

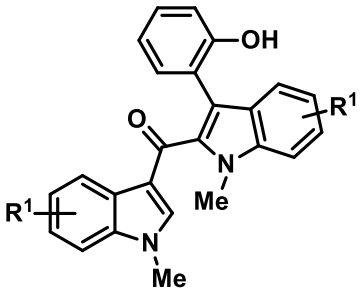


S.No.	R^1	R^2	R^3	R^4	R^5	DIK 2[b]
1	H	H	OH	H	H	n.d.
2	Me	H	H	H	H	n.d.
3	Me	H	OMe	H	H	n.d.
4	Me	H	H	OH	H	n.d.
5	Me	H	H	H	OH	n.d.
6	Me	Me	OH	H	H	n.d.
7	Boc	H	OH	H	H	n.d.

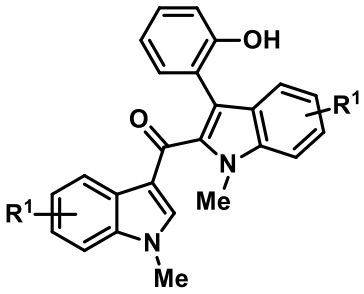
[a] All reactions were conducted using optimized condition; n.d. = not detected

Having the optimized condition and compatible DIPM substrates in hand, we explored the substrate scope of this transformation utilizing an array of DIPMs generated by substituted indoles with N-alkyl variations and substituted salicylaldehydes (Table 4a.3.3). DIPMs with electron-rich *N*-methylindoles underwent rearrangement to produce the desired products DIKs **2b**-**2d** in moderate yields of 51%, 38% and 45%, respectively. DIPMs with 5- or 6- halogenated *N*-methylindoles were also found to be good substrates which afforded DIKs **2e**-**2h** in good yields.

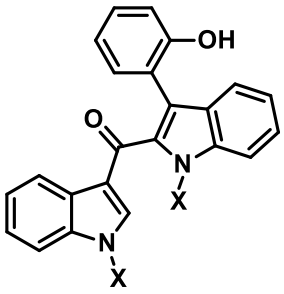
Table 4a.3.3. Generality of the reaction



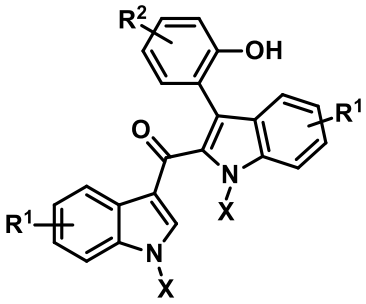
2b (R^1 = 5-OMe, 51%)
2c (R^1 = 6-Me, 38%)
2d (R^1 = 4-OMe, 45%)



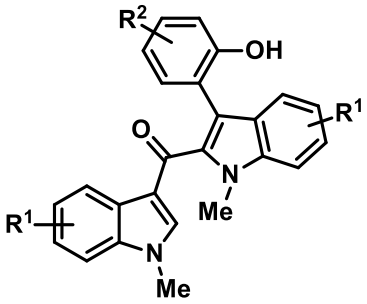
2e (R^1 = 5-I, 73%)
2f (R^1 = 6-Br, 67%)
2g (R^1 = 6-Cl, 63%)
2h (R^1 = 5-Br, 60%)



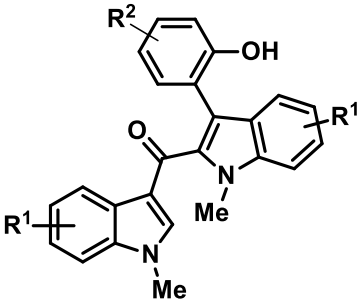
2i (R^1 = H, X = Allyl, 67%)
2j (R^1 = H, X = Butyl, 53%)
2k (R^1 = H, X = Bn, 60%)
2l (R^1 = H, X = PMB, 19%)



2m (R^1 = 5-Br, R^2 = H, X = Allyl, 63%)
2n (R^1 = 5-OMe, R^2 = H, X = Allyl, 67%)
2o (R^1 = 6-Cl, R^2 = 5-Cl, X = Bn, 31%)
2p (R^1 = 5-I, R^2 = 5-Br, X = Bn, 43%)



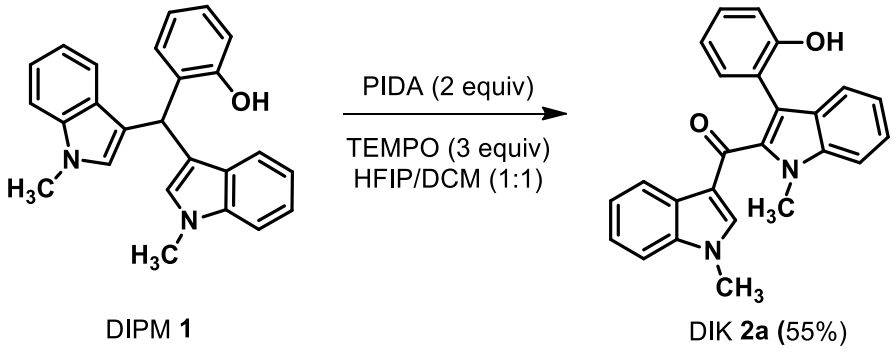
2q (R^1 = H, R^2 = 5-OMe, 19%)
2r (R^1 = H, R^2 = 5-Cl, 41%)
2s (R^1 = H, R^2 = 5-Br, 42%)



2t (R^1 = 5-NO_2, R^2 = H, trace)
2u (R^1 = H, R^2 = 5-NO_2, 0%)

DIPMs with indoles having N-alkyl variations *viz.* allyl, butyl, benzyl and 4-methoxybenzyl (PMB) demonstrated the desirable transformation affording DIKs **2i-2p** in moderate to good yields. The presence of a methoxy group in the para-position of the phenolic moiety of DIPM produced DIK **2q** in 19% yield; however, halogen substituted phenols offered DIKs **2o-2p** and **2r-2s** in moderate yields. The presence of electron-withdrawing substituents such as nitro on either indole or the phenyl ring of DIPM resulted in no product formation (**2t-2u**), indicating the requirement of electron rich indoles as well as ortho-phenols in DIPM substrates.

In order to understand the key steps in the transformation of DIPM **1** to DIK **2**, we carried out density functional theory (DFT) calculations employing the solvation effect included M06-2X/6-311++G(d,p)/SMD method (solvent = 2-methyl-1-propanol) in collaboration with a theoretical chemist, Dr. Suresh C. H. from CSIR-NIIST. HIRs are well known for their oxidative dearomatization reaction on phenolic systems to produce spirocyclic molecules *via* phenoxenium ions in fluoroalcohols such as HFIP.[28] Expecting a similar reaction of PIDA with the phenolic moiety of DIPM, formation of the cationic spirocyclic intermediate $\mathbf{3}^{+}$ is envisaged as the initiation step of DIPM **1** to DIK **2** transformation by the nucleophilic attack of the indole unit (C3) at the *ipso* carbon (C5) (Figure 4a.3B). The reaction proceeds by ionic pathway as DIK **2** formation was observed even in the presence of TEMPO (Scheme 4a.3.2).



DIPM **1** DIK **2a** (55%)

Scheme 4a.3.2. PIDA reaction in the presence of TEMPO

The indole unit orienting right with respect to the spiro carbon (Figure 4a.3B) is referred to as I_R and the other indole unit is labelled as I_L. The relative Gibbs free energy profile in solvent (ΔG_{sol}) starting from $\mathbf{3}^{+}$ is depicted in Figure 4a.3B along with the molecular electrostatic potential (MESP) map of the intermediate structures. The positive charge localized in the deep blue region is easily distinguished from other regions in MESP.

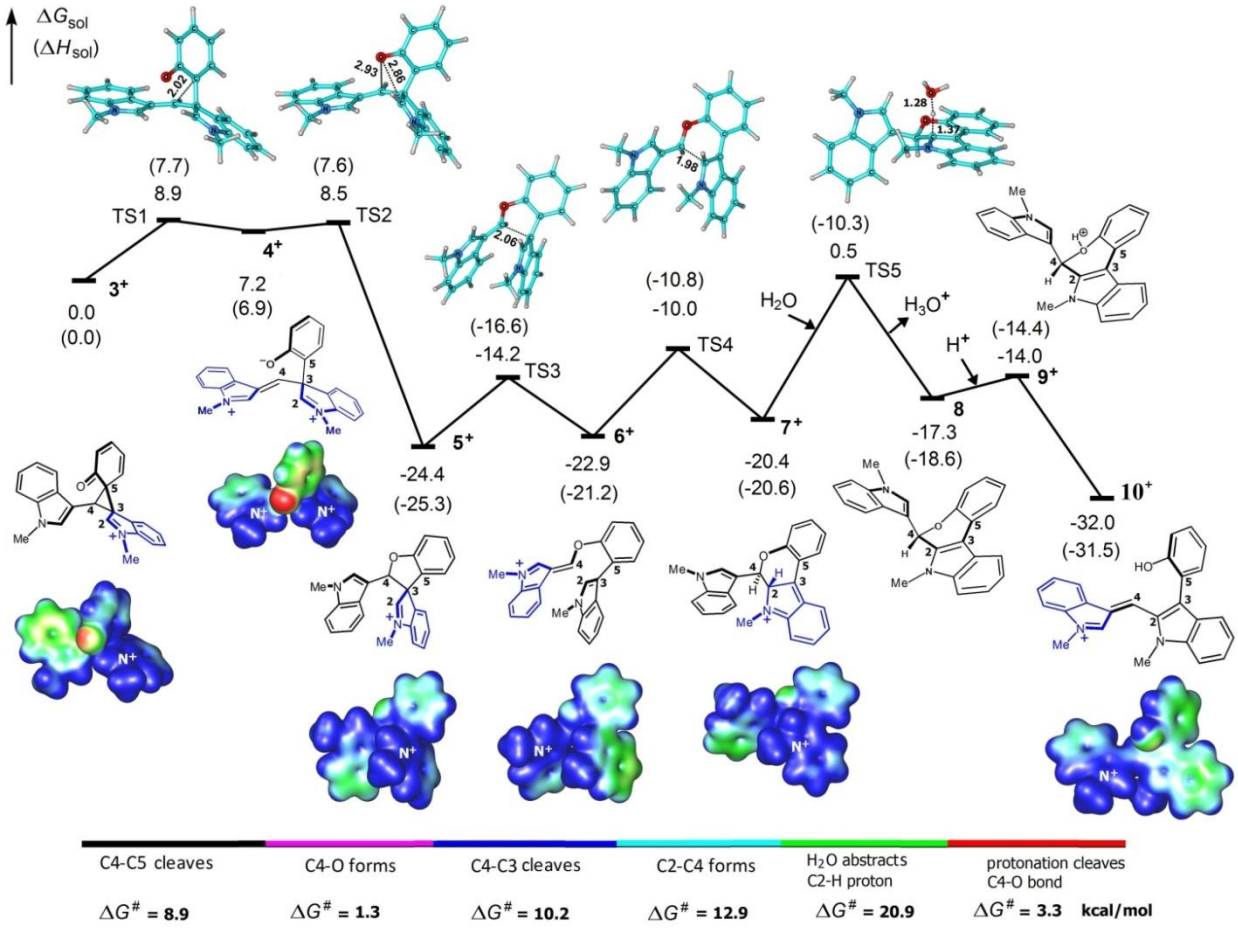
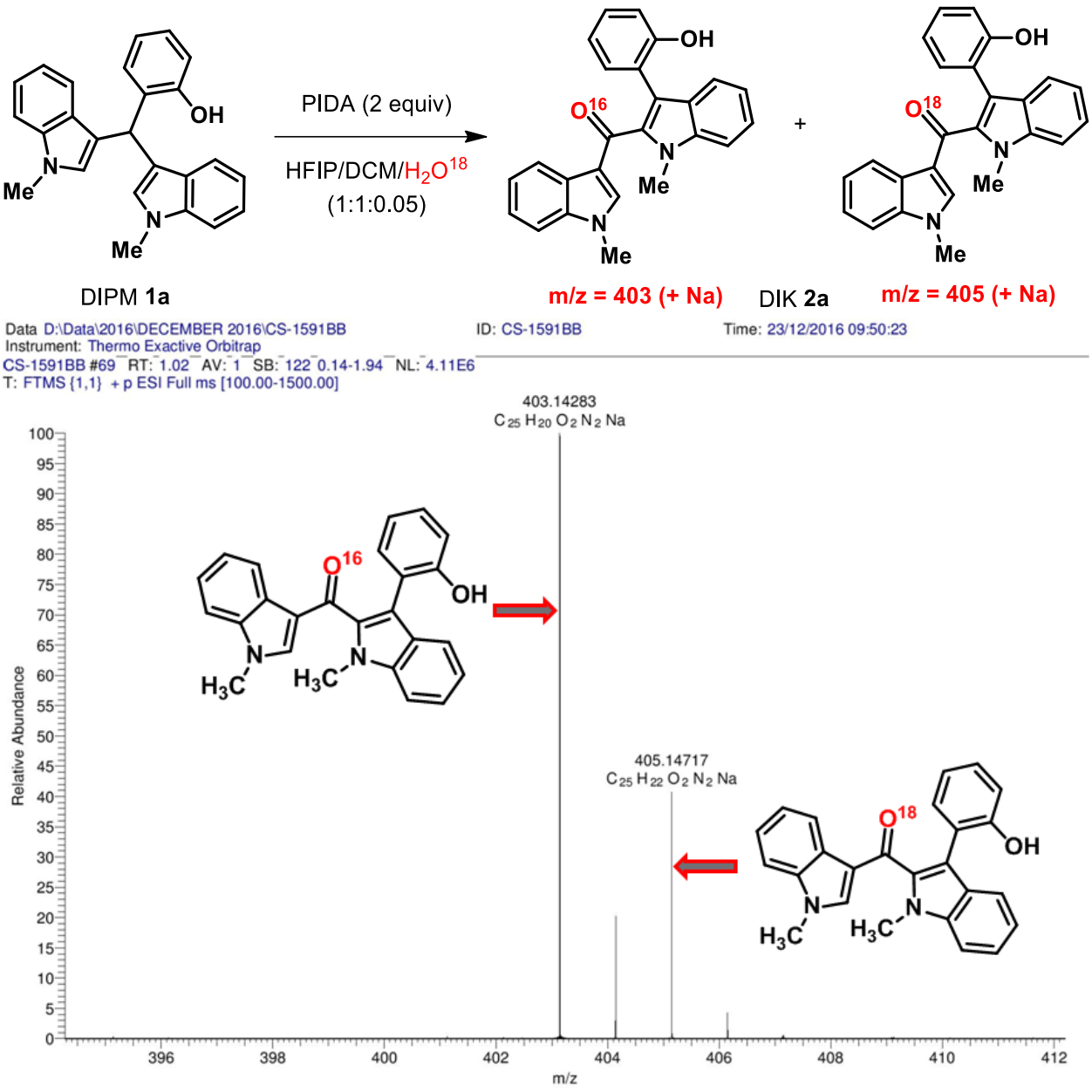


Figure 4a.3B. DFT computed mechanism (in kcal/mol) for the multiple C-C, C-O and C-H bond activations.

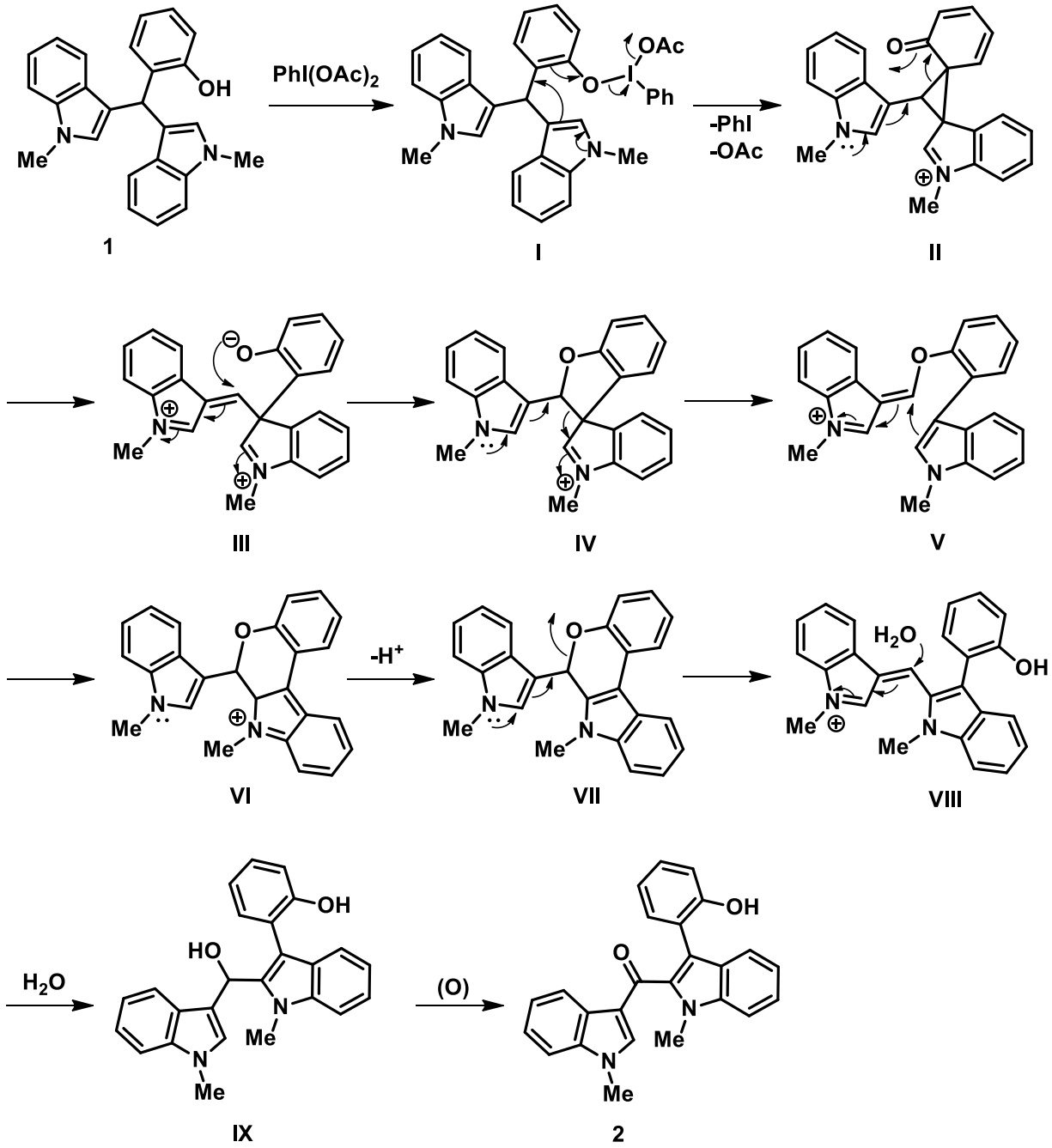
The three-membered ring of the spirocycle and the dearomatized cyclohexa-2,4-dienone portions of $\mathbf{3}^{+}$ indicates its high energy. The strained C4-C5 bond of the spirocycle cleaves *via* the transition state (TS) **TS1** with activation free energy ($\Delta G^{\#}$) 8.9 kcal/mol resulting in the formation of a transient intermediate $\mathbf{4}^{+}$. In $\mathbf{4}^{+}$, both indole moieties show double bond character for the CN bond (1.29 - 1.30 Å), suggesting positive charge on both nitrogen centers and negative charge on phenolic oxygen. The negative charge bearing oxygen center in $\mathbf{4}^{+}$ orients close to the double bond of C4 and a nucleophilic interaction of it occurs easily *via* **TS2** with $\Delta G^{\#}$ 1.3 kcal/mol to yield $\mathbf{5}^{+}$ where the positive charge is mainly localized on I_R. Hitherto, the release of spirocyclic ring strain, aromatization of the phenoxy unit, and C4-O bond formation with significant

charge rearrangement leads to a downhill process by 24.4 kcal/mol. In the next step of the reaction, the key C4-C3 bond cleavage *via* **TS3** ensues $\mathbf{6}^+$ with $\Delta G^{\#}$ 10.2 kcal/mol. The driving force for the low energy involved in C-C bond cleavage is the formation of the fully conjugated $\mathbf{6}^+$, thus, shifting charge from I_R to I_L. The π-character of both C2 and C4 as well as the close orientation of these two atoms in $\mathbf{6}^+$ promotes a ring-closing C-C bond formation *via* **TS4** ($\Delta G^{\#}$ = 12.9 kcal/mol), at a C-C distance 1.98 Å, resulting in intermediate $\mathbf{7}^+$ with concomitant charge shift from I_L to I_R. In $\mathbf{7}^+$, the proximity of C2-H bond to the positive charge bearing indole nitrogen suggests easy heterolytic cleavage of the bond and aromatization of the indole moiety. We modelled this process by abstracting the proton from C2-H by a water molecule present in the medium. The reaction occurs with a moderate $\Delta G^{\#}$ 20.9 kcal/mol (**TS5**) indicating the highly acidic character of the C2-H bond. The product formed in this reaction is the neutral species **8** which upon protonation of the oxygen center ($\mathbf{9}^+$) instantaneously cleaves the C4-O bond to yield the phenolic derivative $\mathbf{10}^+$ with the charge localizing more on I_L than other regions. The $\mathbf{10}^+$ having the lowest relative free energy of 32.0 kcal/mol is the most stable among all the intermediates located in the reaction which can be attributed to the fully conjugated electronic structure of the molecule. Addition of a molecule of water on C4 affords the secondary alcohol which further undergoes oxidation in the presence of excess PIDA to yield DIK **2**. Herein, the source of oxygen has been experimentally confirmed by conducting the reaction using HFIP/DCM/H_2O^{18} solvent system which led to the formation of both [O^{16}] as well as [O^{18}] DIK **2a** (Scheme 4a.3.3).



Scheme 4a.3.3. Confirmation of the source of carbonyl oxygen using H_2O^{18}

The most unique feature of the reaction mechanism is the 'charge-switching' process accompanied with the bond forming and breaking processes between the two indole moieties (Scheme 4a.3.4). Several events occur with low energy barrier to surmount and the reaction is highly exothermic. These features and the metal-free nature of the reaction point towards a new class of reaction in chemistry which we name as indole 'charge-switching' reaction.



Scheme 4a.3.4. Reaction mechanism derived from DFT calculations

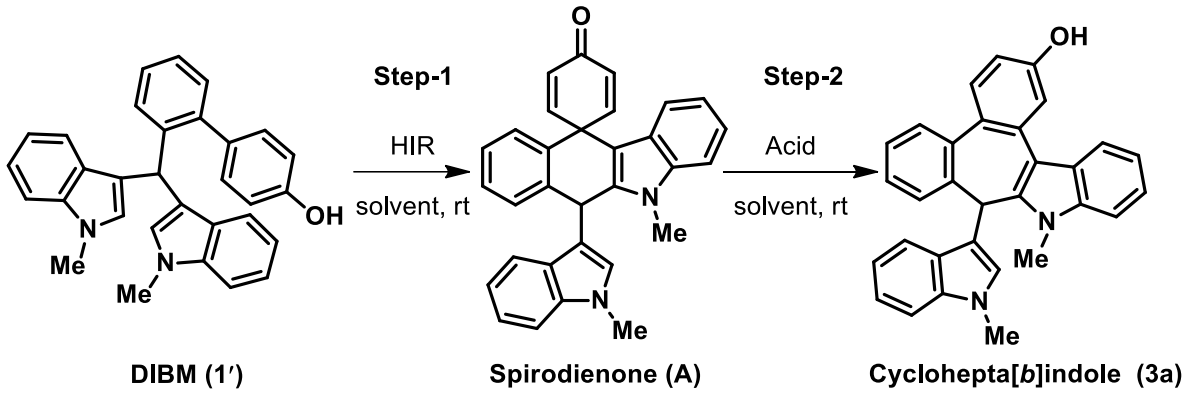
4a.3.2. Synthesis of cyclohepta[*b*]indoles

The unusual "charge-switching" reaction prompted us to explore the other *ortho*-phenol substituted DIPMs under PIDA mediated reaction conditions. Accordingly, we have extended the concept to DIBM **1'** which is a *para*-hydroxy phenyl extension of DIPM **1**. Treatment of DIBM **1'** with PIDA (one equiv) using the optimized solvent

system HFIP/DCM (1:1) afforded the envisaged spiro-compound **A** (Scheme 4a.3.5) produced by one C-C single bond cleavage and one C-C bond formation. Structural confirmation of compound **A** by single crystal X-ray analysis (Figure 4a.3C) further depicts that 'charge-switching' mechanism operates in this reaction as well. To demonstrate the synthetic utility of this transformation, compound **A** was treated under Lewis acid conditions which underwent the known dienone-phenol rearrangement[28] to afford the rearranged product cyclohepta[*b*]indole **3a**, a privileged structural motif in natural products (Figure 4a.3D).[29] The structure of **3a** was unambiguously confirmed by single crystal X-ray analysis of its 4-bromo benzoate derivative **3a'** (Figure 4a.3C). Inspired by this result, we then directed our attention to develop a one-pot method to access **3** under mild conditions (Table 4a.3.4). A detailed optimization by the variation of reagents, solvents, stoichiometry, and acids led us to consider PIDA (1 equiv)/TFE-DCM (1:1) for the step-1 and $BF_3.OEt_2$ (0.25 equiv)/MeCN for the step-2 which gave the desired cyclohepta[*b*]indole **3a** in 95% yield (Table 4a.3.4, entry 22).

Having the optimized condition in hand, we then explored the substrate scope with differently substituted N-alkyl/aryl indoles (Table 4a.3.5). All the substitutions on indoles were well tolerated producing the products **3** in good to excellent yields. Interestingly, moderately electron withdrawing group derived DIBMs also gave the desired products **3h** and **3i** in 71% and 98%, respectively. Based on our previous mechanistic understanding using DFT calculations, we proposed a similar mechanism for the formation of cyclohepta[*b*]indole **3** from DIBM **1'** (Scheme 4a.3.5).

Table 4a.3.4. Optimization of reaction conditions for one-pot synthesis of **3a**[a]



S.No.	HIR (equiv)	Solvent	Acid (equiv) /solvent	Yield of **A**	Yield of **3**
1	PIDA (1)	HFIP/DCM (1:1)	-	90	-
2	PIDA (1)	HFIP	-	73	-
3	PIDA (1)	TFE/DCM (1:1)	-	91	-
4	PIDA (1)	DCM	-	n.r.	-
5	PIDA (1)	TFE/MeCN (1:1)	-	n.r.	-
6	PIDA (0.75)	HFIP/DCM (1:1)	-	41	-
7	PIDA (1.5)	TFE/DCM (1:1)	-	70	-
8	PIFA (1)	TFE/DCM (1:1)	-	71	-
9	PhI(OH)OTs (1)	TFE/DCM (1:1)	-	n.r.	-
10[b]	PIDA (1)	TFE/DCM (1:1)	-	92	-
11[c]	PIDA (1)	TFE/DCM (1:1)	-	36	-
12	PIDA (1)	TFE/DCM (1:1)	$BF_3.OEt_2$ (0.5)/DCM	-	34
13[d]	PIDA (1)	TFE/DCM (1:1)	$BF_3.OEt_2$ (1)/DCM	-	32
14[e]	PIDA (1)	TFE/DCM (1:1)	$BF_3.OEt_2$(1)/DCM	-	39

15	PIDA (1)	TFE/DCM (1:1)	TFA (1)/DCM	-	n.r.
16	PIDA (1)	TFE/DCM (1:1)	$AlCl_3$ (1)/DCM	-	46
17	PIDA (1)	TFE/DCM (1:1)	$FeCl_3$ (1)/DCM	-	54
18	PIDA (1)	TFE/DCM (1:1)	*p*-TsOH (1)/DCM	-	n.r.
19	PIDA (1)	TFE/DCM (1:1)	$BF_3.OEt_2$ (0.5)/MeCN	-	91
20	$PhI(OPiv)_2$ (1)	TFE/DCM (1:1)	$BF_3.OEt_2$ (0.25)/MeCN	-	80
21	PIDA (1)	TFE/DCM (1:1)	$BF_3.OEt_2$ (0.5)/MeCN	-	92
22	**PIDA (1)**	**TFE/DCM (1:1)**	**$BF_3.OEt_2$ (0.25)/MeCN**	**-**	**95**
23	PIDA (1)	TFE/DCM (1:1)	$BF_3.OEt_2$ (0.1)/MeCN	-	86
24	PIDA (1)	TFE/DCM (1:1)	I_2 (0.25)/MeCN	-	95

[a]Unless otherwise mentioned, all HIR reactions were conducted using 0.1 mmol of **1'** (0.07M) at room temperature under open air atmosphere. After one minute, the solvent was evaporated and the crude mixture was dried under vacuum for 5-10 min followed by added solvent (0.05M) and acid in the same pot; [b]PIDA was added in two portions at 10 minute interval; [c]First $BF_3.OEt_2$ (0.3 equiv) was added followed by PIDA; [d]After consumption of **1'**, as monitored by TLC, the crude reaction mixture was passed through a silica pad and proceeded to the second step; [e]After consumption of **1'**, as monitored by TLC, the crude reaction mixture was quenched with sat. aq. $NaHCO_3$ and proceeded to the second step; n.r. = no reaction.

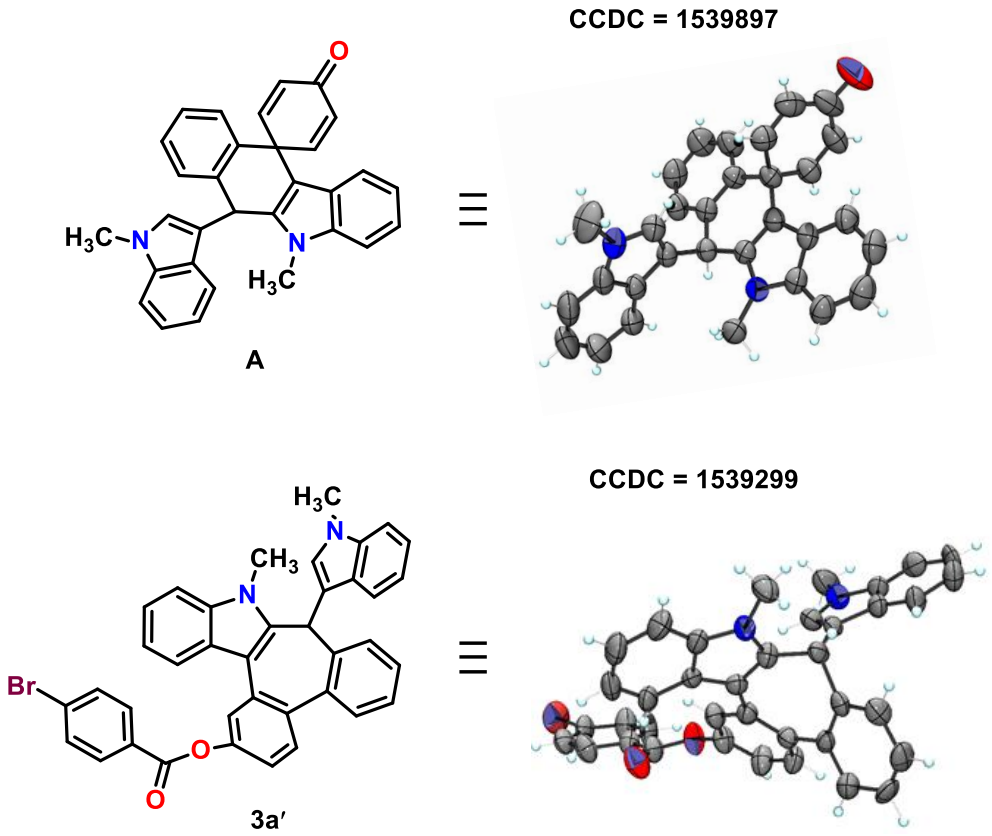


Figure 4a.3C. Ortep drawing of **A** and **3a'**

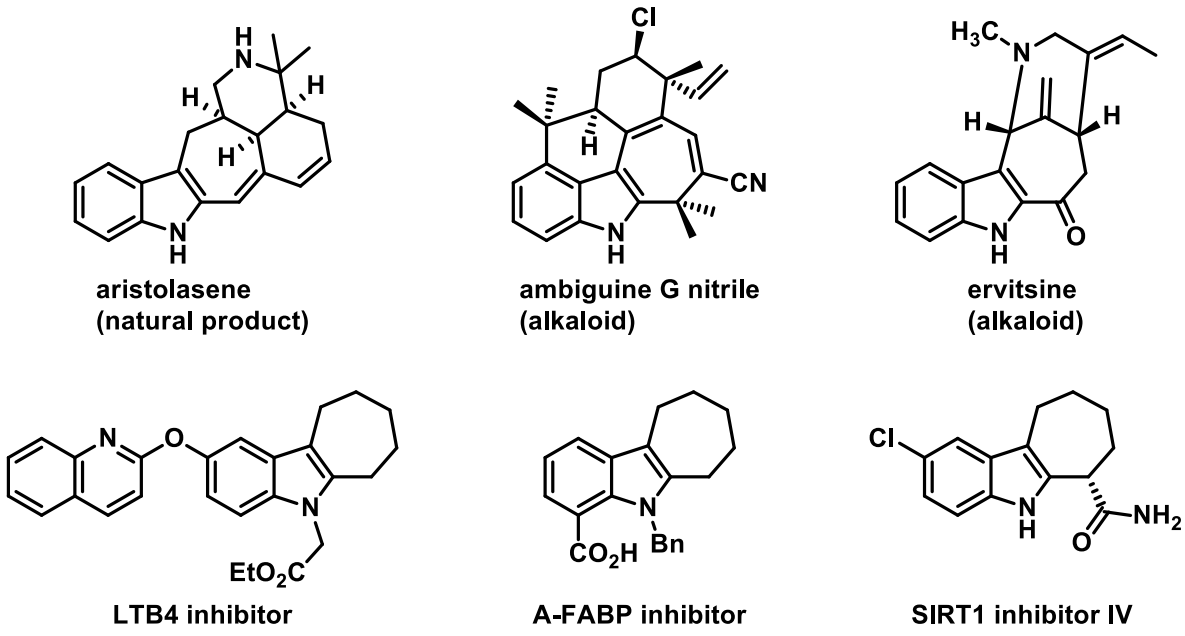
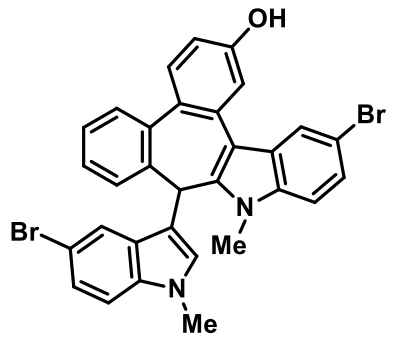
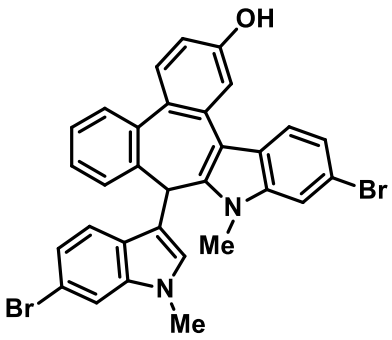


Figure 4a.3D. Important cyclohepta[*b*]indole structural motifs

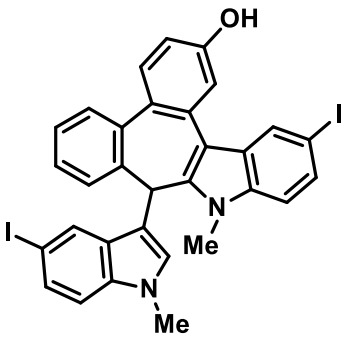
Table 4a.3.5. Scope of cyclohepta[*b*]indole **3**



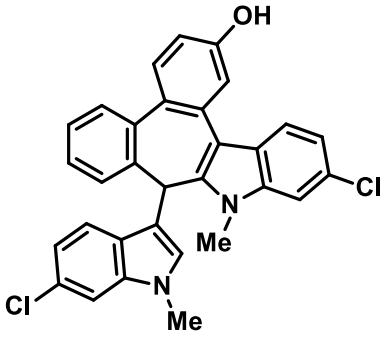
3b (95%)



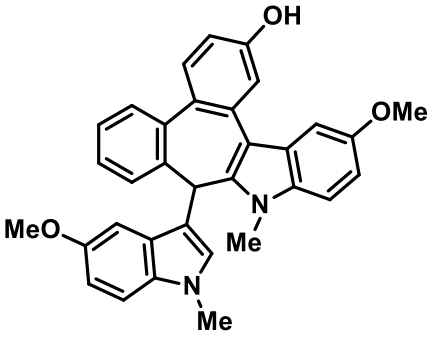
3c (95%)



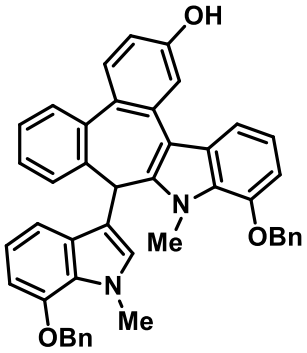
3d (98%)



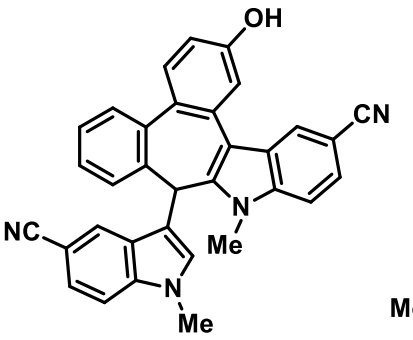
3e (95%)



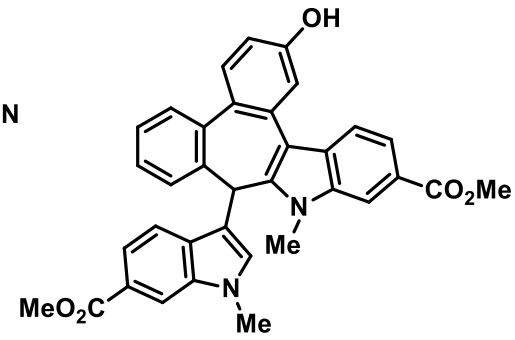
3f (87%)



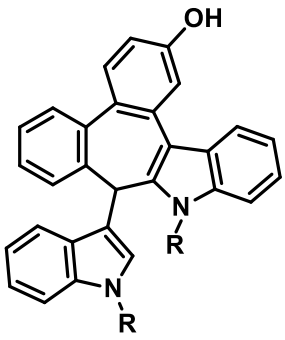
3g (85%)



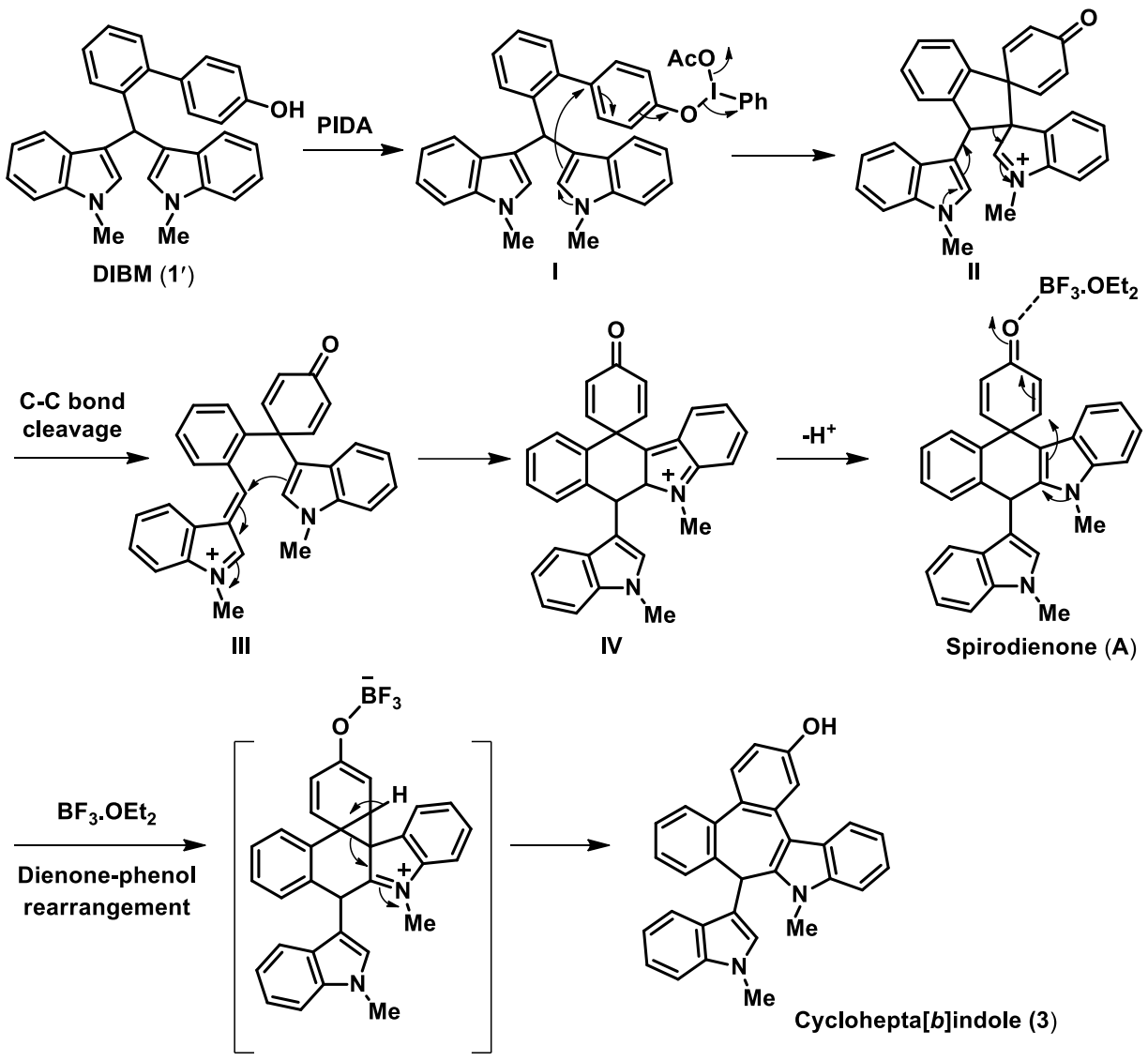
3h (71%)



3i (98%)



3j (R = Allyl, 90%)
3k R = Phenyl, 69%)



Scheme 4a.3.5. Proposed pathway for cyclohepta[*b*]indole synthesis

4a.4. Conclusions

In summary, we have developed a novel oxidation reaction which utilizes an easily accessible DIPM **1** in the presence of an environmentally benign PIDA reagent. Our detailed study revealed that an extension of conjugation to DIK **2** is the driving force behind the rapid oxidative transformation of DIPM **1** as depicted in the energy profile (Figure 4a.3B). The synergy of indoles in shifting the positive charge from one indole unit to the other and vice versa is well evident in the reaction mechanism which is christened as 'charge-switching' mechanism, a new entry in metal-free organic chemistry.

The importance of such a reaction was further demonstrated using DIBM **1'** which indicates that electron rich DIMs or systems with similar electronic features can undergo multiple single bond cleaving and forming events triggered under HIR conditions. The present observation opens up a new avenue in the area of multiple C-C single bond cleavage under metal-free conditions of unactivated and unstrained organic systems.

4a.5. Experimental section

4a.5.1. General information

All chemicals and solvents were purchased as reagent grade and used without further purification. Reactions were monitored by TLC and spots were visualized by short/long wavelength lamps. ^{1}H and ^{13}C NMR were recorded at 500 and 125 MHz, respectively using $CDCl_3$/DMSO-d6 as solvents and chemical shifts were given in ppm. Flash column chromatography was performed using silica gel 100-200 mesh. HRMS analysis was performed by electrospray ionization with ions given in m/z.

4a.5.2. General procedure for the synthesis of DIPM and DIBM

To a solution of salicylaldehyde (1.0 equiv) in ethanol solvent was added N-alkylindole (2.0 equiv) and *p*-TsOH (0.5 equiv) at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with sat. $NaHCO_3$ solution and extracted in DCM solvent (25 mL x 3). The combined DCM extracts were dried over anhydrous Na_2SO_4, concentration and purification by flash column chromatography afforded DIPM in pure form.

DIBMs were also synthesized by following the above procedure by the replacement of *p*-TsOH/EtOH combination with I_2/MeCN and the starting 4'-Hydroxy biphenyl-2-carbaldehyde was synthesized by a reported Suzuki coupling reaction.[31]

4a.5.2. General procedure for PIDA mediated synthesis of DIK 2

To a solution of DIPM **1** (367 mg, 1.0 mmol, 0.07 M) in HFIP/DCM (1:1, 14 mL) was added PIDA (323 mg, 1.0 mmol) at room temperature and after stirring the reaction mixture for 10 minutes in open air one more equivalent of PIDA (323 mg, 1.0 mmol) was added. After complete consumption of the DIPM **1** in less than 5 min, as indicated by TLC, the reaction mixture was diluted with DCM and added silica gel to prepare slurry. After drying on a rotavap, the silica adsorbed reaction mixture was loaded onto a flash column and elution using EtOAc/hexane (2:5) afforded DIK **2** as a grey colored solid.

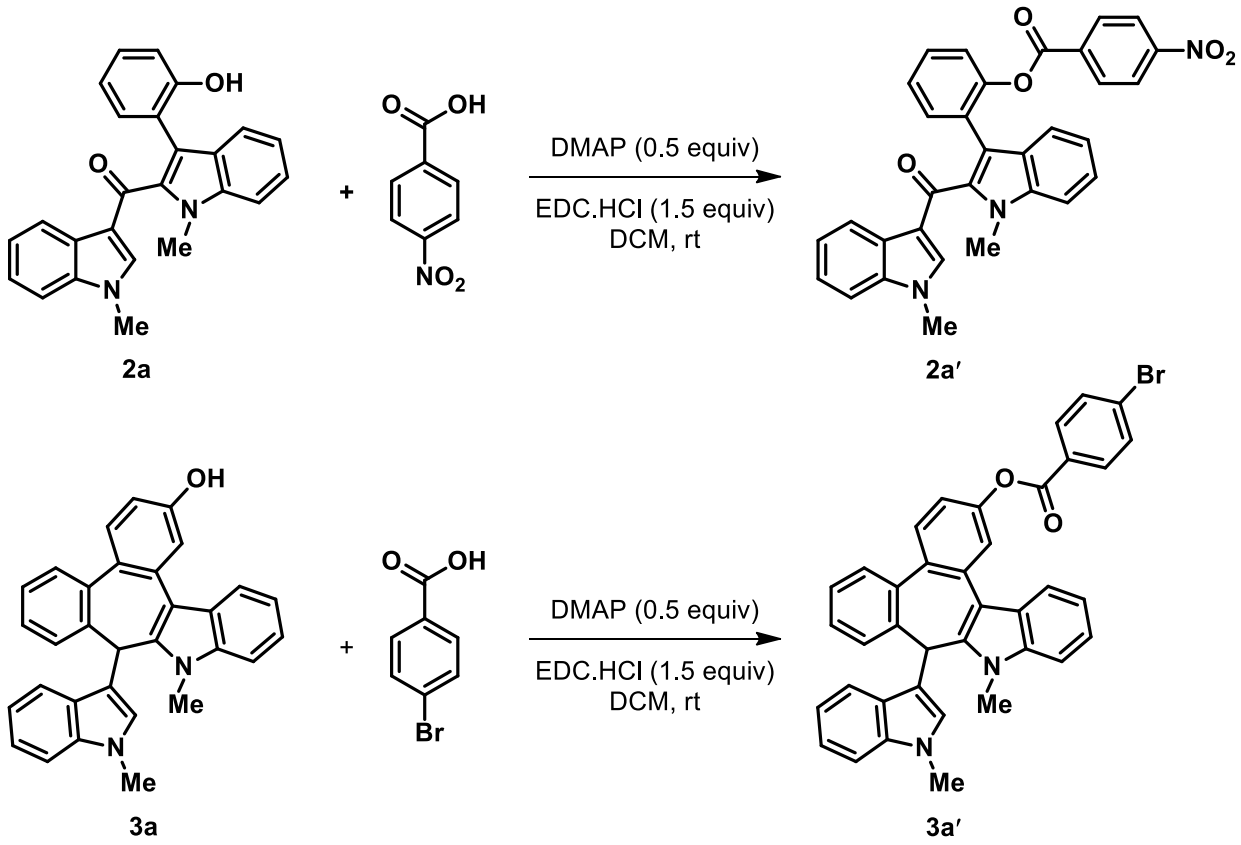
4a.5.3. General procedure for one-pot synthesis of cyclohepta[*b*]indole 3

To a solution of DIBM **1'** (45 mg, 0.1 mmol, 0.07 M) in TFE/DCM solvent (1:1, 1.43 mL) was added PIDA (32.7 mg, 0.1 mmol) at room temperature in open air and within one minute DIBM **1'** consumption took place with the formation of the spiro-intermediate **A**, as observed over TLC. After concentrating the reaction mixture over vacuum for 5-10 minutes, MeCN (2 mL) was added followed by $BF_3.OEt_2$ (0.027mmol in MeCN) at room temperature. After consumption of the spiro-intermediate **A** (15-45 minutes), as indicated by TLC, the reaction mixture was quenched with saturated $NaHCO_3$ and extracted with DCM solvent (3 x 10 mL). The combined DCM extracts were dried over anhydrous Na_2SO_4, concentration and purification by flash column chromatography (EtOAc/hexane 1:3) afforded cyclohepta[*b*]indole **3** as a pale yellow solid (over two steps).

4a.5.4. Synthetic procedure for ester derivatives 2a' and 3a'

To a solution of phenols **2a/3a** (1 equiv) in DCM solvent were added 4-nitrobenzoic acid/4-bromobenzoic acid (1.2 equiv), 4-dimethylaminopyridine (0.5 equiv) and EDCI.HCl (1.5 equiv) in a sequential manner at room temperature. After completion of 2a/3a, as indicated by TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted in DCM (3 x 10 mL). The combined DCM extracts were dried over

anhydrous Na_2SO_4, concentration and purification by flash column chromatography (EtOAc/hexane 1:3) afforded the desired ester products **2a'/3a'**.



4a.5.5. Spectral details of products

(3-(2-hydroxyphenyl)-1-methyl-1*H*-indol-2-yl) (1-methyl-1*H*-indol-3-yl)methanone (2a): Yield: 18 mg, 67%. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.38(s, 1H), 8.24-8.22 (m, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.44-7.42 (m, 2H), 7.33 (td, *J* = 8.0, 1.0 Hz, 1H), 7.26-7.23 (m, 2H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.98 (td, *J* = 8.0, 1.5 Hz, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 3.84 (s, 3H), 3.57 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 182.7, 141.1, 137.1, 135.4, 131.6, 127.9, 126.2, 125.8, 123.3, 123.0, 122.2, 121.6, 121.3, 121.0, 119.8, 118.7, 115.8, 115.0, 114.9, 110.5, 110.2, 32.7, 31.0. HR-ESI-MS calculated for $C_{25}H_{21}N_2O_2$ $[M+H]^+$ 381.1603, found 381.1604.

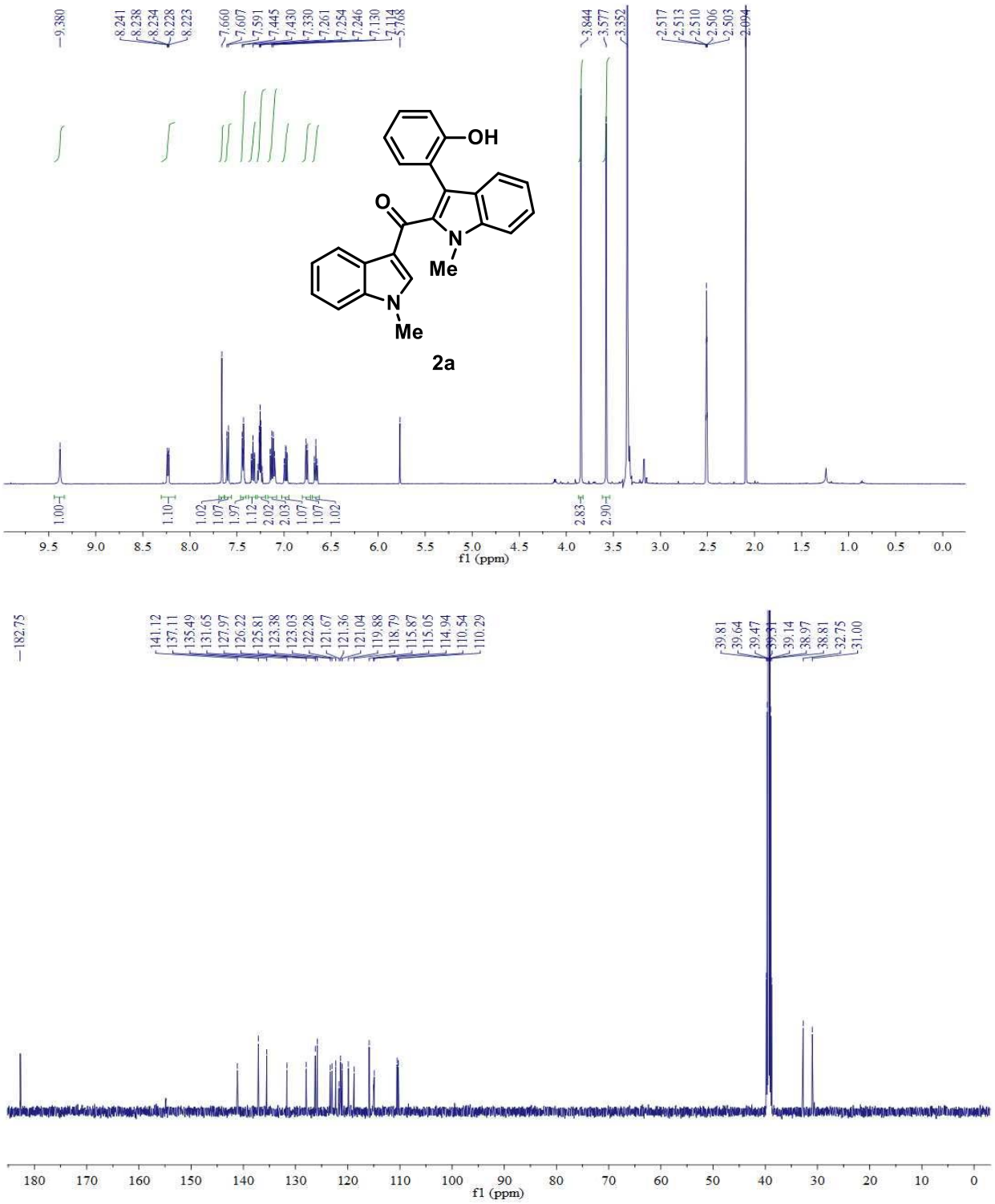
(3-(2-hydroxyphenyl)-5-methoxy-1-methyl-1*H*-indol-2-yl)(5-methoxy-1-methyl-1*H*-indol-3-yl)methanone (2b): Yield: 22 mg, 51%. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.38 (s, 1H), 7.72 (d, *J* = 2.5 Hz, 1H), 7.55 (s, 1H), 7.50 (d, *J* = 9.0 Hz, 1H), 7.33 (d, *J* = 9.0 Hz, 1H), 7.08 (d, *J* = 7.0 Hz, 1H), 7.00-6.96 (m, 2H), 6.87 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.84 (brd, *J* = 2.5 Hz, 1H), 6.79 (d , *J* = 8.0 Hz, 1H), 6.66 (t, *J* = 7.0 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H), 3.53 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 182.5, 155.8, 154.9, 153.9, 136.1, 132.0, 131.6, 127.8, 126.7, 126.5, 118.8, 115.5, 115.2, 114.3, 113.8, 112.5, 111.4, 111.2, 103.1, 101.9, 55.3, 55.2, 32.9, 31.1. HR-ESI-MS calculated for $C_{27}H_{25}N_2O_5$ $[M+H]^+$ 441.1814, found 441.1832.

(1,6-dimethyl-1*H*-indol-3-yl)(3-(2-hydroxyphenyl)-1,6-dimethyl-1*H*-indol-2-yl)methan-one (2c): Yield: 35 mg, 38%. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.32 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.54 (s, 1H), 7.37 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.20 (s, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 7.5 Hz, 2H), 6.76 (d, *J* = 7.0 Hz, 1H), 6.64 (td, *J* = 7.5, 1.0 Hz, 1H), 3.80 (s, 3H), 3.51 (s,3H), 2.49 (s, 3H), 2.41 (s,3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 182.5, 154.9, 140.5, 137.5, 137.4, 135.0, 132.7, 132.3, 131.5, 127.7, 124.2, 123.7, 121.9, 121.7, 121.0, 120.8, 118.6, 115.9, 115.1, 110.3, 109.8, 32.6, 30.9, 21.6, 21.3. HR-ESI-MS calculated for $C_{27}H_{24}N_2O_2Na$ $[M+Na]^+$ 431.1735, found 431.1734.

(3-(2-hydroxyphenyl)-4-methoxy-1-methyl-1*H*-indol-2-yl)(4-methoxy-1-methyl-1*H*-indol-3-yl)methanone (2d): Yield: 23 mg, 45%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 7.02 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.91 (td, *J* = 8.0, 1.5 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.72 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.58-6.53 (m, 3H), 6.08 (br s, 1H), 3.87 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H), 3.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.2, 155.0, 154.2, 153.8, 139.5, 139.2, 137.3, 136.7,132.4, 127.9, 125.2, 123.9, 123.4, 119.4, 118.3, 116.5, 115.7, 115.0,

114.2, 103.2, 103.0, 102.7, 100.7, 55.8, 33.2, 31.9. HR-ESI-MS calculated for $C_{27}H_{25}N_2O_4$ $[M+H]^+$ 441.1814, found 441.1806.

Figure 4a.5A. ^{1}H and ^{13}C-NMR of 2a



(3-(2-hydroxyphenyl)-5-iodo-1-methyl-1*H*-indol-2-yl)(5-iodo-1-methyl-1*H*-indol-3-yl)met-hanone (2e): Yield: 52 mg, 73%. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.47 (s, 1H), 8.57 (d, *J* = 1.5 Hz, 1H), 7.73 (d, *J* = 1.5 Hz, 1H), 7.59 (dd, *J* = 8.5, 1.5Hz, 1H*)*, 7.58 (s, 1H), 7.54(dd, *J* = 8.5, 1.5 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.09 (d, *J* = 7.0 Hz, 1H), 7.00 (td, *J* = 8.5, 2.0 Hz, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.68 (t, *J* = 7.5 Hz, 1H), 3.83 (s, 3H), 3.54 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 182.0, 154.8, 141.5, 136.2, 131.5, 131.0, 129.6, 128.6, 128.3, 128.1, 120.8, 118.9, 115.2, 114.8, 114.2, 113.2, 113.1, 87.1, 83.5, 32.9, 31.1. HR-ESI-MS calculated for $C_{25}H_{19}I_2N_2O_2$ $[M+H]^+$ 632.9536, found 632.9531.

(6-bromo-1-methyl-1*H*-indol-3-yl)(6-bromo-3-(2-hydroxyphenyl)-1-methyl-1*H*-indol-2-yl)methanone (2f): Yield: 35 mg, 67%. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.43 (s,1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 1.5 Hz, 1H), 7.72 (d, *J* = 1.0 Hz, 1H), 7.61 (s, 1H), 7.39-7.37 (m, 2H), 7.27 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.99 (td, *J* = 8.0, 1.5 Hz, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 6.66 (td, *J* = 8.0, 1.0 Hz, 1H), 3.84 (s, 3H), 3.55 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 182.1, 154.8, 141.6, 138.0, 137.9, 135.7, 131.4, 128.2, 125.1, 124.7, 122.9, 122.8, 120.9, 118.7, 116.3, 115.6, 115.5, 115.1, 113.6, 113.2, 32.9, 31.2. HR-ESI-MS calculated for $C_{25}H_{19}Br_2N_2O_2$ $[M+H]^+$ 536.9813, found 536.9817.

(6-chloro-1-methyl-1*H*-indol-3-yl)(6-chloro-3-(2-hydroxyphenyl)-1-methyl-1*H*-indol-2-yl)methanone (2g): Yield: 35 mg, 63%. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.43 (s, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 2.0 Hz, 1H), 7.63 (s, 1H), 7.59 (d, *J* = 1.5 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.27 (dd, *J* = 8.5, 2.0 Hz, 1H) 7.15 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 6.99 (td, *J* = 8.0, 1.5 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.65 (td, *J* = 7.5, 1.0 Hz, 1H), 3.84 (s, 3H), 3.55 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 182.1, 154.8, 141.7, 137.6, 135.8, 131.4, 128.2, 127.6, 124.8, 124.4, 122.5, 120.9,

120.3, 118.7, 115.1, 110.7, 110.2, 32.9, 31.2. HR-ESI-MS calculated for $C_{25}H_{19}Cl_2N_2O_2$ $[M+H]^+$ 449.0823, found 449.0820.

(5-bromo-1-methyl-1*H*-indol-3-yl)(5-bromo-3-(2-hydroxyphenyl)-1-methyl-1*H*-indol-2-yl)methanone (2h): Yield: 34 mg, 60%. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.48 (s, 1H), 8.35 (d, *J* = 1.5 Hz, 1H), 7.64 (s, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.55 (d, *J* = 1.5 Hz, 1H), 7.45 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.42 (s, 1H), 7.40 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.00 (dt, *J* = 8.0, 1.5 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.69 (t, *J* = 7.5 Hz, 1H), 3.85 (s, 3H), 3.56 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 182.1, 154.8, 141.9, 136.1, 135.9, 135.8, 131.4, 128.3, 127.7, 127.4, 125.9, 125.5, 123.4, 123.0, 120.7, 118.9, 115.3, 115.2, 115.0, 114.6, 112.8, 112.7, 112.4, 33.0, 31.2. HR-ESI-MS calculated for $C_{25}H_{19}Br_2N_2O_2$ $[M+H]^+$ 536.9813, found 536.9812.

(**1-allyl-1*H*-indol-3-yl)(1-allyl-3-(2-hydroxyphenyl)-1*H*-indol-2-yl)methanone (2i):** Yield: 34 mg, 67%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.38 (td, *J* = 8.5, 1 Hz, 2H), 7.32 (s, 1H), 7.28-7.26 (m, 1H), 7.25-7.19 (m, 4H), 7.07 (td, *J* = 8.0, 1.5 Hz, 1H), 6.88 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.76 (td, *J* = 8.5, 1.0 Hz, 1H), 6.20 (br s, 1H), 6.02-5.92 (m, 1H), 5.76-5.68 (m, 1H), 5.17 (dd, *J* = 10.5, 1.0 Hz, 1H), 5.11 (dd, *J* = 10.5, 1.0 Hz, 1H), 5.08 (dd, *J* = 17.0, 1.0 Hz, 1H), 5.01-4.99 (m, 2H), 4.92 (dd, *J* = 17.0, 1.0 Hz, 1H), 4.47 (dt, *J* = 5.5, 1.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.7, 153.7, 138,9, 137.6, 136.8, 135.8, 133.6, 131.8, 131.2, 128.7, 126.6, 124.6, 123.6, 123.0, 122.5, 121.3, 121.1, 120.5, 118.9, 117.1, 116.9, 116.2, 113.9, 110.9, 110.1, 49.2, 47.3. HR-ESI-MS calculated for $C_{29}H_{24}N_2O_2Na$ $[M+Na]^+$ 455.1735, found 455.1718.

(1-butyl-1*H*-indol-3-yl)(1-butyl-3-(2-hydroxyphenyl)-1*H*-indol-2-yl)methanone (2j): Yield: 27 mg, 53%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37-8.34 (m, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.5 (d, *J* = 8.5 Hz, 1H), 7.39 (td, *J* = 8.5, 1.0 Hz, 1H), 7.31 (br s, 1H), 7.30-7.28 (m,

1H), 7.27-7.25 (m, 2H), 7.24-7.19 (m, 3H), 7.07 (td, *J* = 8.0, 1.5 Hz, 1H), 6.89 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.77 (td, *J* = 7.5, 1.0 Hz, 1H), 6.25 (br s, 1H), 4.37 (t, *J* = 7.5 Hz, 2H), 3.90 (t, *J* = 7.5 Hz, 2H), 1.81-1.75 (m, 2H), 1.65-1.59 (m, 2H), 1.31-1.25 (m, 2H), 1.19-1.12 (m, 2H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.84 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.0, 153.7, 138.6, 137.4, 136.8, 136.0, 131.8, 128.6, 126.6, 126.3, 124.2, 123.5, 122.9, 122.6, 121.3, 121.0, 120.8, 120.5, 116.8, 116.2, 112.9, 110.9, 109.9, 46.8, 44.6, 32.5, 31.5, 20.2, 19.9, 13.7, 13.5. HR-ESI-MS calculated for $C_{31}H_{33}N_2O_2$ $[M+H]^+$ 465.2542, found 465.2546.

(1-benzyl-1*H*-indol-3-yl)(1-benzyl-3-(2-hydroxyphenyl)-1*H*-indol-2-yl)methanone (2k): Yield: 66 mg, 60%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.36 (m, 3H), 7.29 (m, 5H), 7.21 (m, 4H), 7.14 (m, 4H), 6.87 (m, 3H), 6.81 (td, *J* = 7.5, 1.0 Hz, 1H), 6.08 (s, 1H), 5.63 (s, 2H), 5.05 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.9, 153.7, 139.4, 137.8, 137.6, 136.8, 136.1, 135.2, 131.9, 129.1, 128.9, 128.7, 128.5, 128.4, 128.0, 127.3, 127.2, 126.8, 126.7, 126.5, 124.6, 124.2, 123.7, 123.1, 123.0, 122.6, 122.1, 121.2, 121.1, 120.6, 117.2, 116.2, 111.1, 110.4, 50.8, 48.3. HR-ESI-MS calculated for $C_{37}H_{29}N_2O_2$ $[M+H]^+$ 533.2229, found 533.2235.

(3-(2-hydroxyphenyl)-1-(4-methoxybenzyl)-1*H*-indol-2-yl)(1-(4-methoxybenzyl)-1*H*-indol-3-yl)methanone (2l): Yield: 107 mg, 19%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.36-7.32 (m, 2H), 7.27 (t, *J* = 8.5 Hz, 2H), 7.22-7.19 (m, 2H), 7.15-7.12 (m, 3H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.88 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.82-6.79 (m, 5H), 6.70 (d, *J* = 8.5 Hz, 2H), 6.22 (s, 1H), 5.53 (s, 2H), 4.98 (s, 2H), 3.79 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.0, 159.3, 158.8, 153.7, 139.3, 137.7, 136.8, 136.1, 131.9, 129.7, 128.7, 128.3, 127.1, 126.8, 126.6, 124.5, 123.6, 123.0, 122.5, 121.3, 121.1, 120.6, 117.1, 116.3, 114.2, 114.0,

113.9, 111.1, 110.4, 55.3, 55.1, 50.4, 47.7. HR-ESI-MS calculated for $C_{39}H_{32}N_2O_4Na$ $[M+Na]^+$ 615.2259, found 615.2271.

(1-allyl-5-bromo-1*H*-indol-3-yl)(1-allyl-5-bromo-3-(2-hydroxyphenyl)-1*H*-indol-2-yl)me-thanone (2m): Yield: 65 mg, 63%. ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 1.5 Hz, 1H), 7.70 (d, *J* = 1.5 Hz, 1H), 7.44 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.35-4.33 (m, 2H), 7.25 (d, *J* = 4.0 Hz, 2H), 7.20 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.08-7.05 (m, 2H), 6.84-6.78 (m, 2H), 6.02-5.94 (m, 1H), 5.73 (br s, 1H), 5.71-5.64 (m, 1H), 5.18 (dd, *J* = 10.0, 1.0 Hz, 1H), 5.13 (dd, *J* = 10.0, 1.0 Hz, 1H), 5.06 (dd, *J* = 17.0, 1.0 Hz, 1H), 4.99 (dt, *J* = 5.5, 1.5 Hz, 2H), 4.88 (dd, *J* = 17.0, 1.0 Hz, 1H), 4.44 (dt, *J* = 5.5, 1.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.8, 153.4, 139.3, 133.3, 131.7, 130.8, 129.0, 128.1, 127.9, 127.6, 126.7, 125.2, 123.5, 120.8, 120.5, 119.1, 117.2, 116.8, 116.1, 114.3, 113.5, 112.4, 111.5, 49.2, 47.3. HR-ESI-MS calculated for $C_{23}H_{13}Br_2N_2O_2$ $[M+H]^+$ 506.9343, found 506.9346.

(1-allyl-3-(2-hydroxyphenyl)-5-methoxy-1*H*-indol-2-yl)(1-allyl-5-methoxy-1*H*-indol-3-yl)-methanone (2n): Yield: 61 mg, 67%. ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 2.5 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.25 (d, *J* = 2.5 Hz, 1H), 7.22 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.08 (d, *J* = 9.0 Hz, 2H), 7.04 (dd, *J* = 9.0, 2.5 Hz,1H), 6.94 (d, *J* = 2.5 Hz, 1H), 6.92 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.88 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.78 (td, *J* = 7.5, 1.0 Hz, 1H), 6.33 (br s, 1H), 6.02-5.94 (m, 1H), 5.74-5.67 (m, 1H), 5.17 (dd, *J* = 10.5, 1.0 Hz, 1H), 5.10 (dd, *J* = 10.5, 1.5 Hz, 1H), 5.04 (dd, *J* = 17.0, 1.0 Hz, 1H), 4.96 (app d, *J* = 15.5 Hz, 2H), 4.90 (dd, *J* = 17.0, 1.0 Hz, 1H), 4.43 (app dt, *J* = 5.5, 1.5 Hz, 2H), 3.86 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.3, 178.3, 151.4, 150.0, 148.5, 133.6, 131.1, 128.5, 127.7, 126.5, 126.3, 126.0, 123.9, 123.4, 122.2, 116.2, 115.3, 113.6, 111.7, 111.4, 111.0, 110.4, 108.7, 106.6, 105.7, 98.5, 96.2, 50.6, 50.5, 44.2, 42.0. HR-ESI-MS calculated for $C_{31}H_{28}N_2O_4Na$ $[M+Na]^+$ 515.1946, found 515.1933.

(1-benzyl-6-chloro-1*H*-indol-3-yl)(1-benzyl-6-chloro-3-(5-chloro-2-hydroxyphenyl)-1*H*-indol-2-yl)methanone (2o): Yield: 44 mg, 31%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 1.5 Hz, 1H), 7.23-7.22 (m, 4H), 7.18-7.17 (m, 2H), 7.09-7.05 (m, 6H), 6.97-6.94 (m, 3H), 6.79-6.77 (m, 2H), 6.64 (d, *J* = 8.5 Hz, 1H), 5.41 (s, 2H), 4.91 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.3, 152.5, 139.4, 138.2, 137.3, 136.9, 136.2, 134.5, 130.9, 130.8, 129.9, 129.2, 129.1, 128.8, 128.7, 128.4, 127.6, 127.2, 126.8, 126.6, 125.1, 124.9, 123.8, 123.3, 122.4, 122.3, 122.0, 117.9, 117.0, 113.6, 110.9, 110.4, 50.9, 48.4. HR-ESI-MS calculated for $C_{37}H_{26}N_2O_2Cl_3$ $[M+H]^+$ 635.1059, found 635.1073.

(1-benzyl-3-(5-bromo-2-hydroxyphenyl)-5-iodo-1*H*-indol-2-yl)(1-benzyl-5-iodo-1*H*-indol-3-yl)methanone (2p): Yield: 65 mg, 43%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.5 Hz, 1H), 7.78 (d, *J* = 1.5 Hz, 1H), 7.51 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.25-7.22 (m, 3H), 7.18 (s, 1H), 7.13-7.10 (m, 3H), 7.09-7.06 (m, 2H), 6.97 (dd, *J* = 7.5, 3.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.77 (dd, *J* = 7.5, 3.5 Hz, 2H), 6.60 (d, *J* = 8.5 Hz, 1H), 5.88 (s, 1H), 5.46 (s, 2H), 4.94 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.8, 152.8, 139.1, 136.9, 136.3, 136.0, 134.5, 133.7, 133.3, 132.6, 131.9, 131.3, 129.5, 129.2, 129.1, 129.0, 128.7, 128.5, 128.4, 127.6, 127.1, 126.8, 126.6, 122.6, 118.2, 116.2, 113.1, 112.5, 112.2, 111.8, 87.7, 84.9, 51.0, 48.5. HR-ESI-MS calculated for $C_{37}H_{26}N_2O_2I_2Br$ $[M+H]^+$ 862.9267, found 862.9262.

(3-(2-hydroxy-5-methoxyphenyl)-1-methyl-1*H*-indol-2-yl)(1-methyl-1*H*-indol-3-yl)met-han-one (2q): Yield: 12 mg, 19%. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.90 (s, 1H), 8.24-8.22 (m, 1H), 7.69 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.45-7.43 (m, 1H), 7.33 (td, *J* = 8.0, 1.0 Hz, 1H), 7.28-7.25 (m, 2H), 7.13 (td, *J* = 8.0, 0.5 Hz), 6.67 (br d, *J* = 9.0 Hz, 2H), 6.58(dd, *J* = 8.5, 3.0 Hz, 1H), 3.84 (s, 3H), 3.59 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 182.6, 151.6, 148.9, 141.1, 137.1, 135.5, 126.1, 125.8,

123.3, 122.9, 122.2, 121.2, 121.1, 119.8, 116.7, 115.9, 115.7, 114.9, 113.4, 110.5, 110.2, 55.1, 32.7, 31.0. HR-ESI-MS calculated for $C_{26}H_{22}N_2O_3Na$ $[M+Na]^+$ 433.1528, found 433.1521.

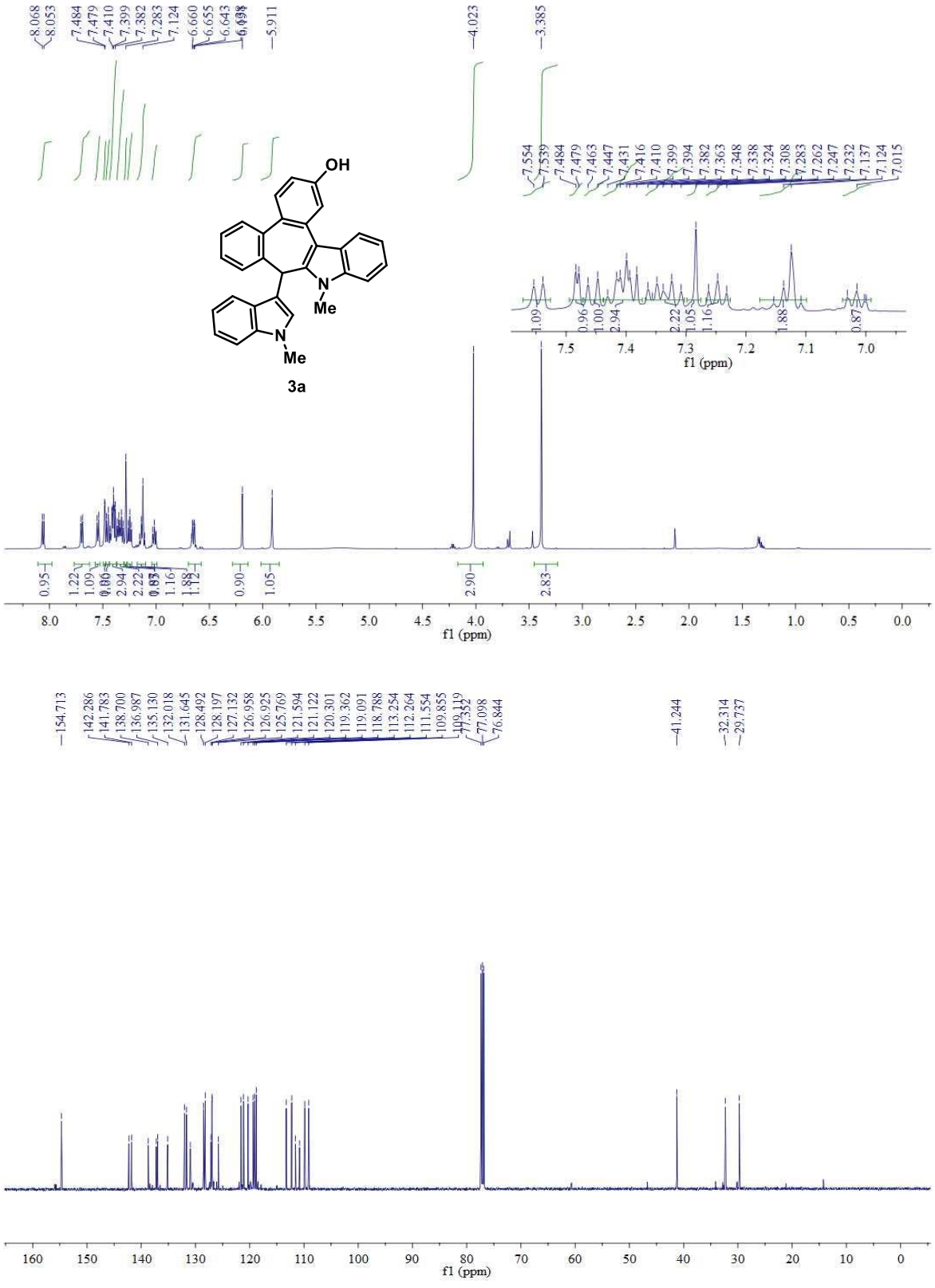
(3-(5-chloro-2-hydroxyphenyl)-1-methyl-1*H*-indol-2-yl)(1-methyl-1*H*-indol-3-yl)methanone (2r): Yield: 46 mg, 45%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 6.5, 2.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.49-7.44 (m, 2H), 7.41 (s, 1H), 7.35-7.29 (m, 4H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.11 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 3.86 (s, 3H), 3.70 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 184.1, 153.2, 139.5, 138.2, 137.5, 136.3, 131.2, 130.2, 128.6, 126.6, 126.2, 124.9, 124.7, 124.0, 123.5, 123.3, 122.2, 121.2, 120.9, 118.8, 116.8, 112.9, 110.2, 109.9, 33.5, 32.2. HR-ESI-MS calculated for $C_{25}H_{20}ClN_2O_2$ $[M+H]^+$ 415.1213, found 415.1218.

(3-(5-bromo-2-hydroxyphenyl)-1-methyl-1*H*-indol-2-yl)(1-methyl-1*H*-indol-3-yl)methanone (2s): Yield: 50 mg, 49%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 7.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.49-7.44 (m, 3H), 7.40 (d, *J* = 6.5 Hz, 2H), 7.34-7.32 (m, 2H), 7.31-7.24 (m, 3H), 6.87 (d, *J* = 8.0 Hz, 1H), 3.86 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.0, 153.7, 139.5, 138.2, 137.5, 136.3, 134.1, 131.5, 126.6, 126.2, 124.8, 124.0, 123.3, 122.2, 121.3, 120.9, 119.3, 116.8, 112.7, 112.1, 110.2, 109.9, 33.5, 32.2. HR-ESI-MS calculated for $C_{25}H_{20}BrN_2O_2$ $[M+H]^+$ 459.0708, found 459.0710.

10-methyl-9-(1-methyl-1*H*-indol-3-yl)-9,10-dihydrodibenzo[3,4:5,6]cyclohepta[1,2-*b*]ind-ol-2-ol (3a): Yield: 43 mg, 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.48 (d, *J* = 2.5 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.43-7.38 (m, 3H), 7.36-7.30 (m, 2H), 7.28 (s, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.15-7.10 (m, 2H), 7.01 (t, *J* = 8.0 Hz, 1H), 6.65 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.19 (s, 1H), 5.91 (s, 1H), 4.02 (s, 3H), 3.38 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 142.2, 141.7, 138.7, 137.2, 136.9, 135.1, 132.0, 131.6, 130.9, 128.4, 128.1, 127.1, 126.9, 125.7,

121.5, 121.1, 120.3, 119.3, 119.0, 118.7, 113.2, 112.2, 111.5, 110.8, 109.8, 109.1, 41.2, 32.3, 29.7. HR-ESI-MS calculated for $C_{31}H_{25}N_2O$ $[M+H]^+$ 441.1966, found 441.1962.

Figure 4a.5B. ^{1}H and ^{13}C-NMR of 3a



13-bromo-9-(5-bromo-1-methyl-1*H*-indol-3-yl)-10-methyl-9,10-dihydrodibenzo-[3,4:5,6]cy-clohepta[1,2-*b*]indol-2-ol (3b): Yield: 47 mg, 95%. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.60 (s, 1H), 7.97 (s, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.35-7.31 (m, 4H), 7.24 (d, *J* = 1.5 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 7.12 (d, *J* = 7.0 Hz, 1H), 6.66 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.22 (s, 1H), 6.05 (s, 1H), 4.03 (s, 3H), 3.38 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 157.0, 143.1, 141.9, 138.6, 136.0, 135.6, 133.7, 131.7, 129.6, 129.2, 129.0, 128.7, 127.5, 127.2, 127.1, 124.2, 123.6, 121.5, 120.9, 113.5, 113.2, 113.1, 112.1, 111.6, 111.2, 110.1, 79.6, 32.7, 30.3. HR-ESI-MS calculated for $C_{31}H_{23}Br_2N_2O$ $[M+H]^+$ 597.0177, found 597.0177.

12-bromo-9-(6-bromo-1-methyl-1*H*-indol-3-yl)-10-methyl-9,10-dihydrodibenzo[3,4:5,6]-cy-clohepta[1,2-*b*]indol-2-ol (3c): Yield: 47 mg, 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 1.5 Hz, 1H), 7.35 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.22 (td, *J* = 7.5, 1.5 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 7.10 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.06 (s, 1H), 6.87-6.82 (m, 2H), 6.51 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.92 (s, 1H), 5.59 (s, 1H), 3.79 (s, 3H), 3.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 141.7, 138.4, 137.9, 137.7, 134.2, 132.0, 131.5, 130.8, 128.6, 128.3, 127.2, 127.1, 125.7, 124.4, 123.4, 122.0, 120.5, 120.2, 114.9, 114.8, 113.0, 112.8, 112.6, 112.1, 111.7, 110.9, 40.9, 32.4, 29.9. HR-ESI-MS calculated for $C_{31}H_{23}Br_2N_2O$ $[M+H]^+$ 597.0177, found 597.0179.

13-iodo-9-(5-iodo-1-methyl-1*H*-indol-3-yl)-10-methyl-9,10-dihydrodibenzo[3,4:5,6]cy-clohepta[1,2-*b*]indol-2-ol (3d): Yield:45 mg, 98%. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.60 (s, 1H), 8.31 (s, 1H), 8.14 (s, 1H), 7.90 (dd, *J* = 8.0,1.0 Hz, 1H), 7.56 (d, *J* = 1.5 Hz, 1H), 7.48-7.46 (m, 2H), 7.44 (td, *J* = 7.5, 1.5 Hz, 1H), 7.39 (td, *J* = 7.5, 1.5 Hz, 1H), 7.33 (td, *J* = 7.0, 1.5 Hz, 1H), 7.25 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.21 (d, *J*

= 2.5 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.65 (d, *J* = 8.5, 2.5 Hz, 1H), 6.16 (s, 1H), 6.04 (s, 1H), 4.01 (s, 3H), 3.37 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 162.7, 157.0, 142.6, 141.9, 138.6, 136.3, 136.0, 133.8, 131.7, 129.7, 129.6, 129.2, 129.1, 129.0, 127.9, 127.8, 127.4, 127.2, 127.0, 113.6, 113.5, 113.1, 112.6, 110.8, 109.8, 84.4, 82.8, 32.6, 30.2. HR-ESI-MS calculated for $C_{31}H_{23}I_2N_2O$ $[M+H]^+$ 692.9899, found 692.9912.

12-chloro-9-(6-chloro-1-methyl-1*H*-indol-3-yl)-10-methyl-9,10-dihydrodibenzo[3,4:5,6]-cy-clohepta[1,2-*b*]indol-2-ol (3e): Yield: 48 mg, 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.5 Hz, 1H), 7.51 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.42 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.28 (td, *J* = 7.5, 1.5 Hz, 1H), 7.24 (td, *J* = 7.5, 1.5 Hz, 2H), 7.19 (d, *J* = 1.5 Hz, 1H), 7.17 (s, 1H), 7.05 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.97 (s, 1H), 6.78 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.57 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.99 (d, *J* = 1.5 Hz, 1H), 5.66 (s, 1H), 3.86 (s, 3H), 3.26 (s, 3H).). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 141.8, 138.4, 137.6, 137.3, 134.3, 131.9, 131.5, 130.9, 128.6, 128.3, 127.4, 127.2, 127.1, 125.4, 124.1, 120.8, 120.1, 119.8, 119.4, 113.1, 112.5, 111.7, 110.9, 109.8, 109.1, 40.9, 32.4, 29.8. HR-ESI-MS calculated for $C_{31}H_{23}Cl_2N_2O$ $[M+H]^+$ 509.1187, found 509.1197.

13-methoxy-9-(5-methoxy-1-methyl-1*H*-indol-3-yl)-10-methyl-9,10-dihydrodibenzo-[3,4:5,6]cyclohepta[1,2-*b*]indol-2-ol (3f): Yield: 43 mg, 87%. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.49 (s, 1H), 7.86 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.49 (d, *J* = 9.0 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.36 (td, *J* = 7.5, 1.5 Hz, 1H), 7.33-7.31 (m, 2H), 7.25 (d, *J* = 2.5 Hz, 1H), 7.08 (d, *J* = 9.0 Hz, 1H), 6.88 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.66 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.62-6.60 (m, 2H), 6.12 (s, 1H), 5.92 (s, 1H), 4.01 (s, 3H), 3.80 (s, 3H), 3.58 (s, 3H), 3.35 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 156.8, 154.7, 153.2, 142.3, 134.6, 132.3, 132.3, 131.6, 129.3, 129.1, 128.6, 127.4, 127.1, 126.9, 125.8, 112.9, 111.6, 111.3, 111.1, 110.6, 110.5, 110.1, 101.6, 101.3, 55.9, 55.5, 32.6, 30.1. HR-ESI-MS calculated for $C_{33}H_{29}N_2O_3$ $[M+H]^+$ 501.2178, found 501.2182.

11-(benzyloxy)-9-(7-(benzyloxy)-1-methyl-1*H*-indol-3-yl)-10-methyl-9,10-dihydrodiben-zo[3,4:5,6]cyclohepta[1,2-*b*]indol-2-ol (3g): Yield: 45 mg, 85%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55-7.52 (m, 2H), 7.45-7.41 (m, 3H), 7.36 (t, *J* = 8.0 Hz, 3H), 7.32-7.22 (m, 10H), 7.19 (s, 1H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.75 (t, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 7.5 Hz, 1H), 6.58 (d, *J* = 8.5, 2.5 Hz, 1H), 6.49 (d, *J* = 7.5 Hz, 1H), 5.94 (s, 1H), 5.72 (s, 1H), 5.19 (d, *J* = 11.5 Hz, 1H), 5.15 (d, *J* = 11.5 Hz, 1H), 4.99 (s, 2H), 4.24 (s, 3H), 3.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 146.8, 146.6, 142.4, 142.3, 138.6, 137.2, 135.1, 131.8, 131.5, 129.5, 128.6, 128.5, 128.4, 128.0, 127.8, 127.6, 127.5, 127.4, 126.8, 126.7, 126.6, 126.5, 120.3, 119.2, 113.2, 112.4, 112.2, 112.1, 111.3, 111.0, 104.1, 103.1, 70.7, 70.2, 40.7, 36.2, 32.8. HR-ESI-MS calculated for $C_{45}H_{37}N_2O_3$ $[M+H]^+$ 653.2804, found 653.2777.

9-(5-cyano-1-methyl-1*H*-indol-3-yl)-2-hydroxy-10-methyl-9,10-dihydrodibenzo[3,4:5,6] cy-clohepta[1,2-*b*]indole-13-carbonitrile (3h): Yield: 36 mg, 71%. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.57 (s, 1H), 8.21 (s, 1H), 7.93 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.77 (d, *J* = 7.0 Hz, 1H), 7.57 (d, *J* = 1.0 Hz, 1H), 7.54 (d, *J* = 8.5, 1.5 Hz, 1H), 7.41-7.39 (m, 1H), 7.37-7.35 (m, 2H), 7.32-7.29 (m, 2H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.23 (d, *J* = 3.0 Hz, 1H), 6.62 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.33 (s, 1H), 6.12 (s, 1H), 4.05 (s, 3H), 3.39 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 157.2, 143.8, 141.6, 138.8, 138.4, 133.1, 131.8, 129.3, 128.9, 127.7, 127.4, 126.6, 125.1, 124.7, 124.2, 124.0, 121.1, 121.0, 113.9, 113.5, 112.6, 112.5, 111.6, 111.3, 102.6, 100.9, 55.3, 32.8, 30.6. HR-ESI-MS calculated for $C_{33}H_{23}N_4O$ $[M+H]^+$ 491.1871, found 491.1862.

Methyl 2-hydroxy-9-(6-(methoxycarbonyl)-1-methyl-1*H*-indol-3-yl)-10-methyl-9,10-di-hydrodibenzo[3,4:5,6]cyclohepta[1,2-*b*]indole-12-carboxylate (3i): Yield: 49 mg, 98%. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.23 (d, *J* = 0.5 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 0.5 Hz, 1H), 7.77 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.46 (dd, *J* = 8.5, 1.5 Hz,

1H), 7.37 (td, *J* = 7.0, 1.0 Hz, 1H), 7.34 (t, *J* = 8.5 Hz, 2H), 7.23-7.21 (m, 2H), 6.66 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.44 (d, *J* = 1.0 Hz, 1H), 6.13 (s, 1H), 4.15 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H), 3.48 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 168.3, 155.4, 144.5, 141.3, 138.6, 136.5, 136.2, 134.0, 132.0, 131.5, 131.3, 130.4, 129.3, 128.3, 127.3, 127.1, 122.6, 121.5, 119.9, 118.9, 118.4, 113.3, 113.0, 112.2, 111.8, 111.6, 111.5, 52.1, 51.9, 41.1, 32.4, 29.9. HR-ESI-MS calculated for $C_{35}H_{29}N_2O_5$ $[M+H]^+$ 557.2076, found 557.2076.

10-allyl-9-(1-allyl-1*H*-indol-3-yl)-9,10-dihydrodibenzo[3,4:5,6]cyclohepta[1,2-*b*]indol-2-ol (3j): Yield: 45 mg, 90%. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.48 (s, 1H), 7.85 (d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 6.5 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 7.5, 1.0 Hz, 1H), 7.35 (td, *J* = 7.5, 1.0 Hz, 1H), 7.30-7.28 (m, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.20 (td, *J* = 8.0, 1.0 Hz, 1H), 7.17-7.14 (m, 2H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.84 (t, *J* = 8.0 Hz, 1H), 6.60 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.20 (s, 1H), 6.01-5.96 (m, 1H), 5.95 (s, 1H), 5.60-5.53 (m,1H), 5.26 (dd, *J* = 17.0, 5.0 Hz, 1H), 5.13 (dd, *J* = 17.0, 5.5 Hz, 1H), 5.07 (dd, *J* = 10.5, 1.0 Hz, 1H), 5.04 (dd, *J* = 17.5, 1.5 Hz, 1H), 4.87 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.43 (td, *J* = 16.5, 5.0 Hz, 1H), 4.33 (dd, *J* = 18.0, 1.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d6) δ 154.6, 142.2, 141.6, 138.6, 136.5, 136.3, 135.1, 133.8, 133.3, 132.9, 131.8, 131.5, 130.9, 130.5, 128.6, 127.4, 127.1, 126.7, 125.8, 121.6, 121.4, 121.0, 120.3, 120.2, 119.3, 118.7, 117.2, 116.6, 116.5, 113.1, 112.1, 111.6, 111.0, 109.9, 109.4, 109.2, 47.9, 45.5, 41.1. HR-ESI-MS calculated for $C_{35}H_{29}N_2O$ $[M+H]^+$ 493.2279, found 493.2264.

10-phenyl-9-(1-phenyl-1*H*-indol-3-yl)-9,10-dihydrodibenzo[3,4:5,6]cyclohepta[1,2-*b*]indol-2-ol (3k): Yield: 34 mg, 69%. ^{1}H NMR (500 MHz, DMSO-d6 + $CDCl_3$) δ 8.03 (d, *J* = 7.5 Hz, 1H),7.63 (br s, 1H), 7.51-7.47 (m, 5H), 7.42 (br, s, 1H), 7.36-7.31 (m, 4H), 7.30-7.23 (m, 4H), 7.20-7.12 (m, 5H), 7.03 (d, *J* = 7.5 Hz, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 6.71 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.52 (s, 1H), 5.58 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d6 + $CDCl_3$) δ 156.5, 142.0, 140.8, 139.5, 138.9, 137.6, 136.9,

135.7, 134.6, 131.8, 131.5, 130.1, 129.3, 128.2, 127.9, 127.8, 127.4, 126.7, 125.9, 123.9, 121.9, 121.7, 120.7, 119.5, 119.4, 119.3, 113.8, 113.6, 113.0, 112.1, 110.8, 110.0. HR-ESI-MS calculated for $C_{41}H_{29}N_2O$ $[M+H]^+$ 565.2279, found 565.2265.

2-(1-methyl-2-(1-methyl-1*H*-indole-3-carbonyl)-1*H*-indol-3-yl)phenyl 4-nitrobenzoate (2a'): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 7.5 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 2H), 8.11 (d, *J* = 9.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.39-7.28 (m, 5H), 7.24-7.19 (m, 3H), 7.13-7.09 (m, 2H), 3.86 (s, 3H), 3.55 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.9, 163.4, 150.6, 148.0, 140.7, 137.9, 137.4, 136.1, 134.5, 132.9, 131.4, 128.2, 127.7, 126.7, 126.4, 125.8, 124.2, 123.5, 123.3, 122.9, 122.7, 122.3, 121.7, 120.6, 116.3, 113.4, 110.1, 109.7, 32.9, 31.5. HR-ESI-MS calculated for $C_{32}H_{24}N_3O_5$ $[M+H]^+$ 530.1716, found 530.1725.

10-methyl-9-(1-methyl-1*H*-indol-3-yl)-9,10-dihydrodibenzo[3,4:5,6]cyclohepta[1,2-*b*]indol-2-yl 4-bromobenzoate (3a'): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.5 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 2.5 Hz, 1H), 7.72 (t, *J* = 8.5 Hz, 3H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 7.0 Hz, 1H), 7.45-7.42 (m, 3H), 7.35 (t, *J* = 7.0 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.15-7.11 (m, 2H), 7.02-6.99 (m, 2H), 6.19 (s, 1H), 5.92 (s, 1H), 4.02 (s, 3H), 3.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 149.7, 143.1, 142.2, 138.1, 137.1, 136.9, 135.5, 135.2, 132.2, 131.9, 131.7, 131.3, 128.5, 128.3, 127.5, 127.0, 126.9, 125.5, 121.7, 121.0, 120.4, 119.8, 119.1, 119.0, 118.7, 117.6, 110.7, 110.4, 109.8, 109.1, 41.1, 32.3, 29.7. HR-ESI-MS calculated for $C_{38}H_{27}N_2O_2Br$ $[M+H]^+$ 622.1255, found 622.1258.

4a.6. References

1. Murakami, M.; Ishida, N. *J. Am. Chem. Soc*. **2016**, *138*, 13759.
2. Straganz, G. D.; Nidetzky, B. *J. Am. Chem. Soc*. **2005**, *127*, 12306.
3. Souillart, L.; Cramer, N. *Chem. Rev*. **2015**, *115*, 9410.

4. Marek, I.; Masarwa, A.; Delaye, P.-O.; Leibeling, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 414.
5. Yu, X.; Wang, J.; Guo, W.; Tian, Y.; Wang, J. *Organometallics* **2016**, *35*, 1876.
6. (a) Chen, F.; Wang, T.; Jiao, N. *Chem. Rev.* **2014**, *114*, 8613. (b) Xia, Y.; Lu, G.; Liu, P.; Dong, G. *Nature* **2016**, *539*, 546. (c) Morioka, T.; Nishizawa, A.; Furukawa, T.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2017**, *139*, 1416. (d) Jia, K.; Pan, Y.; Chen, Y. *Angew. Chem., Int. Ed.* **2017**, *56*, 2478. (e) Liu, T.-L.; Wu, J.; Zhao, Y. *Chem. Sci.* **2017**, *8*, 3885. (f) Shao, Y.; Zhang, F.; Zhang, J.; Zhou, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 11485. (g) Guo, J. J.; Hu, A.; Chen, Y.; Sun, J.; Tang, H.; Zuo, Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 15319.
7. Matsuda, T.; Tsuboi, T.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12596.
8. Fu, X. F.; Xiang, Y.; Yu, Z. X. *Chem. - A Eur. J.* **2015**, *21*, 4242.
9. Kim, S. Y.; Lee, S. I.; Choi, S. Y.; Chung, Y. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 4914.
10. Bowring, M. A.; Bergman, R. G.; Tilley, T. D. *J. Am. Chem. Soc.* **2013**, *135*, 13121.
11. Saidalimu, I.; Suzuki, S.; Tokunaga, E.; Shibata, N. *Chem. Sci*. **2016**, *7*, 2106.
12. Verma, A.; Kumar, S. *Org. Lett*. **2016**, *18*, 4388.
13. Han, C. H.; Kim, E. H.; Colby, D. A. *J. Am. Chem. Soc*. **2011**, *133*, 5802.
14. Shen, J.; Wang, X.; Lin, X.; Yang, Z.; Cheng, G.; Cui, X. *Org. Lett.* **2016**, *18*, 1378.
15. For reviews, see: (a) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328. (b) Singh, F. V.; Wirth, T. *Synth.* **2013**, *45*, 2499.
16. (a) Yadagiri, D.; Anbarasan, P. *Chem. Commun.* **2015**, *51*, 14203. (b) Liu, L.; Zhang, T.; Yang, Y. F.; Zhang-Negrerie, D.; Zhang, X.; Du, Y.; Wu, Y. D.; Zhao, K. *J. Org. Chem.* **2016**, *81*, 4058.
17. (a) Fujioka, H.; Komatsu, H.; Nakamura, T.; Miyoshi, A.; Hata, K.; Ganesh, J.; Murai, K.; Kita, Y. *Chem. Commun. (Camb).* **2010**, *46*, 4133. (b) Beaulieu, M. A.; Sabot, C.; Achache, N.; Guérard, K. C.; Canesi, S. *Chem. - A Eur. J.* **2010**, *16*, 11224. (c) Guérard, K. C.; Chapelle, C.; Giroux, M.-A.; Sabot, C.; Beaulieu, M.-A.; Achache, N.; Canesi, S. *Org. Lett.* **2009**, *11*, 4756.
18. Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927.
19. Shang, S.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 6216.

20. (a) Roche, S. P.; Jr., J. A. P. *Angew. Chemie - Int. Ed.* **2011**, *50*, 4068. (b) Companys, S.; Pouységu, L.; Peixoto, P. A.; Chassaing, S.; Quideau, S. *J. Org. Chem.* **2017**, *82*, 3990.
21. Fujioka, N.; Fritz, V.; Upadhyaya, P.; Kassie, F.; Hecht, S. S. *Mol. Nutr. Food Res.* **2016**, *60*, 1228.
22. Sarkar, F. H.; Li, Y. *Cancer Treat. Rev.* **2009**, *35*, 597.
23. 23. Garbe, T. R.; Kobayashi, M.; Shimizu, N.; Takesue, N.; Ozawa, M.; Yukawa, H. *J. Nat. Prod.* **2000**, *63*, 596.
24. (a) Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Chem. Rev.* **2010**, *110*, 2250. (b) Praveen, P. J.; Parameswaran, P.; Majik, M. *Synthesis* **2015**, *47*, 1827.
25. (a) Sharma, S.; Kundu, B. *Tetrahedron Lett.* **2008**, *49*, 7062. (b) Deb, M. L.; Bhuyan, P. J. *Synlett* **2008**, 325. (c) El Sayed, M. T.; Ahmed, K. M.; Mahmoud, K.; Hilgeroth, A. *Eur. J. Med. Chem.* **2015**, *90*, 845. (d) Chu, X. Q.; Zi, Y.; Lu, X. M.; Wang, S. Y.; Ji, S. J. *Tetrahedron* **2014**, *70*, 232. (e) Huang, L.; Yang, H.-B.; Zhang, D. H.; Zhang, Z.; Tang, X. Y.; Xu, Q.; Shi, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6767.
26. Challa, C.; Vellekkatt, J.; Ravindran, J.; Lankalapalli, R. S. *Org. Biomol. Chem.* **2014**, *12*, 8588.
27. Jamsheena, V.; Shilpa, G.; Saranya, J.; Harry, N. A.; Lankalapalli, R. S.; Priya, S. *Chem.-Biol. Interact.* **2016**, *247*, 11.
28. Dohi, Toshifumi; Kita, Y. *Top. Curr. Chem.* **2016**, *373*, 1.
29. Kita, Yasuyuki; Yakura, Takayuki; Tohma, Hirofumi; Kikuchi, Kazumi; Tamura, Y. *Tetrahedron Lett.* **1989**, *30*, 1119.
30. Stempel, E.; Gaich, T. *Acc. Chem. Res.* **2016**, *49*, 2390.
31. Hille, U. E.; Hu, Q.; Vock, C.; Negri, M.; Bartels, M.; Müller-Vieira, U.; Lauterbach, T.; Hartmann, R. W. *Eur. J. Med. Chem.* **2009**, *44*, 2765.

Chapter-4b

DDQ mediated transformation of 3,3'-diindolylmethanes to indolo[2,3-*b*]quinolines and 3-alkenyl-oxindoles

4b.1. Abstract

This chapter reveals DDQ mediated transformation of readily accessible 3,3'-diindolylmethanes (DIMs) (**1**) to biologically important indolo[2,3-*b*]quinolines (**2**) and 3-alkenyl-oxindoles (**3**) under mild conditions with good to excellent yields. DIMs with *ortho*-NHTs phenyl group afforded indolo[2,3-*b*]quinolines (**2**), whereas DIMs with *ortho*-hydroxy phenyl groups yielded 3-alkenyl-oxindoles (**3**) under identical DDQ reaction conditions (Figure 4b.1A). Two optimized indolo[2,3-*b*]quinolines **2a** and **2n** displayed excellent anti-MRSA activity against clinical isolates. Compound **2a** showed MIC values in the concentration of 1-4 µg/mL, whereas compound **2n** revealed values of 1-2 µg/mL. Furthermore, both the compounds were highly bactericidal and capable of killing MRSA completely within 360 min. Collectively, the results suggested that both the compounds **2a** and **2n** possess enormous potential to be developed as anti-MRSA agents.

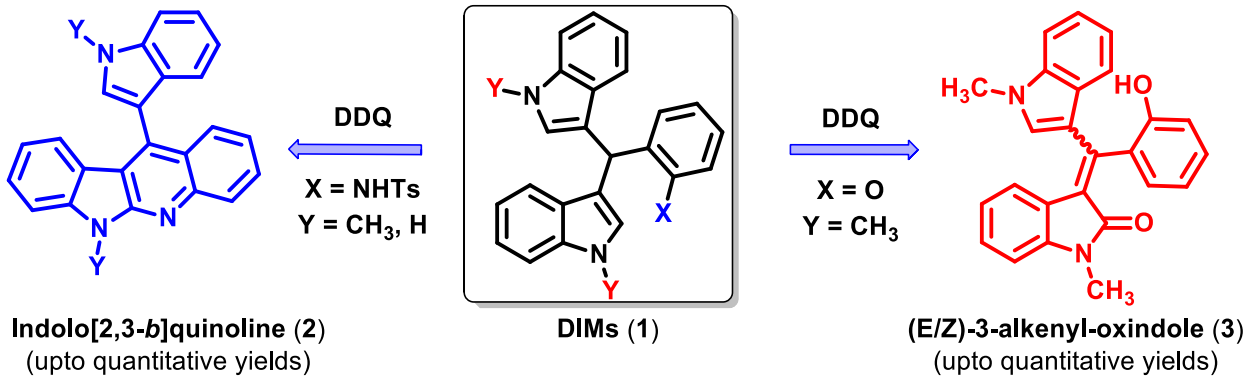


Figure 4b.1A. DDQ mediated synthesis of indolo[2,3-*b*]quinolines and 3-alkenyl-oxindole

4b.2. Introduction

The chemistry and synthetic applications of DDQ were already discussed in chapter-1, whereas the importance and synthetic transformations of DIMs were disclosed in chapter-4a. In this chapter, a brief introduction to indolo[2,3-*b*]quinolines and 3-alkenyl-oxindole will be discussed. Indolo[2,3-*b*]quinoline is a core structure in several natural products which include perophoramidine and communesin alkaloids.[1] 6*H*-Indolo[2,3-*b*]quinoline and its methylated analogs are natural products (e.g. neocryptolepine), known for their DNA intercalation and topoisomerase II inhibition properties.[2] Recently, several neocryptolepine derivatives were synthesized and their antimicrobial and antiproliferative activities were explored.[3] In general most of the analogues were active against Gram-positive bacteria and inactive against Gram-negative bacteria. Similar antibacterial activity trend was observed for other reported indolo[2,3-*b*]quinoline derivatives.[4] Figure 4b.2A represents the structure of neocryptolepine and its synthetic analogues with different biological activities.

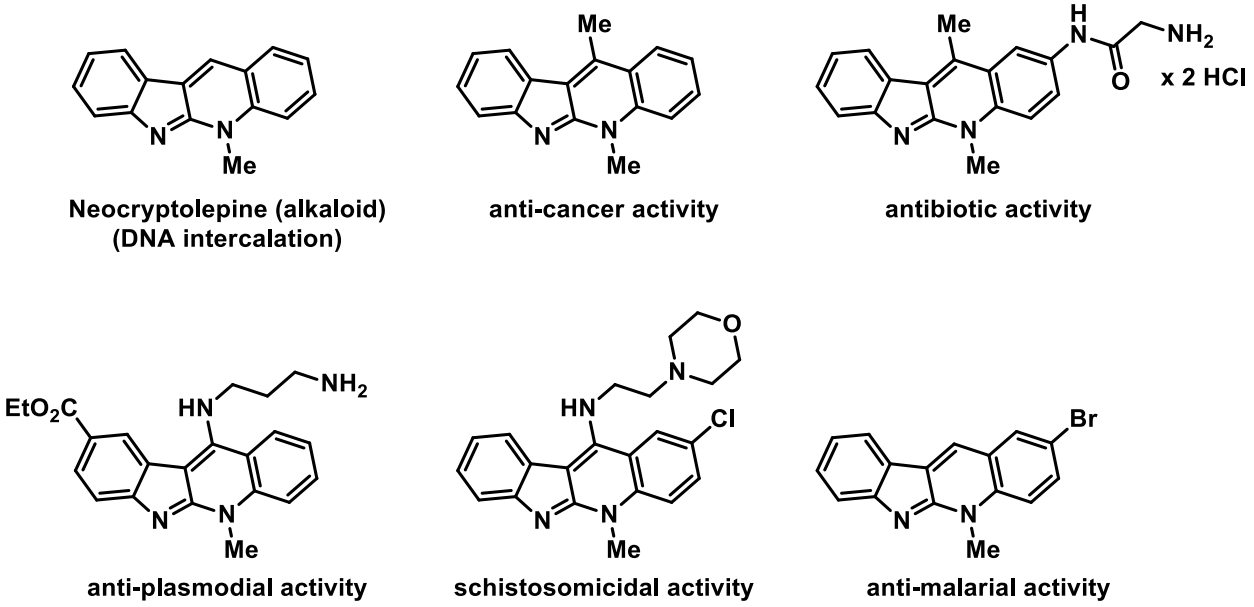
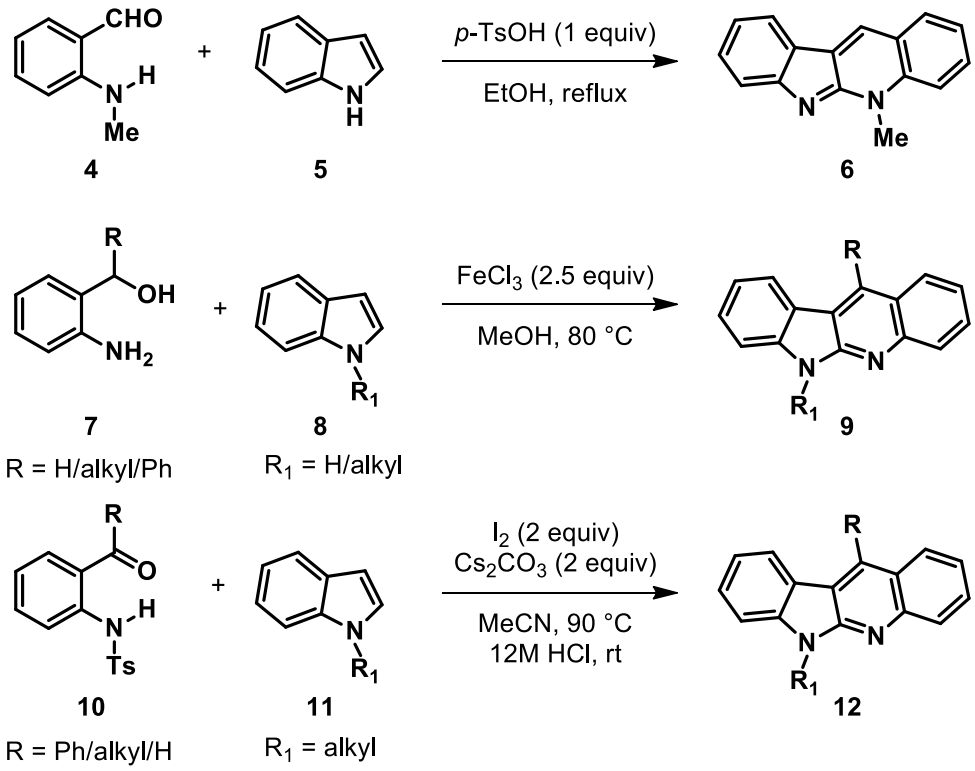


Figure 4b.2A. Neocryptolepine and its important synthetic analogues

Owing to their biological significance in medicinal chemistry research, several efficient methods were reported for the synthesis of indolo[2,3-*b*]quinolines.[2,5] For instance, Seidel et al. reported a simple *p*-TsOH mediated annulation reaction between secondary aminobenzaldehyde **4** and indole **5** to access neocryptolepine **6** (Scheme 4b.2.1).[5a] Wang et al. reported $FeCl_3$ promoted annulation reaction between aminophenyl alcohols **7** and indole **8** for the synthesis of indolo[2,3-b]quinoline analogues **9** (Scheme 4b.2.1).[5c] Liang et al. developed cross-amination/Friedel–Crafts alkylation reaction of 1-(2-tosylaminophenyl)ketones **10** with N-alkylindoles **11** for the synthesis of indolo[2,3-*b*]quinolines **12** under metal-free conditions (Scheme 4b.2.1).[5d]



Scheme 4b.2.1. Representative methods for the synthesis of neocryptolepine analogues

On the other hand, 3-alkenyl-oxindole core represents several natural products and pharmaceuticals.[6] For instance, Sunitinib (SU11248), a receptor tyrosine kinase (RTK) inhibitor approved by FDA in 2006 for the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumors (Figure 4b.2.2). Some of the natural products and

pharmaceutically active molecules contain 3-alkenyl-oxindole core are presented in figure 4b.2B.

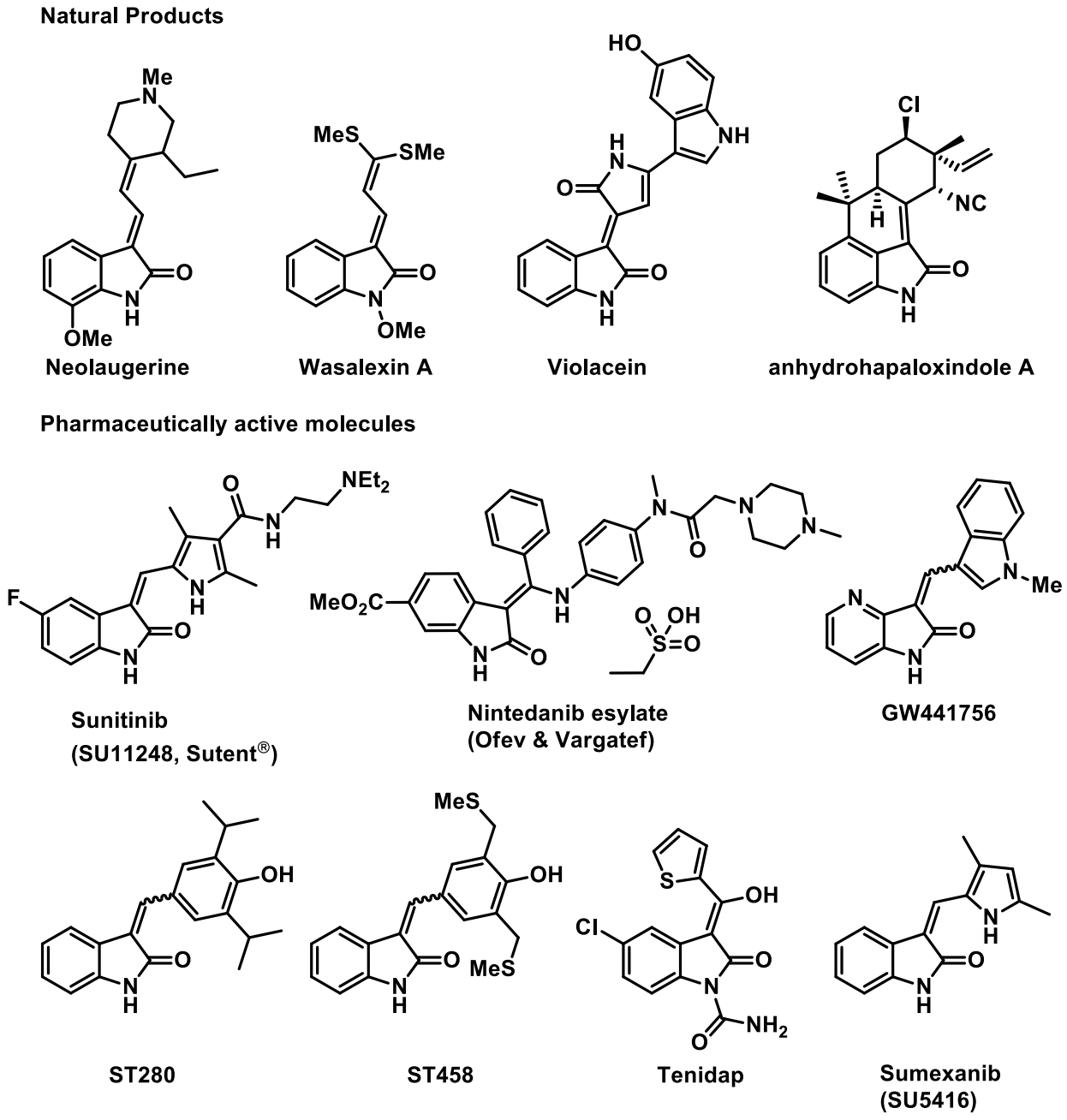
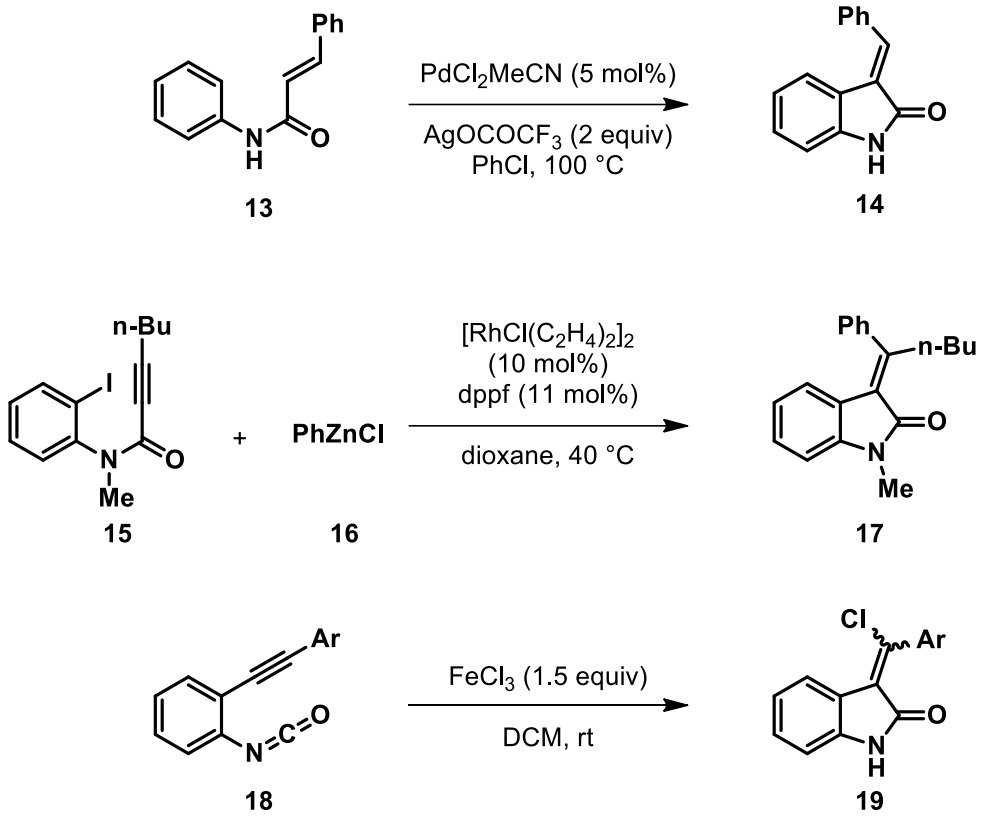


Figure 4b.2B. Representative 3-alkenyl-oxindole structural motifs

Several synthetic methods are available in the literature to access this privileged 3-alkenyl-oxindole motif, and some of the metal catalyzed intramolecular annulation reactions are presented in scheme 4b.2.2. Nagasawa et al. reported palladium-catalyzed C-H activation and intramolecular alkenylation reaction of N-cinnamoylanilines **13** for

the synthesis of 3-alkenyl-oxindoles **14** (Scheme 4b.2.2).[7a] Hayashi et al. developed rhodium catalyzed arylation and cross-coupling sequence between alkyne-tethered iodoarene **15** and organozinc chloride **16** to access the tetrasubstituted 3-alkenyl-oxindole **17** (Scheme 4b.2.2).[7b] Cossy et al. reported, $FeCl_3$ promoted cationic cyclization of *o*-(arylethynyl)aryl isocyanates **18** to access 3-(arylchloromethylene)oxindoles **19** under mild conditions at room temperature (Scheme 4b.2.2).[7c]



Scheme 4b.2.2. Metal-catalyzed /mediated synthesis of 3-alkenyl-oxindoles

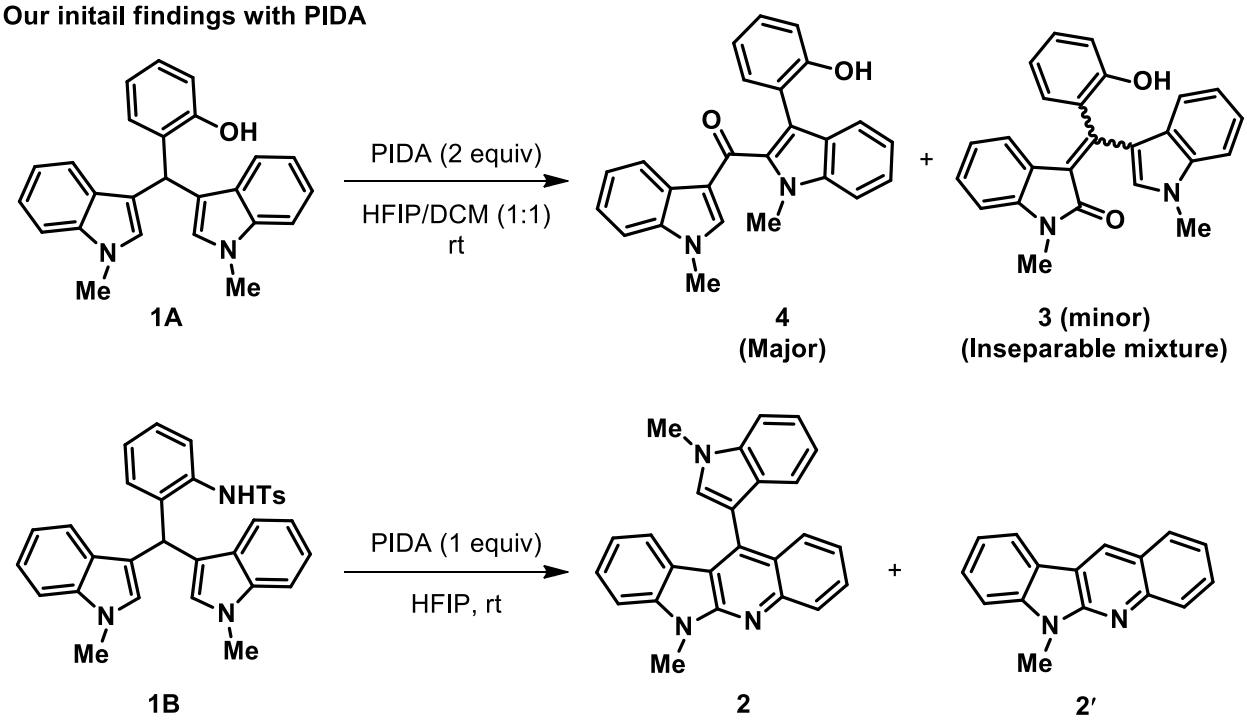
Despite the availability of a vast number of methods, our present method offers a highly efficient route to indolo[2,3-*b*]quinolines and 3-alkenyl-oxindoles from readily accessible DIPMs under mild oxidative reaction conditions. The focused library of these molecules was evaluated for their selective anti-MRSA activity by screening against a range of Gram-positive and Gram-negative bacteria in collaboration with microbiologists Dr. Dileep Kumar B.S. (CSIR-NIIST, TVM) and Prof. Jayanta Haldar (JNCASR, Bangalore).

The zone of inhibition assay suggested that indolo[2,3-*b*]quinolines **2a** and **2n** were highly active against *Staphylococcus aureus*, which causes a wide range of clinical infections. The anti-MRSA efficacy of these two optimized compounds was evaluated by MIC and MBC experiments. The time-kill kinetics was also performed to understand the rate at which the compounds **2a** and **2n** are capable of killing MRSA.

4b.3. Results and discussions

4b.3.1. Synthesis of indolo[2,3-*b*]quinolines

During our PIDA mediated transformation of DIPM **1A** to diindolylketone **4**, we also observed an inseparable E/Z mixture of 3-alkenyl-oxindoles in minor quantities which were difficult to characterize by NMR (Scheme 4b.3.1). This PIDA mediated unusual rearrangement of DIPM **1A** prompted us to check the reactivity of DIPM **1B** generated by the facile condensation of *ortho*-NHTs benzaldehyde and N-methylindole.

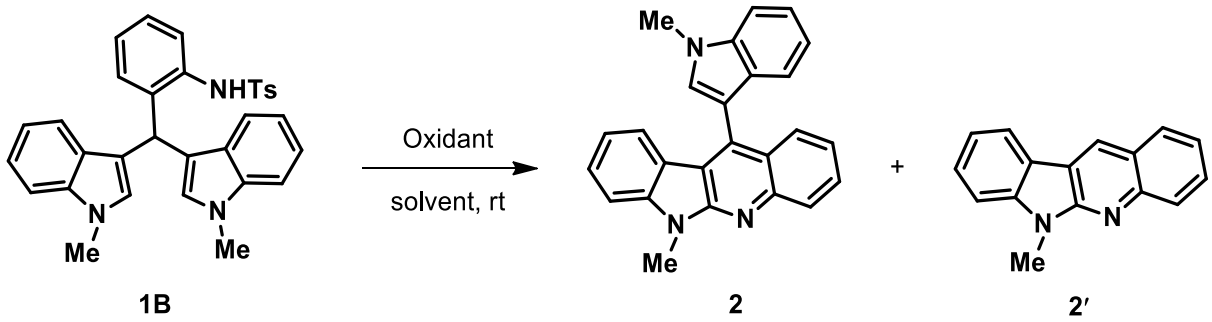


Scheme 4b.3.1. PIDA mediated transformations of DIPMs **1A** and **1B**

To our surprise we did not observe any rearrangement product; instead, the reaction yielded a mixture of indoloquinolines **2** and **2'** in low yields (Scheme 4b.3.1).

The biological importance of indoloquinolines inspired us to develop an efficient method using easily accessible DIPMs under mild oxidative conditions. In our next attempt to get desired product **2** exclusively, we increased the equiv of PIDA, tested different HIRs and solvents, and none of these attempts gave the fruitful results (Table 4b.3.1. entries 1-6). When we changed the oxidant from PIDA to DDQ (1.5 equiv), we were delighted to observe the desired product **2** exclusively despite incomplete reaction. Increase in the stoichiometry of DDQ to 3 equiv afforded indolo[2,3-*b*]quinolines in a quantitative yield either in DCM or DMF solvents (entries 7-8). This reaction was unsuccessful in water, whereas a trace amount of **2** was observed even in the absence of DDQ at 110 °C (entries 9-10).

Table 4b.3.1. Optimization of reaction conditions[a]



1B 2 2′

S.No.	**Oxidant** (equiv)	**Solvent**	**2 (%)**[b]	**2' (%)**[b]
1	PIDA (1.0)	HFIP	30	19
2	PIDA (1.5)	HFIP	23	36
3	PIDA (1.5)	DCE	33	15
4	PIDA (2.0)	HFIP/DCM (1:5)	40	31
5	PIFA (1.5)	HFIP	39	43

6	PhI(OH)OTs (1.0)	HFIP	18	24
7	DDQ (3)	DCM	100	-
8	DDQ (3)	DMF	100	-
9	DDQ (3)	H_2O	n.r.	n.r.
10[c]	-	DMF	trace	
11	CAN (3)	DCM	80	

[a]All reactions were conducted using 0.08 mmol of DIPM **1B** in 1.5 mL of undistilled solvents at room temperature. [b]Isolated yields. [c]Reaction temperature = 110 °C. CAN = ceric ammonium nitrate, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, n.r. = no reaction.

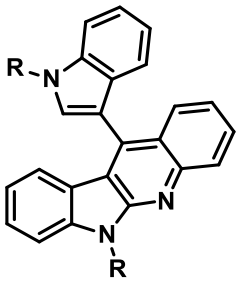
The product formation was even observed in the presence of ceric ammonium nitrate (CAN) (entry 11), albeit less yielding than DDQ.

Having the optimized condition in hand, we extended the present method to DIPMs **1B** with differently substituted 1*H*-indoles and *N*-methylindoles (Table 4b.3.2). DIPMs synthesized using 1*H*-indole and *N*-methyl/phenyl indole underwent facile transformation to the corresponding indolo[2,3-*b*]quinolines **2a** to **2c** in 89%, 100% and 92% yields, respectively. DIPMs with varied halogen, EWG or EDG substituted indoles underwent DDQ mediated transformation to furnish the respective products **2d-2m** and **2o-2p** in good to excellent yields. DIPM with OMe-substituted quinoline afforded indolo[2,3-*b*]quinoline **2n** in 90% yield.

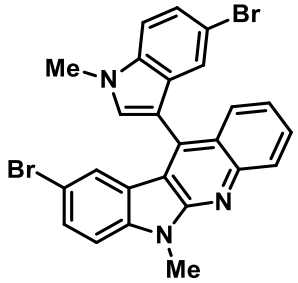
The methodology was further extended to the synthesis of biologically important 11-methylneocryptolepine natural product analog. Most of the indolo[2,3-*b*]quinoline derivatives that were screened for antimicrobial activity possess a simple methyl substitution at the 11-position.[3-4] In this context, the indolyl group at 11-position appears as a spectator substituent in the formation of indolo[2,3-*b*]quinoline **2**, however, its

presence in conjugation with quinoline can bear far stretched implications in biological activity.

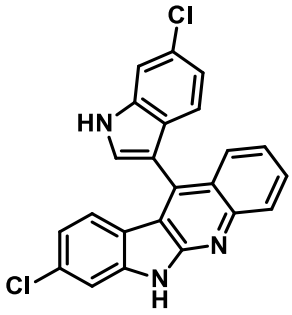
Table 4b.3.2. Substrate scope of indolo[2,3-*b*]quinoline



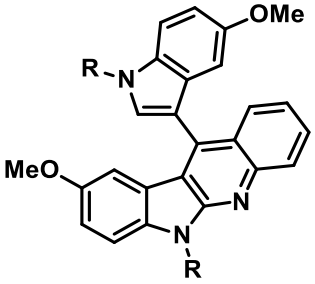
2a (R = H, 89%)
2b (R = Me, quant.)
2c (R = Ph, 92%)



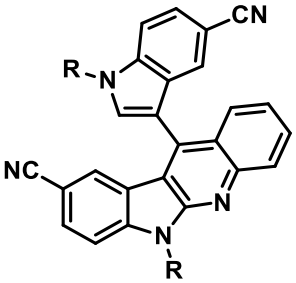
2d (quant.)



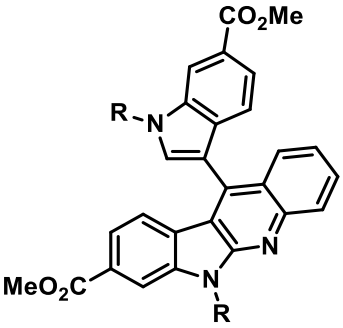
2e (67%)



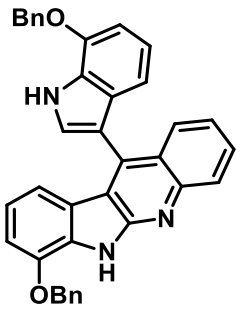
2f (R = H, 99%)
2g (R = Me, quant.)



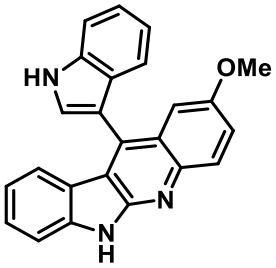
2h (R = H, 90%)
2i (R = Me, 51%)



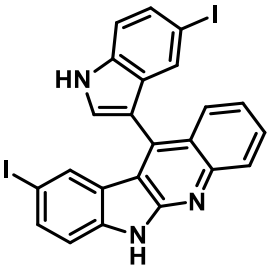
2j (R = H, 90%)
2k (R = Me, quant.)



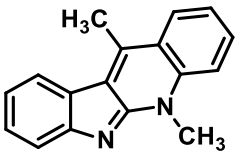
2l (R = H, 94%)
2m (R = Me, 64%)



2n (90%)



2o (X = H, 73%)
2p (X = Me, 94%)



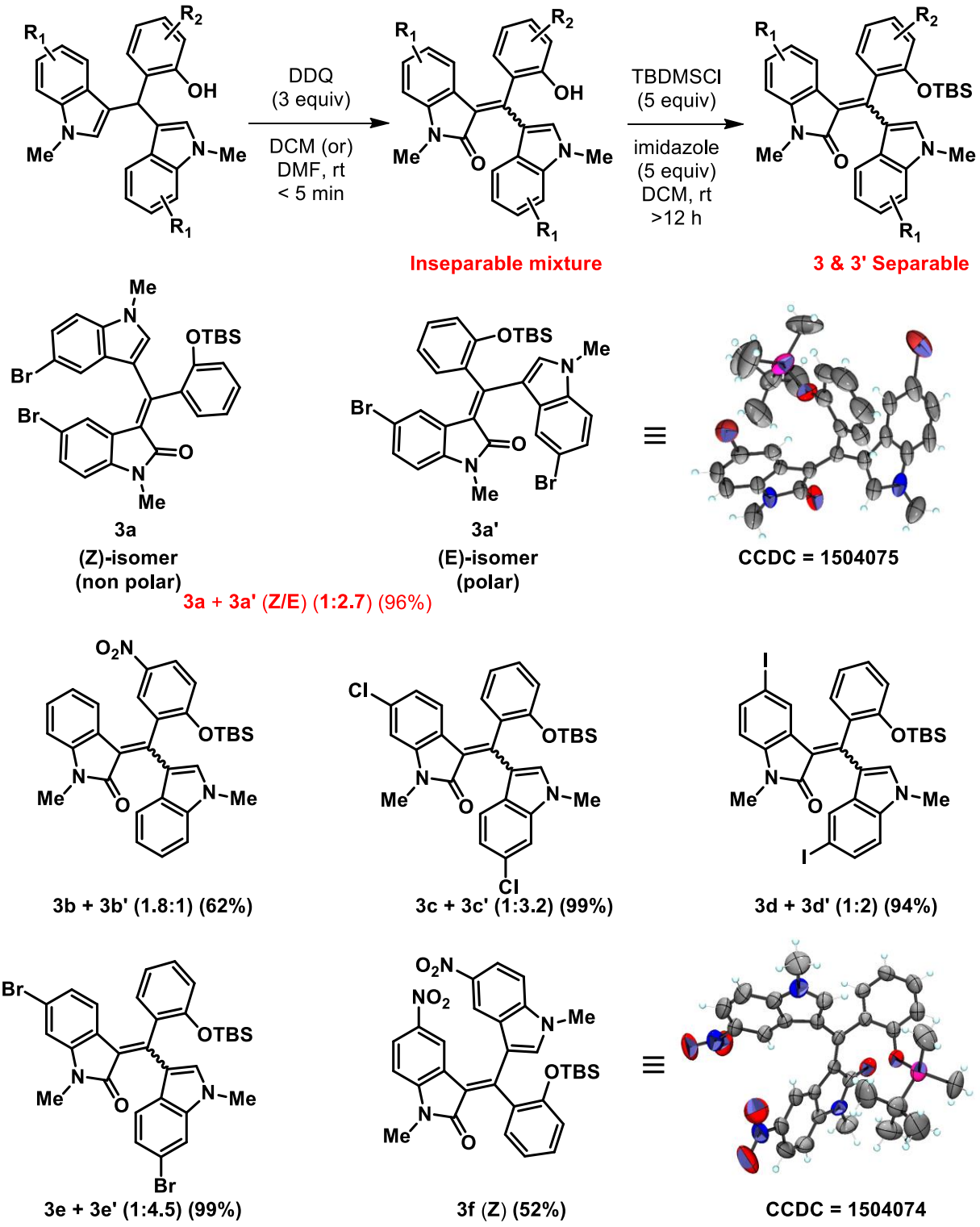
11-Methylneocryptolepine
(95%)

(DNA intercalation & topoisomerase II inhibition)

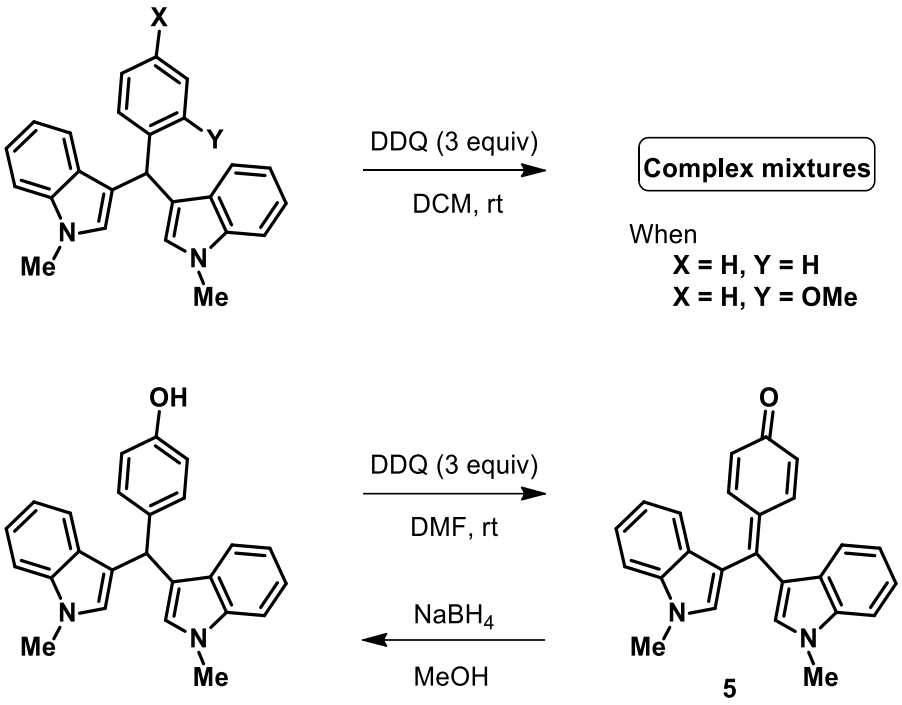
4b.3.2. Synthesis of 3-alkenyl-oxindoles

As described in scheme 4b.3.1, DIPM **1A** afforded an inseparable mixture in minor quantity along with major diindolylketone **4**. Inspired by the above DDQ mediated transformation of DIPM **1B** to indolo[2,3-*b*]quinoline **2**, we became curious to know the reactivity of DIPM **1A** in the presence of DDQ. Accordingly, we have treated DIPM **1A** with the optimized condition i.e DDQ (3 equiv) in DMF or DCM solvent, which surprisingly produced inseparable mixture of **3** in quantitative yields. In order to separate the mixture, we have applied silyl protection (TBDMS) strategy on crude mixture which facilitated the separation over column chromatography and the two TBDMS protected products exhibited same mass values as observed by the high-resolution mass spectrometry. Further, NMR and single-crystal X-ray analyses confirmed the formation of a geometrical mixture of 3-alkenyl-oxindoles **3** (Scheme 4b.3.2). Various substituted DIPMs **1A** were treated under DDQ-mediated oxidative conditions, which furnished 3-alkenyl-oxindole products **3a**, **3a′** to **3e**, **3e′** and **3f** in good to excellent yields over two steps (Scheme 4b.3.2). Based on the X-ray analysis of **3f** and **3b′** and thin-layer chromatography (TLC), compound **3** and **3′** series were identified as Z (nonpolar) and E (polar) isomers, respectively. In the case of **3f**, we were able to isolate only Z-isomer in pure form whereas E-isomer came as inseparable mixture in very low yield.

In order to elucidate the role of ortho-hydroxy group in the phenyl ring, DIPM generated from *para*-hydroxybenzaldehyde and *N*-methylindole were tested under the DDQ conditions which, surprisingly, produced cyclohexa-2,5-dien-1-one **5** which transformed back to the DIPM starting material under $NaBH_4$ reduction. Similarly, treatment of DIPMs synthesized from benzaldehyde or 2-methoxy benzaldehyde and *N*-methylindole under DDQ conditions afforded a mixture of products which decomposed over silica gel column chromatography (Scheme 4b.3.3).



Scheme 4b.3.2. DDQ mediated synthesis of Z/E isomers of 3-alkenyl-oxindoles



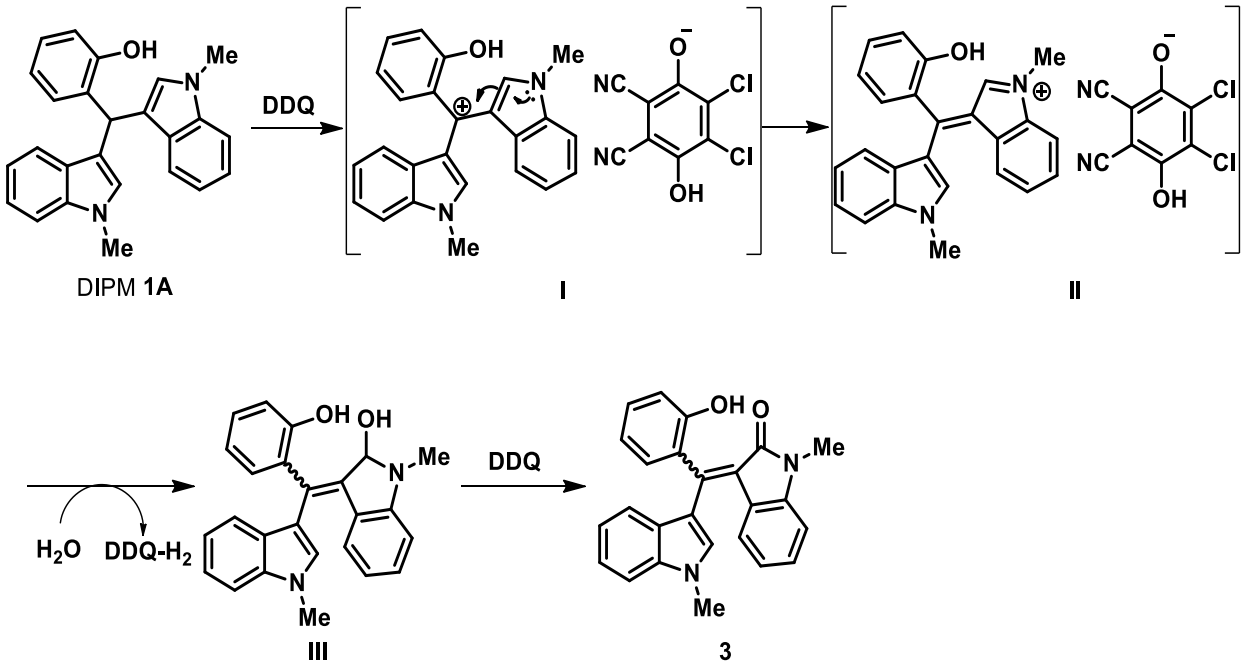
Scheme 4b.3.3. Reactivity of other DIPMs in presence of DDQ

We have proposed a mechanism for the formation of **3** (Scheme 4b.3.4), the initial benzylic C-H oxidation of DIPM **1A** in the presence of DDQ generates ionic intermediate **I** which is stabilized by nitrogen lone pairs to furnish intermediate **II**. The reactive ionic intermediate **II** will be attacked by water molecule to produce secondary alcohol **III** which subsequently undergo oxidation in the presence of excess DDQ and open air atmosphere to afford E/Z mixture of **3**. Formation of **3** can be realized only after quenching as TLC of the reaction mixture indicates formation of highly polar products after immediate consumption of DIPM **1A**. In a similar mechanistic pathway NHTs group of BIPM **1B** attacks the C2 of indole with positively charged nitrogen, subsequent elimination of tosyl group triggers aromatization for the generation of pyridine.

4b.3.3. Antibacterial activity

Having a library of valuable scaffolds in hand, we became interested in evaluating their antibacterial activity in collaboration with microbiologists. Accordingly, we have given

this library of molecules to Dr. Dileep Kumar B.S to check their zone of inhibition (ZOI) efficacy against different gram positive and gram negative bacteria.



Scheme 4b.3.4. Proposed mechanism for the formation of **3**

The primary results suggested that indolo[2,3-*b*]quinolines **2a** and **2n** displayed selective inhibition against *Staphylococcus aureu,* whereas none of the 3-alkenyl-oxindoles (**3)** were active against any tested bacteria (Table 4b.5.1). Based on these results, indolo[2,3-*b*]quinolines **2a** and **2n** were selected to explore their in-depth antibiotic activity in collaboration with Prof. Jayanta Haldar. The results from MIC, MBC and time kill kinetics suggested that compounds **2a** and **2n** have great potential to become anti-MRSA agents (Table 4b.5.2 & Figure 4b.5A).

4b.4. Conclusions

In summary, we have extensively utilized DIPMs under DDQ mediated oxidative transformations to produce biologically relevant molecules. DIPMs generated from *N*-methylindole or 1*H*-indole appended to *ortho*-NHTs phenyl group afforded indolo[2,3-*b*]quinolines **2** in the presence of DDQ, whereas DIPMs with N-methylindole appended

to *ortho*-hydroxy phenyl group afforded geometrical mixture of 3-alkenyl-oxindoles **3** under DDQ mediated conditions. All the reactions were conducted in an expeditious manner at room temperature under mild conditions affording the products in excellent yields. The antibacterial screening through zone of inhibition experiment resulted in two potent and selective anti-MRSA agents. Further detailed studies suggested that compounds **2a** and **2n** were highly bactericidal and displayed excellent MIC and MBC values at lower concentration. Taken together, this study paves the way to identify the lead compounds that possess high potential to be developed as anti-MRSA agents.

4b.5. Experimental section

4b.5.1. General information: All chemicals and solvents were purchased as reagent grade and used without further purification and distillation. Reactions were monitored by TLC and spots were visualized by short/long wavelength UV lamp. ^{1}H and ^{13}C NMR were recorded at 500 and 125 MHz, respectively using $CDCl_3$/DMSO-d6 as solvents and chemical shifts were given in ppm. Flash column chromatography was performed using silica gel 100-200 mesh. HR-ESI-MS analysis was performed using orbitrap analyzer and the ions are given in m/z.

4b.5.2. General procedure for the synthesis of DIPM 1B[8]

To a solution of *N*-Ts-2-aminobenzaldehyde (276 mg, 1.0 mmol) in MeCN solvent (4 mL) was added indole (2.0 equiv) and iodine (0.5 equiv) sequentially at room temperature. After consumption of the aldehyde, as indicated over TLC, the reaction mixture was quenched with saturated $Na_2S_2O_3$ solution and extracted in DCM (30 mL x 3). The combined DCM extracts were dried over anhydrous Na_2SO_4, concentrated and purified by flash column chromatography to afford the desired DIPM **1B**.

4b.5.3. General procedure for DDQ-mediated synthesis of indolo[2,3-b]quinolines 2

To a solution of DIPM **1B** (0.1-0.5 mmol, 0.07 M) in DCM or DMF solvent was added DDQ (3 equiv) at room temperature. After the completion of the starting material, as indicated by TLC (<5 min), the reaction mixture was quenched with a saturated sodium bicarbonate/10 M NaOH solution and extracted in DCM solvent (1 × 3). The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuum. The crude mixture was purified by flash column chromatography using EtOAc/hexane (1:4) or DCM/hexane (1:1 to 1:0) solvent system to afford the desired product **2** as a pale yellow solid.

4b.5.4. General procedure for the synthesis of 3-alkenyl-oxindoles 3

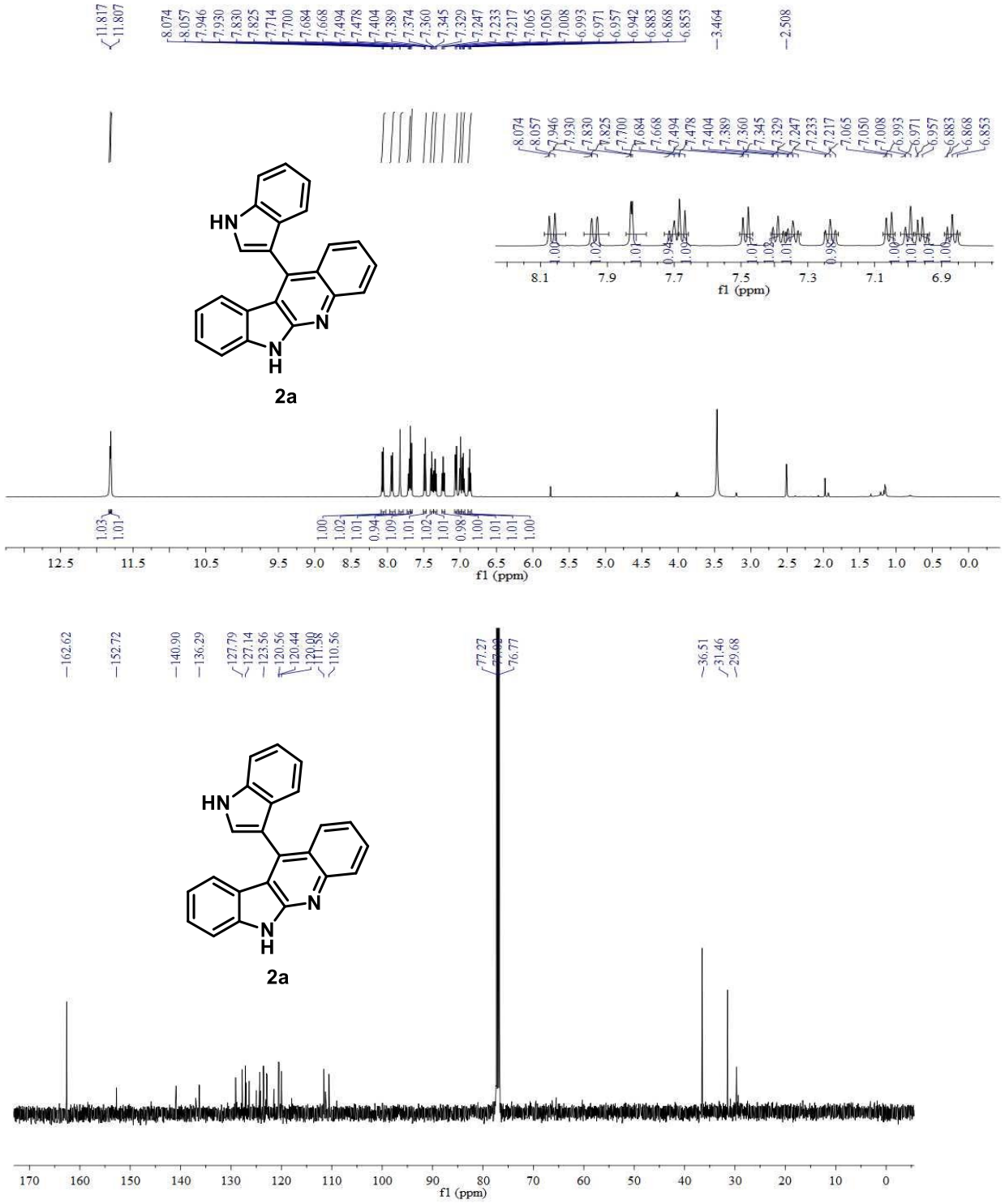
DIPM **1A** was treated with DDQ according to the above-mentioned DDQ-mediated oxidation procedure, and the resulting crude mixture was treated with imidazole (5 equiv) and TBDMSCl (5 equiv) in DCM solvent. After the completion of the reaction, as indicated by TLC, the reaction mixture was quenched with saturated $NaHCO_3$ and extracted in DCM (1 × 3). The combined DCM layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated on a rotavap. The crude mixture was purified by flash column chromatography using EtOAc/hexane (1:4) solvent to afford the TBS-protected 3-alkenyl-oxindole products **3/3'** as red colored solids.

4b.5.5. Spectral details of products

11-(1*H*-indol-3-yl)-6*H*-indolo[2,3-*b*]quinoline (2a): Yield: 30 mg, 89%. ^{1}H NMR (500 MHz, DMSO-d6) δ 11.81 (s, 1H), 11.80 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 2.5 Hz, 1H), 7.71 (d, *J* = 7.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 7.0 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.86 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 1162.9, 152.6, 141.0, 137.7, 136.5, 129.0,

127.9, 127.7, 127.1, 126.4, 125.0, 124.2, 123.6, 122.9, 122.8, 121.4, 120.5, 120.4, 120.0, 111.6, 111.2, 110.5, 109.1. HR-ESI-MS calculated for $C_{23}H_{16}N_3$ $[M+H]^+$ 334.1344, found 334.1345.

Figure 4b.5A. ^{1}H and ^{13}C-NMR images of 2a



6-Methyl-11-(1-methyl-1*H*-indol-3-yl)-6*H*-indolo[2,3-*b*]quinoline (2b): Yield: 67 mg, quantitative. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.5 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.68 (td, *J* = 8.0, 1.0 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.41 (td, *J* = 8.0, 1.0 Hz, 1H), 7.33-7.27 (m, 4H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.03 (t, *J* = 7.0 Hz, 1H), 6.88 (t, *J* = 7.0 Hz, 1H), 4.00 (s, 3H), 3.94 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 146.9, 142.8, 137.1, 136.0, 128.7, 127.6, 127.5, 127.0, 125.0, 123.5, 122.7, 122.5, 122.3, 120.9, 120.7, 120.1, 119.5, 117.2, 109.9, 109.7, 108.2, 33.2, 27.7. HR-ESI-MS calculated for $C_{25}H_{20}N_3$ $[M+H]^+$ 362.1657, found 362.1625.

6-Phenyl-11-(1-phenyl-1*H*-indol-3-yl)-6*H*-indolo[2,3-*b*]quinoline (2c): Yield: 62 mg, 92%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.0 Hz, 1H), 8.07 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.80 (br d, *J* = 7.0 Hz, 3H), 7.71-7.69 (m, 3H), 7.67-7.63 (m, 3H), 7.58 (t, *J* = 8.5 Hz, 2H), 7.49 (t, *J* = 9.0 Hz, 1H), 7.43-7.40 (m, 2H), 7.37-7.32 (m, 4H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 146.9, 142.7, 139.5, 136.5, 136.3, 135.5, 129.9, 129.7, 128.7, 128.5, 128.3, 127.8, 127.6, 126.9, 126.7, 125.4, 124.4, 123.4, 123.3, 123.2, 121.2, 120.9, 120.5, 117.4, 112.5, 111.0, 109.7. HR-ESI-MS calculated for $C_{35}H_{24}N_3$ $[M+H]^+$ 486.1970, found 486.1970.

9-Bromo-11-(5-bromo-1-methyl-1*H*-indol-3-yl)-6-methyl-6*H*-indolo[2,3-*b*]quinoline (2d): Yield: 60 mg, quantitative. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.5 Hz, 1H), 7.91 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.72 (td, *J* = 8.5, 1.5 Hz, 1H), 7.55 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.44-7.40 (m, 2H), 7.35-7.32 (m, 2H), 7.28 (d, *J* = 2.0 Hz, 1H), 7.27-7.26 (m, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 4.01 (s, 3H), 4.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 147.0, 141.5, 135.8, 130.2, 129.7, 129.2, 128.9, 127.7, 126.8, 125.7, 125.5, 124.7, 123.0, 122.8, 122.4, 116.1, 113.8, 112.2, 111.4, 109.7, 109.1, 33.4, 27.8. HR-ESI-MS calculated for $C_{25}H_{18}Br_2N_3$ $[M+H]^+$ 517.9867, found 517.9876.

8-Chloro-11-(6-chloro-1*H*-indol-3-yl)-6*H*-indolo[2,3-*b*]quinoline (2e): Yield: 58 mg, 67%. ^{1}H NMR (500 MHz, DMSO-d6) δ 11.95 (br s, 1H), 11.94 (br s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.89 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.86 (d, *J* = 2.5 Hz, 1H), 7.73-7.69 (m, 2H), 7.49 (t, *J* = 1.5 Hz, 1H), 7.36 (td, *J* = 8.0, 1.0 Hz, 1H), 6.97-6.92 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d6) δ 152.9, 146.7, 142.4, 136.9, 135.4, 132.1, 128.9, 127.4, 126.9, 126.7, 126.4, 125.2, 124.2, 123.9, 123.0, 120.6, 120.2, 119.5, 119.3, 116.0, 112.0, 110.4, 109.1. HR-ESI-MS calculated for $C_{23}H_{14}Cl_2N_3$ $[M+H]^+$ 402.0564, found 402.0566.

9-Methoxy-11-(5-methoxy-1*H*-indol-3-yl)-6*H*-indolo[2,3-*b*]quinoline (2f): Yield: 68 mg, 99%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.72 (br s, 1H), 11.67 (br s, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 2.5 Hz, 1H), 7.74 (td, *J* = 7.5, 1.5 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1Hz), 7.41 (d, *J* = 8.5 Hz, 2H), 7.09 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.92 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.58 (d, *J* = 2.5 Hz, 1H), 6.44 (d, *J* = 2.5 Hz, 1H). 3.46 (s, 3H), 3.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.6, 135.8, 131.4, 128.7, 127.0, 126.6, 123.6, 123.3, 121.0, 116.6, 115.2, 113.0, 112.0, 111.1, 108.5, 107.4, 101.0, 55.2, 54.8. HR-ESI-MS calculated for $C_{25}H_{20}N_3O_2$ $[M+H]^+$ 394.1555, found 394.1573.

9-Methoxy-11-(5-methoxy-1-methyl-1*H*-indol-3-yl)-6-methyl-6*H*-indolo[2,3-*b*]quinoline (2g) Yield: 88 mg, quantitative. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 9.0 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.29 (s, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.72 (s, 1H), 6.58 (s, 1H), 3.99 (s, 3H), 3.94 (s, 3H), 3.51 (s, 3H), 3.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 153.5, 152.9, 146.9, 137.5, 136.1, 132.3, 129.4, 128.7, 127.8, 127.4, 127.1, 124.5, 122.3, 121.1, 117.0, 115.5, 115.4, 113.1, 110.5, 109.3, 108.5, 108.1, 108.0, 102.0, 55.7, 55.5, 33.3, 27.8. HR-ESI-MS calculated for $C_{27}H_{24}N_3O_2$ $[M+H]^+$ 422.1868, found 422.1839.

11-(5-cyano-1*H*-indol-3-yl)-6*H*-indolo[2,3-*b*]quinoline-9-carbonitrile (2h): Yield: 66 mg, 90%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.47 (s, 1H), 12.41 (s, 1H), 8.15 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.87 (dd, *J* = 8.5, 3.5 Hz, 2H), 7.81 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.77 (td, *J* = 7.0, 1.5 Hz, 1H), 7.63 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.52 (s, 1H), 7.43 (td, *J* = 8.5, 1.0 Hz, 1H), 7.15 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 152.9, 147.0, 144.3, 138.3,135.7, 131.2, 129.5, 128.8, 127.7, 126.4, 126.1, 124.9, 124.8, 124.2, 123.6, 120.9, 120.3, 120.0, 115.5, 113.9, 112.0, 109.6, 102.1, 100.8. HR-ESI-MS calculated for $C_{25}H_{14}N_5$ $[M+H]^+$ 384.1249, found 384.1259.

11-(5-cyano-1-methyl-1*H*-indol-3-yl)-6-methyl-6*H*-indolo[2,3-*b*]quinoline-9-carbonitrile (2i) Yield: 51 mg, 51%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.5 Hz, 1H), 7.78 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.71 (td, *J* = 8.5, 1.5 Hz, 1H), 7.67 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.54 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.44 (s, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.37 (br s, 1H), 7.33 (td, *J* = 8.0, 1.0 Hz, 1H), 7.27 (d, *J* = 1.5 Hz, 1H), 4.05 (s, 3H), 4.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 147.3, 145.0, 143.2, 138.6, 135.3, 131.4, 130.4, 129.7, 129.2, 129.0, 128.9, 128.1, 126.9, 126.3, 125.7, 125.6, 124.9, 123.8, 120.9, 120.0, 115.7, 111.5, 110.3, 109.8, 103.8, 102.3, 33.7, 29.6. HR-ESI-MS calculated for $C_{27}H_{18}N_5$ $[M+H]^+$ 412.1562, found 412.1571.

Methyl 11-(6-(methoxycarbonyl)-1*H*-indol-3-yl)-6*H*-indolo[2,3-*b*]quinoline-8-carboxyla-te (2j): Yield: 64 mg, 90%. ^{1}H NMR (500 MHz, DMSO-d6) δ 12.28 (s, 1H), 12.08 (s, 1H), 8.34 (br s, 1H), 8.12 (d, *J* = 2.5 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 8.06 (br s, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.76 (td, *J* = 8.5, 1.5 Hz, 1H), 7.58 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.48 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.40 (td, *J* = 8.5, 1.5 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 167.0, 166.3, 153.2, 147.8, 141.0, 136.6, 135.6, 129.8, 129.7, 129.3, 128.1, 127.4, 124.4, 123.9, 122.9, 120.8, 119.8,

119.0, 115.7, 114.3, 111.1, 109.2, 52.1, 51.8. HR-ESI-MS calculated for $C_{27}H_{20}N_3O_4$ $[M+H]^+$ 450.1453, found 450.1419.

Methyl 11-(6-(methoxy-carbonyl)-1-methyl-1*H*-indol-3-yl)-6-methyl-6*H*-indolo[2,3-*b*]quin-oline-8-carboxylate (2k): Yield: 107 mg, quantitative. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.93 (s, 1H), 7.87 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.63-7.60 (m, 2H), 7.48 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.42 (s, 1H), 7.23 (td, *J* = 8.0, 1.0 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 167.3, 153.0, 147.4, 142.3, 136.5, 136.4, 131.9, 130.7, 129.4, 128.6, 127.7, 126.8, 124.6, 124.5, 124.3, 123.0, 122.8, 121.2, 120.7, 120.1, 116.2, 112.4, 109.9, 109.5, 52.2, 52.0, 33.5, 27.8. HR-ESI-MS calculated for $C_{29}H_{24}N_3O_4$ $[M+H]^+$ 478.1766, found 478.1737.

7-(benzyloxy)-11-(7-(benzyloxy)-1*H*-indol-3-yl)-6*H*-indolo[2,3-*b*]quinoline (2l): Yield: 71 mg, 94%. ^{1}H NMR (500 MHz, DMSO-d6) δ 11.97 (br s, 1H), 11.91 (br s, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.72-7.63 (m, 7H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 4H), 7.33 (app q, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.86 (app q, *J* = 7.5 Hz, 2H), 6.78 (t, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 5.36 (app d, *J* = 7.0 Hz, 4H). ^{13}C NMR (125 MHz, DMSO-d6) δ 152.7, 146.5, 141.5, 143.8, 137.3, 137.1, 135.9, 131.5, 128.4, 128.3, 128.2, 127.3, 127.7, 127.6, 127.2, 126.4, 125.2, 124.1, 122.4, 121.8, 120.1, 119.4, 116.9, 115.5, 112.1, 110.6, 109.6, 103.4, 69.4, 69.3. HR-ESI-MS calculated for $C_{37}H_{28}N_3O_2$ $[M+H]^+$ 546.2181, found 546.2189.

7-(benzyloxy)-11-(7-(benzyloxy)-1-methyl-1*H*-indol-3-yl)-6-methyl-6*H*-indolo[2,3-*b*]quino-line (2m): Yield: 73 mg, 64%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.5 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.70 (td, *J* = 8.5, 1.5 Hz, 1H), 7.59 (d, *J* = 7.0 Hz, 2H), 7.52 (d, *J* = 7.0 Hz, 2H), 7.48 (t, *J* = 7.0 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.31 (td, *J* = 8.0, 1.0 Hz, 1H), 7.20 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.91 (t, *J* =

8.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.31-5.24 (m, 4H), 4.35 (s, 3H), 4.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 147.1, 146.9, 145.4, 137.1, 136.9, 136.1, 132.1, 130.2, 129.7, 128.7, 128.5, 128.0, 127.6, 127.5, 127.0, 126.8, 124.9, 122.7, 122.3, 120.5, 119.6, 117.1, 116.6, 113.7, 111.1, 109.9, 103.9, 71.2, 70.5, 37.1, 31.1. HR-ESI-MS calculated for $C_{39}H_{32}N_3O_2$ $[M+H]^+$ 574.2494, found 574.2476.

11-(1*H*-indol-3-yl)-2-methoxy-6*H*-indolo[2,3-*b*]quinoline (2n): Yield: 37 mg, 90%. ^{1}H NMR (500 MHz, DMSO-d6) δ 11.76 (s, 1H), 11.63 (s, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.84 (d, *J* = 2.5 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 3.0 Hz, 1H), 7.37 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.29 (d, *J* = 3.0 Hz, 1H), 7.23 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 2H), 6.98 (d, *J* = 6.5 Hz, 1H), 6.83 (dt, *J* = 8.0, 0.5 Hz, 1H), 3.63 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6) δ 154.4, 151.6, 142.2, 141.4, 136.3, 134.4, 128.6, 127.4, 126.2, 125.5, 124.5, 122.7, 121.7, 120.4, 119.4, 119.3, 118.7, 116.5, 112.2, 110.4, 109.2, 104.9, 54.9. HR-ESI-MS calculated for $C_{24}H_{18}N_3O$ $[M+H]^+$ 364.1449, found 364.1458.

9-Iodo-11-(5-iodo-1*H*-indol-3-yl)-6*H*-indolo[2,3-*b*]quinoline (2o): Yield: 90 mg, 73%. ^{1}H NMR (500 MHz, DMSO-d6) δ 12.04 (s, 1H), 11.95 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.87-7.85 (m, 2H), 7.75 (td, *J* = 8.0, 1.5 Hz, 1H), 7.70 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.52 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.39 (td, *J* = 8.0, 1.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.28-7.27 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d6) δ 152.3, 146.7, 140.7, 135.5, 135.4, 131.0, 129.9, 128.9, 128.8, 127.3, 126.9, 126.3, 124.0, 123.9, 123.1, 122.8, 115.3, 114.8, 113.1, 108.0, 83.5, 81.8. HR-ESI-MS calculated for $C_{23}H_{14}I_2N_3$ $[M+H]^+$ 585.9277, found 585.9275.

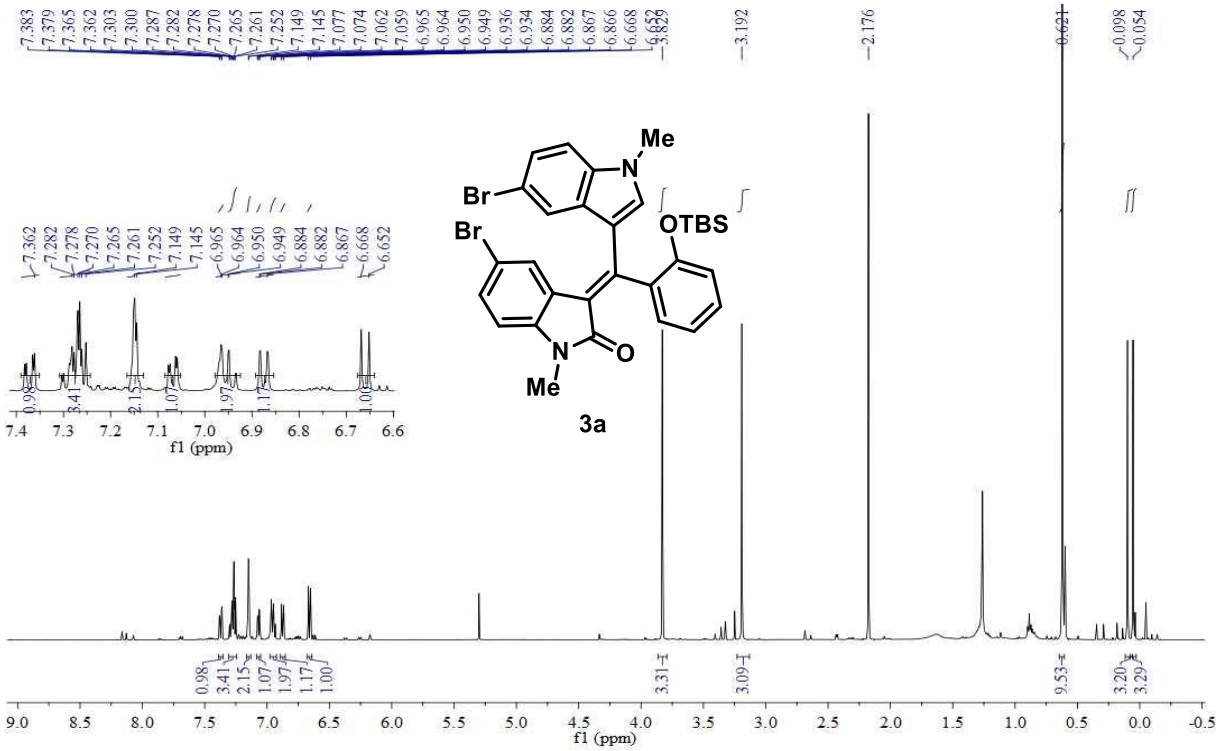
9-Iodo-11-(5-iodo-1-methyl-1*H*-indol-3-yl)-6-methyl-6*H*-indolo[2,3-*b*]quinoline (2p): Yield: 84 mg, 94%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.93 (s, 1H), 7.84 (m, 2H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.65 (dd, *J* = 8.5, 1.5

Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.49 (td, *J* = 8.5, 1.5 Hz, 1H), 7.32 (br s, 2H), 4.11 (s, 3H), 4.02 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d6 + $CDCl_3$) δ 151.5, 146.5, 141.4, 135.7, 135.2, 131.2, 130.2, 129.2, 128.9, 128.5, 128.2, 127.1, 126.2, 124.0, 122.4, 115.1, 111.7, 110.0, 107.9, 37.5, 30.6. HR-ESI-MS calculated for $C_{25}H_{18}I_2N_3$ $[M+H]^+$ 613.9590, found 613.9581.

(Z)-5-Bromo-3-((5-bromo-1-methyl-1*H*-indol-3-yl)(2-((tert-butyldimethylsilyl)oxy)phen-yl)methylene)-1-methylindolin-2-one (3a): Yield: 42 mg, 26%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.29-7.24 (m, 3H), 7.14 (br d, *J* = 2.0 Hz, 2H), 7.06 (dd, *J* = 7.5, 2.0 Hz, 1H), 6.96 (d, *J* = 1.0 Hz, 1H), 6.94 (dd, *J* = 7.5,1.0 Hz, 1H), 6.87 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.66 (d, *J* = 8.5 Hz, 1H), 3.82 (s, 3H), 3.18 (s, 3H), 0.61 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 153.5, 141.4, 136.1, 134.1, 132.8, 131.5, 130.0, 129.9, 127.3, 125.5, 125.0, 124.7, 121.2, 120.9, 118.9, 115.6, 114.4, 113.4, 111.4, 108.4, 33.5, 25.7, 25.2, 25.1, 25.0, 17.7, -4.2, -4.3. HR-ESI-MS calculated for $C_{31}H_{33}Br_2N_2O_2Si$ $[M+H]^+$ 651.0678, found 651.0691.

(E)-5-Bromo-3-((5-bromo-1-methyl-1*H*-indol-3-yl)(2-((tert-butyldimethylsilyl)oxy)-phenyl) methylene)-1-methylindolin-2-one (3a'): Yield: 112 mg, 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.44 (td, *J* = 8.0, 1.5 Hz, 1H), 7.24 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.20 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.16-7.13 (m, 2H), 7.06 (td, *J* = 7.5, 1.0 Hz, 1H), 6.94 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.86 (d, *J* = 1.5 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.17 (d, *J* = 2.0 Hz, 1H), 3.82 (s, 3H), 0.59 (s, 9H), 0.03 (s,3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 152.8, 147.0, 137.2, 135.9, 131.5, 130.9, 130.7, 129.0, 126.8, 125.3, 124.7, 124.2, 121.8, 119.2, 119.1, 114.5, 113.9, 112.4, 111.0, 108.3, 33.5, 25.9, 25.0, 17.7, -4.4, -4.8. HR-ESI-MS calculated for $C_{31}H_{33}Br_2N_2O_2Si$ $[M+H]^+$ 651.0678, found 651.0696.

Figure 4b.5B. ^{1}H and ^{13}C-NMR of 3a



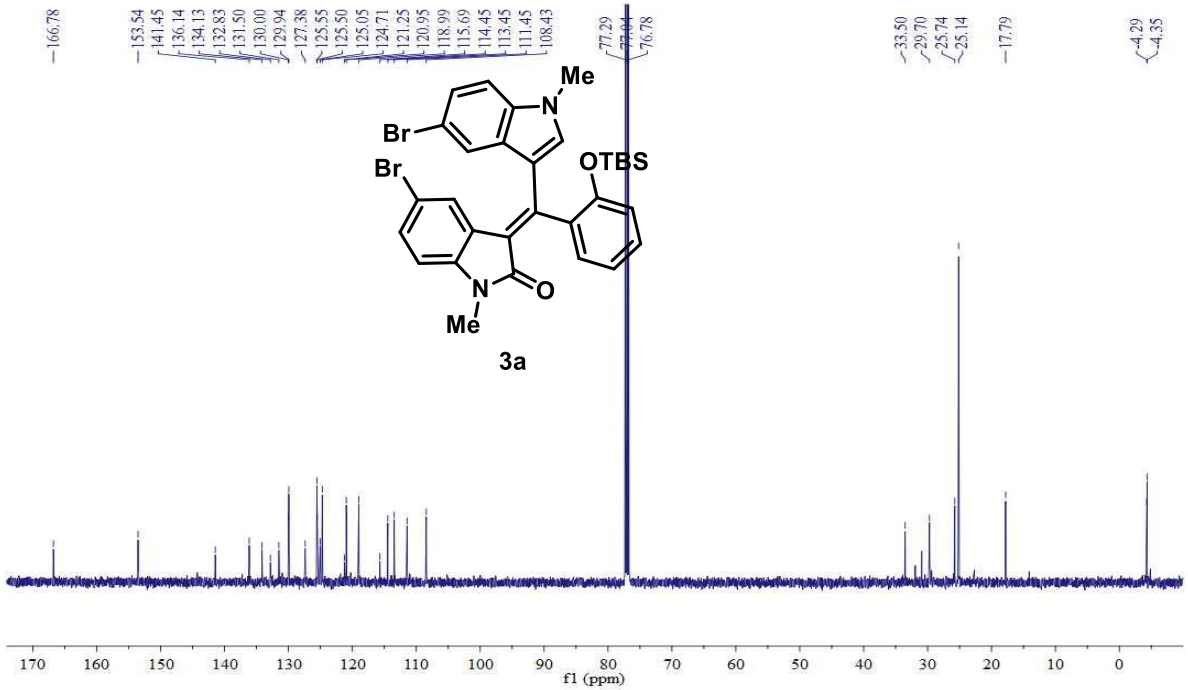
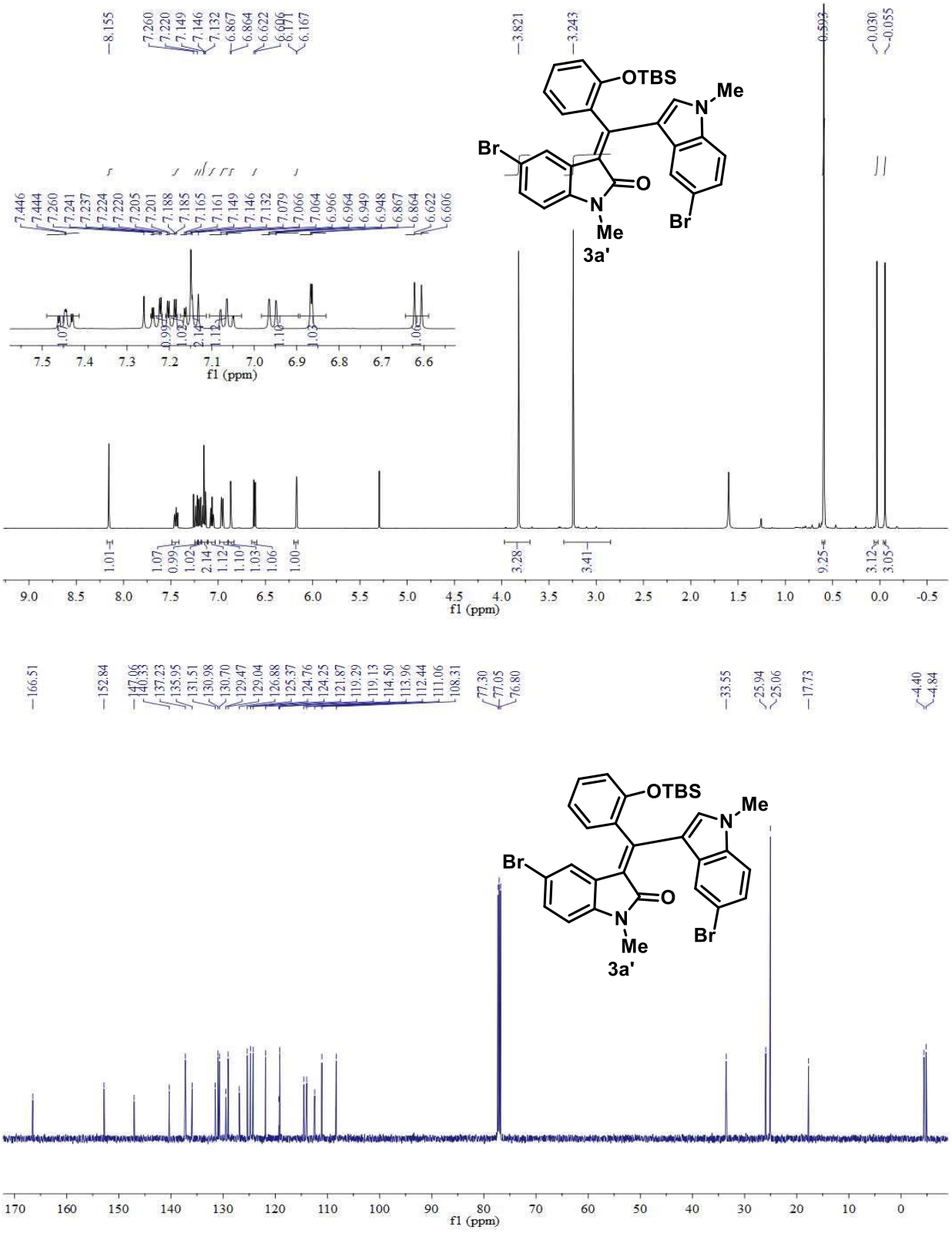


Figure 4b.5C. ^{1}H and ^{13}C-NMR of 3a'



(Z)-3-((2-((tert-butyldimethylsilyl)oxy)-5-nitrophenyl)(1-methyl-1*H*-indol-3-yl)methyl-ene)-1-methylindolin-2-one (3b): Yield: 33 mg, 40%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 9.0, 2.5 Hz, 1H), 8.01 (d, *J* = 2.5 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.28 (td, *J* = 8.0, 1.5 Hz, 1H), 7.17 (td, *J* = 7.5, 1.0 Hz, 1H), 7.11 (br s, 1H), 7.07 (m, 2H), 6.91 (d, *J* = 9.0, 1H), 6.88 (br s, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 6.68 (td, *J* = 7.5, 1.0 Hz, 1H), 3.84 (s, 3H), 3.19 (s, 3H), 0.61 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 159.5, 142.7, 141.6, 137.5, 132.7, 128.1, 127.3, 125.7, 125.3, 123.3, 122.8, 122.7, 122.1, -3.5, -4.3, -4.4. HR-ESI-MS calculated for $C_{31}H_{34}N_3O_4Si$ $[M+H]^+$ 540.2318, found 540.2316.

(E)-3-((2-((tert-butyldimethylsilyl)oxy)-5-nitrophenyl)(1-methyl-1*H*-indol-3-yl)methyl-ene)-1-methylindolin-2-one (3b'): Yield: 19 mg, 23%. ^{1}H NMR (500 M Hz, $CDCl_3$) δ 8.29 (dd, *J* = 9.0, 3.0 Hz, 1H), 8.15 (d, *J* = 3.0, 1H), 8.05 (s, 1 H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.16 (td, *J* = 8.5, 1.0 Hz, 1H), 7.11 (td, *J* = 7.5, 1.0 Hz, 1H), 6.98 (d, *J* = 9.5 Hz, 1H), 6.9 (td, *J* = 8.0, 1.0 Hz, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 6.74 (d, *J* = 8.5 Hz, 1H), 6.64 (td, *J* = 7.5, 1.0 Hz, 1H), 6.13 (d, *J* = 7.5 Hz, 1H), 3.85 (s, 3H), 3.26 (s, 3H), 0.60 (s, 9H), -0.05 (s, 3H), -0.07 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 159.1, 141.8, 136.2, 133.4, 127.8, 127.3, 125.9, 124.4, 122.0, 121.6, 121.2, 120.9, 120.8, 120.7, 118.7, 112.0, 109.9, 107.4, 33.4, 29.7, 25.9, 24.9, 17., -4.4, -4.8. HR-ESI-MS calculated for $C_{31}H_{34}N_3O_4Si$ $[M+H]^+$ 540.2318, found 540.2293.

(Z)-3-((2-((tert-butyldimethylsilyl)oxy)phenyl)(6-chloro-1-methyl-1*H*-indol-3-yl)methyl-ene)-6-chloro-1-methylindolin-2-one (3c): Yield: 43 mg, 23%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 1.5 Hz, 1H), 7.28-7.25 (m, 1 H), 7.06-7.03 (m, 2 H), 7.01 (d, *J* = 1.5 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.93 (td, *J* = 7.5, 1.0 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.77 (d, *J* = 2.0 Hz, 1H), 6.64-6.61 (m, 2H), 3.78 (s, 3H), 3.18 (s, 3H), 0.60 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 153.5, 143.6,

133.8, 133.0, 129.8, 128.6, 124.3, 123.7, 123.1, 121.4, 120.9, 120.5, 119.0, 110.0, 107.6, 33.4, 25.7, 25.1, 25.0, 17.7, -4.2, -4.3. HR-ESI-MS calculated for $C_{31}H_{33}Cl_2N_2O_2Si$ $[M+H]^+$ 563.1688, found 563.1682.

(E)-3-((2-((tert-butyldimethylsilyl)oxy)phenyl)(6-chloro-1-methyl-1*H*-indol-3-yl)methyl-ene) -6-chloro-1-methylindolin-2-one (3c'): Yield: 140 mg, 76%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.37 (td, *J* = 8.5, 2.0 Hz, 1H), 7.27 (d, *J* = 1.5 Hz, 1H), 7.18 (dd, *J* = 7.5, 1.5 Hz,1H), 7.00 (td, *J* = 7.5, 1.0 Hz, 1H), 6.91-6.88 (m, 2H), 6.74 (d, *J* = 2.0 Hz, 1H), 6.64 (d, *J* = 9.0 Hz, 1H), 6.60 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.30 (d, *J* = 8.5 Hz, 1H), 3.77 (s, 3H), 3.24 (s, 3H), 0.58 (s, 9H), -0.05 (s, 3H), -0.08 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 153.1, 146.1, 142.5, 137.7, 136.7, 132.2, 131.3, 130.5, 127.8, 126.3, 123.6, 123.0, 122.4, 121.6, 121.3, 120.9, 119.3, 113.3, 109.7, 107.6, 33.4, 26.0, 25.0, 17.7, -4.3, -4.6. HR-ESI-MS calculated for $C_{31}H_{33}Cl_2N_2O_2Si$ $[M+H]^+$ 563.1688, found 563.1684.

(Z)-3-((2-((tert-butyldimethylsilyl)oxy)phenyl)(5-iodo-1-methyl-1*H*-indol-3-yl)methyle-ne)-5-iodo-1-methylindolin-2-one (3d): Yield: 67 mg, 30%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.46 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.32 (d, *J* = 1.5 Hz, 1H), 7.28 (td, *J* = 8.0, 1.5 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.12 (br s, 1H), 7.09 (s, 1H), 7.07 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.94 (td, *J* = 7.5, 1.0 Hz, 1H), 6.88 (dd, *J* = 8.0, 0.5 Hz, 1H), 6.57 (d, *J* = 8.0, 1H), 3.81 (s, 3H), 3.18 (s, 3H), 0.62 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 152.7, 146.9, 140.8, 136.9, 136.3, 134.9, 131.5, 131.2, 130.9, 130.6, 130.5, 130.2, 130.1, 127.3, 121.8, 119.1, 119.0, 112.1, 111.6, 109.3, 85.1, 84.0, 33.5, 25.9, 25.1, 17.7, -4.2, -4.7. HR-ESI-MS calculated for $C_{31}H_{33}I_2N_2O_2Si$ $[M+H]^+$ 747.0400, found 747.0394.

(E)-3-((2-((tert-butyldimethylsilyl)oxy)phenyl)(5-iodo-1-methyl-1*H*-indol-3-yl)methyle-ne)-5-iodo-1-methylindolin-2-one (3d'): Yield: 142 mg, 64%. ^{1}H NMR (500

MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.45 (td, *J* = 8.0, 1.5 Hz, 1H), 7.37 (td, *J* = 8.0, 1.5 Hz, 2H), 7.14 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.08-7.04 (m, 2H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 3.79 (s, 3H), 3.22 (s, 3H), 0.60 (s, 9H), 0.06 (s, 3H), -0.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 153.5, 141.9, 136.5, 135.8, 134.0, 132.8, 131.5, 131.3, 130.9, 129.9, 127.8, 125.4, 120.9, 120.8, 118.9, 115.4, 111.9, 109.0, 84.6, 83.1, 83.4, 25.7, 25.1, 17.8, -4.2. HR-ESI-MS calculated for $C_{31}H_{33}I_2N_2O_2Si$ $[M+H]^+$ 747.0400, found 747.0392.

(Z)-6-Bromo-3-((6-bromo-1-methyl-1*H*-indol-3-yl)(2-((tert-butyldimethylsilyl)oxy)phe-nyl) methylene)-1-methylindolin-2-one (3e): Yield: 33 mg, 18%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 1.5 Hz, 1H), 7.24 (td, *J* = 8.0, 1.5 Hz, 1H), 7.12 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.02-7.01 (m, 2H), 6.92-6.88 (m, 3H), 6.84 (dd, *J* = 8.0, 0.5 Hz, 1H), 6.57 (d, *J* = 7.0 Hz, 1H), 3.75 (s, 3H), 3.15 (s, 3H), 0.58 (s, 9H), 0.04 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 153.5, 143.7, 138.2, 133.8, 133.2, 131.7, 129.9, 124.6, 124.0, 123.4, 122.4, 121.5, 121.0, 119.0, 116.9, 116.2, 113.0, 110.4, 33.4, 25.7, 25.1, 17.8, -4.2, -4.3. HR-ESI-MS calculated for $C_{31}H_{33}Br_2N_2O_2Si$ $[M+H]^+$ 651.0678, found 651.0676.

(E)-6-Bromo-3-((6-bromo-1-methyl-1*H*-indol-3-yl)(2-((tert-butyldimethylsilyl)oxy)phe-nyl) methylene)-1-methylindolin-2-one (3e'): Yield: 151 mg, 81%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.43 (d, *J* = 1.5 Hz, 1H), 7.37 (td, *J* = 8.5, 2.0 Hz, 1H), 7.18 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.04 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.00 (td, *J* = 7.5, 1.0 Hz, 1H), 6.90-6.88 (m, 2H), 6.77 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.58 (d, *J* = 9.0 Hz,1H), 6.97 (d, *J* = 8.5 Hz, 1H), 3.78 (s, 3H), 3.24 (s, 3H), 0.58 (s, 9H), -0.05 (s, 3H), -0.08 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 153.1, 146.2, 142.6, 138.0, 136.7, 132.0, 131.2, 130.5, 126.6, 124.0, 123.9, 123.8, 123.4, 122.8, 121.6, 120.1, 119.3, 115.5,

113.4, 112.7, 110.4, 33.4, 25.9, 25.0, 17.7, -4.3, -4.6. HR-ESI-MS calculated for $C_{31}H_{33}Br_2N_2O_2Si$ $[M+H]^+$ 651.0678, found 651.0679.

(Z)-3-((2-((tert-butyldimethylsilyl)oxy)phenyl)(1-methyl-5-nitro-1*H*-indol-3-yl)methyl-ene)-1-methyl-5-nitroindolin-2-one (3f): Yield: 113 mg, 52%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.10 (dd, *J* = 8.5, 2.0 Hz, 2H), 7.82 (d, *J* = 2.0 Hz, 1H), 7.53 (td, *J* = 8.0, 1.5 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.18 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.11 (td, *J* = 7.5, 1.0 Hz, 1H), 7.06 (d, *J* = 2.5 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 1H), 3.91 (s, 3H), 3.33 (s, 3H), 0.54 (s, 9H), 0.04 (s, 3H), -0.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 153.7, 147.5, 142.6, 142.0, 140.3, 136.3, 131.4, 130.8, 125.2, 124.6, 123.2, 121.1, 119.1, 118.3, 117.6, 110.7, 106.9, 33.9, 26.1, 25.1, 17.7, -4.3. HR-ESI-MS calculated for $C_{31}H_{33}N_4O_6Si$ $[M+H]^+$ 585.2169, found 585.2177.

Table 4b.5A. Zone of inhibition (diameter in mm) studies of indolo[2,3-*b*]quinolines **2**, and 3-alkenyl-oxindoles **3**[a]

Comp-ound name	*Bacillus cereus*	*Staphylo-coccus aureus*	*Staphylo-coccus epidermidis*	*Staphylo-coccus simulans*	*Escherichia coli*	*Klebsiella pneumoniae*	*Proteus mirabilis*
2a	0	18 ± 0	0	6 ± 0	0	5 ± 0	0
2b	0	0	0	0	0	0	0
2c	0	0	0	0	0	0	0
2d	0	0	0	0	0	0	0
2e	0	0	9±1	9.66 ± 0.57	9.33 ± 0.57	10.33 ± 0.57	0
2f	0	0	0	0	0	17 ± 0	0
2g	0	0	0	0	0	0	0
2h	0	0	0	0	0	0	0
2i	0	0	0	0	0	0	0
2j	0	0	0	0	0	0	0
2k	0	0	0	0	0	0	0

2l	0	0	0	0	0	0	0
2m	0	0	0	0	0	0	0
2n	0	15 ± 0	0	0	0	0	0
2o	9.66 ± 0.57	0	0	0	8 ± 1	0	0
2p	0	7±1	0	7.66 ± 0.57	0	0	0
3a-f	0	0	0	0	0	0	0

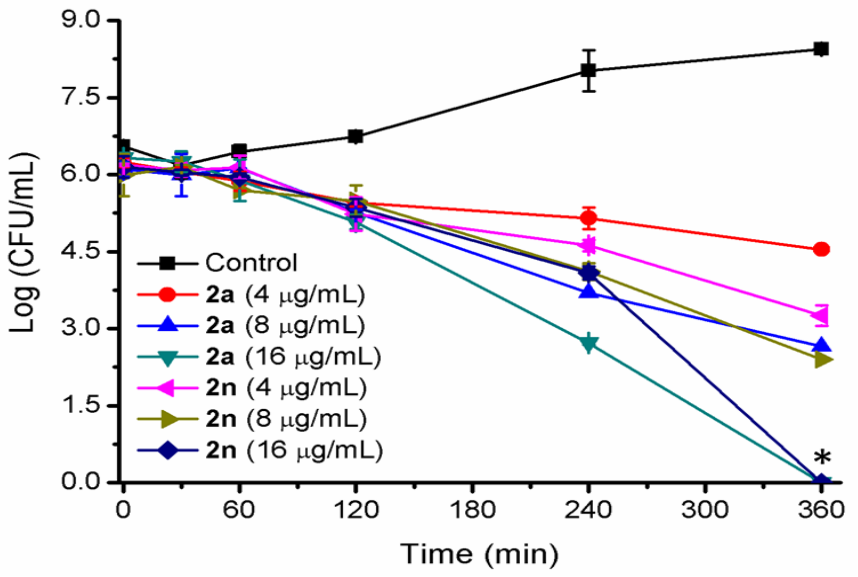
[a]Zone of inhibition was an average of three replications ± standard deviation.

Table 4b.5B. Antibacterial activity of compounds **2a** and **2n**[a]

Bacteria	MIC (µg/mL)			MBC (µg/mL)		
	2a	**2n**	Methicillin	**2a**	**2n**	Methicillin
Staphylococcus aureus-MTCC737	1	1	1	4	2	4
MRSA-ATCC33591	2	2	>64	4	4	>64
MRSA-R3545	2	1	32	4	2	>64
MRSA-R3889	2	1	32	8	4	>64
MRSA-R3890	4	1	>64	8	8	>64
Escherichia coli-MTCC443	>64	>64	ND[a]	>64	>64	ND
Acinetobacter baumannii-MTCC1425	>64	>64	ND	>64	>64	ND
Klebsiella pneumniae-ATCC700603	>64	>64	ND	>64	>64	ND

[a] ND stands for not determined.

Figure 4b.5D. Time-kill kinetics of compounds **2a** and **2n** against MRSA-ATCC33591[a]



[a]The symbol (*) represents complete killing (detection limit is 50 CFU/mL).

4b.6. References

1. Trost, B. M.; Osipov, M. *Chem. - Eur. J.* **2015**, *21*, 16318.
2. Bracca, A. B. J.; Heredia, D. A.; Larghi, E. L.; Kaufman, T. S. *Eur. J. Org. Chem.* **2014**, *2014*, 7979.
3. Sidoryk, K.; Jaromin, A.; Edward, J. A.; Świtalska, M.; Stefańska, J.; Cmoch, P.; Zagrodzka, J.; Szczepek, W.; Peczyńska-Czoch, W.; Wietrzyk, J.; Kozubek, A.; Zarnowski, R.; Andes, D. R.; Kaczmarek, Ł. *Eur. J. Med. Chem.* **2014**, *78*, 304.
4. (a) Kaczmarek, L.; Peczynska-Czoch, W.; Osiadacz, J.; Mordarski, M.; Sokalski, W. A.; Boratynski, J.; Marcinkowska, E.; Glazman-Kusnierczyk, H.; Radzikowski, C. *Bioorg. Med. Chem.* **1999**, *7*, 2457. (b) Godlewska, J.; Luniewski, W.; Zagrodzki, B.; Kaczmarek, L.; Bielawska-Pohl, A.; Dus, D.; Wietrzyk, J.; Opolski, A.; Siwko, M.; Jaromin, A.; Jakubiak, A.; Kozubek, A.; Peczynska-Czoch, W. *Anticancer Res.* **2005**, *25*, 2857.
5. (a) Vecchione, M. K.; Sun, A. X.; Seidel, D. *Chem. Sci.* **2011**, *2*, 2178. (b) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *J. Org. Chem.* **2009**, *74*, 8369. (c) Yan, Z.;

Wan, C.; Wan, J.; Wang, Z. *Org. Biomol. Chem.* **2016**, *14*, 4405. (d) Ali, S.; Li, Y.; Anwar, S.; Yang, F.; Chen, Z.; Liang, Y. *J. Org. Chem.* **2012**, *77*, 424. (e) Sundaram, G. S. M.; Venkatesh, C.; Kumar, U. K. S.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2004**, *69*, 5760. (f) Dhanabal, T.; Sangeetha, R.; Mohan, P. S. *Tetrahedron* **2006**, *62*, 6258.

6. Millemaggi, A.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2010**, 4527.
7. (a) Ueda, S.; Okada, T.; Nagasawa, H. *Chem. Commun.* **2010**, *46*, 2462. (b) Shintani, R.; Yamagami, T.; Hayashi, T. *Org. Lett.* **2006**, *8*, 4799. (c) Cantagrel, G.; Carne-Carnavalet, B. de; Meyer, C.; Cossy, J. *Org. Lett.* **2009**, *11*, 4262.
8. Bandgar, B. P.; Shaikh,K. A. *Tetrahedron Lett.* **2003**, *44*, 1959.

Summary and Conclusions

In the first chapter, a brief introduction to multicomponent reactions (MCRs) and importance of hypervalent iodine reagents (HIRs) and DDQ oxidants in organic synthesis has been described. Briefly, Multicomponent reactions (MCRs) are considered as ideal reactions because they combine more than two components to generate molecular complexity in one-pot. The first MCR reaction was reported by Adolph Strecker in 1850 when he synthesized α-amino acids from aldehyde, ammonia and hydrogen cyanide. However, the introduction of isocyanide based MCRs (IMCRs) such as Passerini 3CR and Ugi 4CR has changed the paradigm of MCR. MCRs are successfully applied in several natural product synthesis, generation of novel scaffolds and drug discovery.

Hypervalent iodine reagents (HIRs) are considered as mild and green alternatives to heavy toxic metal oxidants. The most commonly used HIR is Dess-Martin periodinane (DMP) for the oxidation of alcohols to carbonyl compounds. The general reactivity pattern of HIR involves ligand exchange, reductive elimination and ligand coupling. One of the most important applications of HIR is generation of an umpolung of phenolic substrates by dearomatization. The concept of oxidative dearomatization by HIR was successfully applied in several natural products synthesis. Apart from this HIRs were frequently utilized in oxidative aryl-aryl couplings, electrophilic arylation, trifluoromethylation, synthesis of heterocycles and rearrangement reactions. On the other hand DDQ is considered as a mild and ecofriendly oxidant mainly used for the functionalization of allylic, propargylic and benzylic SP_3 C-H bonds in inter and intramolecular Cross Dehydrogenative Coupling reactions (CDC).

The second chapter describes an efficient three component approach (3CR) for the synthesis of 1,2-dihydropyridines (1,2-DHP) (**5**). 1,4-DHP based drugs are best known

for their calcium channel modulating properties, whereas 1,2-DHPs are less explored in medicinal chemistry but utilized as useful intermediates for the synthesis of pyridines, pyridones and as diene component in Diels-Alder reaction. Isoquinuclidine is the key intermediate in the synthesis of Tamiflu an influenza drug which is obtained from 1,2-DHP. Several reports are available in the literature for the synthesis of 1,2-DHPs, most of them utilizes transition metal catalysts, high temperatures and tedious starting material synthesis. Our present method utilizes easily accessible dienaminodioate (**2**) and readily available aldehydes (**3**) and amines (**4**) in the presence trifluoroacetic acid (TFA) to make diversely substituted 1,2-DHP (**5**) (Figure. 2.1A). Several optimization reactions were conducted and found that one equivalent of TFA in acetonitrile solvent at room temperature and in open air atmosphere is the best condition for this reaction. The substrate scope was demonstrated with variously substituted aromatic, hetero aromatic and polycyclic aromatic aldehydes as well as aromatic and benzyl amines. Most of the electronic effects in the substrates were well tolerated and products were usually observed in good to excellent yields.

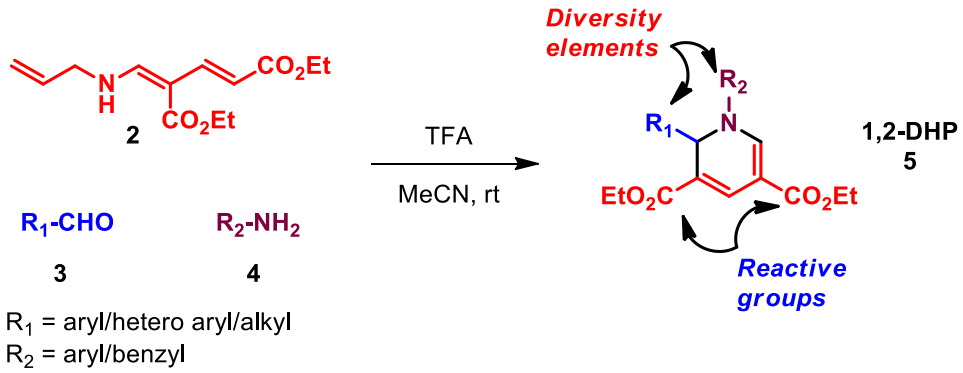


Figure 2.1A. Synthesis of 1,2-DHP by a cascade 3CR approach

Third chapter explains the serendipitous discovery of biaryl (**5**) formation from dienaminodioate (**1**), cinnamaldehydes (**2**) and allyl amine (**3**) in presence of excess TFA (Figure. 3.1A). When we replaced the aromatic aldehydes with cinnamaldehydes in the synthesis of 1,2-DHP, we obtained a red colored compound which upon storing for long

time in $CDCl_3$ solvent converted to a new product. This product was identified as biaryl-2-carbaldehyde by using extensive 1D, 2D-NMR and X-ray single crystal analysis. The red colored intermediate was found to be trienamine (**4**) instead of 1,2-DHP. To develop a one-pot method for the synthesis of biaryl-2-carbaldehydes we have tested several reaction conditions which revealed 3 equivalents of TFA in 1:1 $CH_3CN/CHCl_3$ solvent combination as the best condition. We have checked the generality with variously substituted cinnamaldehydes such as electron rich, electron poor and with multi substituents. In most of the reactions we obtained the desired biaryls in moderate to good yields. Furthermore, we have successfully utilized the biarl-2-carbaldehydes to synthesize molecules of biology and material relevance.

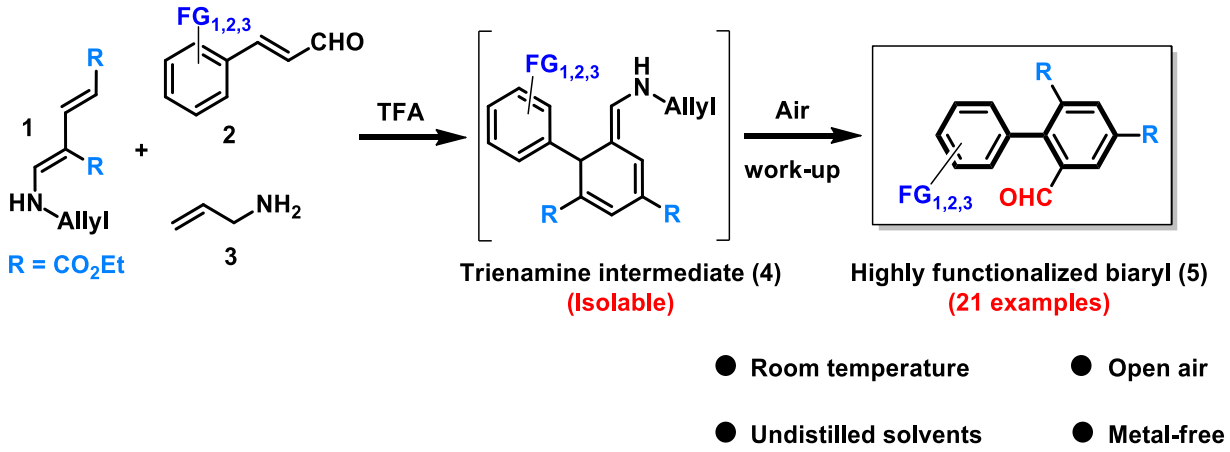


Figure 3.1A. Cascade synthesis of biaryl-2-carbaldehyde

In the fourth chapter, we have successfully transformed an easily accessible diindolylmethanes (DIMs) to synthesize a diverse library of scaffolds under mild and metal-free oxidative reaction conditions. Diindolylmethanes (DIMs) or bisindolylmethanes (BIMs) are best known for their anti-cancer property. The ease of synthesis and our previous experience in chapter 3 to make biaryl appended DIMs and subsequent anti-cancer exploration in our laboratory prompted us to utilize DIMs as suitable starting materials for our metal-free transformations. This chapter is further divided into two parts.

Chapter-4a reveals an unusual PIDA mediated transformation of DIPM (**1**) derived from salicylaldehyde and 1-alkyl indole to 2,3'-diindolyl ketones (**2**) (Figure 4a.1A). The optimized condition for this transformation was two equivalents of PIDA and 1:1 HFIP/DCM solvent combination at room temperatures. Different halo- and electron rich substituents containing DIMs gave the desired products in moderate to good yields whereas DIMs with electron withdrawing substituents were not suitable for this transformation. In order to investigate the underlying mechanism behind this transformation we have taken a theoretical route and with the help of Dr. Suresh C.H. from NIIST, DFT calculations were performed by him and it was found that the reaction involves multiple C-C single bonds and C-H functionalizations by a 'charge-switching' mechanism which is unprecedented under metal-free conditions.

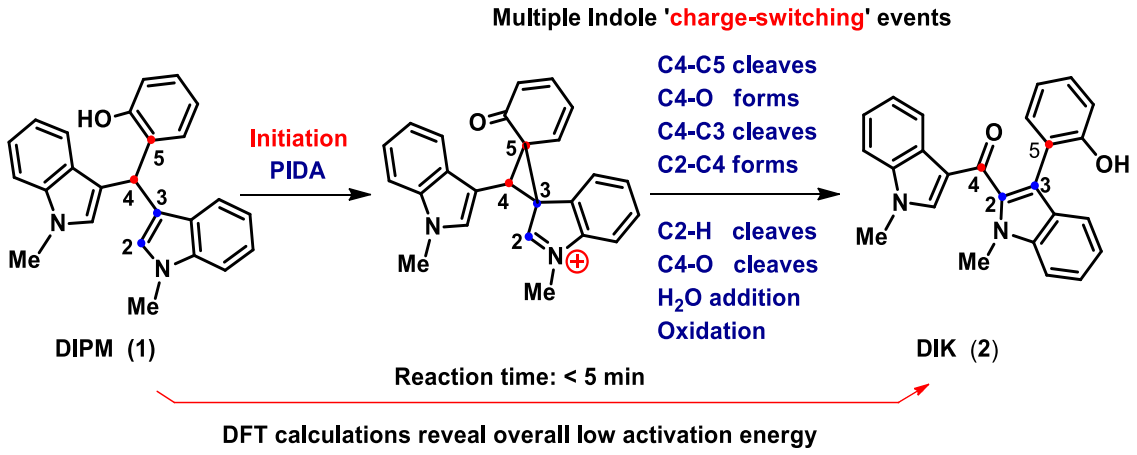


Figure 4a.1A. PIDA mediated indole "charge-switching" reaction in DIPM

Furthermore, the charge-switching concept was successfully applied to DIBM derived from biphenyl aldehydes and 1-alkyl indoles which resulted in the formation of a highly important cyclohepta[*b*]indole motif in good to excellent yields. The DIMs underwent PIDA mediated charge-switching mechanism to generate a spiro dienone intermediate which upon treatment with $BF_3.OEt_2$ yielded cyclohepta[*b*]indoles via dienone-phenol rearrangement (Figure 4a.1B).

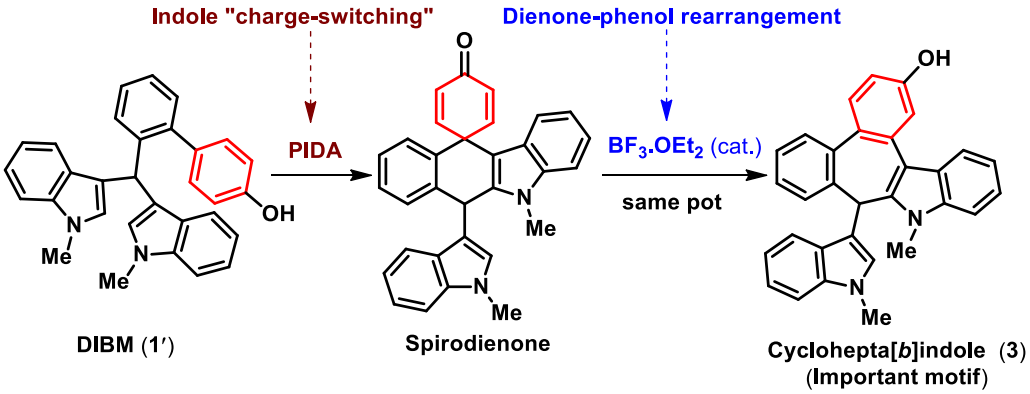


Figure 4a.1B. Extension of "charge-switching" concept for cyclohepta[*b*]indole synthesis

Chapter-4b describes DDQ mediated transformation of DIMs to indolo[2,3-*b*]quinolines and 3-alkenyl-oxindoles under mild conditions. DIMs generated from *ortho*-NHTs substituted benzaldehydes and NH or 1-alkyl indoles underwent an intramolecular C-N bond formation reaction to form indolo[2,3-*b*]quinolines under DDQ mediated oxidation conditions. Indoloquinolines are very important scaffolds present in several natural alkaloids. All reactions were performed at room temperatures under open air atmosphere to get variously substituted indoloquinolines in good to excellent yields (Figure 4b.1A). Under the same DDQ conditions *ortho*-hydroxy DIMs derived from salicylaldehyde and 1-alkyl indole gave an inseparable mixture of 3-alkenyl-oxindoles which were separated by column after TBS protection of hydroxy group (Figure 4b.1A). Here also the products were usually obtained in good to excellent yields. 3-Alkenyloxindoles are also important structural motifs present in several bioactive molecules.

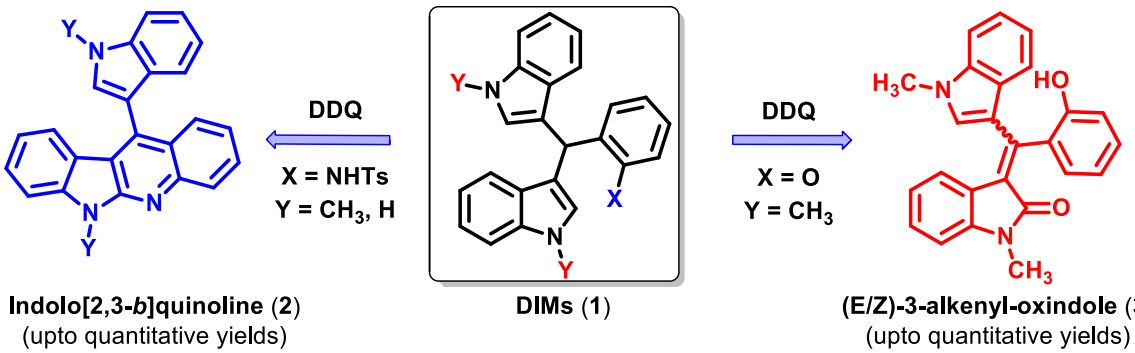


Figure 4b.1A. DDQ mediated synthesis of indolo[2,3-*b*]quinolines and 3-alkenyl-oxindole

List of Publications

1. Cascade synthesis of 1,2-dihydropyridine from dienaminodioate and an imine: a three-component approach - *Tetrahedron Lett*. **2013**, *54*, 3810-3812.
   Chandrasekhar Challa, Manju John, Ravi S. Lankalapalli*
2. A comparative study of antimicrobial properties of cyclo(L-Pro-L-Asp) with its 2-ketopiperazine analog -*Med. Chem. Res*. **2014**, *23*, 2377–2385.
   Chandrasekhar Challa, Nishanth Kumar, Manju John, Ravi S. Lankalapalli*
3. A metal-free one-pot cascade synthesis of highly functionalized biaryl-2-carbaldehydes - *Org. Biomol. Chem*.**2014**, *12*, 8588-8592.
   Chandrasekhar Challa, Jamsheena Vellekkatt, Jaice Ravindran, Ravi S. Lankalapalli*
4. Metal-free multiple carbon-carbon and carbon-hydrogen bond activations via charge-switching mechanism in unstrained diindolylmethanes - *Org. Lett.* **2017**, *19*, 4219-4222.
   Chandrasekhar Challa, Sunil Varughese, Cherumuttathu H. Suresh, Ravi S. Lankalapalli*
5. Expedient synthesis of indolo[2,3-*b*]quinolines, chromeno[2,3-*b*]indoles, and 3-alkenyl-oxindoles from 3,3'-diindolylmethanes and evaluation of their antibiotic activity against methicillin-resistant *Staphylococcus aureus*- *ACS Omega* **2017**, *2*, 5187-5195.
   Chandrasekhar Challa, Jaice Ravindran, Mohini Mohan Konai, Sunil Varughese, Jubi Jacob, B. S. Dileep Kumar, Jayanta Haldar, Ravi S. Lankalapalli*

Conferences/Posters

1. A metal-free one-pot cascade synthesis of highly functionalized biaryl-2-carbaldehydes. Poster Presentation in a 1st National symposium on Transcending Frontiers in Organic Chemistry (TFOC), organized by CSIR-NIIST, Trivandrum, Kerala, October 09-11, 2014.
   Chandrasekhar Challa and Ravi S. Lankalapalli*
2. Metal-Free Cascade Synthesis of 1,2-DHPs and Biaryl-2-Carbaldehydes.
   Poster presentation at 17th CRSI-National Symposium in Chemistry, organized by CSIR-NCL, Pune, India, February 06-08, 2015.
   Chandrasekhar Challa and Ravi S. Lankalapalli*