Construction of Carbocycles and Heterocycles Utilizing the Steric Strain in Heterobicyclic Olefins

Thesis Submitted to AcSIR for the Award of the Degree of
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November 2017

.....To My Beloved Parents

DECLARATION

*I hereby declare that the Ph.D. thesis entitled "**Construction of Carbocycles and Heterocycles Utilizing the Steric Strain in Heterobicyclic Olefins**" is an independent work carried out by me at Organic Chemistry Section, Chemical Sciences and Technology Division, CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST), Thiruvananthapuram under the supervision of **Dr. K. V. Radhakrishnan**, Principal Scientist and Head, Organic Chemistry Section, and it has not been submitted anywhere else for any other degree, diploma or title.*

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*This is to certify that the work incorporated in this Ph.D. thesis entitled "**Construction of Carbocycles and Heterocycles Utilizing the Steric Strain in Heterobicyclic Olefins**" submitted by **Mr. Ajesh Vijayan** to Academy of Scientific and Innovative Research (AcSIR), in fulfilment of the requirements for the award of the **Degree of Doctor of Philosophy in Chemical Sciences**, embodies original research work under my guidance. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in this thesis. Any text, illustration, table, etc. used in this thesis from other sources have been duly cited and acknowledged.*

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Ajesh Vijayan

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ABBREVIATIONS

Ac	:	acetyl	*ee*	:	enantiomeric excess
Ar	:	aryl	ESI	:	electron spray ionisation
BINAP	:	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl	Et	:	ethyl
			EWG	:	electron withdrawing group
Bn	:	Benzyl	equiv.	:	equivalents
Boc	:	tertiary butyloxycarbonyl	FT	:	fourier transform
brs	:	broad singlet	g	:	gram
^{t}Bu	:	tertiary butyl	h	:	hours
^{o}C	:	degree Celsius	HRMS	:	high resolution mass spectra
calcd	:	calculated	Hz	:	hertz
cm	:	centimetre	^{i}Pr	:	isopropyl
cod	:	cyclooctadiene	IR	:	infrared
Cp*	:	pentamethylcyclopentadienyl	*J*	:	coupling constant
d	:	doublet	L	:	litre
dba	:	dibenzylidene acetone	LA	:	Lewis acid
DCE	:	dichloroethane	LAH	:	lithium aluminium hydride
DCM	:	dichloromethane	M	:	molar
dd	:	doublet of a doublet	m	:	multiplet
DIPA	:	diisopropylamine	*m*	:	meta
DIPEA	:	diisopropylethylamine	M. P.	:	melting point
DMDO	:	dimethyldioxirane	Me	:	methyl
DME	:	1,2-dimethoxyethane	Mg	:	milligram
DMF	:	dimethylformamide	MHz	:	megahertz
DMSO	:	dimethylsulfoxide	mL	:	millilitre
dppe	:	bis(diphenylphosphino)ethane	mmole	:	millimole
dppf	:	bis(diphenylphosphino) ferrocene	MS	:	molecular sieves
			MW	:	microwave
dppm	:	bis(diphenylphosphino)methane	NMO	:	*N*-methylmorpholine-*N*-oxide
dppp	:	bis(diphenylphosphino)propane	NMR	:	nuclear magnetic resonance

Nu	:	Nucleophile
o	:	ortho
p	:	para
Ph	:	phenyl
ppm	:	parts per million
q	:	quartet
rac	:	racemic
R_f	:	retention factor
rt	:	room temperature
s	:	singlet
t	:	triplet
tert	:	tertiary
Tf	:	trifluoro methane sulfonyl
TFA	:	trifluoro acetic acid
THF	:	tetrahydrofuran
TLC	:	thin layer chromatography
TMS	:	tetramethylsilane
Tol	:	tolyl
Ts	:	tosyl

PREFACE

The synthesis and functionalization of biologically important functionalized carbocycles and heterocycles using simple precursors is one of the most challenging goals in synthetic organic chemistry. Different research groups have developed various attractive synthetic approaches including both transition metal catalyzed as well as metal free strategies in this regard. One of the simplest methods to achieve this is through the synthetic transformations of heterobicyclic olefins such as oxa/aza, oxaza or diazabicyclic olefins, Vince lactams and so forth.

The desymmetrization reactions of diazabicyclic olefins have grabbed a lot of attention in the construction of functionalized hetero/carbocyclic motifs appended or fused with cyclopentene derivatives. However, the presence of hydrazine derivatives having considerable toxicity in the products is a serious drawback of the strategy. Replacing such toxic moieties with more biologically significant motifs such as urea derivatives pose a convenient remedy to this problem. This thesis entitled "**Construction of Carbocycles and Heterocycles Utilizing the Steric Strain in Heterobicyclic Olefins**", describes our entire effort towards the development of such metal free as well as transition metal catalyzed transformations of diazabicyclic and urea-derived bicyclic olefins.

The thesis is divided into five chapters. Relevant references are given at the end of each chapter. Also, each chapter of the thesis is presented as an independent unit and therefore the structural formulae, schemes and figures are numbered chapter wise. The first chapter of the thesis gives an overview of the heterocyclic olefins, its reactivity and various synthetic transformations developed so forth. Out of the various heterobicyclic olefins, the chapter mainly focuses on the synthetic manipulations of oxa/azabicyclic olefins, oxaza bicyclic olefins, diazabicyclic olefins, Vince lactams and urea-derived bicyclic olefins. The definition of the present research problem is also incorporated in this chapter.

The second chapter outlines the synthesis of cyclopenta[*b*]chromene derivatives by the base catalyzed intramolecular transformation of phenol substituted fulvene derived diazabicyclic olefins. Even though there are limited reports on the palladium/Lewis acid mediated desymmetrization of fulvene derived azabicyclic olefins, the synthetic

transformations of phenol-substituted fulvene derived azabicyclic olefins have not been investigated so far.

Urea and its cyclic derivatives represent a class of biologically relevant molecules, widely occurring in natural products and have been studied for various biological activities such as antibiotic hypoglycemic effects, anti-cancer, anti-diabetic, antimicrobial, antibacterial activities *etc.* The urea-derived bicycles grabbed our attention because of their tremendous synthetic potential. The reactivity of urea-derived bicyclic olefins under different transition metal catalysis such as rhodium, palladium and iridium are described in the following chapters. The synthesis of chromanone fused urea derivatives through the oxidative coupling of salicylaldehydes and urea-derived bicyclic olefins in the presence of Rh/Cu catalyst system is described in the third chapter.

The fourth chapter, which is divided into three parts deals with the hydro(hetero) arylation reactions and annulation reactions of urea-derived bicyclic olefins. Part A describes an efficient method for the hydroarylation of these bicycles via the palladium catalyzed reductive Heck reaction. The presence of functional groups in the *ortho*-position of aryl iodides can trap the palladium species intramolecularly resulting in a cascade reaction and forms annulated products. The reaction of bi-functional aryl iodides such as 2-iodophenol, 2-iodobenzylbromide and 2-iodobenzonitrile towards the synthesis of benzofuran, indane and indanone derivatives forms the core of Part B. The iridium catalyzed hydroheteroarylation using *N*-free indoles, benzofurans and pyrroles is illustrated in Part C.

Chapter five outlines the results of our investigations on the rhodium catalyzed synthesis of azaheterocycles, and is divided into two parts. Recent advances in transition metal catalyzed reactions have paved a way to the facile syntheses of azaheterocycles *via* the functionalization of omnipresent carbon–hydrogen bonds. Our investigations on the rhodium catalyzed reaction of urea-derived bicyclic olefins with *O*-acetyl ketoximes toward the synthesis of isoquinoline fused bicycles is described in Part A of chapter 5 whereas the isoquinolone synthesis using the C-H activation of *N*-methoxybenzamides is dealt in Part B.

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

CHAPTER 1

Heterobicyclic Olefins: An Overview

1.1. Introduction

One of the ultimate challenges in synthetic organic chemistry is to develop novel and efficient transformations for the creation of functionalized molecules with structural diversity. Transition metal catalyzed reactions have revolutionized the area of synthetic organic chemistry by providing facile and efficient routes toward the construction of carbocycles and heterocycles.[1–9] In this regard, the discovery of novel synthons and their useful synthetic transformations have been an interesting prospect for many synthetic chemists. Among the different synthons utilized so far, heterobicyclic alkenes achieved considerable attention because of their intrinsic angle strain, unfavorable bond angles, eclipsing interactions, and thus exhibiting different reactivity patterns.[10] The steric strain present in these bicycles can be attributed to ring strain energy (RSE) which is defined as the destabilization or increase in energy created upon ring closure of an acyclic molecule.[10] The introduction of a heteroatom in the bicyclic structure greatly influences the reactivity of these molecules because of the electronegative nature of the heteroatom. One example that demonstrates this fact include the increase in the ring strain energy of 7-heteroatom substituted analogues of norbornadiene containing oxygen or nitrogen atoms compared to norbornadiene and norbornene. The electronegativity of the heteroatom substituents and degree of saturation of the molecule are the important factors determining the ring strain of bicyclic olefins.[11] Other than ring strain, the reactivity of these bicyclic systems is also influenced by its unique geometry, which is responsible for the exclusive facial selectivity. Steric considerations indicate that the *exo* face is more accessible to reactants.

Among the various heterobicyclic systems explored, majority of the investigations have been made on oxa/aza norbornadiene derivatives, oxazabicycles, Vince lactams, diazabicyclic olefins and urea derived bicyclic olefins (Figure 1).[12–14] Various transformations of heterobicyclic olefins have been reported using a variety of transition metals such as palladium, rhodium, ruthenium, nickel, cobalt, copper, gold and so on. However, reactions catalyzed by palladium, rhodium, ruthenium, and iridium will be the

primary focus in the following sections considering its relevance to the content of the thesis.

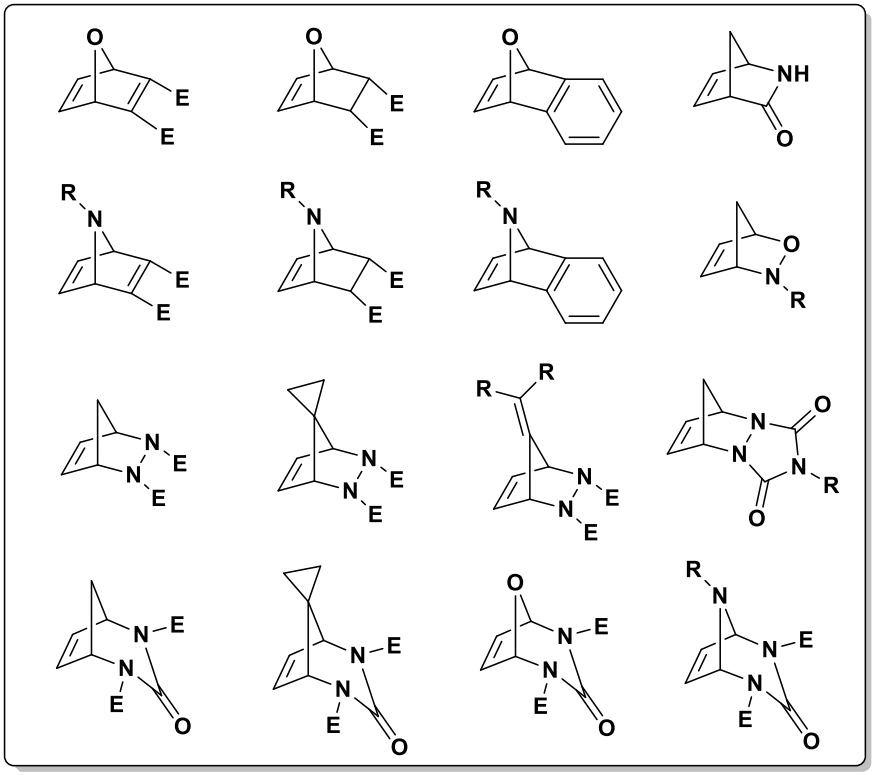
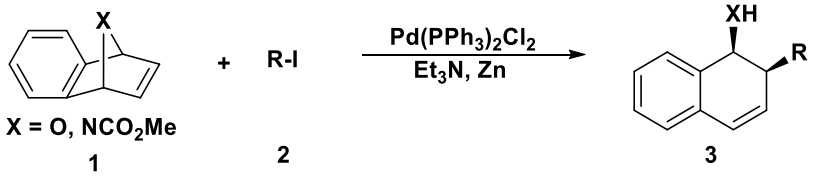


Figure 1.1. Various heterobicyclic alkenes

1.2. Transition Metal Catalyzed Reactions of Oxa or Azabicyclic Alkenes

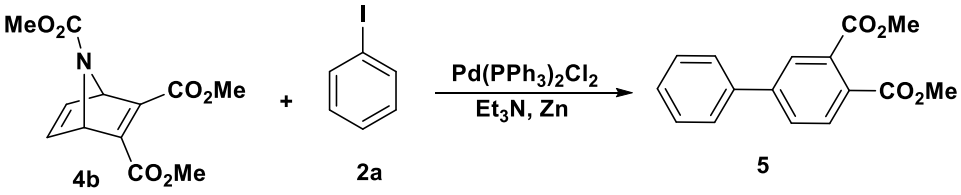
1.2.1. Palladium Catalyzed Reactions

Palladium is one of the most versatile, useful and important metals in synthetic organic chemistry which has significantly improved the art of organic synthesis over the past few decades. First report on the stereoselective palladium-catalyzed reactions of 7-heteroatom norbornadiene derivatives **1** with organic halides **2** to give substituted aryls, *cis*-1,2-dihydro-l-naphthyl alcohols and carbamates was by Cheng *et al.* in 1993 (Scheme 1.1).[15]



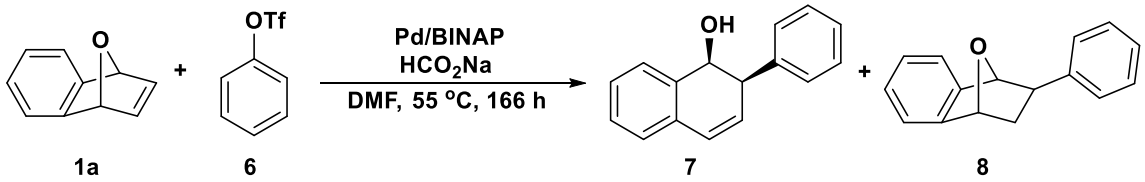
Scheme 1.1

Later the same group extended this strategy to 7-aza or oxa norbornadiene derivatives **4b**, which gave biphenyl derivatives **5** (Scheme 1.2).[16]



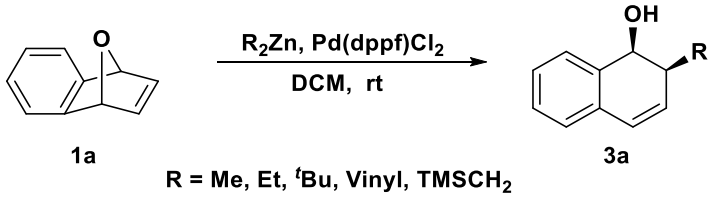
Scheme 1.2

The asymmetric version of the above reaction facilitating the ring opening of benzoxanorbornadienes **1a** using palladium (0) BINAP complex, phenyl triflate **6**, and sodium formate in dimethylformamide (DMF) at 55 °C for 166 h was developed by Fiaud *et al*. The ring opened product **7** as well as the hydroarylated product **8** were formed in this reaction (Scheme 1.3).[17]



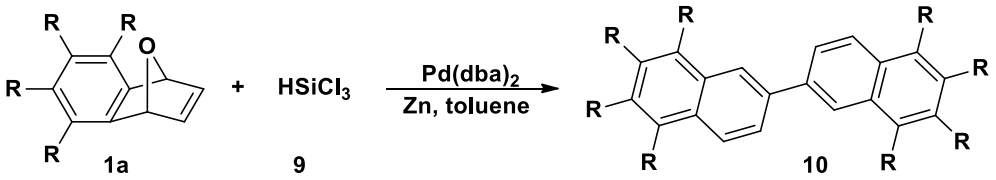
Scheme 1.3

The palladium catalyzed enantioselective alkylative ring opening reaction of oxabenzonorbornadiene **1a** with dialkylzinc reagents was reported by Lautens' group. This method is applicable to the enantioselective synthesis of cyclohexenols, cycloheptenol and dihydronaphthols **3a** (Scheme 1.4).[18]



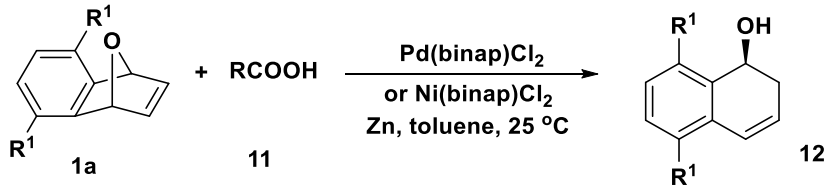
Scheme 1.4

Cheng *et al*. reported an unusual deoxygenative dimerization of the 7-oxabenzonorbornadiene derivatives **1a** with trichlorosilane **9** in the presence of palladium and zinc catalysts to afford the corresponding biaryl products **10** in good to excellent yields (Scheme 1.5). The process appears to occur *via* a novel palladium-catalyzed hydrosilylative dimerization of 1,4-epoxy-1,4-dihydroarenes and subsequent elimination of $HOSiCl_3$ and H_2O.[19]



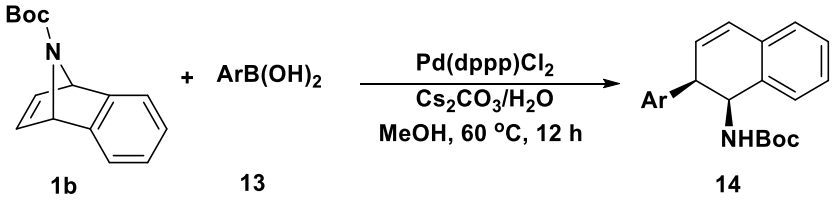
Scheme 1.5

Cheng *et al*. reported the asymmetric reductive ring opening reaction of oxa- and azabenzonorbornadienes **1a** with organic acids **11** and zinc powder under mild conditions catalyzed by Ni(binap)Cl_2 or Pd(binap)Cl_2 to furnish the corresponding 1,2-dihydronaphth-1-ols **12** in good to excellent yields with high enantioselectivity (Scheme 1.6).[20]



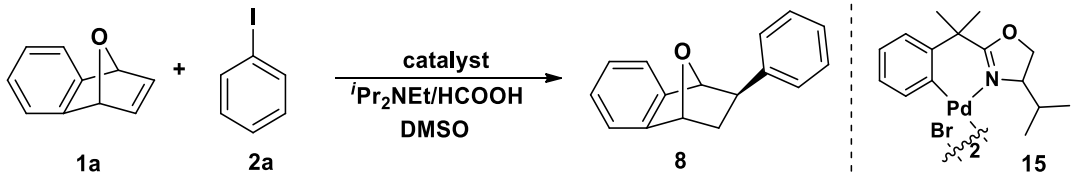
Scheme 1.6

Lautens' group reported palladium catalyzed ring opening of heterobicyclic alkenes **1b** with arylboronic acids **13**.[21] The addition of a variety of aryl groups proceeded in excellent yield, including heteroaryl groups, which can be problematic with other catalyst systems (Scheme 1.7).



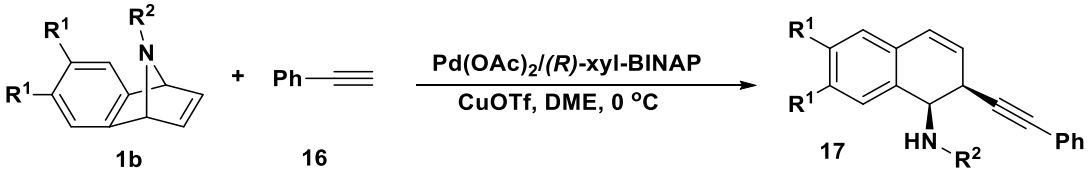
Scheme 1.7

Hydrophenylation of a wide range of bicyclic alkenes, not only norbornene and norbornadiene but also oxa- and aza-bicyclic alkenes **1a** with iodobenzenes **2a** under aerobic conditions using a highly efficient palladacycle catalyst **15** was reported by Hou and coworkers (Scheme 1.8).[22]



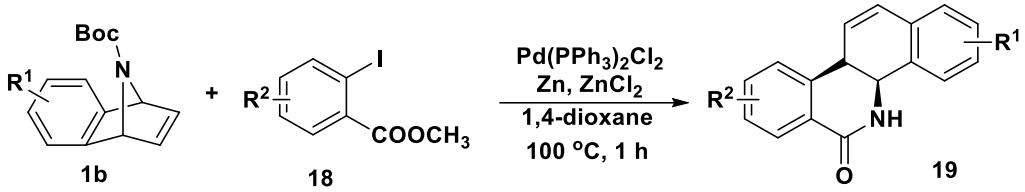
Scheme 1.8

Palladium-catalyzed asymmetric ring opening reaction of substituted azabenzonorbornadienes **1b** with terminal alkynes **16** was explored by Fan & Wang *et al*. This chiral palladium/copper co-catalytic system which comprised of palladium(II) acetate/(*R*)-xylBinap and copper(I)triflate (CuOTf) exhibited wide substrate compatibility and good functional group tolerance (Scheme 1.9).[23]



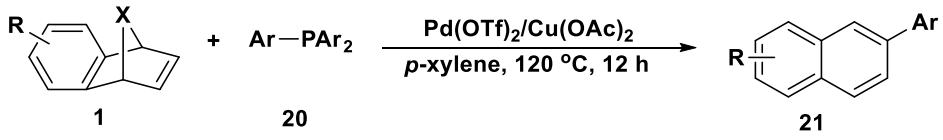
Scheme 1.9

The palladium-catalyzed annulation reaction of methyl-*o*-halobenzoates **18** with azabicyclic alkenes **1b** proceeded efficiently to furnish the corresponding benzo[*c*]phenanthridine derivatives **19** in good to excellent yields (Scheme 1.10). In this report by Xu *et al*., they developed an improved and generally applicable base free methodology which may be applied in the functionalized synthesis of both fully aromatized-type and partially hydrogenated-type alkaloids.[24]



Scheme 1.10

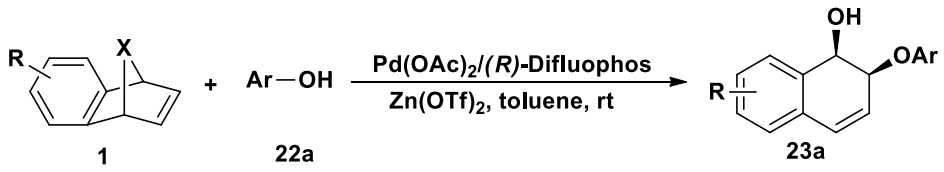
A new approach for the Pd(II)-catalyzed aromatic coupling of oxabenzonorbornadienes **1** with triarylphosphines **20** as both ligands and aryl donors was developed by Jiang and coworkers (Scheme 1.11). The catalytic process underwent stable C−P bond cleavage and tolerated diverse functional groups, which allowed new potential in the application of phosphines.[25]



Scheme 1.11

In a report by Fan and Wang *et al*., they developed a new palladium/zinc co-catalyst system associated with chiral (*R*)-Difluorphos for asymmetric ring-opening reaction of

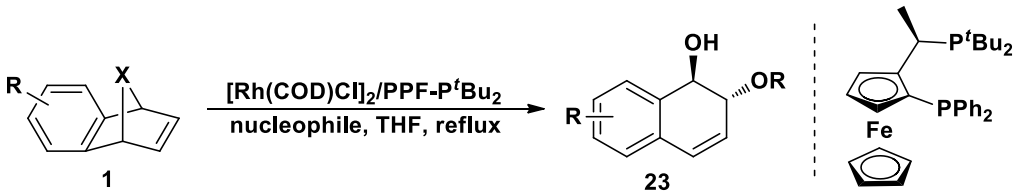
oxabenzonorbornadienes **1** with phenols **22a** to form *cis*-2-aryloxy-1,2-dihydronaphthalen-1-ol products **23a** in good yields (Scheme 1.12). This reaction represents the first example in ring-opening reactions of bicycloalkenes with heteronucleophiles in a *syn*-stereoselective manner.[26]



Scheme 1.12

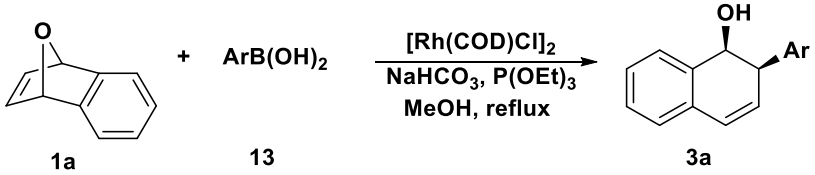
1.2.2. Rhodium Catalyzed Reactions

The first rhodium-catalyzed asymmetric ring opening (ARO) reaction of oxabenzonorbornadienes **1** using alcohol and amine nucleophiles to produce *trans*-2-alkoxy-1,2-dihydronaphthalenols **23** in good yields and excellent *ee*'s was developed by Lautens and coworkers in 2000 (Scheme 1.13).[27]



Scheme 1.13

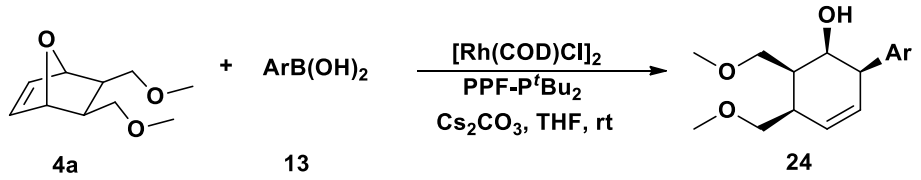
Murakami *et al*. reported the facile addition reaction of boronic acids **13** to oxabenzonorbornadienes **1a** using a catalytic amount of a rhodium complex, $Rh[(COD)Cl]_2$ having $P(OEt)_3$ ligands, to synthesize *cis*-2-aryl-1,2-dihydro-1-naphthol **3a** stereoselectively and in good yields without concomitant deboronation of the boronic acid (Scheme 1.14).[28]



Scheme 1.14

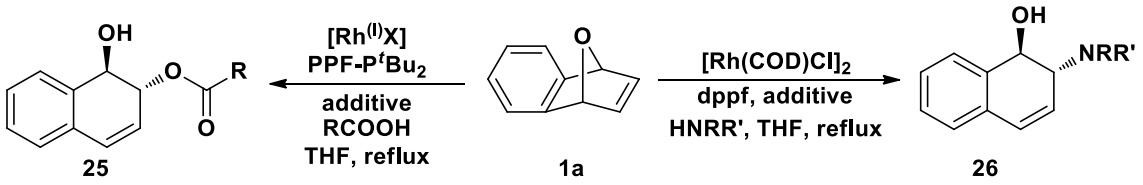
The rhodium-catalyzed asymmetric ring opening of oxabicyclic alkenes **4a** with organoboronic acids **13** was developed by Lautens *et al.* (Scheme 1.15). This asymmetric ring opening (ARO) reaction proceeded in high yield under very mild conditions with electronically diverse organoboronic acids, in a highly diastereoselective and enantioselective

manner.[29]



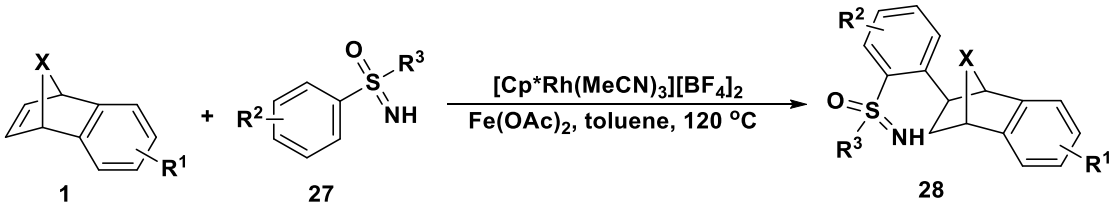
Scheme 1.15

The same group extended the scope of this reaction to other substrates such as aromatic amines, malonate and carboxylate nucleophiles by modifying catalysts and other additives (Scheme 1.16).[30]



Scheme 1.16

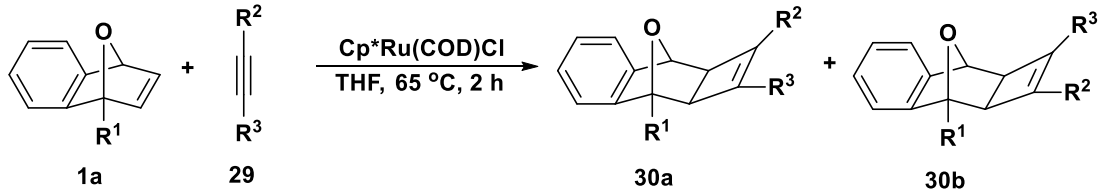
Hydroarylation reactions of heterobicyclic alkenes **1** through rhodium-catalyzed directed C-H functionalizations of *S*-aryl sulfoximines **27** was reported by Bolm *et al.* (Scheme 1.17).[31] The products are synthetically useful, as demonstrated by the *N*-phosphorylations providing potential ligands for metal catalysis and ring-closing reactions leading to aryl-fused thiazine derivatives.



Scheme 1.17

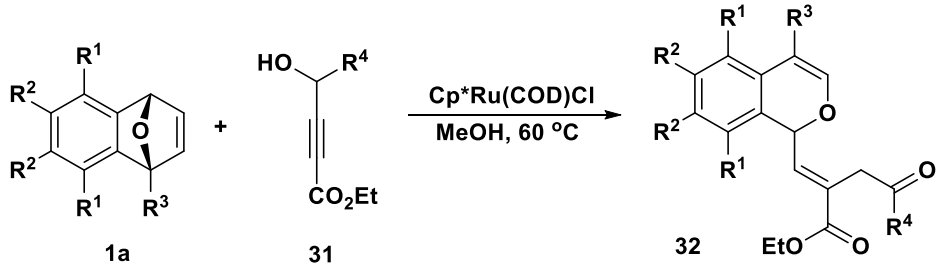
1.2.3. Ruthenium Catalyzed Reactions

The reactivity of oxabicyclic olefins **1a** in the ruthenium-catalyzed [2+2] cycloadditions with alkynes **29** was checked by Tam *et al.* (Scheme 1.18). They proved that the presence of oxygen atom in the bridgehead of the bicyclic alkene significantly enhanced the rate of ruthenium-catalyzed [2 + 2] cycloadditions.[32] The *exo* product is always formed due to the complexation of Ru catalyst to more electron-rich *exo* face of the bicyclic structure.



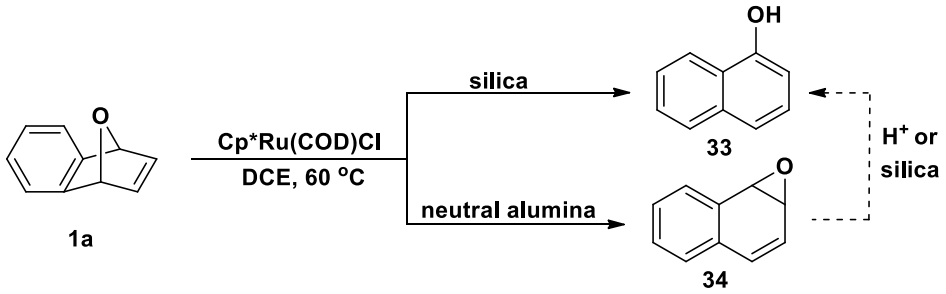
Scheme 1.18

An unprecedented ruthenium catalyzed construction of isochromene framework **32** from propargylic alcohol **31** and an oxabenzonorbornene **1a** was disclosed by Tam and coworkers (Scheme 1.19).[33] The catalytic cycle involved the oxidative cyclization of the two unsaturated partners with the ruthenium catalyst, followed by a *β*-hydride elimination, tautomerization and hydroruthenation. The ruthenacyclobutane obtained further undergoes [2 + 2] cycloreversion to form a Ru-carbene intermediate that uncommonly rearranges through a [1,3]-alkoxide shift and finally reductively eliminates to produce the desired compound.



Scheme 1.19

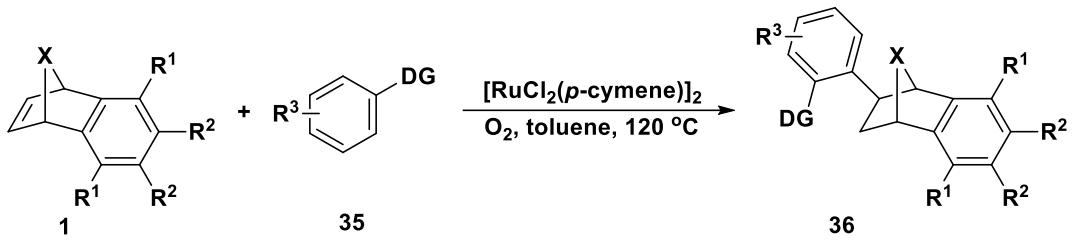
An expedient route towards the synthesis of 1,2-naphthalene oxides **34** and imines *via* the ruthenium-catalyzed isomerization of oxa/azabicyclic alkenes **1a** was explored by Tam *et al*. This method illustrates a mild, simple and efficient experimental procedure for the preparation of corresponding vinyl epoxides or aziridines (Scheme 1.20).[34]



Scheme 1.20

Ruthenium-catalyzed hydroarylations of oxa- and azabicyclic alkenes **1** with (hetero)arenes **35** by the C−H bond activation was discovered by Bolm *et al*. Substituted 2-

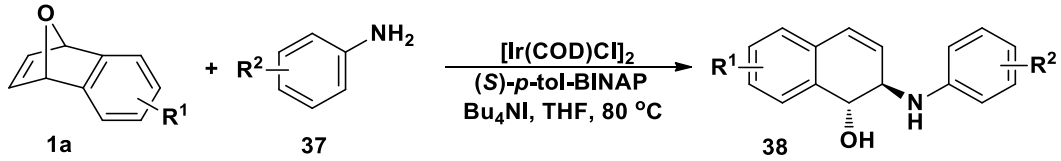
phenyl pyridines in the presence of $[RuCl_2(p\text{-cymene})]_2$ as catalyst and O_2 in dry toluene at 120 °C for 6-12 h furnished the hydroarylated products **36** in moderate to good yields (Scheme 1.21).[35]



Scheme 1.21

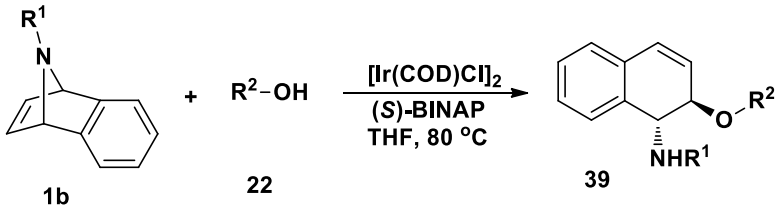
1.2.4. Iridium Catalyzed Reactions

An iridium-catalyzed ring-opening reaction of oxabenzonorbornadienes **1a** with a variety of primary aromatic amine **37** or *N*-substituted piperazine nucleophiles to afford the corresponding products **38** in excellent yields was illustrated by Yang and Long *et al.* (Scheme 1.22).[36]



Scheme 1.22

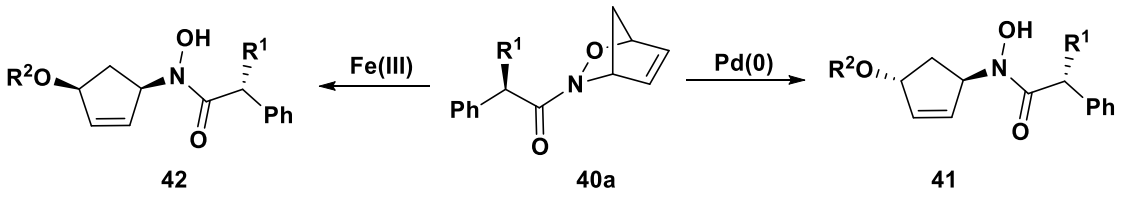
Yang and coworkers reported a novel asymmetric ring-opening reaction of *N*-substituted azabenzonorbornadienes **1b** with a wide variety of substituted benzyl alcohols **22**. The addition reaction of *N*-substituted azabenzonorbornadienes with alcohols and thiols in the presence of an iridium catalyst afforded the corresponding 1,2-*trans*-alkoxyamino products **39** in moderate yields and the corresponding thiol addition products in high yields (Scheme 1.23).[37]



Scheme 1.23

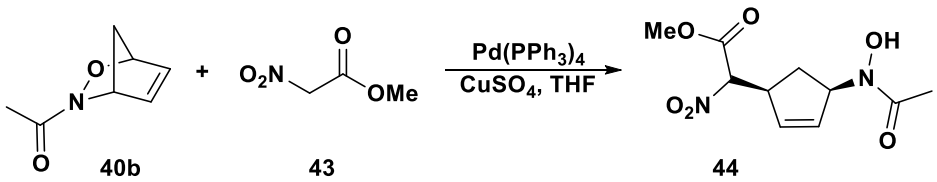
1.3. Transition Metal Catalyzed Reactions of Oxaza Bicyclic Olefins

The first report on the regio- and stereoselective Lewis acid and Pd(0)/Brønsted acid-mediated ring opening reactions of 3-aza-2-oxabicyclo[2.2.1]hept-5-ene systems **40a** to selectively afford versatile *anti*-1,4- (**41**) and *syn*-1,4- (**42**) disubstituted cyclopentene-derived hydroxamic acids, respectively was developed by Miller and coworkers (Scheme 1.24).[38]



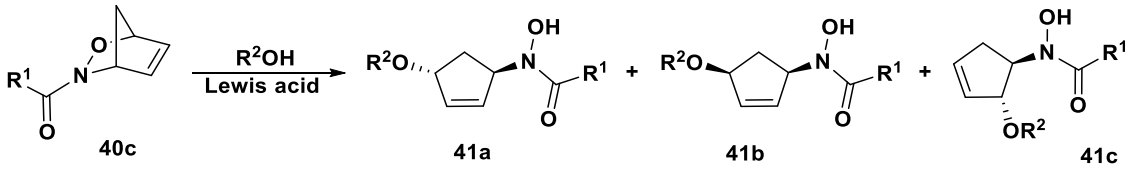
Scheme 1.24

In a report by the same group, treatment of *N*-acetyl cycloadduct **40b** with methyl nitroacetate **43** and Pd(0) in the presence of $CuSO_4$ gave the 1,4-*syn* amino acid precursor **44** in 70 % yield (Scheme 1.25).[39]



Scheme 1.25

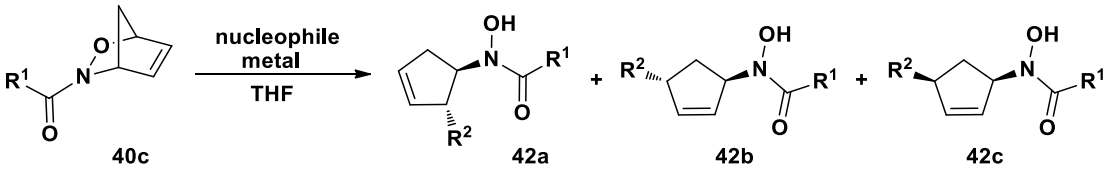
They also illustrated that the treatment of acyl nitroso hetero Diels-Alder cycloadducts **40c** with iron (III) or copper (II) in an alcohol solvent induces ring opening to afford predominantly monocyclic *anti*-1,4-hydroxamic acids **41a** (Scheme 1.26). Also, by varying the size of the nucleophile and/or by changing the Lewis acid, either the *anti*-1,4- or the *syn*-1,4-hydroxamic acid products **41b** can be obtained selectively.[40]



Scheme 1.26

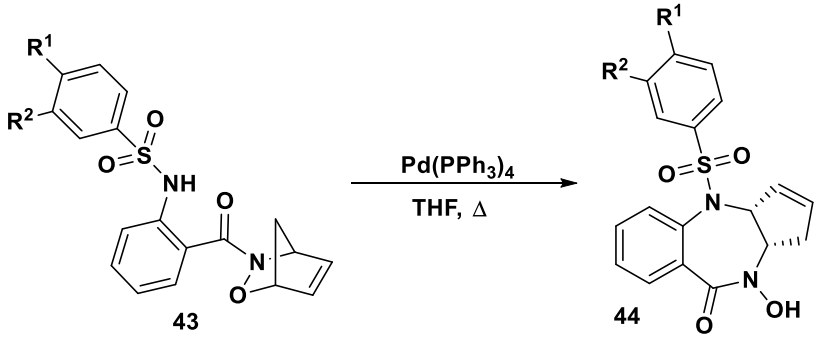
The same group reported the ring opening reaction of acylnitroso Diels-Alder cycloadducts **40c** with organomagnesium reagents (RMgBr) in the presence of a catalytic amount of copper to provide hydroxamic acids **42** in up to 93 % yield and with selectivities

of up to 18:2:1 for the *anti*-1,2-: *anti*-1,4-: *syn*-1,4-products (**42a**:**42b**:**42c**) (Scheme 1.27).[41]



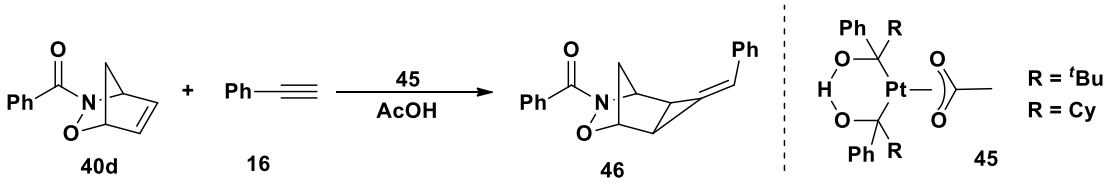
Scheme 1.27

The palladium catalyzed single step synthesis of *N*-hydroxy-1,4-benzodiazepines **44** from synthetically versatile acylnitroso-derived hetero-Diels-Alder cycloadducts **43** was unraveled by Miller and coworkers (Scheme 1.28).[42]



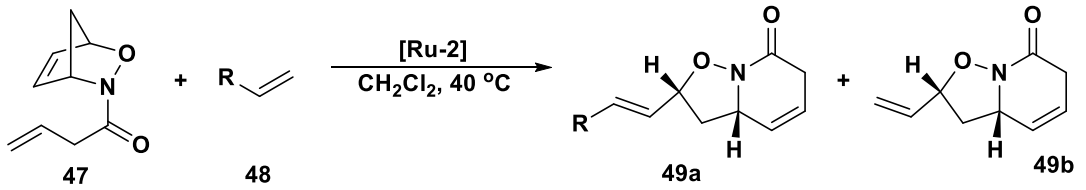
Scheme 1.28

The construction of benzylidenecyclopropanes **46** using novel Pt(η^2-acetato){[(R)(Ph)PO]$_2$H} complexes **45** prepared from $PtCl_2(CH_3CN)_2$ and secondary phosphine oxides *via* the [2 + 1] cycloaddition of phenylethyne **16** with oxazanorbornene derivatives **40d** was explored by Buono and coworkers (Scheme 1.29).[43]



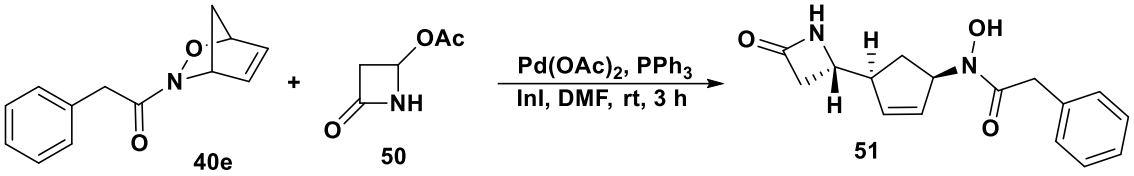
Scheme 1.29

Blanchard and Kouklovsky *et al*. showed that properly substituted nitroso Diels-Alder cycloadducts **47** underwent domino metathesis with an external alkene **48** in the presence of a catalytic quantity of second generation Grubbs carbene [Ru]-2 to form isoxazolo[2,3-a]pyridin-7-ones **49a** and **49b** (Scheme 1.30).[44]



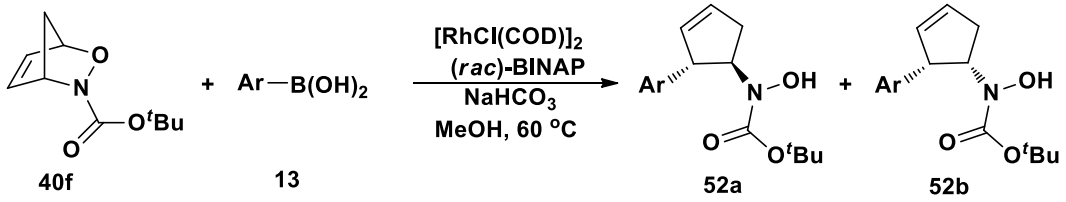
Scheme 1.30

Miller *et al*. reported the reaction of phenylacetyl cycloadduct **40e** with 4-acetoxy-2-azetidinone **50** in the presence of Pd(0) and InI to afford *syn*-1,4-substituted-*β*-lactam derived carbocyclic scaffold **51** (Scheme 1.31). This reaction can also be considered as the diastereoselective allylation of 4-acetoxy-2-azetidinone with an allylic indium(III) species generated from cycloadduct.[45]



Scheme 1.31

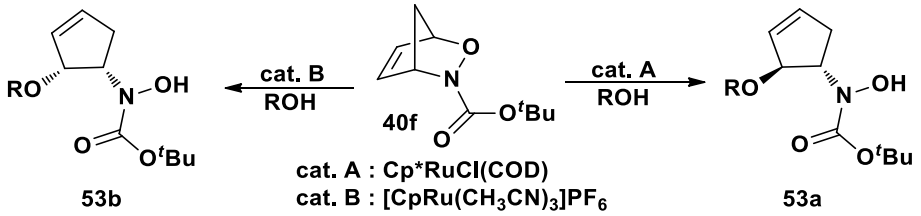
Tam and coworkers investigated the rhodium-catalyzed ring-opening reactions of 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **40f** with arylboronic acids **13** using $[RhCl(COD)]_2$, (*rac*)-BINAP, and $NaHCO_3$ in MeOH at 60 °C to give both *trans*-**52a** and *cis*-1,2-ring-opened products **52b** in low to moderate yields (Scheme 1.32). The *trans* and *cis* isomers could be generated selectively by using either a neutral Cp*RuCl(COD) catalyst or a cationic $[CpRu(CH_3CN)]PF_6$ catalyst.[46]



Scheme 1.32

The same group developed the ruthenium-catalyzed nucleophilic ring-opening reactions of 3-aza-2-oxabicyclo[2.2.1]hept-5-ene **40f** with alcohols to give only the 1,2-cyclopentene ring-opening products. When a neutral ruthenium(II) catalyst, Cp*RuCl(COD), was used in MeOH, the *trans*-1,2-ring opened product **53a** was formed as the only regio- and stereoisomer. On the other hand, when a cationic ruthenium(II) catalyst,

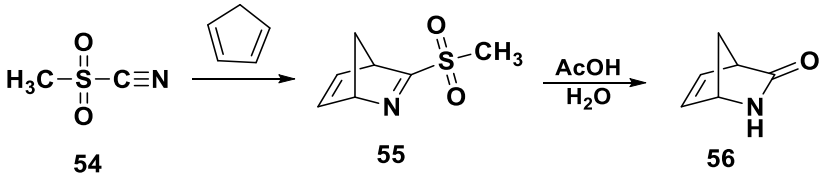
$[CpRu(CH_3CN)_3]PF_6$, was used in MeOH, the *cis*-1,2-ring opened product **53b** was formed exclusively (Scheme 1.33).[47]



Scheme 1.33

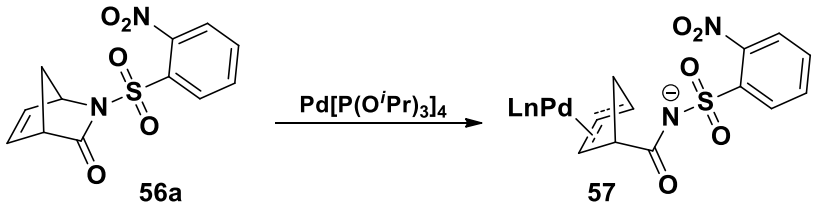
1.4. Transition Metal Catalyzed Reactions of Vince Lactam

2-Azabicyclo[2.2.1]hept-5-en-3-one, a bicyclic-γ-lactam, generally known by the name "Vince lactam", coined by Chemical and Engineering News in 2003, is one of the best synthons for a variety of functionalized cyclopentene derivatives.[14] Vince lactam **56** can be conveniently synthesized by the Diels Alder reaction of methanesulfonyl cyanide **54** and cyclopentadiene, followed by the hydrolysis with $AcOH/H_2O$ (Scheme 1.34).[48]



Scheme 1.34

The presence of amide bond and an olefin makes the bicyclic system a highly strained molecule. Various transformations of this olefin such as cyclopropylation, hydroxylation, epoxidation, fluorination, selenylation, aziridation *etc*. have been reported.[14] The versatile metal that has been studied for ring opening of the lactams is palladium. In the application of Trost's chemistry to Vince lactams, Katagiri *et al*. reported the formation of a π-allyl palladium complex **57** on reaction with the palladium source (Scheme 1.35).[49]

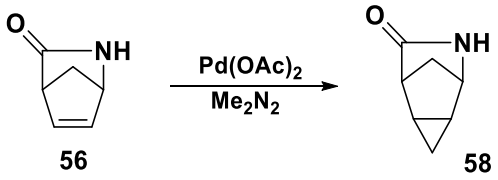


Scheme 1.35

The metal center approaches preferentially from the *exo*-side of the lactam and leads to an increase in the ring strain. Interestingly, the ring undergoes cleavage of C-N bond with

N-sulfonyl group acting as an intramolecular leaving group.

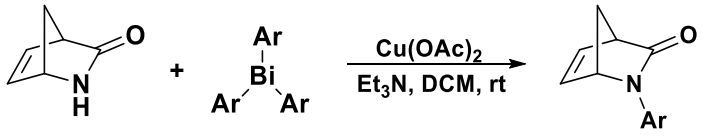
Katagiri *et al*. introduced cyclopropyl ring on the double bond of Vince lactam by exposure of the lactam to excess diazomethane in the presence of $PdCl_2(PhCN)_2$ in dry reaction conditions (Scheme 1.36).[50]



56 58

Scheme 1.36

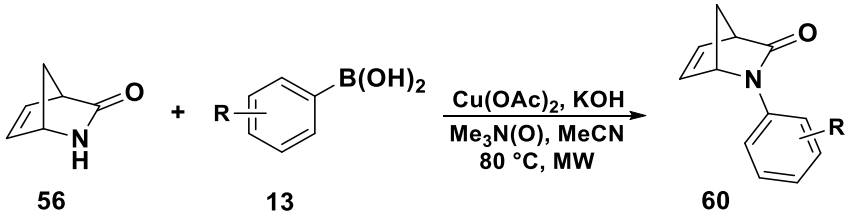
The *N*-arylation of Vince lactam **56** by the use of triaryl-bismuth reagents **59** in a copper mediated system was reported by Chan *et al.* in 1996 (Scheme 1.37).[51] They demonstrated that a tertiary amine promoter can greatly enhance the scope and yield of Barton's copper(II)-mediated organobismuth *N*-arylation.



56 59 60

Scheme 1.37

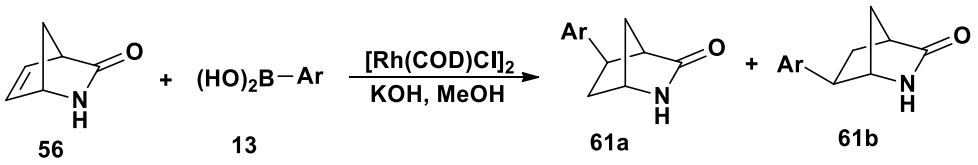
Later, in 2008, Ishikura and coworkers extended Chan's strategy by employing catalytic amount of $Cu(OAc)_2$ in the presence of KOH and trimethylamine-*N*-oxide under microwave radiation (Scheme 1.38).[52]



56 13 60

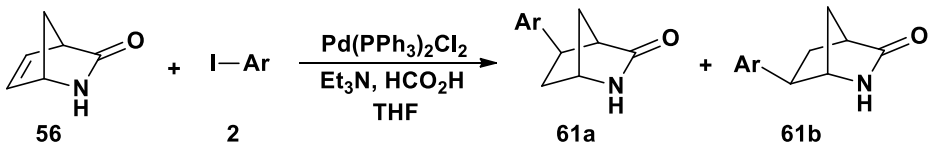
Scheme 1.38

They also explored rhodium-catalyzed arylation of Vince lactam **56** and its various analogues with arylboronic acids **13** (Scheme 1.39). The rhodium catalyst furnished only the products formed by the *C*-arylation on olefinic carbons of Vince lactam, even though with copper catalyst, exclusive formation of *N*-arylated Vince lactam was observed.[53]



Scheme 1.39

Pietrowski and Polivkova have revealed the *C*−arylation of Vince lactam **56** using aryl iodides **2** in palladium mediated reaction system (Scheme 1.40). The reactions furnished the coupling products **61a** and **61b** in excellent yields with 5 mol% palladium catalyst loadings at 65 °C and the substrate scope of the reaction was explored with electron-rich as well as electron deficient aryl iodides.[54]



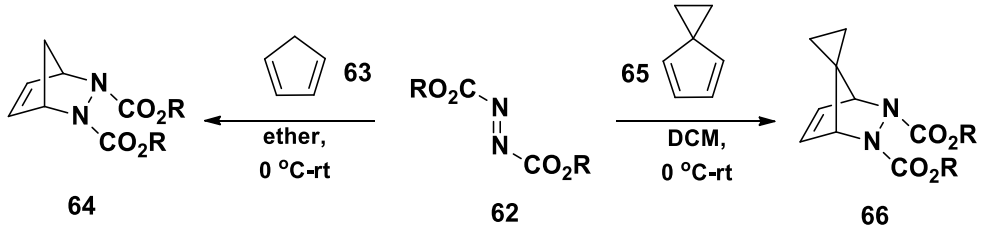
Scheme 1.40

1.5. Transition Metal Catalyzed Reactions of Diazabicyclic Olefins

Diazabicyclic olefins, being versatile synthons, have received considerable attention among the synthetic organic chemists as they open a way to compounds of synthetic and biological interest.[13,55] These alkenes can be readily activated by transition metal complexes, face-selectively due to their bicyclic structure and the intrinsic angle strain on the carbon–carbon double bond. Numerous synthetic transformations of these building blocks have been developed, involving the electrophilicity of their strained double bond and ring-opening reactions or skeletal rearrangements *via* β-nitrogen elimination or N-N bond cleavage. The transition metal catalyzed desymmetrization reactions of these strained olefins have been investigated by different research groups viz. Micouin *et al*., Kaufmann *et al*., Pineschi *et al*., Lautens *et al*. and our group providing efficient methodologies toward the construction of carbocycles and heterocycles. Reactions of diazanorbornenes with mono- and bi-functional aryl iodides, soft nucleophiles such as phenol, oxidative coupling with salicylaldehyde *etc*. will be discussed in the following chapters to avoid repetition.

Diazanorbornenes (**64** or **66**) can be conveniently prepared *via* the Diels-Alder cycloaddition of cyclopentadiene derivatives (**63** or **65**) and the corresponding dialkylazodicarboxylates **62** (Scheme 1.41).[56,57] This chemistry was extended to fulvenes

toward the synthesis of fulvene derived diazabicylic olefins by Marullo and Alford.[58]

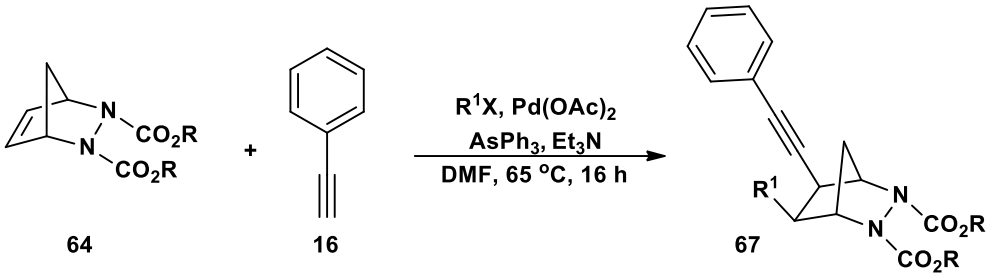


Scheme 1.41

A brief discussion on the synthetic transformations of diazanorbornenes is presented in the following sections.

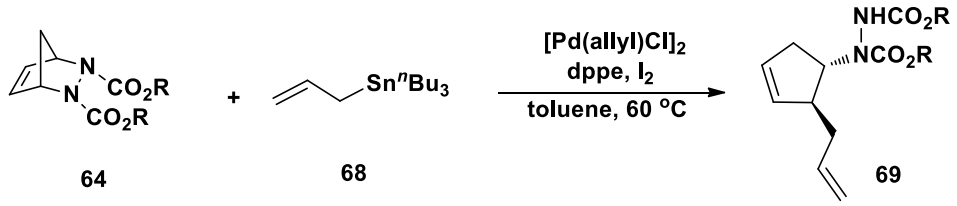
1.5.1. Palladium Catalyzed Reactions

Kaufmann *et al*. showed that, in hydroarylation reactions, it is possible to substitute the hydride reagent by the nucleophilic phenylacetylene **16** which enabled the tandem coupling of aryl halide and phenylacetylene onto the diazabicyclic alkene **64** resulting in the formation of a bis-coupled product **67** (Scheme 1.42).[59]



Scheme 1.42

The pioneering investigations on the palladium catalyzed ring opening of diazabicyclic olefins **64** with organometallic reagents were done by our group in 2006.[60] We unraveled the synthesis of allylated hydrazinocyclopentenes **69** utilizing scandium triflate as the Lewis acid (Scheme 1.43).

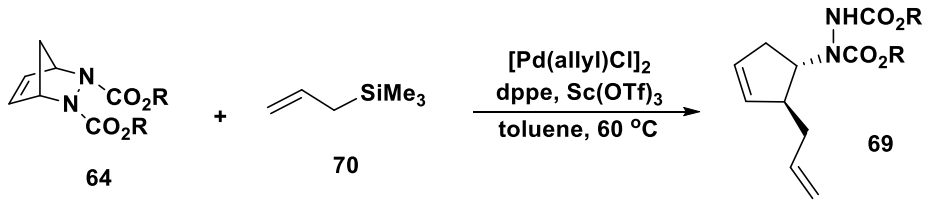


Scheme 1.43

This mild reaction is the first general methodology developed for the stereoselective synthesis of *trans*-vicinal disubstituted cyclopentenes. The results showed that

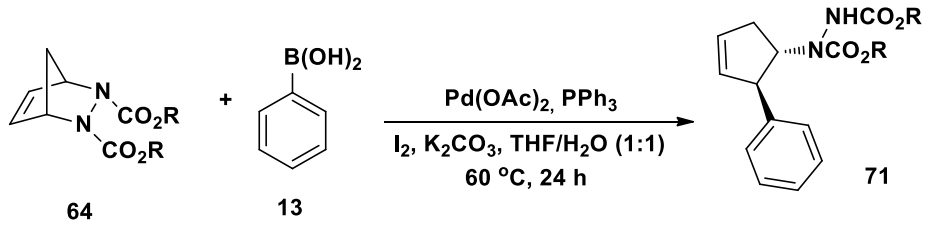
organostannanes **68** with easily functionalizable moieties can be efficiently utilized in the ring opening of bicyclic olefins leading to the stereoselective formation of 3,4-disubstituted cyclopentenes.

The reaction of allyltrimethylsilane **70** with bicyclic hydrazine **64** was also tested that afforded the allyl substituted hydrazinocyclopentenes **69** in moderate yield in the presence of Pd/Lewis acid catalyst (Scheme 1.44).[61]



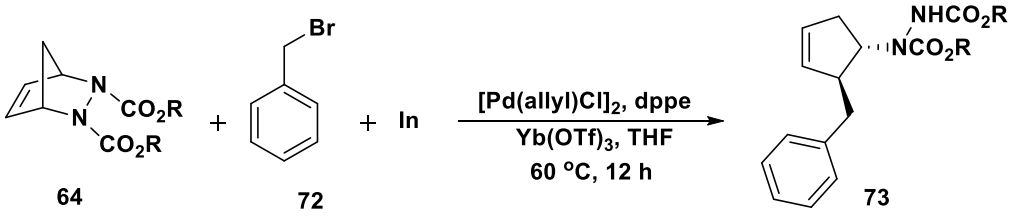
Scheme 1.44

Our group unraveled the reaction of organoboronic acids **13** with diazabicyclic olefins **64** leading to the stereoselective formation of *trans*-vicinal disubstituted cyclopentenes **71** in good to excellent yields in 2006 (Scheme 1.45). This was the first report on the use of modified Suzuki reaction for the synthesis of functionalized cyclopentenes.[62,63]



Scheme 1.45

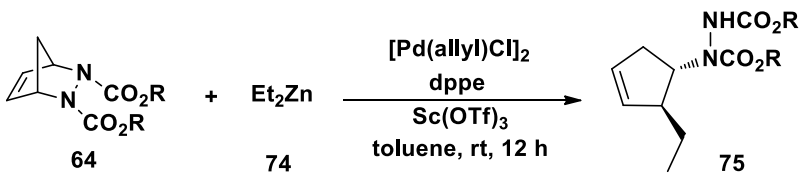
We also demonstrated the use of *in situ* generated allyl and benzyl indium species utilizing organoindiums as nucleophiles which induced the palladium (II) catalyzed ring-opening of diazabicyclic olefins **64** (Scheme 1.46).[64,65]



Scheme 1.46

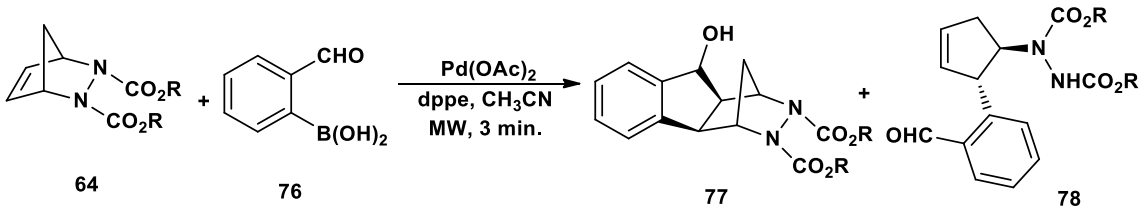
Investigations from our laboratory also proved that the palladium/Lewis acid mediated ring-opening reactions using alkylzinc reagents **74** can be used for the

desymmetrization of diazabicyclic olefins **64** leading to alkylated hydrazinocyclopentenes **75** in low yields (Scheme 1.47).



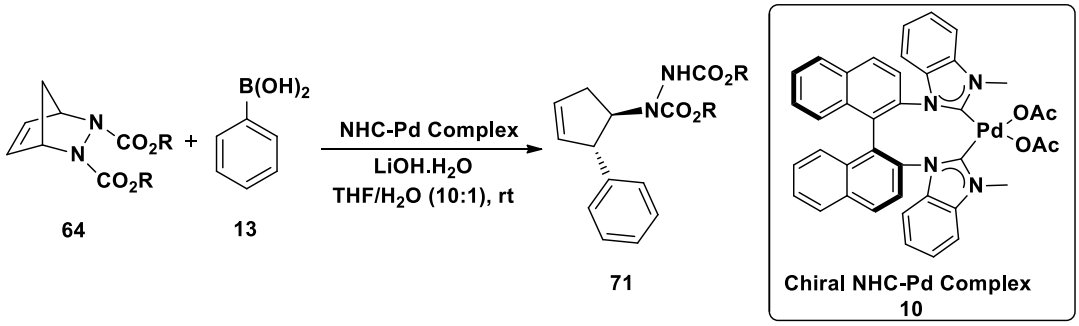
Scheme 1.47

A simple and efficient palladium catalyzed method for the synthesis of indanol fused bicyclic hydrazines **77** using 2-formylphenylboronic acid **76** under microwave irradiation was reported by our group (Scheme 1.45). The reactions afforded 3,4-disubstituted cyclopentenes **78** as a minor product along with indanols **77**.[66]



Scheme 1.48

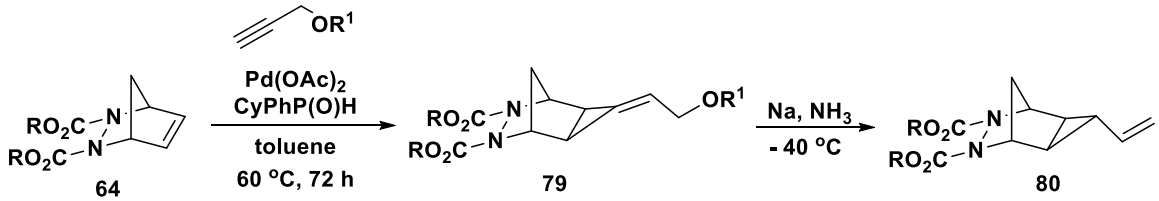
Xu-Shi *et al*. reported the first example of palladium-catalyzed enantioselective desymmetrization of 2,3-bicyclic hydrazines **64** with arylboronic acids **13** using a chiral C2-symmetric *N*-heterocyclic carbene (NHC) palladium complex as the catalyst (Scheme 1.49).[67] The reaction can be performed under convenient conditions to give *trans*-1,2-disubstituted 3-cyclopentenes **71** with high regioselectivity in good to excellent yields (up to 95 %) and moderate to good enantioselectivities (up to 88 % *ee*) (Scheme 1.49).



Scheme 1.49

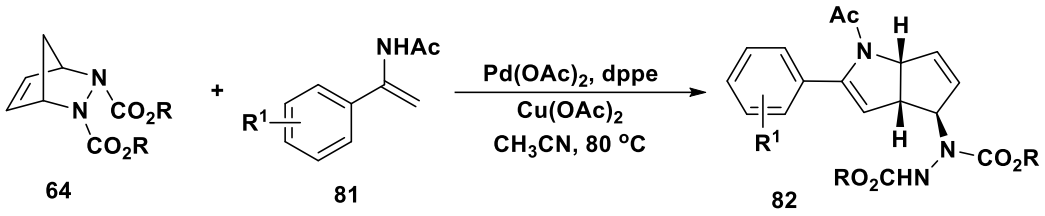
Clavier and coworkers developed a palladium-promoted [2 + 1] cycloaddition between diazabicyclic olefins **64** with alkynes to synthesize methylenecyclopropanes **79**.

Later, the reductive isomerization of methylenecyclopropanes (MCPs) to vinylcyclopropanes **80** was achieved by treating with sodium metal in liquid ammonia wherein, MCPs bearing a C−O bond at allylic position undergo both a reductive cleavage of the C−O bond and an isomerization of the C−C double bond giving rise to VCPs (Scheme 1.50).[68]



Scheme 1.50

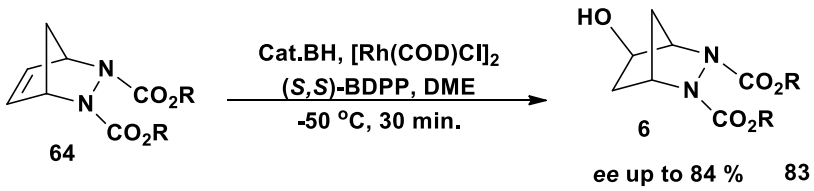
An efficient stereoselective route for the synthesis of cyclopentene fused 2-pyrrolines **82** *via* the palladium-catalyzed C–H activation/oxidative coupling of aryl enamides **81** with diazabicyclic olefins **64** was established by our group. This was the first report on the ring opening-ring closing of diazabicyclic olefins using transition metal catalyzed C–H activation reaction (Scheme 1.51).[69]



Scheme 1.51

1.5.2. Rhodium Catalyzed Reactions

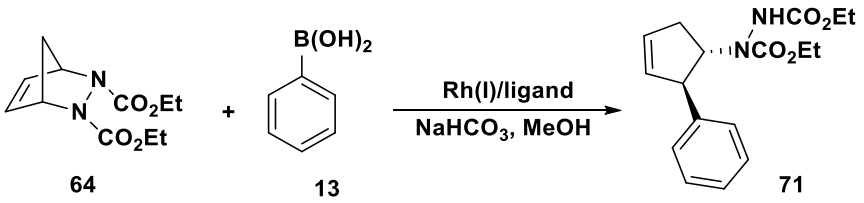
Micouin and co-workers have shown the catalytic asymmetric hydroboration reactions of *meso*-diazabicyclic alkenes **64** at low temperature using $[Rh(COD)Cl]_2$ as the rhodium source and (*S,S*)-BDPP as chiral diphosphine in DME as solvent (Scheme 1.52).[70]



Scheme 1.52

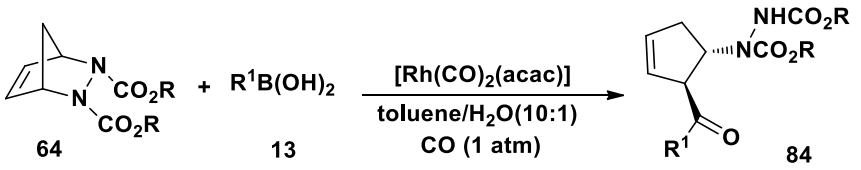
Pineschi *et al*. developed a rhodium-catalyzed asymmetric arylative ring opening of these bicyclic hydrazines **64** with aryl boronic acids **13** to provide new and practical access to chiral nonracemic arylated hydrazinocyclopentenes **71** with excellent regio- and

stereoselectivities (Scheme 1.53).[71]



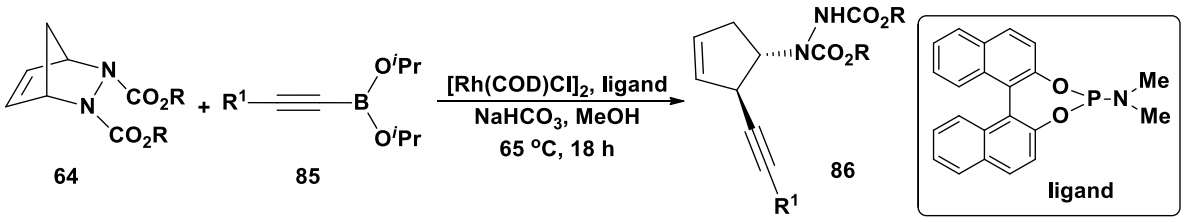
Scheme 1.53

Lautens and co-workers reported the catalytic desymmetrization of strained alkenes **64** *via* a formal allylic substitution reaction with acyl anion nucleophiles, which is generated *in situ* under very mild conditions from readily available organoboron precursors **13**, to obtain functionalized *trans*-1,2-hydrazinoacyl cyclopentene building blocks **84** (Scheme 1.54).[72]



Scheme 1.54

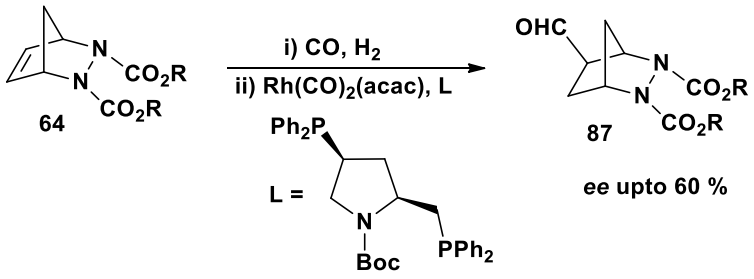
The first successful unprecedented asymmetric transfer of rhodium–alkynyl species to symmetrical strained alkenes was realized by Pineschi and co-workers starting from bicyclic hydrazines **64** and alkynylboronic esters **85** (Scheme 1.55). This protocol offers a new and straightforward regio- and stereoselective entry to valuable alkynyl cyclopentenic hydrazines **86**.[73]



Scheme 1.55

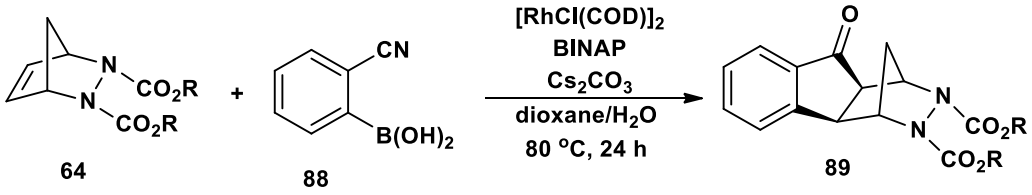
In 2008, Micouin *et al*. explored the rhodium-catalyzed enantioselective hydroformylation of *meso*-azabicyclic componds **64** wherein the reaction afforded the *exo* products **87** exclusively with a high diastereoselectivity (Scheme 1.56). The asymmetric transformation was done with the combination of $Rh(CO)_2(acac)$ and diphosphine ligand which enabled the hydroformylation to proceed with excellent conversion and *ee* up to 60 %

(Scheme 1.56).[74]



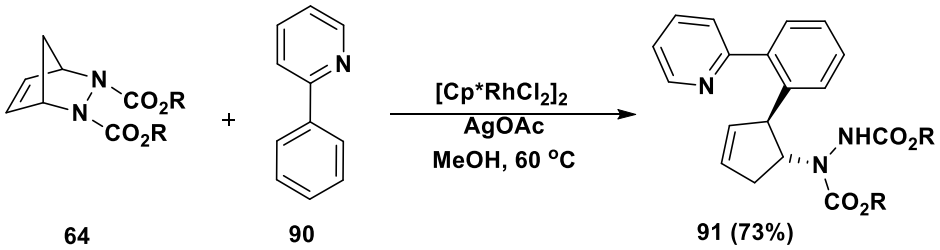
Scheme 1.56

Our laboratory developed a rhodium catalyzed efficient strategy for the synthesis of highly functionalized indanones **89** using 2-cyanophenylboronic acid **88** (Scheme 1.57).[66]



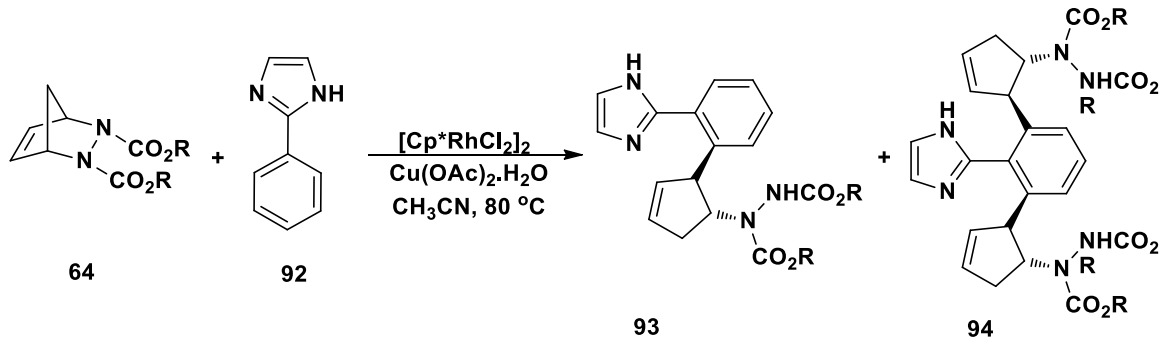
Scheme 1.57

A novel and efficient strategy for the desymmetrization of diazabicycles *via* the Rh(III)-catalyzed C–H activation with heteroarenes such as 2-aryl-pyridines **90**, pyrimidines, pyrazoles and imidazoles, as an expedient approach to functionalized cyclopentenes **91** was reported by Cui *et al*. This protocol utilizes simple starting materials, mild reaction conditions and has high efficiency and broad substrate scope (Scheme 1.58).[75]



Scheme 1.58

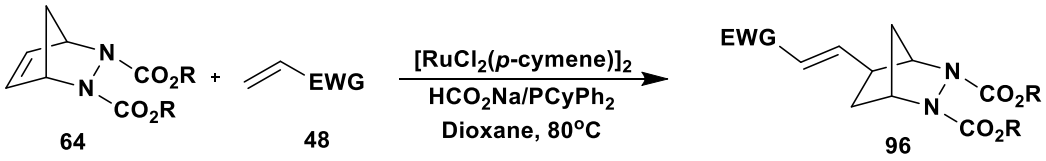
During the same period, we also reported the rhodium-catalysed ring opening of diazabicyclic olefins **64** with aza-heteroaromatics such as substituted imidazoles **92** and benzimidazoles to furnish mono- (**93**) or bis-cyclopentenyl (**94**) functionalized azaheteroaromatics (Scheme 1.59).[76]



Scheme 1.59

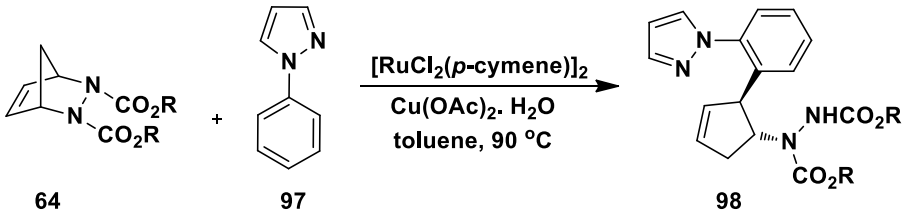
1.5.3. Ruthenium Catalyzed Reactions

Darses *et al*. demonstrated the co-dimerization of bicyclic alkenes **64** and Michael acceptors **48** using a ruthenium based catalytic system to provide the *exo-(E)* adducts **96** (Scheme 1.60).[77]



Scheme 1.60

The ruthenium-catalyzed desymmetrisation of diazabicyclic olefins with azaheteroaromatics were utilized by our group in the synthesis of heteroaryl substituted cyclopentenes. This was the first report of a ruthenium catalyzed redox-neutral C–H activation of phenylazoles **97** towards the ring-opening of diazabicyclic olefins **64** providing efficient access to heteroaryl substituted cyclopentenes **98** by employing less-expensive ruthenium catalyst (Scheme 1.61).[78]

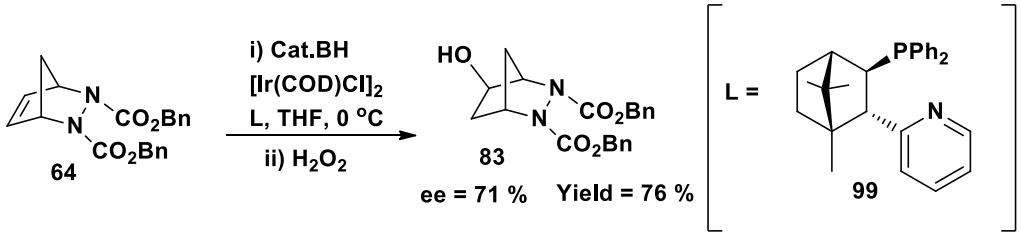


Scheme 1.61

1.5.4. Iridium Catalyzed Reactions

Micouin *et al*. employed phosphoramidites or phosphite ligands in the iridium-catalyzed hydroboration of mesobicyclic hydrazines **64** with enantiomeric excesses of up to 67 % in moderate to good yields. They also showed that the use of phosphoramidite ligands

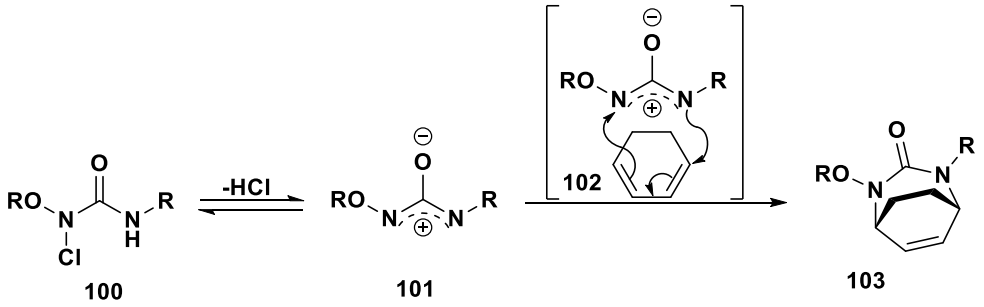
in such a transformation can deliver the final compound with enantiomeric excesses between 50 % and 60 %, with chemical yields up to 75 % (Scheme 1.62).[79]



Scheme 1.62

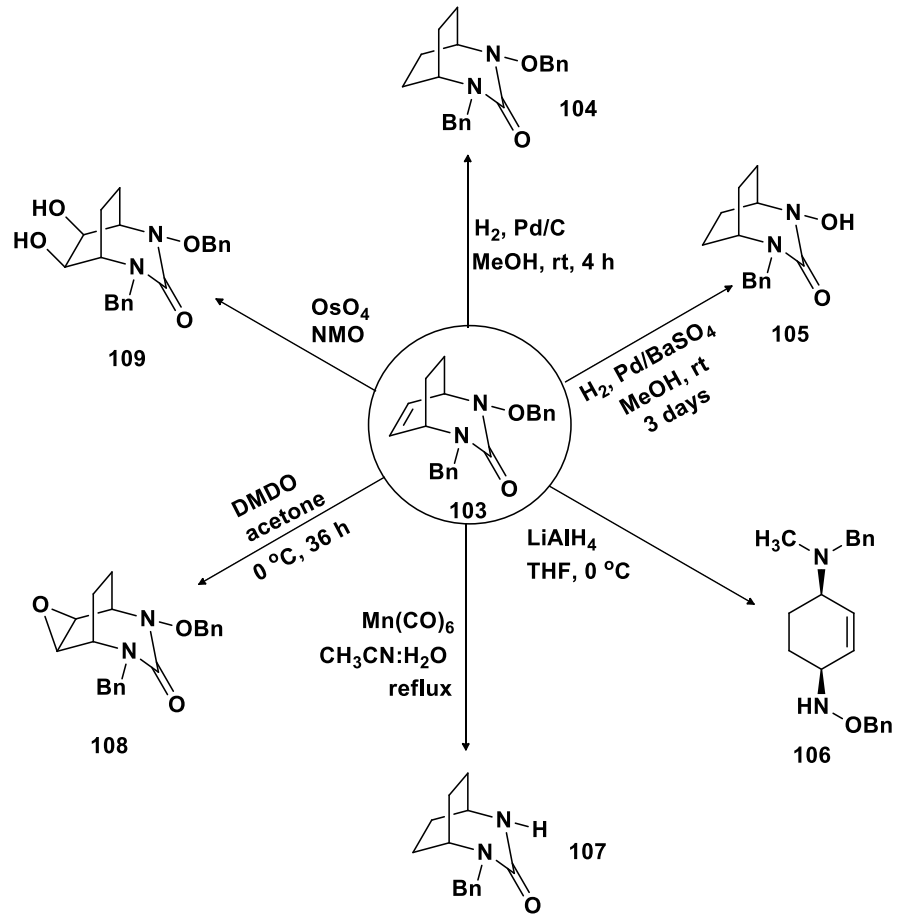
1.6. Urea Derived Bicyclic Olefins and Reactions

It was Jeffrey *et al*., who for the first time in 2012, demonstrated the hetero (4 + 3) type cycloaddition of a diaza-oxyallyl cation **101** as a method for the chemoselective 1,4-diamination of dienes **102** to deliver cyclic urea derivatives **103** using *N*-chloroureas **100** (Scheme 1.63).[80]



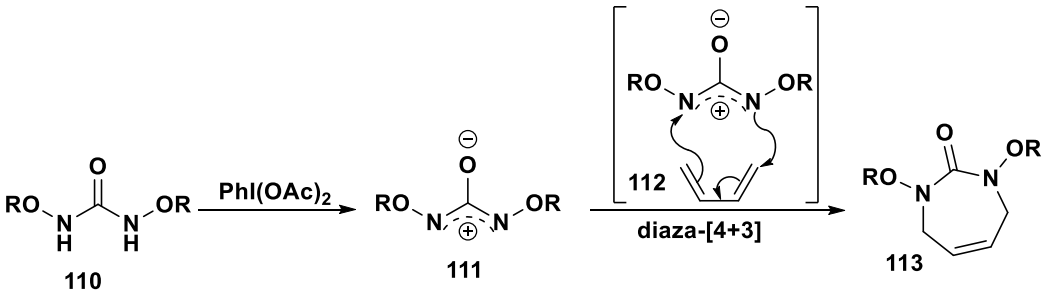
Scheme 1.63

They also treated the [3.2.2] diaza-bicyclononene **103** under a variety of conditions to prove the versatility of the cycloaddition such as hydrogenation of the alkene without the cleavage of either of the benzyl groups or the N-O bond, chemo-selective reduction of the N-O bond using $Mo(CO)_6$ in the presence of the N-Bn and alkene, oxidation of the alkene to the diol or the epoxide, reductive ring opening of the urea using $LiAlH_4$ to obtain *N*-methyl diamine, etc. Under harsh hydrogenation conditions, the *O*-benzyl and *N*-benzyl group were cleaved to provide the hydroxamic acid (Scheme 1.64).



Scheme 1.64

Later in 2014, the same group reported the direct oxidative 1,4-diamination of dienes **112** using simple urea derivatives using phenyl iododiacetate as the oxidant because the previous reported reaction conditions suffered from a limited substrate scope and poor regioselectivity in reactions with monosubstituted furans. This reaction was even found to be general with cycopentadiene, spiro cyclopentadiene, furan and protected pyrroles (Scheme 1.65).[81]



Scheme 1.65

1.7. Conclusion & Present Work

Strained heterobicyclic alkenes are potentially reactive and versatile synthons for the construction of biologically active carbocycles and heterocycles. Even though different groups have investigated the ring opening and ring closing reactions of diazabicyclic olefins using transition metal catalysis, reports on the base catalyzed functionalization of these versatile synthons are scant. We have unraveled the synthesis of chromene fused cyclopentene derivatives *via* the base catalyzed ring opening and ring closing of phenol substituted fulvene derived diazabicyclic olefins, which is described in the second chapter.

Urea and its cyclic derivatives represent a class of biologically relevant molecules, widely occurring in natural products and have been studied for various biological activities such as antibiotic, anti-cancer, antidiabetic, antimicrobial, antibacterial activities *etc*.[82–85] As hydrazine derivatives are toxic, the urea derived bicycles synthesized by Jeffrey *et al*. grabbed our attention because of their tremendous synthetic potential. Moreover, the investigations on the synthetic transformations of urea derived bicyclic olefins are limited. Our continued interest in the chemistry of transition metal catalyzed synthetic transformations of strained bicyclic systems coupled with the aim of constructing biologically significant motifs prompted us to investigate the reactivity of bicyclic urea adduct with salicylaldehydes under rhodium catalysis, which is discussed in Chapter 3.

Among the complexes of a variety of transition metals for carbon-carbon bond formation employed previously, palladium complexes have been most often used in cross coupling reactions such as the Heck, Negishi, Suzuki, Stille, Sonogashira and so on. The palladium-catalyzed hydroarylation of urea derived bicyclic olefins performed *via* the reductive Heck reaction using aryl iodides and annulation reactions using 2-iodophenols, 2-iodobenzylbromide and 2-iodobenzonitrile toward the synthesis of benzofuran, indane and indolone fused urea derivatives are described in the part A and part B of fourth chapter respectively. Transition metal catalyzed aromatic C-H activation reactions have provided efficient methodologies for a variety of site-selective functionalization of indoles, an ubiquitous heterocyclic core in numerous natural products and pharmaceuticals. Part C of Chapter 4 deals with the heterohydroarylation of these bicyclic olefins utilizing iridium catalyzed C-H activation of indoles.

The formation of azaheterocycles through the transition metal catalyzed reactions largely depends upon the directing groups present in the starting materials. Among these attempts, those involving oximes and benzamides have emerged as a promising synthetic protocol toward the construction of azaheterocycles such as isoquinolines and isoquinolines. The fifth chapter describes the rhodium catalyzed C-H activation followed by the annulation reactions of *O*-acetyl ketoximes and *N*-methoxybenzamides. The reaction of *O*-acetyl ketoximes generated isoquinoline derivatives, which is described in part A of the fifth chapter whereas part B gives an idea about the synthesis of isoquinolone derivatives using *N*-methoxybenzamides.

1.8. References

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CHAPTER 2

Base Catalyzed Synthesis of Cyclopenta[*b*]chromene Derivatives from Phenol Substituted Fulvene Derived Azabicyclic Olefins

2.1. Introduction

Chromenes, an important class of heterocycles are structural components in many natural products, pharmaceutical drugs and photosensitive materials (Figure 2.1).[1] The 2*H*-chromene skeleton containing heterocyclic compounds display anticancer, antioxidant, anti-inflammatory, antitubercular, antiviral, antitumour, antibacterial, antidiabetic *etc*.[2]

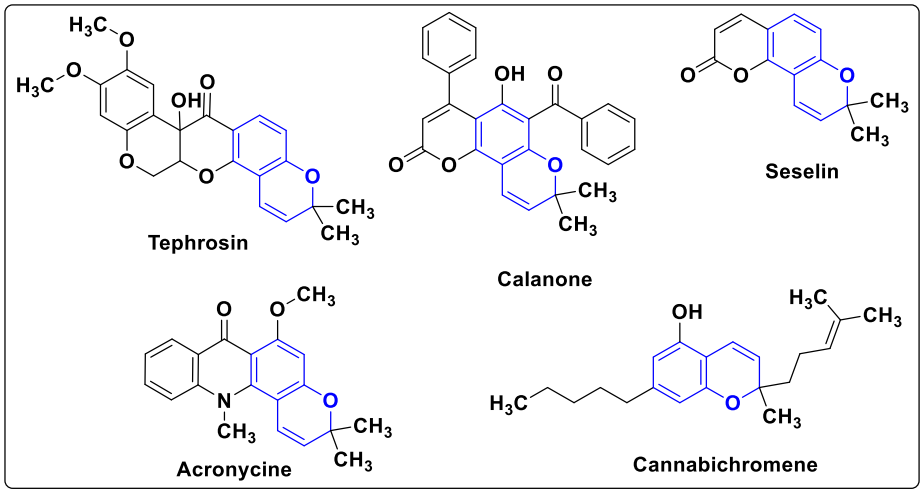


Figure 2.1. Natural products containing chromene skeleton

Due to the prevalence of these functional moieties in natural products, a great deal of interest has been elicited in the field of organic synthesis and chemical biology to develop new and improved synthetic methods to obtain these molecular skeletons.

2.2. Synthetic Approaches toward Chromene Derivatives

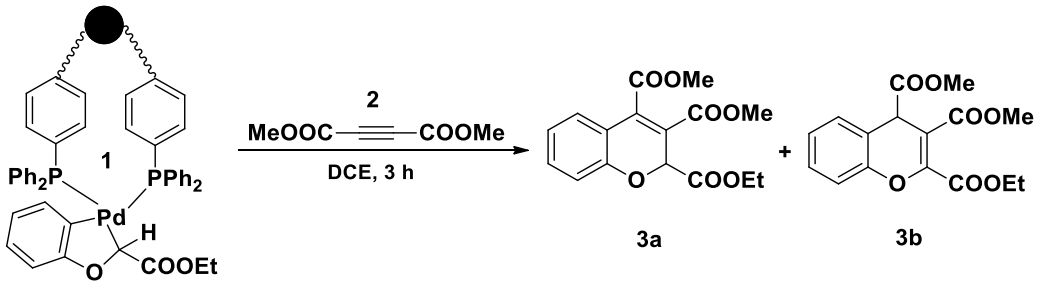
Among the various methods developed for the synthesis of 2*H*-chromene skeletons such as transition metal catalyzed reactions, metal free transformations and intramolecular approaches, a few important strategies are illustrated in the following sections.

2.2.1. Transition Metal Catalyzed Reactions

The synthesis of chromene derivatives using transition metals like Pd, Cu, Au, Fe *etc.* have been developed by different research groups, of which some are described below.

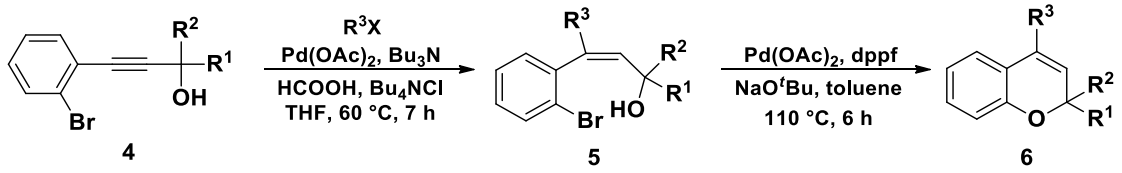
2.2.1.1. Using Palladium

Malinakova *et al.* synthesized immobilized palladacycles **1** by treating oxapalladacycles with polystyrene-divinylbenzene resins, which were subsequently reacted with alkynes **2** to furnish 2*H*-1-benzopyrans **3a** or **3b**.[3] They also showed that resins loaded with medium amount of phosphorus and high amount of palladium gave maximum yield for the reaction (Scheme 2.1).



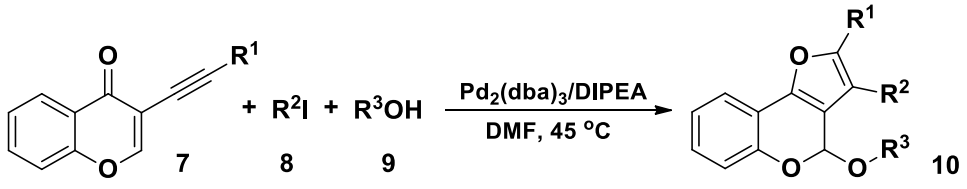
Scheme 2.1

Cacchi and Marinelli *et al.* developed a one pot synthesis of chromene derivatives **6** *via* the coupling of tertiary 3-(*o*-bromophenyl)propynols **4** with aryl iodides or vinyl triflates.[4] The strategy involves two palladium-catalyzed reactions, a hydroarylation or hydrovinylation step followed by intramolecular C–O bond forming reaction (Scheme 2.2).



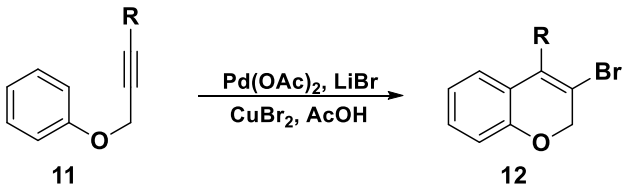
Scheme 2.2

The synthesis of multisubstituted furo[3,2-*c*]chromenes **10** *via* Pd-catalyzed cascade 1,4-addition and cyclization using 3-(1-alkynyl)chromones **7**, aryl iodides **8**, and alcohols **9** was reported by Hu *et al.* This one-pot three-component reaction efficiently generates two C–O bonds and one C–C bond (Scheme 2.3).[5]



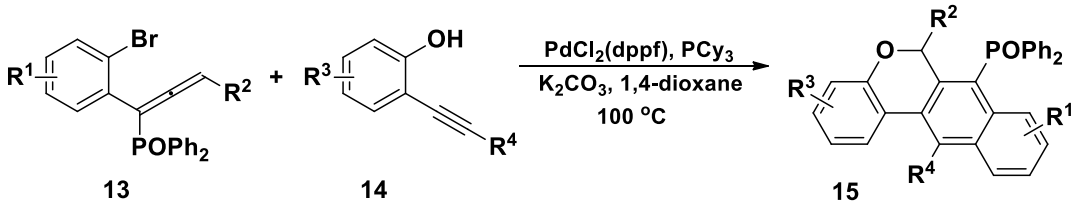
Scheme 2.3

A palladium catalyzed intramolecular approach for the synthesis of 3-bromo-2*H*-chromene derivatives **12** was achieved by Perumal *et al*.[6] A variety of aryl propargyl ethers **11** underwent the reaction smoothly furnishing the corresponding chromene derivatives in good yields (Scheme 2.4).



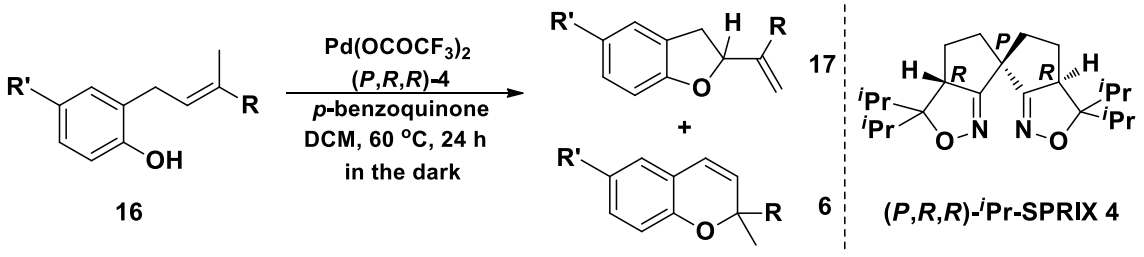
Scheme 2.4

Wu *et al*. demonstrated the synthesis of naphthochromene derivatives **15** by the palladium-catalyzed reaction of 2-haloaryl allene **13** with 2-alkynylphenol **14**.[7] All the products were synthesized in good to excellent yields with excellent chemoselectivity and regioselectivity (Scheme 2.5).



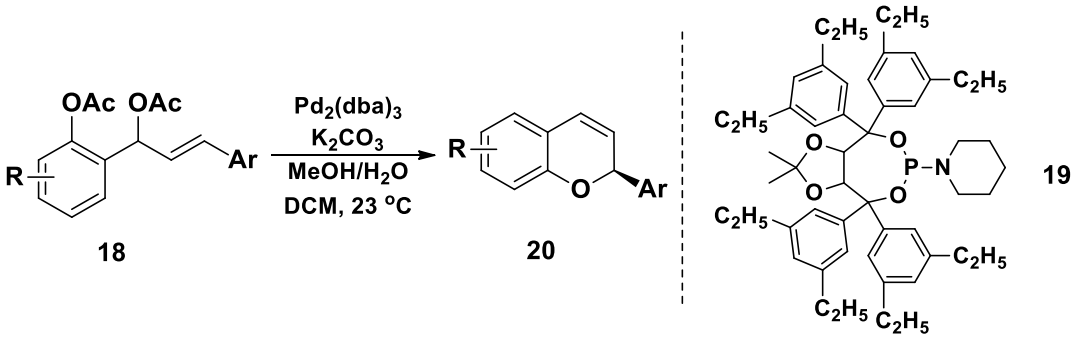
Scheme 2.5

Sasai *et al*. reported the enantioselective synthesis of chromenes **6** or dihydrobenzofurans **17** *via* intramolecular Wacker-type cyclization of 2-geranylphenols **16** (Scheme 2.6). The palladium catalyzed cyclization proceeds in a 6-*endo*-trig manner to give chromene derivatives in reasonable yields.[8]



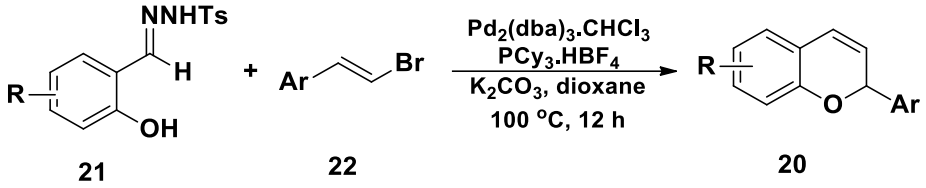
Scheme 2.6

The palladium catalyzed synthesis of 2-aryl-2*H*-chromenes **20** from the 1,3-disubstituted allyl substrates **18** *via* 6-*endo*-trig type closure was developed by Scheidt *et al*. (Scheme 2.7).[9]



Scheme 2.7

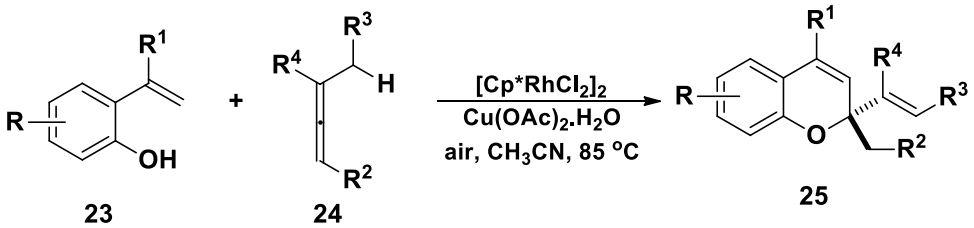
A highly efficient approach towards 2*H*-chromenes **20** was developed by Wang and coworkers based on the palladium-catalyzed coupling of *N*-tosylhydrazones **21** and *β*-bromostyrenes **22** (Scheme 2.8). The mechanism of this reaction involves the formation of vinyl palladium by carbene migratory insertion and the intramolecular nucleophilic substitution.[10]



Scheme 2.8

2.2.1.2. Using Rhodium

Mascarenas-Gulias and coworkers developed the rhodium catalyzed reaction of 2-alkenylphenols **23** with allenes **24** to provide valuable 2,2-disubstituted 2*H*-chromenes **25** (Scheme 2.9).



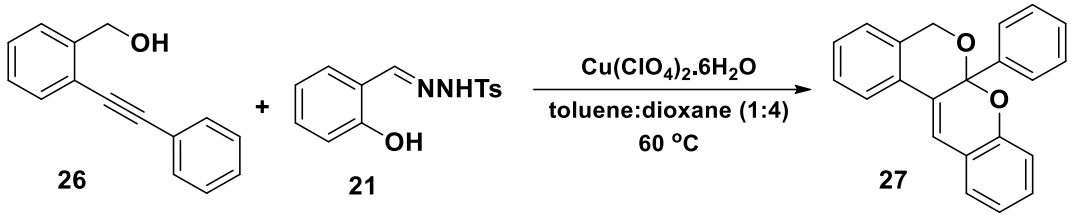
Scheme 2.9

The whole process, which involves the cleavage of one C-H bond of the alkenyl moiety and the participation of the allene as a one-carbon cycloaddition partner, can be considered a simple, versatile, and atom-economical (5+1) heteroannulation.[11] The reaction, which tolerated a broad range of substituents, proposes a straightforward and atom-

economical access to highly appealing chromene skeletons and is operationally simple, permitting the use of non-dried solvents and air, and requires trivial starting materials.

2.2.1.3. Using Copper

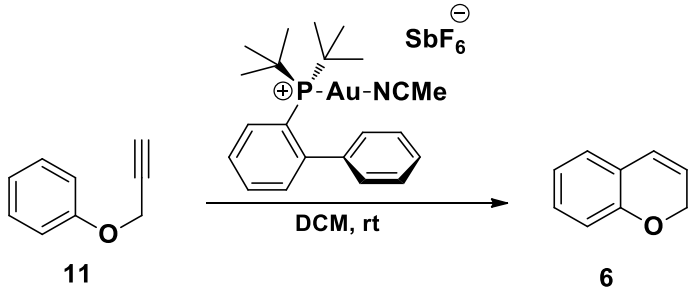
The use of copper catalysts in the synthesis of chromene derivatives by the reaction of internal alkynols **26** and salicyl *N*-tosylhydrazones **21** was shown by Liu *et al*.[12] They reported a copper (II) perchlorate-promoted tandem reaction involving cycloisomerization, formal [4 + 2] cycloaddition and an elimination process to provide isochromenochromene derivatives **27** in moderate to good yields (Scheme 2.10).



Scheme 2.10

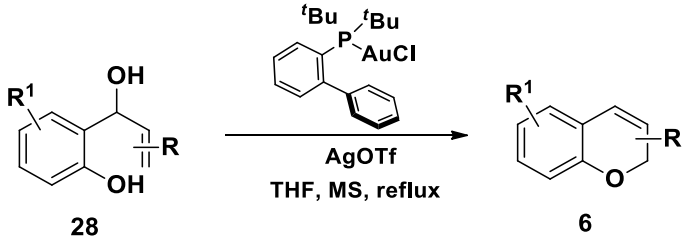
2.2.1.4. Using Gold

Banwell and coworkers developed the Au(I)-catalyzed intramolecular hydroarylation of terminal alkynes **11** toward the synthesis of 2*H*-chromenes **6**.[13] They illustrated a simple method that proceeds under exceptionally mild conditions and in a time-efficient manner. They were also successful in synthesizing a number of other important heterocyclic motifs such as coumarins, benzofurans, and dihydroquinolines (Scheme 2.11).



Scheme 2.11

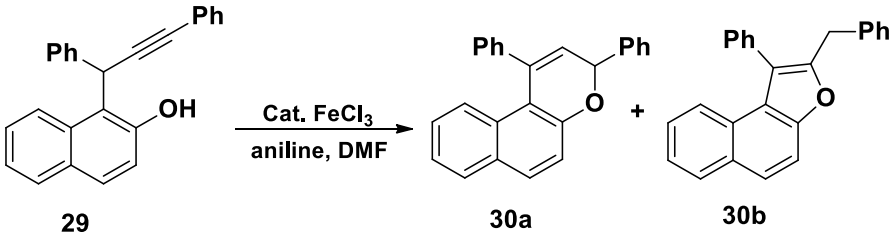
Aponick *et al*. reported the gold(I)-catalyzed endo-cyclization of *ortho*-(1-hydroxyallyl)-phenols **28** to furnish chromenes **6** (Scheme 2.12).[14] The role of the catalyst was found to change depending up on the nature of the substrate as the catalyst functions as a Lewis acid when ionization is facile and as a π-acid when the substrate is not readily ionized.



Scheme 2.12

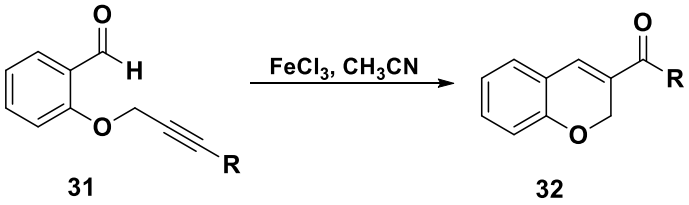
2.2.1.5. Using Iron

The intramolecular hydroaryloxylation of 2-propargylphenols or naphthols **29** was developed by Li *et al*. wherein the *endo*-dig cyclization afforded the benzopyran or naphthopyran derivatives **30a** using iron (III) chloride as the catalyst with the assistance of aniline in DMF (Scheme 2.13).[15] The formation of benzofuran derivatives **30b** was also observed in the reaction as a side product.



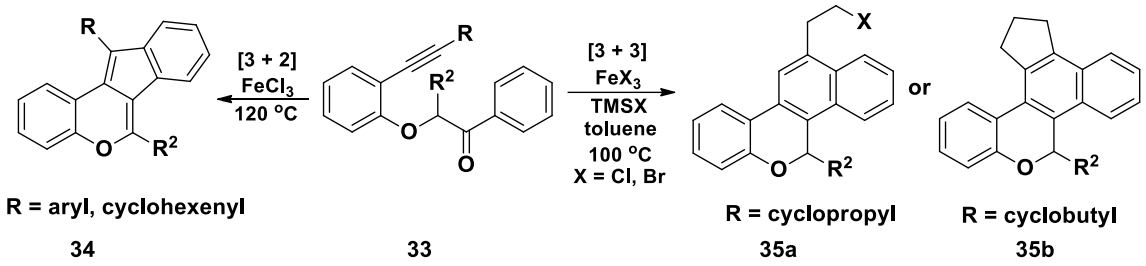
Scheme 2.13

$FeCl_3$-catalyzed intramolecular alkyne-aldehyde metathesis strategy of the alkynyl ether of salicylaldehyde derivatives **31** for the synthesis of functionalized 2*H*-chromenes **32** was reported by Jana and coworkers (Scheme 2.14).[16]



Scheme 2.14

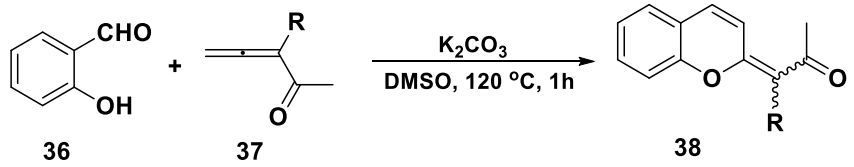
Li and coworkers developed an iron-mediated method through sequential electrophilic addition of a ketone to an alkyne followed by an annulation tandem reaction toward the synthesis of indeno[1,2-*c*]chromenes **34** and 5H-naphtho[1,2-*c*]chromenes **35**.[17] A halide group is introduced into the products by a ring-opening process among the annulation of alkynylcyclopropanes (Scheme 2.15).



Scheme 2.15

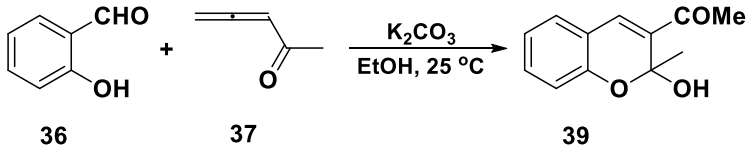
2.2.2. Metal Free Transformations

Among different versatile methods for the construction of chromene derivatives **38**, potassium carbonate-catalyzed reactions of salicylaldehydes **36** with substituted allenic ketones **37** and esters to synthesize functionalized 2*H*-chromenes **38** were explored by Shi *et al*. (Scheme 2.16).[18]



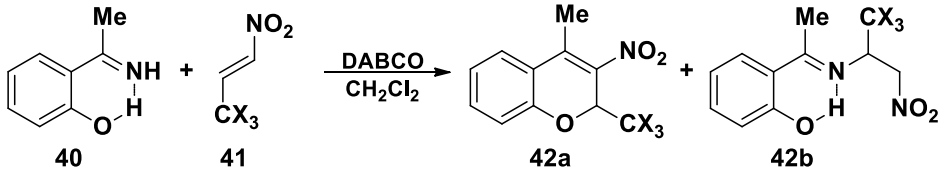
Scheme 2.16

The same group later developed the synthesis of different types of 2*H*-chromenes using unsubstituted allenic esters or ketones **37** *via* the same strategy (Scheme 2.17).[19]



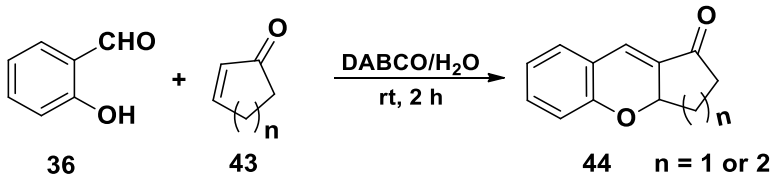
Scheme 2.17

A simple and convenient synthesis of 2*H*-chromenes **42a** from *N*-unsubstituted imines of 2-hydroxyacetophenones **40** and trichloro or trifluoro ethylidene nitromethanes **41** were developed by Sosnovskikh *et al*.[20] The reaction works well with DABCO as a base and under the optimized conditions a small amount of the imine (*E*-isomer) **42b** was also seen (Scheme 2.18).



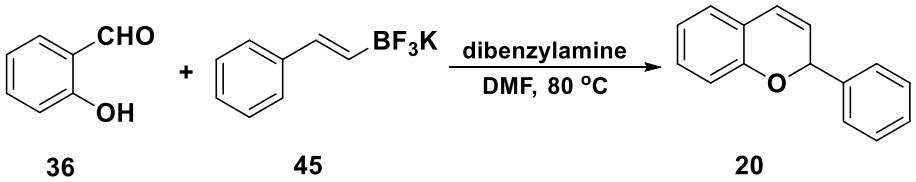
Scheme 2.18

Ravichandran *et al*. also reported the synthesis of chromene derivatives **44** by the reaction of salicylaldehyde **36** with 2-cyclohexen-1-one or 2-cyclopenten-1-one **43** in the presence of DABCO (Scheme 2.19).[21]



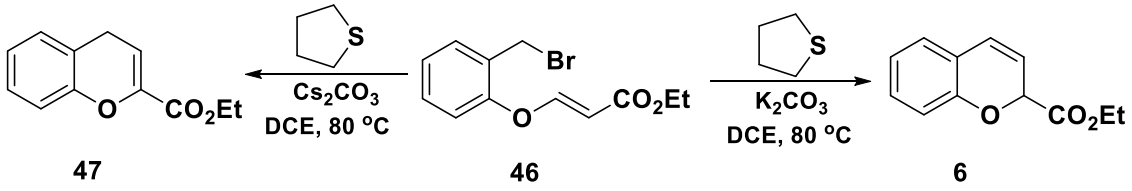
Scheme 2.19

The synthesis of 2*H*-chromenes **20** from salicylaldehyde **36** using potassium vinylic borates **45** in the presence of secondary amines at 80 ^{o}C was explored by Das and co-workers.[22] The reaction gave higher yields with electron withdrawing groups in the *para* position of salicylaldehydes, as compared to unsubstituted functional groups (Scheme 2.20).



Scheme 2.20

Tang *et al*. unraveled an efficient strategy for the synthesis of 2*H*-chromenes and 4*H*-chromenes by an unexpected tandem ylide annulation reaction (Scheme 2.21).[23] The tandem Michael addition/elimination/substitution reaction gave 2*H*-chromenes **6** using K_2CO_3 as base and 4*H*-chromenes **47** using Cs_2CO_3 from the same ester as the starting material.

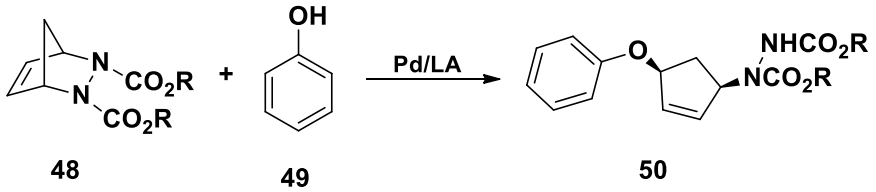


Scheme 2.21

2.3. Background to the Present Work

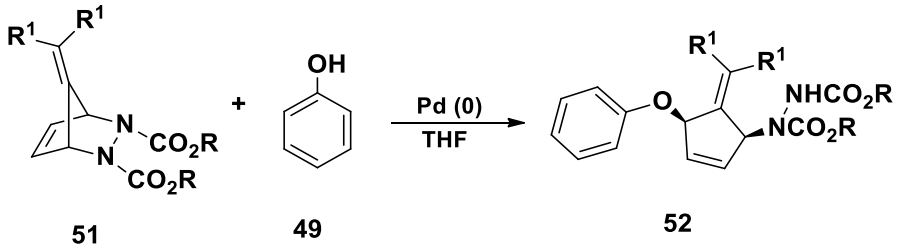
As described in the first chapter, the desymmetrization of diazabicyclic olefins provides an easy way toward the synthesis of carbocycles and heterocycles that are of both synthetic and biological interest, and thus they have been widely exploited. In 2003, Micouin and coworkers reported the palladium catalyzed ring opening of diazabicyclic olefins **48** with soft nucleophiles such as phenols **49** toward the synthesis of *cis*-3,5-disubstituted

cyclopentenes **50** for the first time (Scheme 2.22).[24]



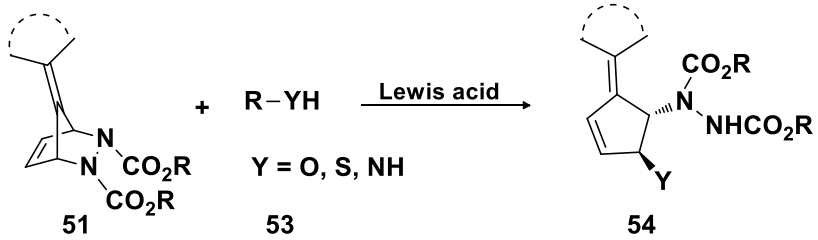
Scheme 2.22

Followed by that our group utilized the same strategy for the ring opening of fulvene derived bicyclic hydrazines **51** and spirotricyclic diazanorbornene analogues (Scheme 2.23).[25,26]



Scheme 2.23

We had also demonstrated the Lewis acid catalyzed ring opening of pentafulvene derived diazabicyclic olefins **51** with external nucleophiles such as alcohols, phenols, thiophenols and anilines **53** (Scheme 2.24).



Scheme 2.24

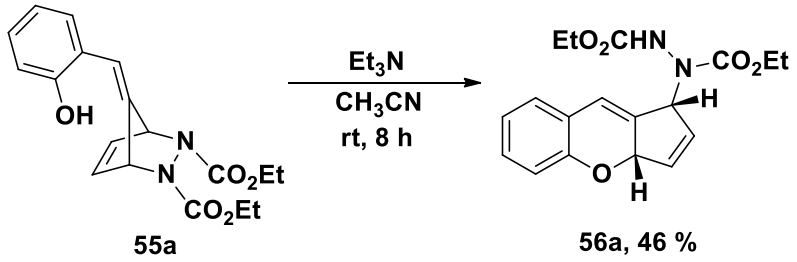
2.4. Statement of the Problem

The development of catalytic, clean, efficient and mild synthetic methods to create C-C, C-N and C-O bond formation remains one of the important topics in the field of organic chemistry. Despite the availability of these existing methods for the synthesis of chromene derivatives, there remains a continued demand for developing novel strategies that can more efficiently provide diverse chromene systems. Even though there are limited reports on the Pd/LA mediated desymmetrization of fulvene derived azabicyclic olefins, the synthetic

transformations of phenol substituted fulvene derived azabicyclic olefins have not been investigated so far. Intrigued by the promising results of our investigations on the ring opening of fulvene derived azabicyclic olefins with soft nucleophiles like phenols, we were interested to check the reactivity pattern of phenol substituted fulvene derived azabicyclic olefins. A detailed investigation on the base mediated intramolecular reactions of various phenol substituted fulvene derived bicyclic hydrazines was carried out and the results of these studies are presented in the following sections.

2.5. Results and Discussion

In order to validate our hypothesis, we commenced our studies with the reaction of salicylaldehyde derived fulvene adduct **55a** in the presence of Et_3N as base in CH_3CN at room temperature for 8 hours. The reaction afforded cyclopentene fused chromene derivative **56a** in 46 % yield (Scheme 2.25).



Scheme 2.25. Base induced intramolecular cyclization

The structure of the product **56a** was assigned based on various spectroscopic analyses such as ^{1}H NMR, ^{13}C NMR and further confirmation was obtained from HRMS-ESI analysis. The IR spectrum showed characteristic carbonyl absorption at 1749 and 1692 cm^{-1}, a strong broad C-O stretching vibration at 1237 cm^{-1} and the absorption indicative of the N-H stretching at 3266 cm^{-1}.

In the ^{1}H NMR spectrum (Figure 2.2), the four aromatic protons appeared as multiplet in the region δ 7.15-6.90 ppm. Three alkenic protons and the –NH proton appeared as a multiplet in the region δ 6.40-6.25 ppm. The proton adjacent to the nitrogen atom appeared as a broad mutiplet at δ 6.13-5.84 ppm. The proton nearer to oxygen atom resonated at δ 5.35 ppm as a singlet. The multiplet in the region δ 4.28-4.09 ppm was assigned to methylene protons of carboethoxy groups. The methyl protons of the carboethoxy group resonated as a multiplet in the region δ 1.31-1.20 ppm.

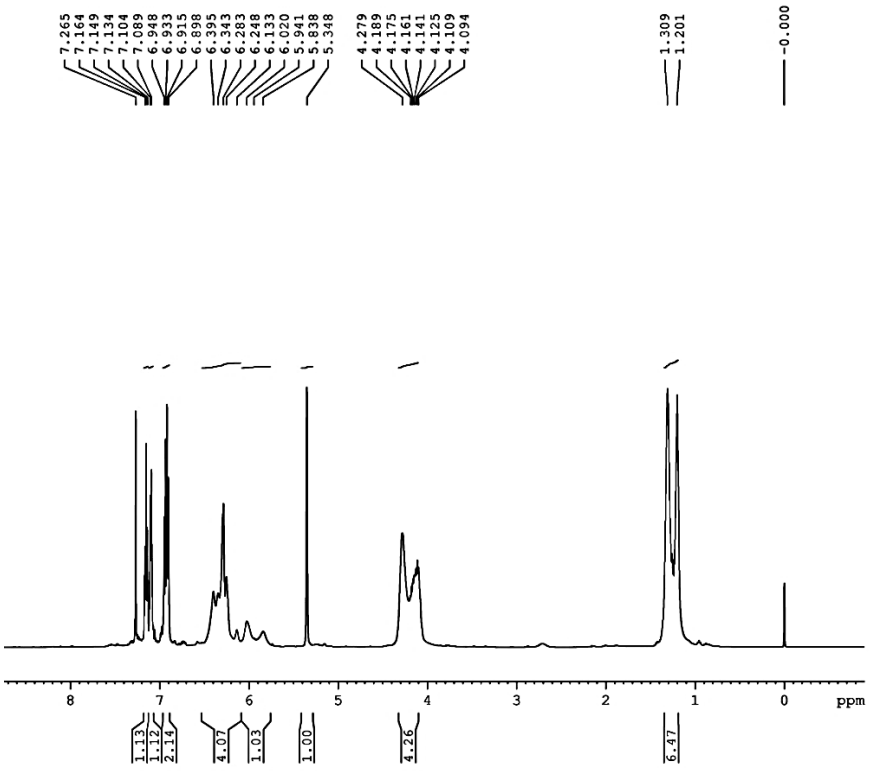


Figure 2.2. ^{1}H NMR spectrum of compound **56a**

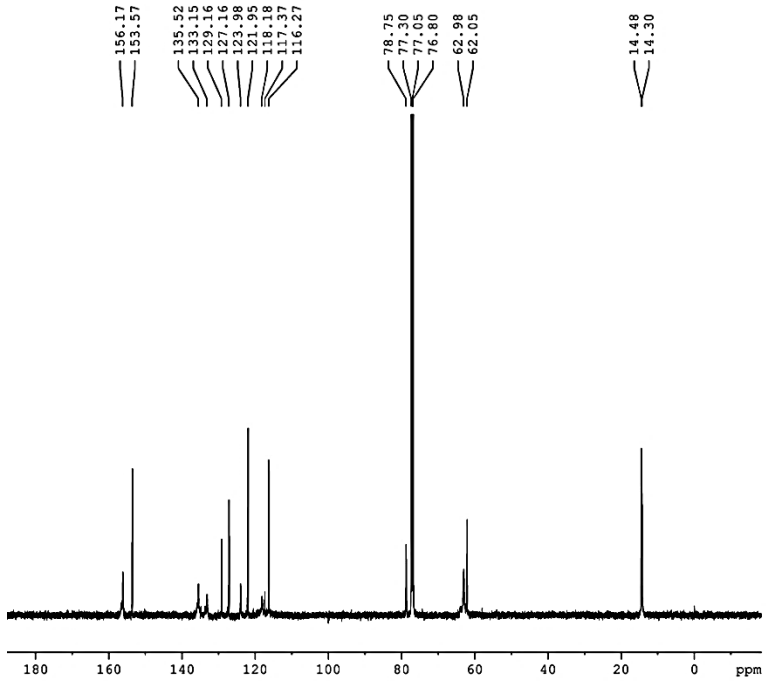


Figure 2.3. ^{13}C NMR spectrum of compound **56a**

The ^{13}C NMR spectrum showed peak due to ester carbonyl carbons at δ 156.2 ppm. The carbon adjacent to oxygen was discernible at δ 78.8 ppm. The carbon attached to the

nitrogen group resonated at δ 63.0 ppm. The methylene carbons of the ester group resonated at δ 63.0 and 62.1 ppm. The methyl carbons of the carboethoxy group showed sharp peaks at δ 14.5 and 14.3 ppm. All other signals in ^{13}C NMR spectra were in agreement with the proposed structure (Figure 2.3).

The structure of the product **56a** assigned was further supported by high resolution mass spectral analysis which showed $[M+Na]^+$ peak at *m/z* = 367.12756.

The chromene derivative **56a** was crystallized from ethyl acetate/hexane mixture, and the stereochemistry was unambiguously confirmed by single crystal X-ray analysis (CCDC 1438504) (Figure 2.4).

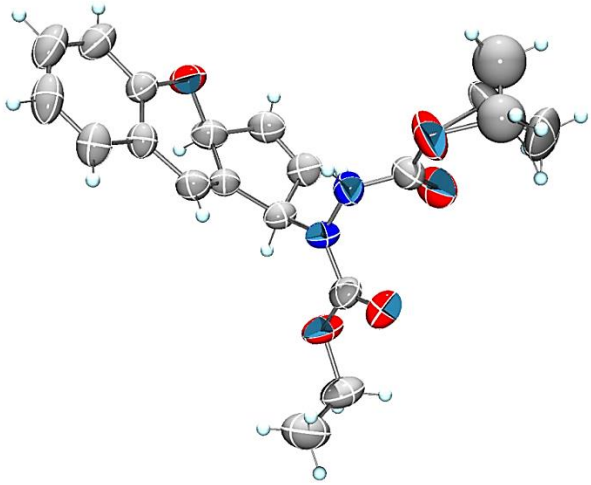
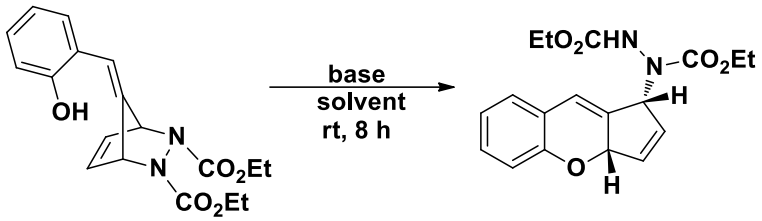


Figure 2.4. Single crystal X-ray structure of **56a**

2.5.1. Optimization Studies

To explore the best condition for this reaction, we have performed detailed optimization studies with different organic and inorganic bases (Table 2.1, entries 1-11). Among them, DMAP was found to be the efficient base. Reaction was found to be effective even after adding the base in catalytic amount (entry 12). To check the effect of different solvents on the outcome of this organocatalytic transformation, the reaction was carried out in different solvents (entries 12-17). The highest yield (66 %) for **56a** was obtained with CH_3CN as the solvent (entry 12). After the detailed investigation, the best condition was found to be with 1 equiv. of bicyclic hydrazine in the presence of 20 mol% DMAP at room temperature for 8 h furnishing the product **56a** in 66 % yield (entry 12).

Table 2.1. Reaction optimization studies[a]



Entry	Base	Solvent	Yield (%)[b]
1	Et_3N	CH_3CN	46
2	DIPA	CH_3CN	31
3	KO^tBu	CH_3CN	20
4	K_2CO_3	CH_3CN	23
5	Cs_2CO_3	CH_3CN	24
6	NaOAc	CH_3CN	48
7	KOAc	CH_3CN	40
8	DMAP	CH_3CN	68
9	DBU	CH_3CN	15
10	Imidazole	CH_3CN	54
11	DABCO	CH_3CN	21
12[c]	**DMAP**	**CH_3CN**	**66**
13[c]	DMAP	ether	38
14[c]	DMAP	DCM	27
15[c]	DMAP	THF	34
16[c]	DMAP	toluene	4
17[c]	DMAP	DMF	34

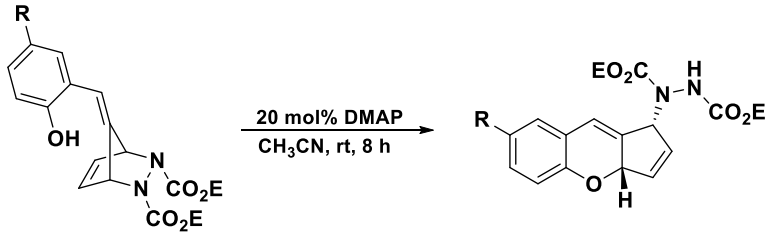
[a]**Reaction conditions:** adduct (1 equiv.), base (1 equiv.), rt, 8 h. [b]Isolated yields. [c]base (20 mol%).

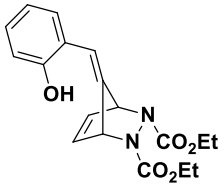
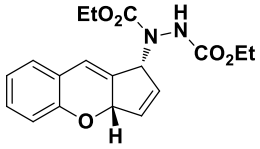
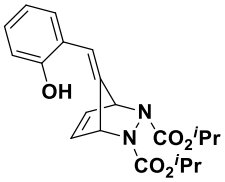
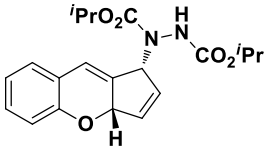
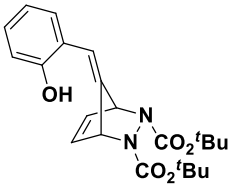
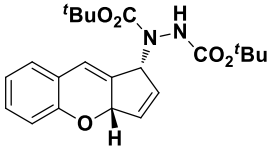
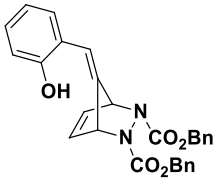
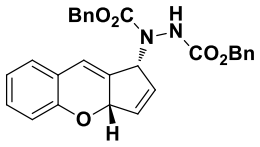
2.5.2. Scope of the Reaction

Under the optimal condition, various bicyclic olefins derived from different dialkyl azadicarboxylates underwent ring opening followed by intramolecular cyclization and gave the corresponding cyclopentene fused chromene derivatives (Table 2.2, **56a-56d**) in moderate to good yields. The reactivity of bicyclic hydrazines derived from various

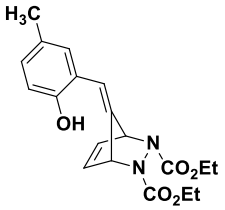
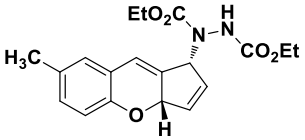
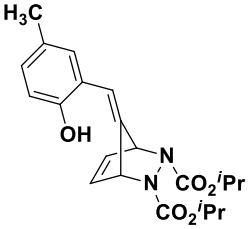
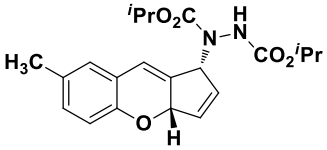
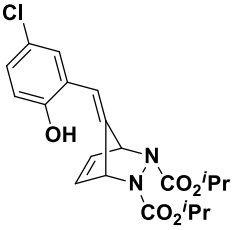
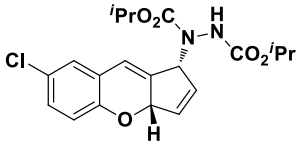
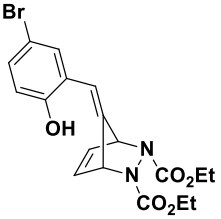
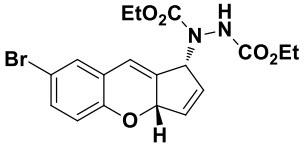
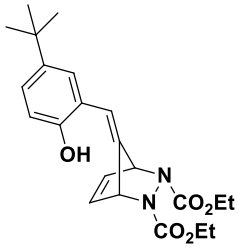
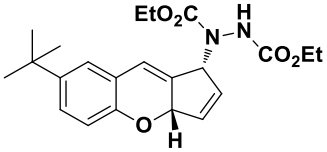
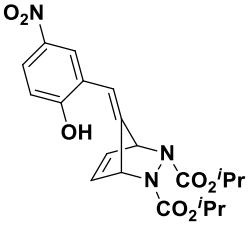
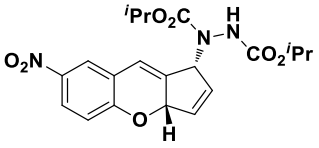
substituted salicylaldehydes was also explored under similar conditions. Both electron donating and electron withdrawing substituents present on the aromatic ring of fulvene adducts at *para* position to the hydroxyl group delivered the fused chromene derivatives in comparable yields (Table 2.2, **56e**-**56l**). However, further scope of the reaction could not be expanded to substituents at other positions of the aromatic ring due to the instability of the fulvene synthesized.

Table 2.2. Substrate scope for intramolecular cyclisation[a]

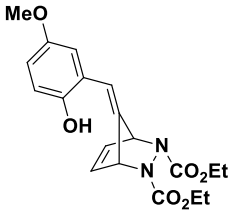
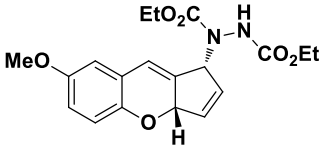
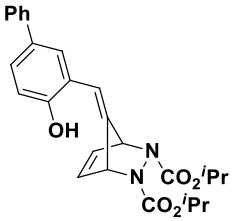
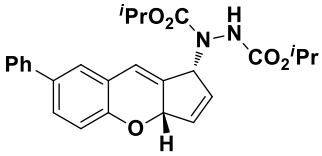


Entry	Bicyclic olefin	Product	Yield (%)[b]
1	 **55a**	 **56a**	66
2	 **55b**	 **56b**	54
3	 **55c**	 **56c**	49
4	 **55d**	 **56d**	43

Continued..

5	 **55e**	 **56e**	59
6	 **55f**	 **56f**	51
7	 **55g**	 **56g**	48
8	 **55h**	 **56h**	50
9	 **55i**	 **56i**	53
10	 **55j**	 **56j**	41

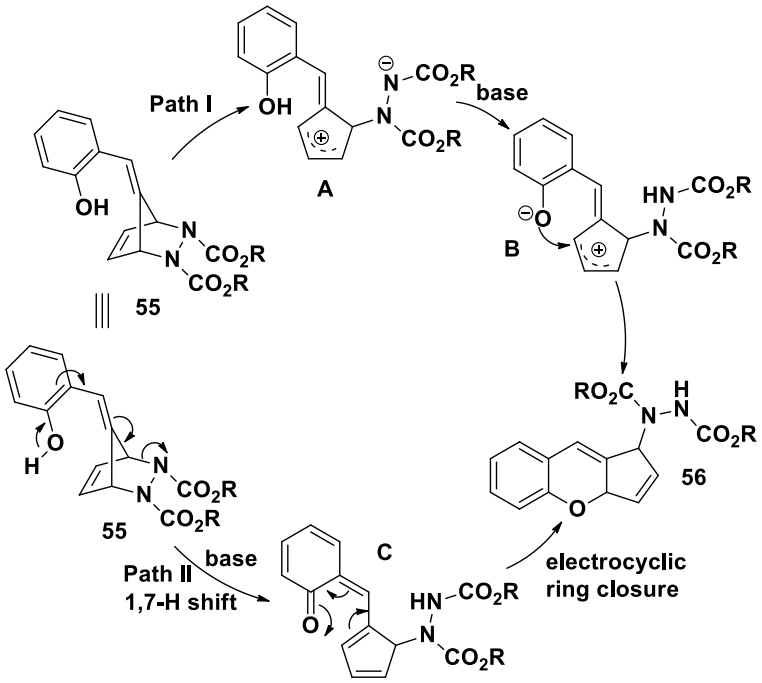
Continued..

11	 **55k**	 **56k**	61
12	 **55l**	 **56l**	52

[a]**Reaction conditions:** azabicyclic olefin (1 equiv.), DMAP (20 mol%), CH_3CN, rt, 8 h. [b]Isolated yield.

2.6. Proposed Mechanism

The mechanism for the reaction can be shown in two different pathways *viz.* a zwitter ion mechanism (Path I) or an electrocyclic ring closure mechanism (Path II) as illustrated in Scheme 2.26.



Scheme 2.26. Proposed mechanistic pathways

Path I commences with the formation of zwitter ion **A** by the ring opening of pentafulvene derived diazabicyclic olefin due to its inherent instability.[27] Subsequent base

induced proton transfer to the hydrazinium ion from the hydroxyl group results in the formation of **B**. Then the intramolecular attack of phenoxide ion to the allylic cation furnishes cyclopentene fused chromene derivative **56**. In electrocyclic ring closure mechanism (Path II), the diazabicyclic olefin undergoes a base induced 1,7-hydrogen shift to furnish the intermediate **C**. Further, the 6π electrocyclic ring closure of **C** delivers cyclopentene fused chromene derivative **56**.[28,29]

2.7. Conclusion

In conclusion, we have unraveled a versatile route for the synthesis of cyclopentene fused chromenes *via* base catalyzed transformation of phenol substituted fulvene derived azabicyclic olefins. To the best of our knowledge, this is the first report on transition metal free ring opening of pentafulvene-derived diazabicyclic alkenes. These results may prove useful for further investigations on the reactivity of heterobicyclic analogues appended with other nucleophilic moieties toward the synthesis of biologically important molecules. Moreover the importance of chromene derivatives shows promise in future applications with respect to its biological activity.

2.8. Experimental Section

2.8.1. General Methods

All reactions were conducted in oven-dried glasswares. All chemicals were of the best grade commercially available and are used without further purification. All the solvents were purified according to standard procedure; dry solvents were obtained according to the literature methods and stored over molecular sieves. All reactions were monitored by TLC (Silica gel 60 F254, 0.25 mm, Merck), visualization was effected with UV and/or by staining with Mc Gill or Enholm yellow solution. Gravity column chromatography was performed using 100-200 mesh silica gel or neutral alumina and mixtures of hexane-ethyl acetate were used for elution. Melting point was determined on a Buchi Melting Point apparatus and is uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker Avance AMX 500 spectrophotometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.25 ppm, singlet). Multiplicities were given as: s (singlet); bs (broad singlet); d (doublet); t (triplet); q (quartet); dd (double doublet); ddd (doublet of double doublet); m (multiplet). Coupling constants are reported as *J* value in Hz.

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

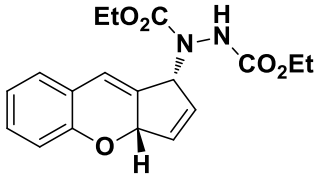
2.8.2. General Procedure for the Intramolecular Cyclization

The phenol substituted fulvene derived azabicyclic olefin (1 equiv.) and base DMAP (20 mol%) were taken in a Schlenk tube. The mixture was then dissolved in dry CH_3CN (2 mL) and allowed to stir at room temperature for 8 hours. The solvent was evaporated in *vacuo* and the residue on silica gel column chromatography using mixtures of EtOAc/hexane yielded cyclopentene fused chromene derivatives in moderate to good yields.

2.8.3. Characterization of the Products

Compound 56a

Following general procedure for the intramolecular cyclization 2.8.2, compound **56a** (53 mg, 66 %) was synthesised from phenol substituted fulvene derived azabicyclic olefin **55a** (80 mg, 0.2323 mmol) using 20 mol% DMAP (6 mg, 0.0465 mmol) as pale reddish orange crystals.



R_f: 0.26 (3:7 hexane/ethyl acetate).

M. P. = 147-149 ^{o}C.

IR (neat) ν_{max}: 3266, 2981, 2928, 2850, 1749, 1692, 1604, 1519, 1480, 1412, 1384, 1310, 1269, 1237, 1130, 1099, 1060, 1000, 858, 758, 664, 608, 555 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (t, *J* = 7.5 Hz, 1 H), 7.09 (d, *J* = 7.5 Hz, 1 H), 6.95-6.90 (m, 2 H), 6.40-6.13 (m, 4 H), 6.02-5.83 (m, 1 H), 5.35 (s, 1 H), 4.28-4.09 (m, 4 H), 1.31-1.20 (m, 6 H).

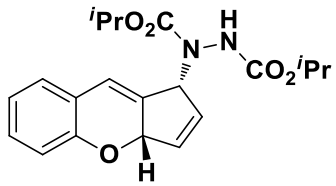
^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 153.6, 135.5, 133.2, 129.2, 127.2, 124, 122, 118.2, 117.4, 116.3, 78.8, 63, 62.1, 14.5, 14.3.

HRMS (ESI): *m/z* calcd for $C_{18}H_{20}N_2O_5Na$: 367.12699; Found: 367.12756.

Compound 56b

Following general procedure for the intramolecular cyclization 2.8.2, compound **56b** (43 mg,

54 %) was synthesised from phenol substituted fulvene derived azabicyclic olefin **55b** (80 mg, 0.2148 mmol) using 20 mol% DMAP (5 mg, 0.0429 mmol) as reddish brown viscous liquid.



R_f: 0.39 (3:7 hexane/ethyl acetate).

IR (neat) ν_{max}: 3340, 2983, 2928, 1711, 1606, 1460, 1381, 1305, 1233, 1179, 1107, 1039, 951, 834, 789, 758, 664, 610 cm^{-1}.

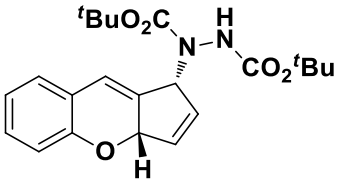
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15-7.12 (m, 1 H), 7.08 (d, *J* = 7.0 Hz, 1 H), 6.93-6.88 (m, 2 H), 6.28 (bs, 4 H), 6.14-5.79 (m, 1 H), 5.35 (s, 1 H), 5.02-4.89 (m, 2 H), 1.32-1.2 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 155.7, 153.6, 135.6, 132.9, 129.8, 129.6, 129, 127.1, 124, 121.8, 118.2, 117.4, 116.2, 78.7, 70.5, 69.8, 69.5, 62.7, 22.1.

HRMS (ESI): *m/z* calcd for $C_{20}H_{24}O_5N_2Na$: 395.15829; Found: 395.15825.

Compound 56c

Following general procedure for the intramolecular cyclization 2.8.2, compound **56c** (39 mg, 49 %) was synthesised from phenol substituted fulvene derived azabicyclic olefin **55c** (80 mg, 0.1998 mmol) using 20 mol% DMAP (5 mg, 0.0399 mmol) as reddish brown viscous liquid.



R_f: 0.53 (3:7 hexane/ethyl acetate).

IR (neat) ν_{max}: 3330, 2979, 2929, 2350, 1707, 1608, 1480, 1457, 1391, 1369, 1314, 1244, 1157, 1102, 1056, 1022, 999, 944, 912, 857, 757, 660, 609, 556 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16-7.12 (m, 1 H), 7.09 (d, *J* = 7.0 Hz, 1 H), 6.94-6.89 (m, 2 H), 6.34-6.13 (m, 4 H), 5.99-5.87 (m, 1 H), 5.36 (s, 1 H), 1.53-1.43 (m, 18 H).

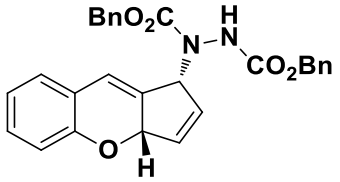
^{13}C NMR (125 MHz, $CDCl_3$): δ 155.1, 153.6, 136.9, 136, 135.3, 132.6, 129, 127.1, 124.1, 121.9, 117.4, 116.2, 81.7, 80.9, 78.9, 62.2, 28.2, 28.1.

HRMS (ESI): *m/z* calcd for $C_{22}H_{28}O_5N_2Na$: 423.18959; Found: 423.19023.

Compound 56d

Following general procedure for the intramolecular cyclization 2.8.2, compound **56d** (34 mg, 43 %) was synthesised from phenol substituted fulvene derived azabicyclic olefin **55d** (80

mg, 0.1708 mmol) using 20 mol% DMAP (4 mg, 0.0342 mmol) as pale yellow solid.



R_f: 0.42 (30% hexane/ethyl acetate).

M. P. = 151-153 ^oC.

IR (neat) ν_{max}: 3395, 2924, 1713, 1588, 1526, 1497, 1479, 1456, 1409, 1368, 1305, 1263, 1128, 1102, 1056, 998, 910, 891, 871, 791, 756, 697, 662, 608, 556 cm^{-1}.

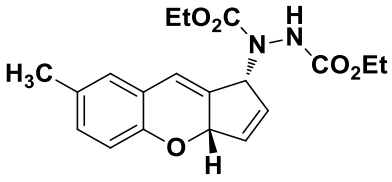
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.26 (m, 10 H), 7.17-7.14 (m, 1 H), 7.06 (s, 1 H), 6.95-6.90 (m, 2 H), 6.52 (s, 1 H), 6.30-6.26 (m, 3 H), 6.07-5.88 (m, 1 H), 5.35-5.01 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.0, 153.6, 135.5, 128.6, 128.5, 128.3, 128, 123.9, 122, 118.4, 116.3, 78.7, 68.5, 67.7, 63.2.

HRMS (ESI): *m/z* calcd for $C_{28}H_{24}O_5N_2Na$: 491.15829; Found: 491.15908.

Compound 56e

Following general procedure for the intramolecular cyclization 2.8.2, compound **56e** (47 mg, 59 %) was synthesised from *p*-cresol substituted fulvene derived azabicyclic olefin **55e** (80 mg, 0.2232 mmol) using 20 mol% DMAP (5 mg, 0.0446 mmol) as reddish brown viscous liquid.



R_f: 0.33 (3:7 hexane/ethyl acetate).

IR (neat) ν_{max}: 3329, 2923, 2853, 1712, 1584, 1486, 1413, 1380, 1307, 1226, 1125, 1059, 861, 819, 762, 662, 609, 556 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.94 (d, *J* = 8.0 Hz, 1 H), 6.89 (s, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 6.37-6.24 (m, 4 H), 6.12-5.82 (m, 1 H), 5.31 (s, 1 H), 4.33-4.11(m, 4 H), 2.28 (s, 3 H), 1.34-1.22 (m, 6 H).

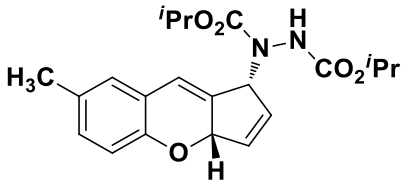
^{13}C NMR (125 MHz, $CDCl_3$): δ 156.1, 151.4, 135.4, 133.2, 131, 129.7, 128.9, 127.6, 123.8, 118.1, 115.9, 78.8, 62.8, 61.9, 20.6, 14.5, 14.3.

HRMS (ESI): *m/z* calcd for $C_{19}H_{22}O_5N_2Na$: 381.14264; Found: 381.14276.

Compound 56f

Following general procedure for the intramolecular cyclization 2.8.2, compound **56f** (41 mg, 51 %) was synthesised from *p*-cresol substituted fulvene derived azabicyclic olefin **55f** (80 mg, 0.2070 mmol) using 20 mol% DMAP (5 mg, 0.0414 mmol) as reddish brown viscous

liquid.



R_f: 0.44 (3:7 hexane/ethyl acetate).

IR (neat) ν_{max}: 3316, 2985, 2926, 2308, 1732, 1486, 1381, 1304, 1216, 1180, 1109, 1037, 951, 897, 818, 763, 714, 664, 609, 556 cm^{-1}.

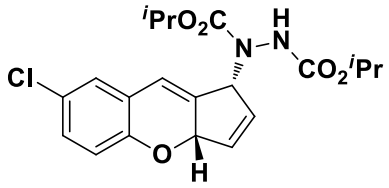
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (d, *J* = 8.0 Hz, 1 H), 6.88 (s, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.50-6.25 (m, 4 H), 6.12-5.77 (m, 1 H), 5.29 (s, 1 H), 5.01-4.88 (m, 2 H), 2.27(s, 3 H), 1.32-1.19 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7, 151.4, 136.2, 135.5, 133.1, 131, 129.5, 127.5, 123.8, 118.2, 115.9, 78.8, 70.5, 69.6, 62.8, 22.1, 21.8, 20.6.

HRMS (ESI): *m/z* calcd for $C_{21}H_{26}O_5N_2Na$: 409.17394; Found: 409.17424.

Compound 56g

Following general procedure for the intramolecular cyclization 2.8.2, compound **56g** (38 mg, 48 %) was synthesised from 4-chlorophenol substituted fulvene derived azabicyclic olefin **55g** (80 mg, 0.1966 mmol) using 20 mol% DMAP (5 mg, 0.0393 mmol) as reddish brown viscous liquid.



R_f: 0.46 (3:7 hexane/ethyl acetate)

IR (neat) ν_{max}: 3304, 2982, 2935, 1712, 1589, 1495, 1473, 1404, 1386, 1304, 1266, 1235, 1202, 1181, 1130, 1145, 1107, 1057, 1000, 953, 926, 892, 819, 764 cm^{-1}.

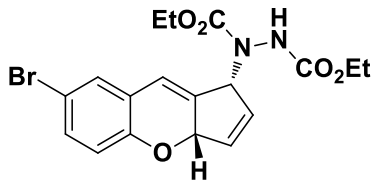
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10-7.06 (m, 2 H), 6.83 (d, *J* = 8.5 Hz, 1 H), 6.40-6.15 (m, 4 H), 6.00-5.8 (m, 1 H), 5.34 (s, 1 H), 5.03-4.9 (m, 2 H), 1.32-1.22 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6, 154.9, 152.1, 135.6, 132.8, 131.3, 129.3, 128.6, 126.8, 126.7, 125.3, 125.0, 117.5, 116.6, 79.0, 70.8, 69.9, 63.1, 22.1, 21.8.

HRMS (ESI): *m/z* calcd for $C_{20}H_{23}O_5N_2ClNa$: 429.11932; Found: 429.11951.

Compound 56h

Following general procedure for the intramolecular cyclization 2.8.2, compound **56h** (40 mg, 50 %) was synthesised from 4-bromophenol substituted fulvene derived azabicyclic olefin **55h** (80 mg, 0.1890 mmol) using 20 mol% DMAP (5 mg, 0.0378 mmol) as reddish brown viscous liquid.



R_f: 0.32 (3:7 hexane/ethyl acetate).

IR (neat) ν_{max}: 3296, 2981, 2927, 1710, 1471, 1411, 1382, 1305, 1226, 1129, 1106, 1059, 999, 913, 817, 761, 662, 609, 556 cm^{-1}.

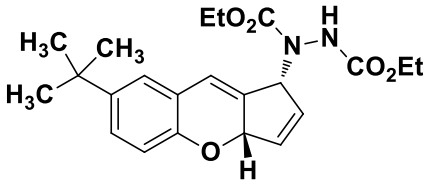
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.21 (m, 2 H), 6.78 (d, *J* = 8.5 Hz, 1 H), 6.26 (bs, 4 H), 6.13-5.81 (m, 1 H), 5.33 (s, 1 H), 4.28-4.11(m, 4 H), 1.32-1.23 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 152.6, 135.6, 132.6, 131.7, 129.6, 129, 125.9, 118, 117.2, 114, 78.9, 63.1, 62.1, 14.4, 14.5, 14.4.

HRMS (ESI): *m/z* calcd for $C_{18}H_{19}O_5N_2BrNa$: 445.03750; Found: 445.03810.

Compound 56i

Following general procedure for the intramolecular cyclization 2.8.2, compound **56i** (42 mg, 53 %) was synthesised from 4-*tert*-butyl phenol substituted fulvene derived azabicyclic olefin **55i** (80 mg, 0.1998 mmol) using 20 mol% DMAP (5 mg, 0.0399 mmol) as pale yellowish red viscous liquid.



R_f: 0.38 (3:7 hexane/ethyl acetate).

IR (neat) ν_{max}: 3302, 2962, 1713, 1488, 1412, 1382, 1307, 1263, 1229, 1135, 1061, 830, 762, 663, 609, 555 cm^{-1}.

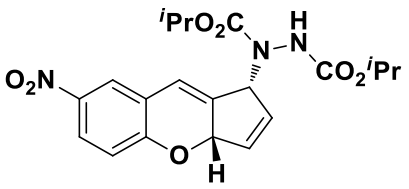
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18-7.16 (m, 1 H), 7.11 (s, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 6.35-6.25 (m, 4 H), 6.13-5.83 (m, 1 H), 5.33 (s, 1 H), 4.29-4.10 (m, 4 H), 1.31-1.21 (m, 15 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156, 151.3, 144.6, 135.4, 133.4, 126.0, 124.0, 123.3, 118.5, 115.7, 78.8, 62.8, 61.9, 34.2, 31.5, 14.5, 14.3.

HRMS (ESI): *m/z* calcd for $C_{22}H_{28}O_5N_2Na$: 423.18959; Found: 423.18915.

Compound 56j

Following general procedure for the intramolecular cyclization 2.8.2, compound **56j** (33 mg, 41 %) was synthesised from 4-nitrophenol substituted fulvene derived azabicyclic olefin **55j** (80 mg, 0.1917 mmol) using 20 mol% DMAP (5 mg, 0.0383 mmol) as reddish orange viscous liquid.



R_f: 0.53 (2:3 hexane/ethyl acetate).

IR (neat) ν_{max}: 3307, 2982, 2930, 1712, 1611, 1580, 1520, 1473, 1384, 1341, 1302, 1236, 1180, 1108, 1049, 994, 952, 908, 835, 800, 756, 665, 610, 556 cm^{-1}.

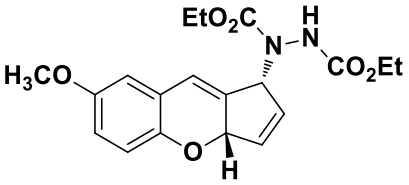
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.5 Hz, 1 H), 7.98 (s, 1 H), 6.94 (d, *J* = 8.5 Hz 1 H), 6.52-6.19 (m, 4 H), 6.02-5.79 (m, 1 H), 5.46 (s, 1 H), 5.02-4.89 (m, 2 H), 1.31-1.19 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8, 156.4, 156, 155.6, 142.2, 137.5, 136.2, 132.0, 124.8, 124.0, 122.6, 116.6, 79.6, 70.8, 69.9, 62.7, 22.0, 21.9.

HRMS (ESI): *m/z* calcd for $C_{20}H_{23}O_7N_3Na$: 440.14337; Found: 440.14310.

Compound 56k

Following general procedure for the intramolecular cyclization 2.8.2, compound **56k** (49 mg, 61 %) was synthesised from 4-hydroxyanisole substituted fulvene derived azabicyclic olefin **55k** (80 mg, 0.2137 mmol) using 20 mol% DMAP (5 mg, 0.0427 mmol) as reddish brown viscous liquid.



R_f: 0.26 (3:7 hexane/ethyl acetate).

IR (neat) ν_{max}: 3301, 2983, 2933, 2348, 1710, 1611, 1578, 1485, 1412, 1382, 1305, 1264, 1207, 1160, 1127, 1103, 1059, 1036, 1004, 939, 864, 817, 762, 712, 662, 609, 555 cm^{-1}.

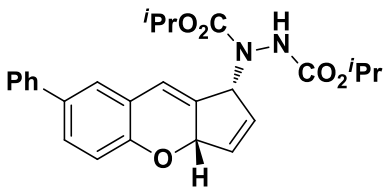
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.8 (d, *J* = 8.5 Hz, 1 H), 6.67-6.6 (m, 3 H), 6.25 (bs, 3 H), 6.10-5.80 (m, 1 H), 5.27 (s, 1 H), 4.28-4.08 (m, 4 H), 3.73 (s, 3 H), 1.32-1.2 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156, 154.3, 147.4, 135.4, 134.7, 133.1, 124.6, 118.3, 116.6, 114.2, 112.0, 78.9, 62.0, 61.9, 55.5, 14.5, 14.3.

HRMS (ESI): *m/z* calcd for $C_{19}H_{22}O_6N_2Na$: 397.13756; Found: 397.13828.

Compound 56l

Following general procedure for the intramolecular cyclization 2.8.2, compound **56l** (42 mg, 52 %) was synthesised from 4-phenylphenol substituted fulvene derived azabicyclic olefin **55l** (80 mg, 0.1784 mmol) using 20 mol% DMAP (4 mg, 0.0357 mmol) as pale yellow viscous liquid.



R_f: 0.66 (3:7 hexane/ethyl acetate).

IR (neat) ν_{max}: 3303, 3031, 2981, 2933, 1711, 1607, 1477, 1385, 1304, 1228, 1181, 1108, 1058, 999, 952, 901, 832, 765, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.50 (m, 2 H), 7.41-7.35 (m, 3 H), 7.31-7.28 (m, 2 H), 6.96 (d, *J* = 8.5 Hz, 1 H), 6.34-6.29 (m, 4 H), 6.14-5.81 (m, 1 H), 5.38 (s, 1 H), 5.02-4.89 (m, 2 H), 1.32-1.20 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7, 153.2, 140.6, 135.7, 135.1, 133.0, 128.7, 127.7, 126.9, 126.7, 125.8, 124.3, 118.1, 116.5, 79.0, 70.6, 69.7, 62.9, 22.0, 21.8.

HRMS (ESI): *m/z* calcd for $C_{26}H_{28}O_5N_2Na$: 471.18959; Found: 471.19067.

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CHAPTER 3

Rhodium Catalyzed Oxidative Coupling of Salicylaldehydes with Urea Derived Bicyclic Olefins

3.1. Introduction

Chromanones constitute an important class of heterocycles in view of their close resemblance with naturally occurring compounds like flavones, chromones and coumarins.[1,2] These heterocycles exhibit versatile biological activities such as antiviral, antimicrobial, antiarrhythmic and antidiabetic activities.[3] Due to their biological and pharmaceutical importance, more facile and convenient methods for their construction are still in the domain. Even though there exist many strategies for the synthesis of chromanones, attempts toward the synthesis of fused chromanone systems are limited.[4] Fused ring chromanone skeletons are abundant in natural products like cryptosporioptide, preussochromones and diaportheone (Figure 1).[5–7]

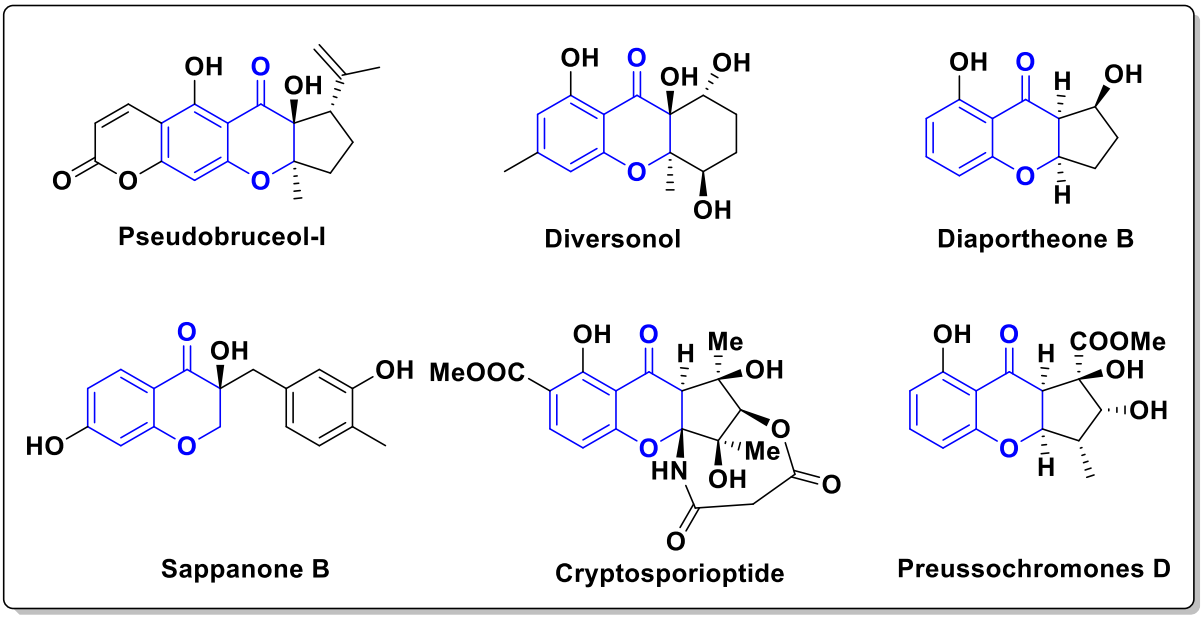
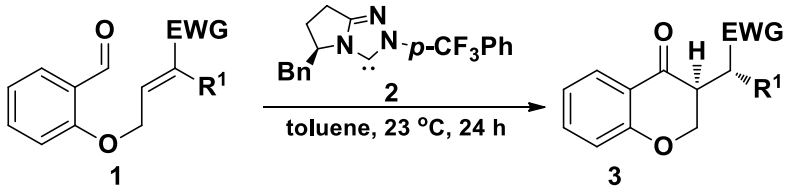


Figure 3.1. Natural products containing chromanone skeleton

3.2. Synthetic Approaches toward Chromanone Derivatives

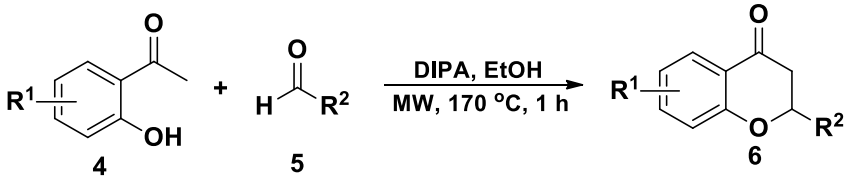
Various groups have reported several strategies toward the synthesis of substituted chromanone derivatives. The synthesis of substituted chromanones **3** using a highly enantio- and diastereoselective intramolecular Stetter reaction on a variety of tri-substituted Michael

acceptors **1** was developed by Rovis *et al.* in 2005 (Scheme 3.1).[8]



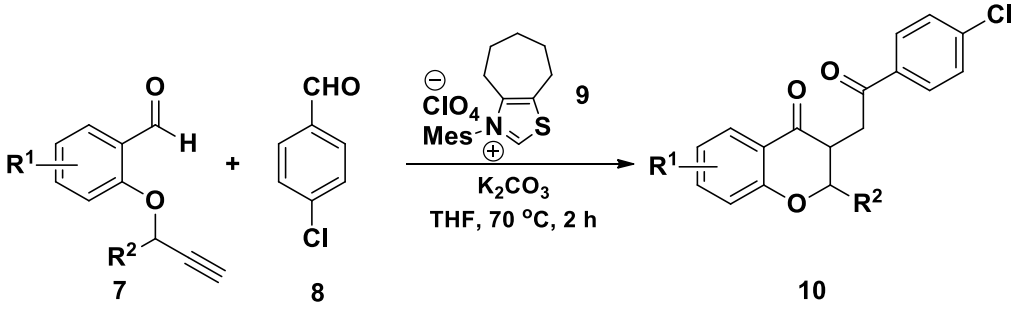
Scheme 3.1

Luthman and coworkers reported the base promoted condensation of 2-hydroxy acetophenones **4** and aliphatic aldehydes **5** towards the synthesis of a diverse set of 2-alkyl-substituted 4-chromanones **6** (Scheme 3.2).[9]



Scheme 3.2

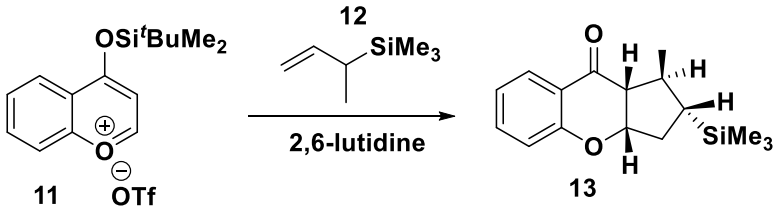
Glorius *et al*. developed the NHC-organo catalyzed hydroacylation of unactivated alkynes **7** to furnish α,β-unsaturated ketones **10** (Scheme 3.3). They even extended this strategy to synthesize benzopyranopyrrole derivative *via* subsequent intermolecular Stetter reaction.[10]



Scheme 3.3

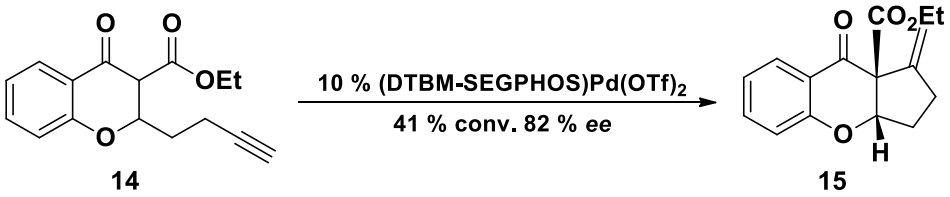
3.3. Synthetic Approaches toward Fused Chromanone Derivatives

As mentioned in afore sections, the synthesis of fused ring chromanones has also gained considerable attention and some of these strategies are mentioned below. Tandem reaction of 4-silyloxy-1-benzopyrylium salts **11** with 3-(trimethylsilyl)-1-butene **12** was reported by Akiba *et al*. to afford cyclopentane fused chromanone derivative **13** (Scheme 3.4).[11]



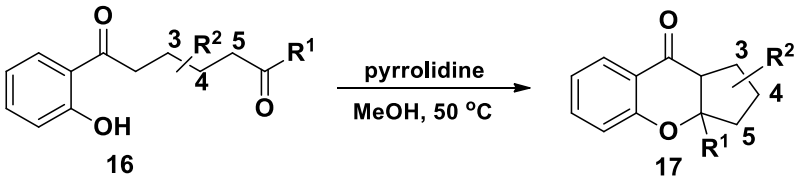
Scheme 3.4

Toste and co-workers reported the synthesis of cyclopentane fused chromanone derivatives **15** *via* the palladium-catalyzed intramolecular Conia-ene reaction of a β-dicarbonyl compound and alkyne (Scheme 3.5).[12]



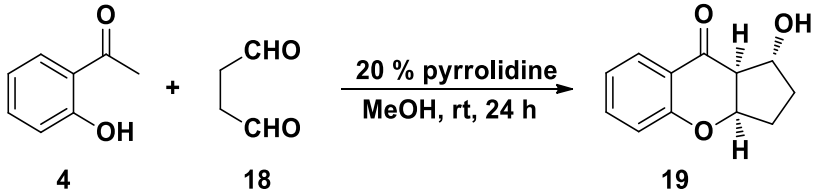
Scheme 3.5

An efficient diastereoselective organocatalytic aldol/oxa-Michael reaction has been developed by Kurth *et al.* to deliver medicinally relevant 2,3-ring-substituted chromanones **17** (Scheme 3.6).[13]



Scheme 3.6

The reaction of *o*-hydroxyacetophenone **4** with succinaldehyde **18** in the presence of 20 mol% of pyrrolidine to furnish the desired tricyclic core structure (chromanone fused cyclopentane **19**) was reported by Reddy and co-workers (Scheme 3.7).[14]

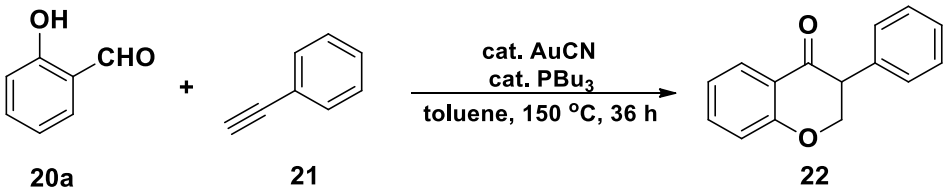


Scheme 3.7

3.4. Reactions of Salicylaldehydes

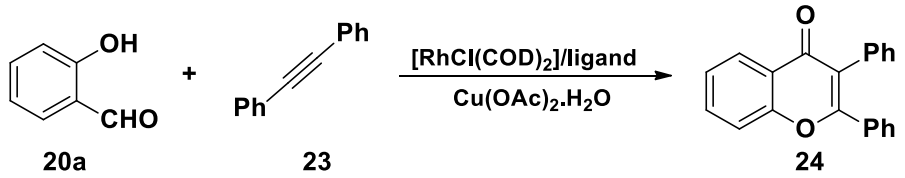
Among the various substrates for the chelation-controlled hydroacylation reactions,

salicylaldehydes have been well utilized as a potent precursor for developing efficient and atom economic routes for the regioselective construction of ketones.[15–24] Li *et al*. developed the gold (I)-catalyzed annulation of salicylaldehydes **20a** and aryl acetylenes **21** to generate isoflavanone-type structures **22** (Scheme 3.8).[25] This annulation incorporates all atoms in both starting materials into the product and thus has a theoretical atom economy of 100 %.



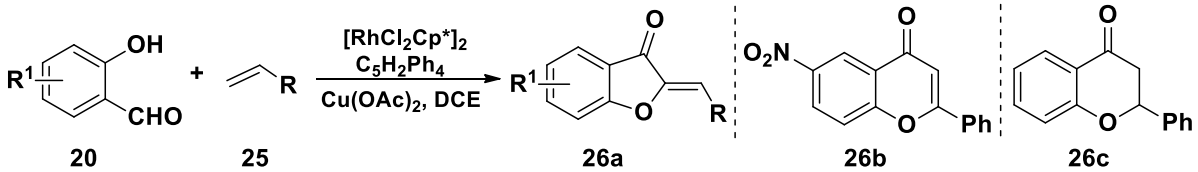
Scheme 3.8

Miura-Satoh *et al*. reported the direct oxidative coupling of salicylaldehydes **20a** with internal alkynes **23** proceeding efficiently with the cleavage of the aldehyde C-H bond to produce the corresponding chromone derivatives **24** which are prevalent in a wide variety of naturally occurring compounds that exhibit a broad range of interesting biological activities (Scheme 3.9).[26]



Scheme 3.9

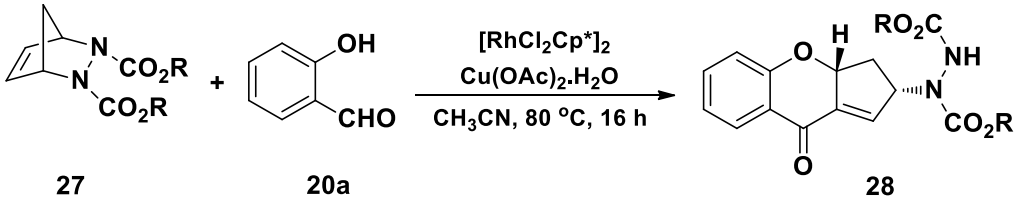
Rhodium (III) catalyzed dehydrogenative Heck reaction of salicylaldehydes **20** with olefins **25** was reported by Glorius *et al*. With the most electron-poor substrate, 5-nitrosalicylaldehyde, the reaction selectively afforded the chromanone derivative **26b** in 44 % yield. The use of Ag_2CO_3 as oxidant also afforded only the flavanone **26c** (Scheme 3.10).[27]



Scheme 3.10

Recently, our group reported an efficient one pot strategy for the synthesis of cyclopentene fused chromanone derivatives **28** through the direct oxidative coupling of

salicylaldehydes **20a** with azabicyclic olefins **27** in the presence of rhodium catalyst (Scheme 3.11).[28]



Scheme 3.11

3.5. Statement of the Problem

Even though the above-mentioned rhodium catalyzed transformations of bicyclic hydrazines yields cyclopentene fused chromanone derivatives, the presence of hydrazine in these products demands further exploration of these results. Hydrazine is considered as a toxic compound and the presence of hydrazine moiety in these products makes them biologically inactive.[29] We envisaged that the hydrazine moiety in these adducts can be replaced with more biologically active urea derivatives. Urea and its cyclic derivatives represent a class of biologically relevant molecules, widely occurring in natural products and have been studied for various biological activities such as antibiotic hypoglycemic effects, anti-cancer, anti-diabetic, antimicrobial, antibacterial activities *etc*. (Figure 3.2).[30–36]

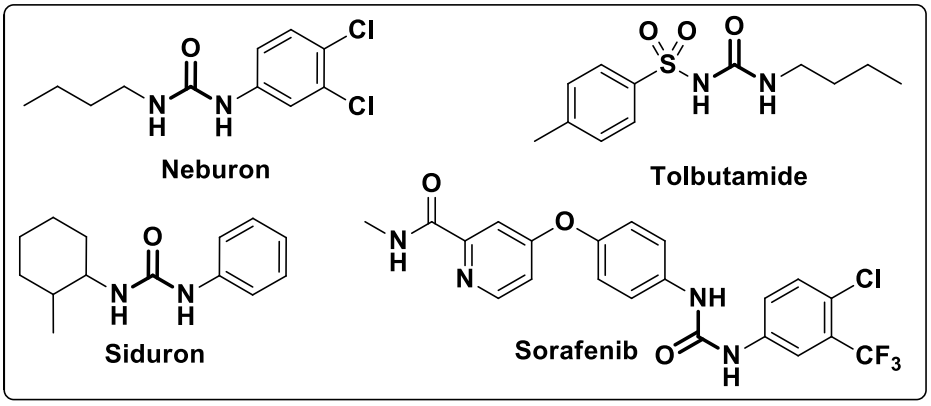


Figure 3.2. Some biologically important urea derivatives

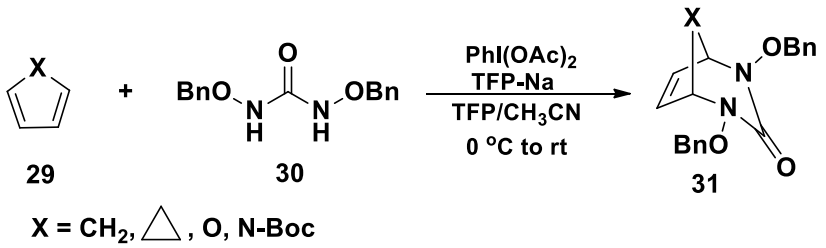
In this perspective, the urea derived bicycles synthesized by Jeffrey *et al*. grabbed our attention because of their tremendous synthetic potential.[37] Our continued interest in the chemistry of transition metal catalyzed synthetic manipulation of strained bicyclic systems coupled with the aim of constructing biologically significant fused chromanones prompted us to investigate the reactivity of bicyclic urea adduct with salicylaldehyde under rhodium

catalysis which is discussed in the following sections.

3.6. Results and Discussion

3.6.1. Synthesis of Urea-derived Bicyclic Olefins

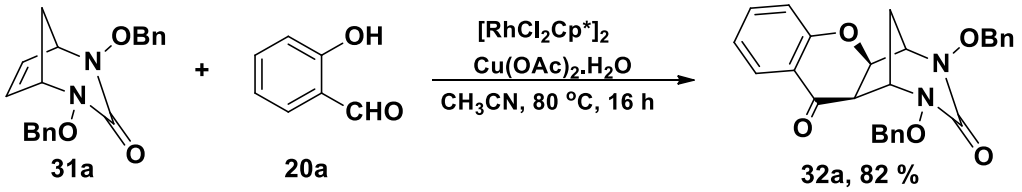
The urea-derived bicyclic olefins were synthesised according to the reported literature procedure.[37] The direct oxidative 1,4-diamination of dienes **29** such as cycopentadiene, spiro cyclopentadiene, furan and protected pyrrole using 1,3-bis(benzyloxy)urea **30** and phenyl iododiacetate as the oxidant furnished these bicyclic akenes **31** in good yields (Scheme 3.12).



Scheme 3.12

3.6.2. Synthesis of Chromanone Fused Urea-derived Bicyclic Olefins

In an initial experiment, we carried out the reaction of urea derived bicyclic adduct **31a** with salicylaldehyde **20a** under the same optimized conditions that we had performed for diazabicyclic olefins. The reaction afforded fused chromanone derivative **32a** in 82 % yield (Scheme 3.13).



Scheme 3.13. Oxidative coupling of salicylaldehyde with bicyclic olefin

The structure of the product **32a** was assigned based on various spectroscopic techniques like ^{1}H NMR, ^{13}C NMR and HRMS (ESI) analysis. The IR spectrum of **32a** showed characteristic carbonyl absorption of chromanone and urea at 1717 and 1677 cm^{-1} respectively. In the ^{1}H NMR (Figure 3.3), the aromatic protons were discernible in the region δ 7.68–6.80 ppm. The proton on the carbon attached to the oxygen atom of the chromanone appeared as a doublet at δ 5.13 ppm. The multiplets in the region δ 5.07-5.03 and δ 4.93-4.90 ppm were assigned to the methylene protons of the benzyloxy groups. The proton on each carbon attached to nitrogen atom of the urea group appeared at δ 4.03 and δ 3.80 ppm. The

protons attached to the carbon bearing the carbonyl group of chromanone appeared as a doublet at δ 3.56 ppm. The bridge protons resonated as a multiplet in the region δ 2.05-2.03 and δ 1.87-1.83 ppm.

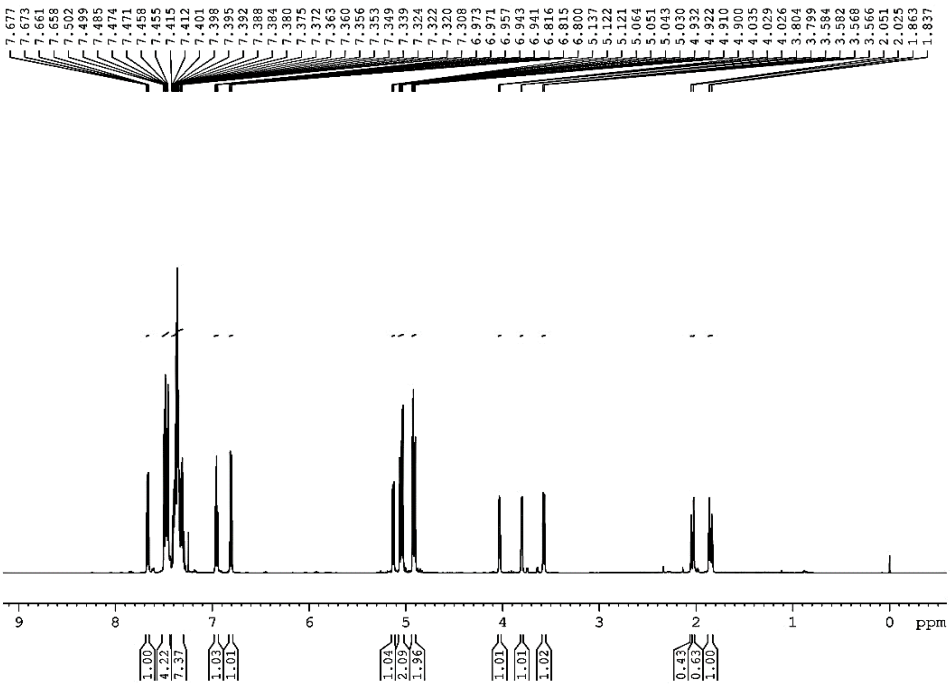


Figure 3.3. ^{1}H NMR spectrum of compound **32a**

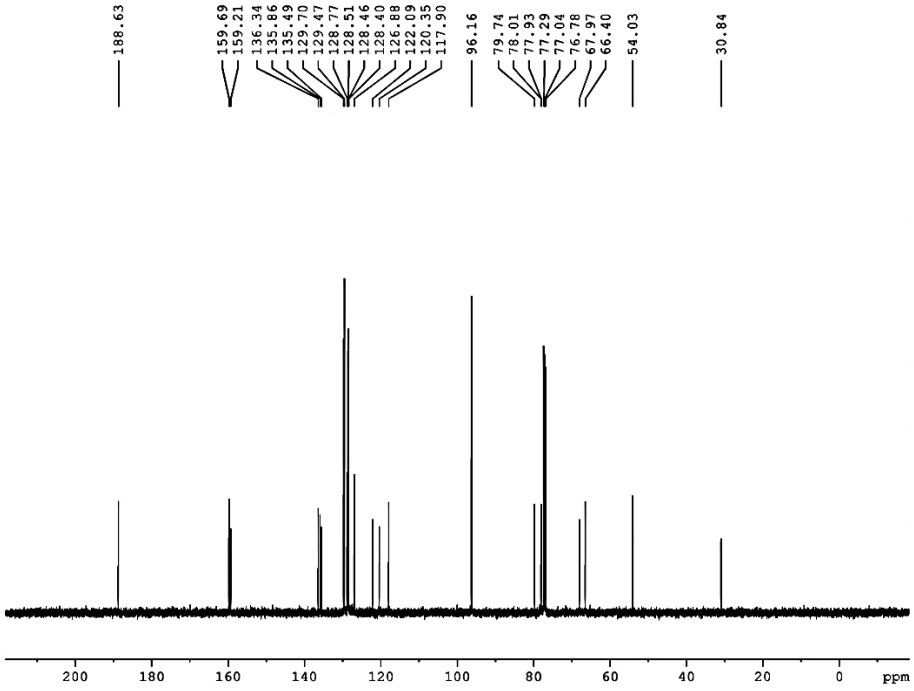


Figure 3.4. ^{13}C NMR spectrum of compound **32a**

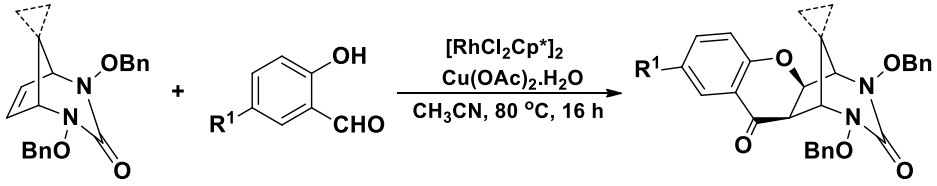
^{13}C NMR of **32a** (Figure 3.4) displayed the carbonyl peak of the chromanone at 188.6 ppm and of the amide at δ 159.7 ppm. The peak at δ 79.7 ppm was assigned to the carbon attached to the oxygen atom of the chromanone. The methylene carbons of the benzyloxy groups were identified at δ 78.0 and 77.9 ppm. Each carbon bearing the nitrogen atom resonated at δ 68.0 and 66.4 ppm. The carbon bearing the carbonyl group of chromanone appeared at δ 54.0 ppm. The methylene carbon resonated at δ 30.8 ppm.

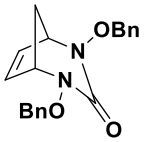
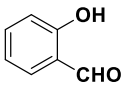
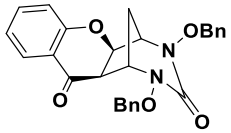
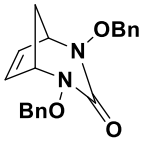
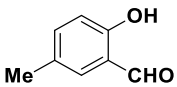
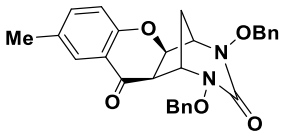
The structure was also supported by high resolution mass spectral analysis which showed $[M+H]^+$ peak at *m/z* 457.17712.

3.6.2.1. Scope of the Reaction

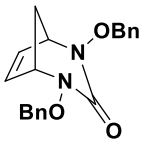
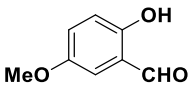
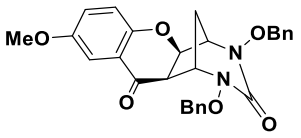
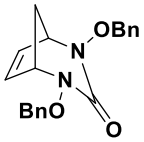
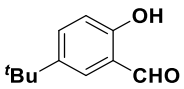
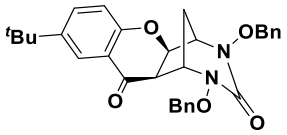
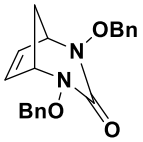
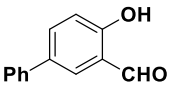
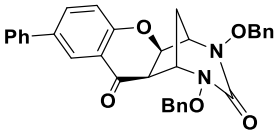
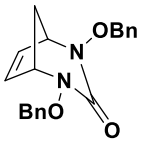
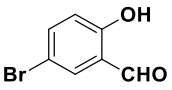
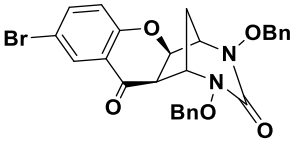
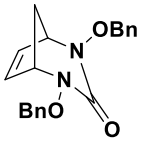
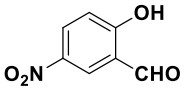
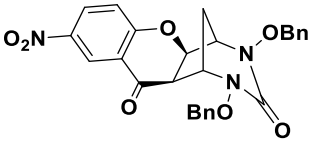
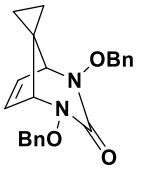
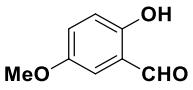
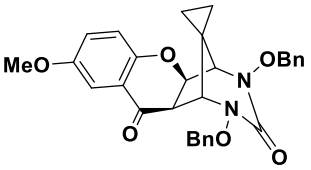
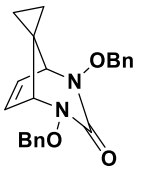
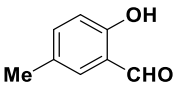
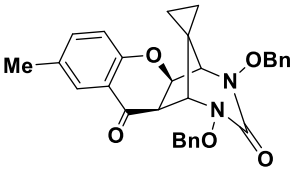
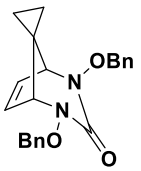
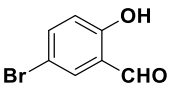
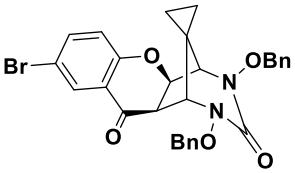
To illustrate the broad scope of the present method, we have examined the reactivity of various urea-derived bicyclic olefins and different salicylaldehydes under the optimized reaction conditions. The bicyclic urea adducts derived from cyclopentadiene and spiro[2.4]hepta-4,6-diene underwent annulation reaction with various salicylaldehydes and provided the corresponding fused chromanone derivatives in good yields. The results obtained are summarized in Table 3.1 (entry 1-12). Also, the reaction was found to be compatible with different salicylaldehydes substituted with electron donating and electron withdrawing groups such as Me, OMe, ^{t}Bu, Ph, Br and NO_2.

Table 3.1. Oxidative coupling of substituted salicylaldehydes with bicyclic olefins[a]



Entry	Bicyclic olefin	Salicylaldehyde	Product	Yield (%)[b]
1				82
	31a	**20a**	**32a**	
2				59
	31a	**20b**	**32b**	

Continued..

3	 **31a**	 **20c**	 **32c**	81
4	 **31a**	 **20d**	 **32d**	64
5	 **31a**	 **20e**	 **32e**	80
6	 **31a**	 **20f**	 **32f**	62
7	 **31a**	 **20g**	 **32g**	82
8	 **31b**	 **20c**	 **32h**	93
9	 **31b**	 **20b**	 **32i**	67
10	 **31b**	 **20f**	 **32j**	63

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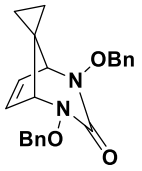
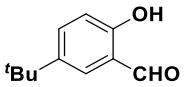
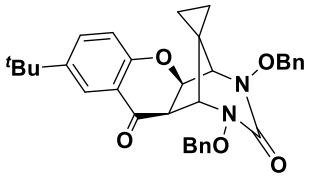
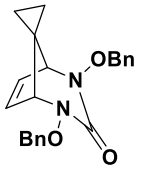
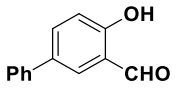
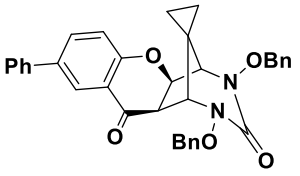
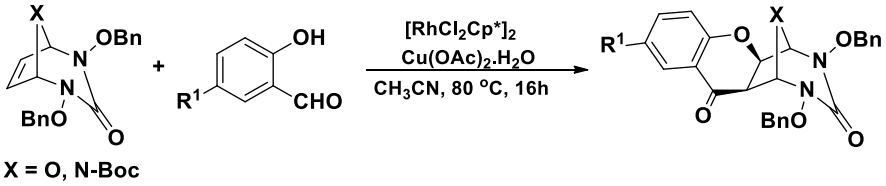
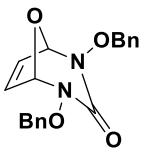
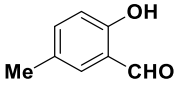
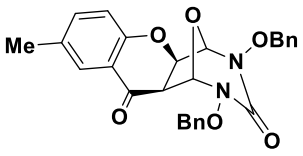
11	 **31b**	 **20d**	 **32k**	65
12	 **31b**	 **20e**	 **32l**	81

[a]**Reaction Conditions:** urea-derived bicyclic alkene (1 equiv.), salicylaldehyde (1 equiv.), $[RhCl_2Cp^*]_2$ (3 mol%), $Cu(OAc)_2.H_2O$ (2 equiv.), CH_3CN (2 mL), 80 ^oC. [b]Isolated yield.

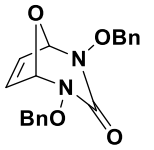
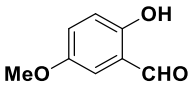
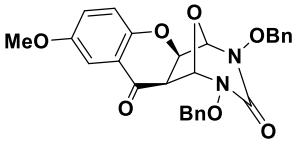
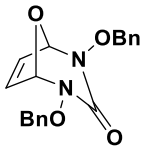
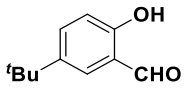
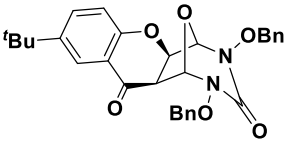
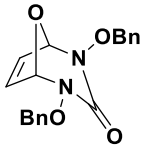
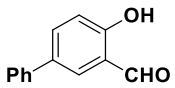
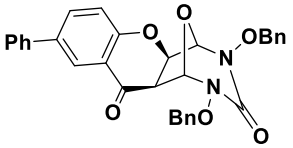
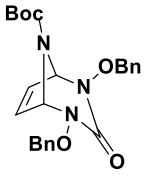
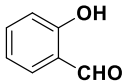
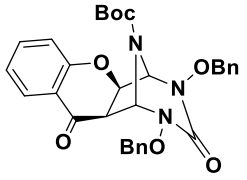
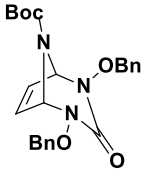
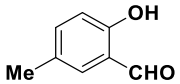
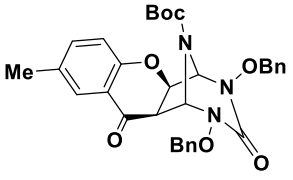
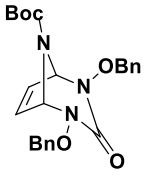
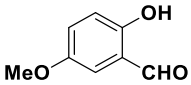
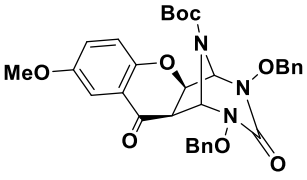
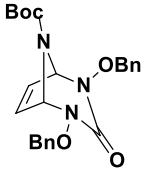
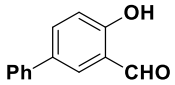
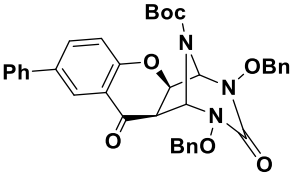
The importance of oxa/azabicyclic alkenes in the construction of synthetically versatile building blocks *via* the transition metal catalyzed ring opening or annulation reactions and hydro(hetero)arylation reactions, prompted us to expand the generality of this oxidative coupling reaction to oxa/aza-bridged bicyclic urea derivatives. These heterobicyclic urea adducts also underwent smooth oxidative coupling reactions with different substituted salicylaldehydes under the optimized condition and afforded the heteroatom enriched fused chromanone derivatives in good yields (Table 3.2, entry 1-8).

Table 3.2. Oxidative coupling of various salicylaldehydes with oxa/aza bridged heterobicyclic urea derivatives[a]



Entry	Bicyclic olefin	Salicylaldehyde	Product	Yield (%)[b]
1	 **31c**	 **20b**	 **32m**	58

Continued..

2	 **31c**	 **20c**	 **32n**	85
3	 **31c**	 **20d**	 **32o**	53
4	 **31c**	 **20e**	 **32p**	63
5	 **31d**	 **20a**	 **32q**	64
6	 **31d**	 **20b**	 **32r**	70
7	 **31d**	 **20c**	 **32s**	52
8	 **31d**	 **20e**	 **32t**	60

[a]**Reaction Conditions:** urea-derived bicyclic alkene (1 equiv.), salicylaldehyde (1 equiv.), $[RhCl_2Cp^*]_2$ (3 mol%), $Cu(OAc)_2.H_2O$ (2 equiv.), CH_3CN (2 mL), 80 ^oC. [b]Isolated yield.

We were successful in obtaining the single crystal X-ray of compound **32q** from ethylacetate/hexane mixture (CCDC 1449575) (Figure 3.5).

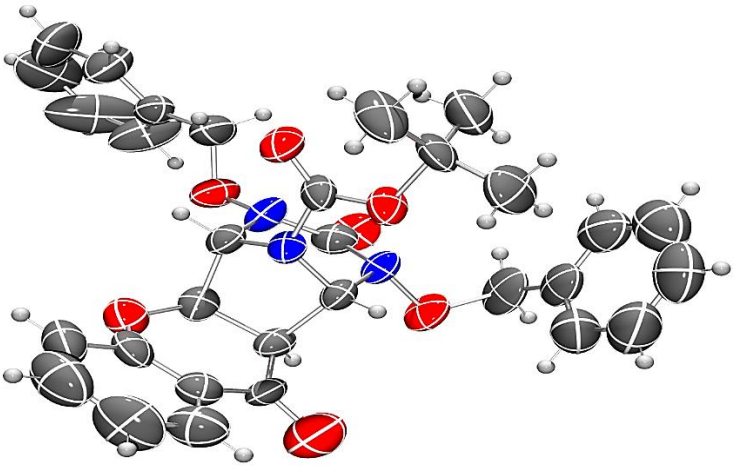
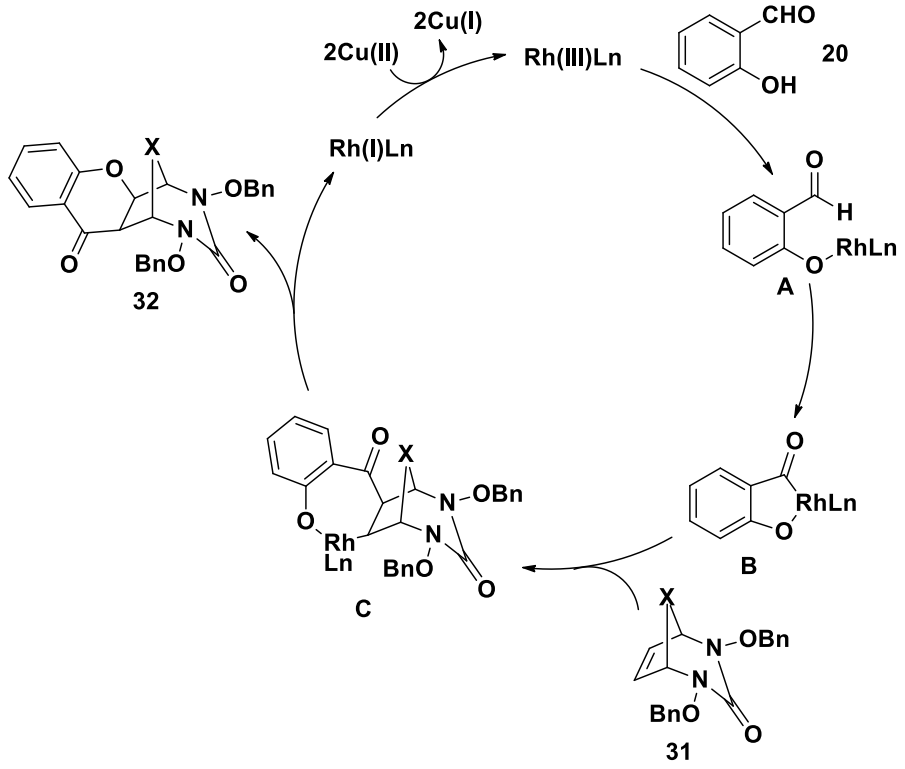


Figure 3.5. Single crystal X-ray structure of compound **32q**

3.7. Proposed Mechanistic Pathway

In accordance with the previous studies, a reasonable reaction mechanism is proposed and is presented in Scheme 3.14.



Scheme 3.14. Proposed reaction mechanism

The coordination of hydroxyl group of salicylaldehyde **20** to $Rh^{III}Ln$ species gives a rhodium (III) phenolate **A**. Subsequently, the intermediate **A** undergoes selective C-H bond

cleavage and generates five-membered rhodacycle **B**. This is followed by alkene insertion to the rhodacycle furnishing the intermediate **C**, and successive reductive elimination provides the fused chromanone product **32**. The active $Rh^{III}Ln$ catalyst is regenerated by the oxidation of $Rh^{I}Ln$ species in the presence of Cu(II) salt.

3.8. Conclusion

In summary, we have developed an efficient one-pot strategy for the synthesis of fused chromanone derivatives through the rhodium catalyzed direct oxidative coupling of salicylaldehydes with urea derived bicyclic olefins. It is notable that the reaction performs well with different oxa/aza-bridged bicyclic urea derivatives. To the best of our knowledge, urea-derived bicyclic olefins have not been utilized for the synthesis of fused chromanone derivatives *via* Rh-catalyzed oxidative coupling reactions.

3.9. Experimental Section

3.9.1. General Methods

General information about the experiments is given in Section 2.8.1 of Chapter 2.

3.9.2. General Procedure for the Synthesis of Urea Derived Bicyclic Olefins

(Diacetoxyiodo)benzene (DIB) (2.0 equiv.) and corresponding cyclic dienes **29** (5.0 equiv.) were added dropwise to a solution of $CHF_2CF_2CH_2OH$ (13 mL) and $CHF_2CF_2CH_2ONa$ (2.0 equiv) at 0 ^oC. To this, a solution of 1,3-bis(benzyloxy)urea **30** (1.0 equiv.) in anhydrous CH_3CN (40 mL) was added dropwise slowly at 0 ^oC using a pressure equalizer. The reaction mixture was stirred until the complete consumption of urea, which was monitored by TLC (4-5 h). The residue obtained after removing the volatiles under reduced pressure was dissolved in ethyl acetate, washed with water and separated the two layers. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product **31** was purified *via* silica gel (100-200 mesh) column chromatography using hexane/ethyl acetate mixture.

3.9.3. General Procedure for the Rhodium Catalyzed Oxidative Coupling

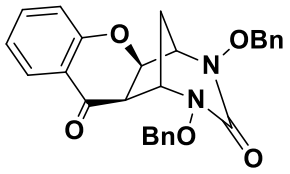
A mixture of bicyclic olefin **31** (1.0 equiv.), salicylaldehyde **20** (1.0 equiv.), $[RhCl_2Cp^*]_2$ (3 mol%) and $Cu(OAc)_2.H_2O$ (2.0 equiv.) were weighed in a Schlenk tube and degassed for 10 minutes. Dry acetonitrile was added and the reaction mixture was purged with argon and allowed to stir at 80 ^oC for 16 hours. The solvent was evaporated in *vacuo* and the residue on silica gel (100-200 mesh) column chromatography yielded fused

chromanone derivatives **32**.

3.9.4. Characterization of the Products

Compound 32a

Following the general procedure 3.9.3, compound **32a** (89 mg, 82 %) was synthesised from bicyclic olefin **31a** (80 mg, 0.2378 mmol) and salicylaldehyde **20a** (29 mg, 0.2378 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0071 mmol) and $Cu(OAc)_2.H_2O$ (95 mg, 0.4756 mmol) as white solid.



M. P. = 156-158 ^oC.

R_f: 0.54 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3063, 3032, 2925, 2874, 2391, 2353, 1717, 1677, 1605, 1582, 1498, 1463, 1374, 1312, 1275, 1219, 1155, 1114, 1082, 1029, 919, 883, 752, 698, 675 cm^{-1}.

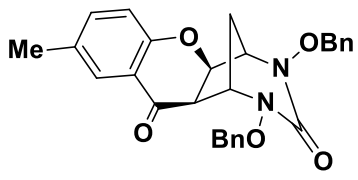
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 7.50-7.46 (m, 4 H), 7.42-7.31 (m, 7 H), 6.97-6.94 (m, 1 H), 6.82-6.80 (m, 1 H), 5.13 (d, J = 7.5 Hz, 1 H), 5.06-5.03 (m, 2 H), 4.93-4.90 (m, 2 H), 4.04-4.03 (m, 1 H), 3.8 (d, J = 2.5 Hz, 1 H), 3.6 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1 H), 2.04 (d, J = 13.0 Hz, 1 H), 1.86-1.84 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 188.6, 159.7, 159.2, 136.3, 135.9, 135.5, 129.7, 129.5, 128.8, 128.5, 128.4, 126.9, 122.1, 120.4, 117.9, 79.7, 78.0, 77.9, 68.0, 66.4, 54.0, 30.8.

HRMS (ESI): *m/z* calcd for $C_{27}H_{25}N_2O_5$: 457.17635; Found: 457.17712.

Compound 32b

Following the general procedure 3.9.3, compound **32b** (66 mg, 59 %) was synthesised from bicyclic olefin **31a** (80 mg, 0.2378 mmol) and 5-methylsalicylaldehyde **20b** (32 mg, 0.2378 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0071 mmol) and $Cu(OAc)_2.H_2O$ (95 mg, 0.4756 mmol) as pale yellow viscous liquid.



R_f: 0.67 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3033, 2923, 2348, 1717, 1673, 1618, 1584, 1542, 1492, 1454, 1421, 1373, 1300, 1220, 1156, 1081, 1018, 915, 832, 750, 699, 677 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.46 (m, 5 H), 7.41-7.33 (m, 6 H), 7.23 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 6.73 (d, J = 8.5 Hz, 1 H), 5.11 (d, J = 7.5 Hz, 1 H), 5.08-5.05 (m, 2 H),

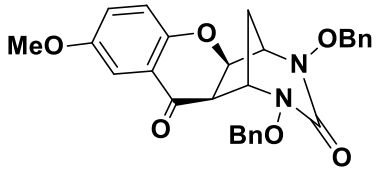
4.95-4.92 (m, 2 H), 4.05-4.04 (m, 1 H), 3.81 (d, J = 3.0 Hz, 1 H), 3.57 (dd, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1 H), 2.27 (s, 3 H), 2.05 (d, J = 13.0 Hz, 1 H), 1.89-1.84 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 189.0, 159.2, 157.7, 137.4, 135.9, 135.5, 131.6, 129.7, 129.5, 128.8, 128.5, 128.4, 126.5, 120.1, 117.7, 115.3, 79.6, 78.0, 78.0, 67.9, 66.3, 54.1, 30.8, 20.4.

HRMS (ESI): *m/z* calcd for $C_{28}H_{27}N_2O_5$: 471.19200; Found: 471.19293.

Compound 32c

Following the general procedure 3.9.3, compound **32c** (94 mg, 81 %) was synthesised from bicyclic olefin **31a** (80 mg, 0.2378 mmol) and 5-methoxysalicylaldehyde **20c** (36 mg, 0.2378 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0071 mmol) and $Cu(OAc)_2.H_2O$ (95 mg, 0.4756 mmol) as yellow viscous liquid.



R_f: 0.56 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3063, 3031, 2939, 2878, 2837, 1716, 1675, 1616, 1588, 1489, 1454, 1432, 1372, 1290, 1207, 1174, 1157, 1121, 1083, 1059, 1032, 915, 885, 862, 831, 750, 698, 675, 621, 582 cm^{-1}.

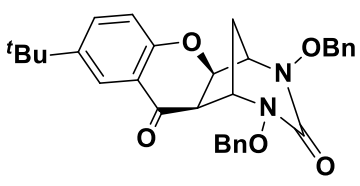
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.48 (m, 4 H), 7.40-7.33 (m, 6 H), 7.10 (d, J = 3.5 Hz, 1 H), 7.03 (dd, J_1 = 9.0 Hz, J_2 = 3.0 Hz, 1 H), 6.77 (d, J = 9.0 Hz, 1 H), 5.11-5.05 (m, 3 H), 4.96-4.92 (m, 2 H), 4.06 (dd, J_1 = 4.5 Hz, J_2 = 1.5 Hz, 1 H), 3.83 (d, J = 3.0 Hz, 1 H), 3.74 (s, 3 H), 3.56 (dd, J_1 = 7.5 Hz, J_2 = 1 Hz, 1 H), 2.06 (d, J = 13.0 Hz, 1 H), 1.90-1.86 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 189.1, 159.2, 154.5, 154.3, 135.9, 135.4, 129.7, 129.5, 128.8, 128.6, 128.5, 128.5, 125.4, 120.3, 119.3, 107.4, 79.6, 78.1, 78.0, 67.8, 66.3, 55.8, 54.1, 30.9.

HRMS (ESI): *m/z* calcd for $C_{28}H_{27}N_2O_6$: 487.18691; Found: 487.18811.

Compound 32d

Following the general procedure 3.9.3, compound **32d** (78 mg, 64 %) was synthesised from bicyclic olefin **31a** (80 mg, 0.2378 mmol) and 5-*tert*-butylsalicylaldehyde **20d** (42 mg, 0.2378 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0071 mmol) and $Cu(OAc)_2.H_2O$ (95 mg, 0.4756 mmol) as pale yellow viscous liquid.



R_f: 0.66 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3063, 3032, 2960, 2872, 1958, 1717, 1677, 1612, 1492, 1455, 1422, 1367, 1300, 1255, 1218, 1142, 1107, 1082, 1013, 911, 832, 748, 698, 676 cm^{-1}.

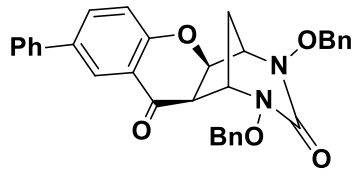
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 2.5 Hz, 1 H), 7.53-7.48 (m, 5 H), 7.42-7.33 (m, 6 H), 6.78 (d, *J* = 8.5 Hz, 1 H), 5.13-5.11 (m, 1 H), 5.11-5.05 (m, 2 H), 4.96-4.92 (m, 2 H), 4.06-4.05 (m, 1 H), 3.83 (d, *J* = 3 Hz, 1 H), 3.59 (dd, J_1 = 8 Hz, J_2 = 1.5 Hz, 1 H), 2.06 (d, *J* =12.5 Hz, 1 H), 1.89-1.86 (m, 1 H), 1.26 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 189.3, 159.2, 157.7, 145.2, 135.9, 135.4, 134.3, 129.7, 129.5, 128.8, 128.6, 128.5, 128.5, 127.6, 127.0, 122.8, 119.5, 117.6, 79.7, 78.1, 78.0, 68.0, 66.5, 54.1, 34.3, 31.2.

HRMS (ESI): *m/z* calcd for $C_{31}H_{33}N_2O_5$: 513.23895; Found: 513.23906.

Compound 32e

Following the general procedure 3.9.3, compound **32e** (101 mg, 80 %) was synthesised from bicyclic olefin **31a** (80 mg, 0.2378 mmol) and 5-phenylsalicylaldehyde **20e** (47 mg, 0.2378 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0071 mmol) and $Cu(OAc)_2.H_2O$ (95 mg, 0.4756 mmol) as pale brown viscous liquid.



R_f: 0.53 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3061, 3032, 2924, 2876, 1955, 1716, 1678, 1612, 1540, 1506, 1478, 1453, 1416, 1373, 1299, 1275, 1258, 1211, 1157, 1137, 1082, 1026, 1008, 914, 833, 749, 698 cm^{-1}.

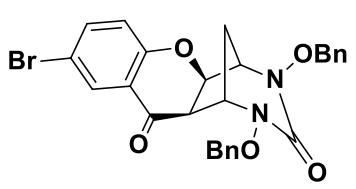
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 2.5 Hz, 1 H), 7.67 (dd, J_1 = 9 Hz, J_2 = 2.5 Hz, 1 H), 7.53-7.49 (m, 6 H), 7.42-7.32 (m, 9 H), 6.91 (d, *J* = 9.0 Hz, 1 H), 5.18-5.17 (m, 1 H), 5.10-5.06 (m, 2 H), 4.97-4.94 (m, 2 H), 4.09-4.08 (m, 1 H), 3.87 (d, *J* = 2.5 Hz, 1 H), 3.63 (dd, J_1 = 8 Hz, J_2 = 1.0 Hz, 1 H), 2.09 (d, *J* =13.0 Hz, 1 H), 1.91-1.87 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 189.0, 159.2, 159.1, 139.2, 135.9, 135.5, 135.3, 135.2, 129.8, 129.5, 129.0, 128.9, 128.6, 128.6, 128.5, 127.6, 126.7, 124.8, 120.2, 118.5, 80.0, 78.1, 78.0, 68.0, 66.5, 54.1, 30.9.

HRMS (ESI): *m/z* calcd for $C_{33}H_{29}N_2O_5$: 533.20765; Found: 533.20819.

Compound 32f

Following the general procedure 3.9.3, compound **32f** (79 mg, 62 %) was synthesised from bicyclic olefin **31a** (80 mg, 0.2378 mmol) and 5-bromosalicylaldehyde **20f** (48 mg, 0.2378 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0071 mmol) and $Cu(OAc)_2.H_2O$ (95 mg, 0.4756 mmol) as pale yellow viscous liquid.



R_f: 0.70 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3063, 3031, 2932, 2876, 1717, 1680, 1598, 1494, 1467, 1417, 1373, 1286, 1215, 1158, 1131, 1082, 1010, 916, 858, 819, 749, 699, 655 cm^{-1}.

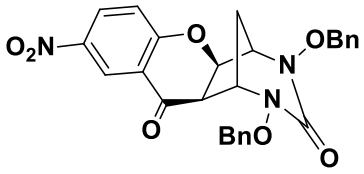
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 2.5 Hz, 1 H), 7.52-7.47 (m, 5 H), 7.41-7.34 (m, 6 H), 6.74 (d, *J* = 9.0 Hz, 1 H), 5.14-5.13 (m, 1 H), 5.08-5.05 (m, 2 H), 4.95-4.92 (m, 2 H), 4.03-4.02 (m, 1 H), 3.83 (d, *J* = 2.5 Hz, 1 H), 3.59 (dd, J_1 = 9 Hz, J_2 = 1.0 Hz, 1 H), 2.08 (d, *J* =12.5 Hz, 1 H), 1.86-1.81 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 187.8, 159.1, 158.6, 139.1, 135.7, 135.4, 129.7, 129.5, 129.3, 128.9, 128.6, 128.5, 121.3, 120.1, 114.7, 80.0, 78.1, 78.1, 67.9, 66.4, 53.8, 30.9.

HRMS (ESI): *m/z* calcd for $C_{27}H_{24}BrN_2O_5$: 535.08686; Found: 535.08771.

Compound 32g

Following the general procedure 3.9.3, compound **32g** (98 mg, 82 %) was synthesised from bicyclic olefin **31a** (80 mg, 0.2378 mmol) and 5-nitrosalicylaldehyde **20g** (40 mg, 0.2378 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0071 mmol) and $Cu(OAc)_2.H_2O$ (95 mg, 0.4756 mmol) as pale yellow solid.



M. P. = 101-103 °C.

R_f: 0.40 (hexane/ethyl acetate = 7:3).

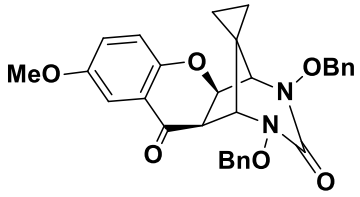
IR (neat) ν_{max}: 3090, 3033, 2930, 2876, 1685, 1617, 1587, 1523, 1475, 1440, 1343, 1290, 1222, 1158, 1107, 1080, 1008, 917, 876, 835, 747, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.59 (s, 1 H), 8.27 (dd, J_1 = 9 Hz, J_2 = 3.0 Hz, 1 H), 7.51-7.47 (m, 4 H), 7.41-7.34 (m, 6 H), 6.97 (d, *J* = 9.0 Hz, 1 H), 5.27-5.26 (m, 1 H), 5.09-5.06 (m, 2 H), 4.95-4.92 (m, 2 H), 4.03-4.02 (m, 1 H), 3.85 (d, *J* = 2.5 Hz, 1 H), 3.70 (dd, J_1 = 8 Hz, J_2 = 1.0 Hz, 1 H), 2.13-2.11 (m, 1 H), 1.82-1.77 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 186.8, 163.5, 158.9, 142.5, 135.6, 135.3, 130.7, 129.7, 129.5, 128.9, 128.7, 128.6, 128.5, 123.4, 119.3, 118.8, 81.0, 78.2, 78.1, 68.0, 66.8, 53.4, 30.9.
HRMS (ESI): *m/z* calcd for $C_{27}H_{23}N_3O_7Na$: 524.14337; Found: 524.14337.

Compound 32h

Following the general procedure 3.9.3, compound **32h** (105 mg, 93 %) was synthesised from bicyclic olefin **31b** (80 mg, 0.2207 mmol) and 5-methoxysalicylaldehyde **20c** (34 mg, 0.2207 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0066 mmol) and $Cu(OAc)_2.H_2O$ (88 mg, 0.4414 mmol) as brown viscous liquid.

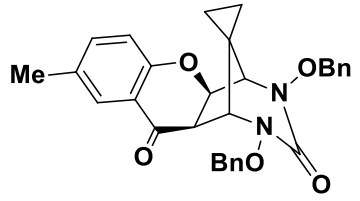


R_f: 0.58 (hexane/ethyl acetate = 7:3).
IR (neat) ν_{max}: 3065, 3032, 2925, 1716, 1672, 1618, 1541, 1490, 1456, 1432, 1368, 1292, 1227, 1202, 1177, 1121, 1057, 1029, 919, 828, 752, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.45 (m, 4 H), 7.38-7.31 (m, 6 H), 7.09 (d, *J* = 3.0 Hz, 1 H), 7.02 (dd, J_1 = 9.0 Hz, J_2 = 3.0 Hz, 1 H), 6.74 (d, *J* = 9.0 Hz, 1 H), 5.21 (d, *J* = 8.0 Hz, 1 H), 5.07-5.04 (m, 2 H), 4.92-4.90 (m, 2 H), 3.75 (s, 3 H), 3.69 (d, *J* = 8.5 Hz, 1 H), 3.25 (d, *J* = 2.5 Hz, 1 H), 2.96 (d, *J* = 2.0 Hz, 1 H), 0.52-0.49 (m, 2 H), 0.47-0.44 (m, 1 H), 0.31-0.28 (m, 1 H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 189.1, 159.7, 154.2, 135.8, 135.6, 129.9, 129.8, 128.7, 128.5, 128.4, 128.3, 128.2, 125.4, 119.7, 119.1, 107.2, 80.3, 78.0, 78.0, 73.6, 72.2, 55.6, 54.6, 26.2, 10.3, 4.5.
HRMS (ESI): *m/z* calcd for $C_{30}H_{29}N_2O_6$: 513.20256; Found: 513.20319.

Compound 32i

Following the general procedure 3.9.3, compound **32i** (74 mg, 67 %) was synthesised from bicyclic olefin **31b** (80 mg, 0.2207 mmol) and 5-methylsalicylaldehyde **20b** (30 mg, 0.2207 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0066 mmol) and $Cu(OAc)_2.H_2O$ (88 mg, 0.4414 mmol) as pale yellow viscous liquid.



R_f: 0.42 (hexane/ethyl acetate = 7:3).
IR (neat) ν_{max}: 3031, 3005, 2932, 2875, 1955, 1717, 1676, 1617, 1583, 1492, 1454, 1422, 1369, 1299, 1225, 1185, 1161, 1136, 1057, 1009, 952, 916, 823, 750, 699 cm^{-1}.

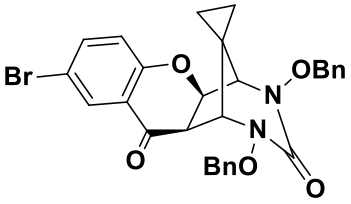
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.46 (m, 5 H), 7.38-7.31 (m, 6 H), 7.22 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1 H), 6.71 (d, *J* = 8.5 Hz, 1 H), 5.22 (d, *J* = 8.5 Hz, 1 H), 5.07-5.04 (m, 2 H), 4.92-4.90 (m, 2 H), 3.69 (d, *J* = 8.5 Hz, 1 H), 3.25 (d, *J* = 2.0 Hz, 1 H), 2.97 (d, *J* = 2.0 Hz, 1 H), 2.26 (s, 3 H), 0.52-0.42 (m, 3 H), 0.30-0.26 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 189.2, 159.7, 157.7, 137.4, 135.8, 135.6, 131.1, 129.9, 129.8, 128.7, 128.5, 128.4, 128.4, 128.3, 128.2, 126.4, 119.5, 117.6, 80.3, 78.0, 77.9, 73.7, 72.2, 54.7, 26.2, 20.4, 10.3, 4.5.

HRMS (ESI): *m/z* calcd for $C_{30}H_{29}N_2O_5$: 497.20765; Found: 497.20840.

Compound 32j

Following the general procedure 3.9.3, compound **32j** (78 mg, 63 %) was synthesised from bicyclic olefin **31b** (80 mg, 0.2207 mmol) and 5-bromosalicylaldehyde **20f** (44 mg, 0.2207 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0066 mmol) and $Cu(OAc)_2.H_2O$ (88 mg, 0.4414 mmol) as pale brown viscous liquid.



R_f: 0.64 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3065, 3033, 2931, 2877, 1673, 1599, 1469, 1419, 1370, 1288, 1231, 1204, 1163, 1132, 1056, 1023, 952, 897, 856, 824, 748, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 2.5 Hz, 1 H), 7.49-7.45 (m, 5 H), 7.38-7.32 (m, 6 H), 6.72 (d, *J* = 9.0 Hz, 1 H), 5.25 (d, *J* = 8.5 Hz, 1 H), 5.06-5.04 (m, 2 H), 4.92-4.89 (m, 2 H), 3.71 (d, *J* = 8.0 Hz, 1 H), 3.20 (d, *J* = 2.0 Hz, 1 H), 2.94 (d, *J* = 2.5 Hz, 1 H), 0.52-0.49 (m, 2 H), 0.43-0.39 (m, 1 H), 0.28-0.24 (m, 1 H).

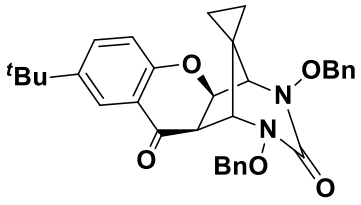
^{13}C NMR (125 MHz, $CDCl_3$): δ 187.6, 159.5, 158.5, 138.9, 135.7, 135.6, 129.9, 129.8, 129.2, 128.8, 128.6, 128.4, 128.3, 120.7, 119.8, 114.3, 80.7, 78.0, 78.0, 73.6, 72.3, 54.3, 26.2, 10.3, 4.6.

HRMS (ESI): *m/z* calcd for $C_{29}H_{26}BrN_2O_5$: 561.10251; Found: 561.10284.

Compound 32k

Following the general procedure 3.9.3, compound **32k** (77 mg, 65 %) was synthesised from bicyclic olefin **31b** (80 mg, 0.2207 mmol) and 5-*tert*-butylsalicylaldehyde **20d** (39 mg, 0.2207 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0066 mmol) and $Cu(OAc)_2.H_2O$ (88 mg, 0.4414

mmol) as white solid.



M. P. = 170-172 ^{o}C.

R_f: 0.61 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3063, 3032, 3005, 2961, 2872, 1956, 1715, 1676, 1613, 1581, 1492, 1455, 1423, 1366, 1301, 1258, 1227, 1196, 1164, 1143, 1106, 1077, 1056, 1005, 952, 913, 831, 776, 748, 700, 622, 597, 528 cm^{-1}.

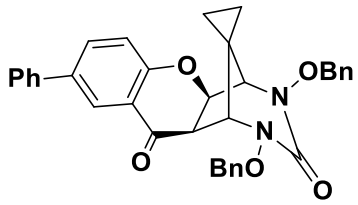
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 3.0 Hz, 1 H), 7.50-7.47 (m, 5 H), 7.39-7.32 (m, 6 H), 6.76 (d, *J* = 8.5 Hz, 1 H), 5.23 (d, *J* = 8.0 Hz, 1 H), 5.08-5.05 (m, 2 H), 4.94-4.91 (m, 2 H), 3.71 (d, *J* = 8.5 Hz, 1 H), 3.27 (d, *J* = 2.0 Hz, 1 H), 2.99 (d, *J* = 2.5 Hz, 1 H), 1.27 (s, 9 H), 0.53-0.47 (m, 3 H), 0.33-0.29 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 189.4, 159.8, 157.7, 144.7, 135.8, 135.6, 134.1, 129.9, 129.8, 128.7, 128.5, 128.4, 128.3, 122.7, 119.2, 117.4, 80.4, 78.0, 78.0, 73.6, 72.2, 54.8, 34.3, 31.2, 26.2, 10.3, 4.4.

HRMS (ESI): *m/z* calcd for $C_{33}H_{35}N_2O_5$: 539.25460; Found: 539.25555.

Compound 32l

Following the general procedure 3.9.3, compound **32f** (100 mg, 81 %) was synthesised from bicyclic olefin **31b** (80 mg, 0.2207 mmol) and 5-phenylsalicylaldehyde **20e** (44 mg, 0.2207 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0066 mmol) and $Cu(OAc)_2.H_2O$ (88 mg, 0.4414 mmol) as yellow viscous liquid.



R_f: 0.54 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3063, 3033, 2934, 2877, 1957, 1885, 1674, 1613, 1506, 1478, 1454, 1417, 1369, 1310, 1266, 1203, 1161, 1137, 1058, 1005, 900, 833, 805, 746, 699, 622 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J* = 2.5 Hz, 1 H), 7.66 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1 H), 7.50-7.47 (m, 5 H), 7.41-7.30 (m, 10 H), 6.88 (d, *J* = 9.0 Hz, 1 H), 5.29 (d, *J* = 8.5 Hz, 1 H), 5.08-5.05 (m, 2 H), 4.94-4.91 (m, 2 H), 3.75 (d, *J* = 8.5 Hz, 1 H), 3.27 (d, *J* = 2.0 Hz, 1 H), 2.99 (d, *J* = 2.0 Hz, 1 H), 0.53-0.46 (m, 3 H), 0.33-0.29 (m, 1 H).

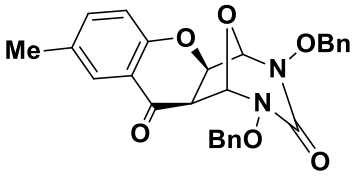
^{13}C NMR (125 MHz, $CDCl_3$): δ 188.8, 159.7, 159.0, 139.3, 135.8, 135.6, 135.0, 134.9, 130.0, 129.8, 128.9, 128.7, 128.5, 128.4, 128.3, 127.4, 126.6, 124.8, 119.7, 118.3, 80.6, 78.0,

78.0, 73.7, 72.3, 54.6, 26.2, 10.3, 4.6.

HRMS (ESI): *m/z* calcd for $C_{35}H_{31}N_2O_5$: 559.22330; Found: 559.22375.

Compound 32m

Following the general procedure 3.9.3, compound **32m** (65 mg, 58 %) was synthesised from bicyclic olefin **31c** (80 mg, 0.2364 mmol) and salicylaldehyde **20b** (32 mg, 0.2364 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0071 mmol) and $Cu(OAc)_2.H_2O$ (94 mg, 0.4729 mmol) as pale yellow solid.



M. P. = 120-122 ^oC.

R_f: 0.57 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3033, 2936, 1720, 1679, 1619, 1586, 1492, 1455, 1422, 1374, 1304, 1217, 1133, 1076, 1005, 918, 855, 825, 749, 699 cm^{-1}.

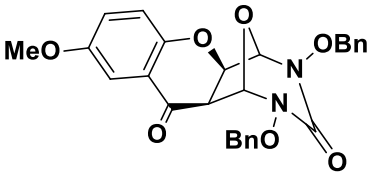
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.46 (m, 5 H), 7.42-7.35 (m, 6 H), 7.25 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1 H), 6.72 (d, J = 8.5 Hz, 1 H), 5.31 (s, 1 H), 5.16 (s, 1 H), 5.10-5.07 (m, 2 H), 5.03-4.99 (m, 2 H), 4.92 (d, J = 8.0 Hz, 1 H), 3.43 (d, J = 8.0 Hz, 1 H), 2.26 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 186.5, 157.4, 156.6, 137.9, 135.3, 135.2, 131.7, 129.9, 129.8, 129.6, 129.1, 128.8, 128.7, 128.6, 126.7, 126.4, 119.0, 117.7, 96.3, 95.3, 79.7, 78.9, 78.7, 53.6, 20.4.

HRMS (ESI): *m/z* calcd for $C_{27}H_{24}N_2O_6Na$: 495.15321; Found: 495.15332.

Compound 32n

Following the general procedure 3.9.3, compound **32n** (98 mg, 85 %) was synthesised from bicyclic olefin **31c** (80 mg, 0.2364 mmol) and 5-methylsalicylaldehyde **20c** (36 mg, 0.2364 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0071 mmol) and $Cu(OAc)_2.H_2O$ (94 mg, 0.4729 mmol) as brown solid.



M. P. = 98-100 ^oC.

R_f: 0.63 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3032, 2937, 1730, 1680, 1617, 1590, 1541, 1489, 1456, 1433, 1372, 1297, 1206, 1124, 1071, 1031, 918, 856, 749, 699, 625, 584 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.5-7.46 (m, 4 H), 7.41-7.33 (m, 7 H), 7.09 -7.08 (m, 1 H),

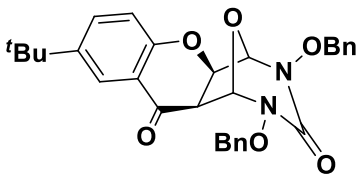
6.75 (d, *J* = 9.0 Hz, 1 H), 5.29 (s, 1 H), 5.13 (s, 1 H), 5.09 -5.06 (m, 2 H), 5.02-4.01 (m, 2 H), 4.91 (d, *J* = 8.0 Hz, 1 H), 3.75 (s, 3 H), 3.41 (d, *J* = 10.0 Hz, 1 H) .

^{13}C NMR (125 MHz, $CDCl_3$): δ 186.5, 156.7, 154.6, 153.9, 135.3, 135.1, 129.8, 129.6, 129.1, 128.8, 128.7, 128.6, 126.1, 119.2, 107.1, 96.3, 95.3, 79.7, 78.9, 78.7, 55.7, 53.5.

HRMS (ESI): *m/z* calcd for $C_{27}H_{24}N_2O_7Na$: 511.14812; Found: 511.14883.

Compound 32o

Following the general procedure 3.9.3, compound **32o** (65 mg, 53 %) was synthesised from bicyclic olefin **31c** (80 mg, 0.2364 mmol) and 5-*tert*-butylsalicylaldehyde **20d** (42 mg, 0.2364 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0071 mmol) and $Cu(OAc)_2.H_2O$ (94 mg, 0.4729 mmol) as reddish brown viscous liquid.



R_f: 0.63 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3063, 3032, 2961, 2872, 2031, 1728, 1679, 1639, 1613, 1583, 1492, 1456, 1424, 1367, 1304, 1259, 1211, 1143, 1111, 1075, 1000, 914, 855, 747, 699, 622, 586 cm^{-1}.

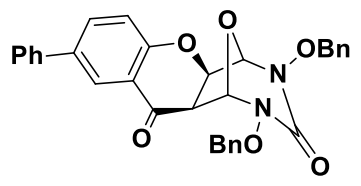
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 2.5 Hz, 1 H), 7.52-7.47 (m, 5 H), 7.43-7.36 (m, 6 H), 6.77 (d, *J* = 9.0 Hz, 1 H), 5.33 (s, 1 H), 5.18 (s, 1 H), 5.11-5.07 (m, 2 H), 5.04-5.00 (m, 2 H), 4.92 (d, *J* = 8.0 Hz, 1 H), 3.44 (d, *J* = 8.0 Hz, 1 H), 1.26 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 186.7, 157.4, 156.7, 145.2, 135.3, 134.7, 129.8, 129.6, 129.1, 128.9, 128.7, 128.6, 127.0, 122.8, 118.5, 117.5, 96.4, 95.4, 79.7, 78.9, 78.7, 53.6, 34.3, 31.2.

HRMS (ESI): *m/z* calcd for $C_{30}H_{31}N_2O_6$: 515.21821; Found: 515.21906.

Compound 32p

Following the general procedure 3.9.3, compound **32p** (79 mg, 63 %) was synthesised from bicyclic olefin **31c** (80 mg, 0.2364 mmol) and 5-phenylsalicylaldehyde **20e** (47 mg, 0.2364 mmol) using $[RhCl_2Cp^*]_2$ (4 mg, 0.0071 mmol) and $Cu(OAc)_2.H_2O$ (94 mg, 0.4729 mmol) as yellow viscous liquid.



R_f: 0.64 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3062, 3033, 2940, 2881, 1731, 1681, 1614, 1541, 1505, 1478, 1454, 1417, 1354, 1313, 1212, 1138, 1075, 1000, 915, 855, 781, 748, 698, 620, 587, 565 cm^{-1}.

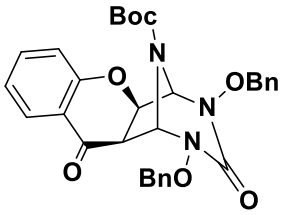
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, *J* = 2.0 Hz, 1 H), 7.69 (dd, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1 H), 7.52-7.48 (m, 6 H), 7.43-7.33 (m, 9 H), 6.91 (d, *J* = 9.0 Hz, 1 H), 5.34 (s, 1 H), 5.20 (s, 1 H), 5.12-5.09 (m, 2 H), 5.05-5.01 (m, 2 H), 4.97 (d, *J* = 8.0 Hz, 1 H), 3.49 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 186.3, 158.7, 156.6, 153.3, 139.1, 135.5, 135.5, 129.9, 129.8, 129.7, 129.6, 129.2, 129.1, 128.9, 128.9, 128.8, 128.6, 126.7, 124.8, 119.2, 118.3, 96.4, 95.4, 79.9, 78.9, 78.7, 53.6.

HRMS (ESI): *m/z* calcd for $C_{32}H_{27}N_2O_6$: 535.18691; Found: 535.18799.

Compound 32q

Following the general procedure 3.9.3, compound **32q** (65 mg, 64 %) was synthesised from bicyclic olefin **31d** (80 mg, 0.1829 mmol) and salicylaldehyde **2a** (22 mg, 0. 1829 mmol) using $[RhCl_2Cp^*]_2$ (3 mg, 0.0055 mmol) and $Cu(OAc)_2.H_2O$ (73 mg, 0.3658 mmol) as reddish brown solid.



M. P. = 112-114 ^oC.

R_f: 0.67 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3064, 3033, 2977, 2934, 2880, 1960, 1727, 1682, 1607, 1583, 1496, 1464, 1370, 1325, 1222, 1157, 1116, 1073, 1001, 942, 915, 890, 834, 750, 699, 592 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 7.51-7.45 (m, 5 H), 7.40-7.33 (m, 6 H), 7.03-6.99 (m, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 5.49 (brs, 1 H), 5.40 (brs, 1 H), 5.25 (d, *J* = 8.0 Hz, 1 H), 5.09-5.05 (m, 2 H), 4.97-4.93 (m, 2 H), 3.72 (d, *J* = 8.0 Hz, 1 H), 1.42 (s, 9 H).

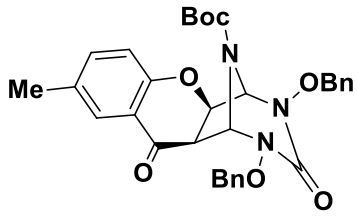
^{13}C NMR (125 MHz, $CDCl_3$): δ 187.0, 159.5, 159.2, 152.2, 136.9, 135.3, 134.9, 129.5, 129.2, 128.8, 128.6, 128.5, 127.6, 127.0, 127.0, 122.3, 119.6, 118.0, 83.1, 78.4, 78.2, 65.3, 53.2, 28.0.

HRMS (ESI): *m/z* calcd for $C_{31}H_{32}N_3O_7$: 558.22403; Found: 558.22534.

Compound 32r

Following the general procedure 3.9.3, compound **32r** (74 mg, 70 %) was synthesised from bicyclic olefin **31d** (80 mg, 0.1829 mmol) and 5-methylsalicylaldehyde **20b** (25 mg, 0. 1829 mmol) using $[RhCl_2Cp^*]_2$ (3 mg, 0.0055 mmol) and $Cu(OAc)_2.H_2O$ (73 mg, 0.3658 mmol)

as reddish brown solid.



M. P. = 126-128 ^{o}C.

R_f: 0.60 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3064, 3033, 2977, 2931, 2880, 1726, 1680, 1618, 1587, 1492, 1455, 1422, 1370, 1333, 1302, 1223, 1158, 1075, 1002, 944, 832, 748, 699 cm^{-1}.

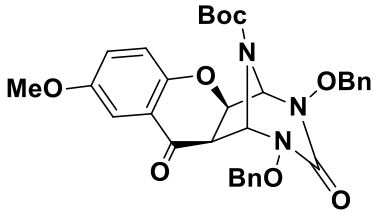
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.47 (m, 5 H), 7.39-7.33 (m, 6 H), 7.27 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1 H), 6.79 (d, J = 8.5 Hz, 1 H), 5.46 (brs, 1 H), 5.36 (brs, 1 H), 5.20 (d, J = 8.0 Hz, 1 H), 5.07-5.04 (m, 2 H), 4.96-4.92 (m, 2 H), 3.68 (d, J = 8.0 Hz, 1 H), 2.28 (s, 3 H), 1.42 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 187.0, 159.2, 157.6, 152.2, 137.9, 135.4, 134.9, 131.7, 129.9, 129.5, 129.2, 128.8, 128.6, 128.5, 128.5, 126.9, 126.5, 119.3, 117.8, 82.9, 78.3, 78.1, 65.2, 53.3, 28.0, 20.4.

HRMS (ESI): *m/z* calcd for $C_{32}H_{34}N_3O_7$: 572.23968; Found: 572.23860.

Compound 32s

Following the general procedure 3.9.3, compound **32q** (56 mg, 52 %) was synthesised from bicyclic olefin **31d** (80 mg, 0.1829 mmol) and 5-methoxysalicylaldehyde **20c** (28 mg, 0. 1829 mmol) using $[RhCl_2Cp^*]_2$ (3 mg, 0.0055 mmol) and $Cu(OAc)_2.H_2O$ (73 mg, 0.3658 mmol) as yellow viscous liquid.



R_f: 0.62 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3064, 3033, 2977, 2936, 2881, 2838, 1722, 1677, 1618, 1490, 1455, 1433, 1370, 1332, 1293, 1231, 1204, 1158, 1123, 1061, 1033, 943, 832, 786, 749, 699 cm^{-1}.

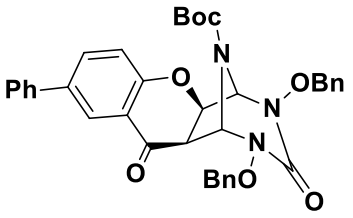
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.47 (m, 4 H), 7.41-7.34 (m, 6 H), 7.15 (d, J = 3.5 Hz, 1 H), 7.07 (dd, J_1 = 9.0 Hz, J_2 = 3.5 Hz, 1 H), 6.83 (d, J = 9.0 Hz, 1 H), 5.48 (brs, 1 H), 5.38-5.37 (m, 1 H), 5.20 (d, J = 3.0 Hz, 1 H), 5.08-5.05 (m, 2 H), 4.97-4.93 (m, 2 H), 3.77 (s, 3 H), 3.69 (d, J = 8.0 Hz, 1 H), 1.43 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 186.8, 159.2, 154.6, 154.1, 152.2, 135.3, 134.9, 129.5, 129.1, 128.8, 128.6, 128.5, 128.5, 127.0, 125.9, 119.5, 119.4, 107.3, 83.0, 78.3, 78.2, 65.2, 55.8, 53.2, 28.0.

HRMS (ESI): *m/z* calcd for $C_{32}H_{34}N_3O_8$: 588.23459; Found: 588.23566.

Compound 32t

Following the general procedure 3.9.3, compound **32t** (70 mg, 60 %) was synthesised from bicyclic olefin **31d** (80 mg, 0.1829 mmol) and 5-phenylsalicylaldehyde **20e** (36 mg, 0. 1829 mmol) using $[RhCl_2Cp^*]_2$ (3 mg, 0.0055 mmol) and $Cu(OAc)_2.H_2O$ (73 mg, 0.3658 mmol) as reddish brown solid.



R_f: 0.58 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3063, 3033, 2977, 2933, 2879, 1953, 1726, 1683, 1614, 1541, 1506, 1479, 1454, 1417, 1370, 1332, 1259, 1236, 1207, 1157, 1075, 1002, 943, 909, 872, 836, 786, 748, 698, 620, 598, 569 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 2.5 Hz, 1 H), 7.71 (dd, J_1 = 9.0 Hz, J_2 = 1.0 Hz, 1 H), 7.52-7.49 (m, 6 H), 7.42-7.31 (m, 9 H), 6.97 (d, *J* = 9.0 Hz, 1 H), 5.51 (brs, 1 H), 5.42 (brs, 1 H), 5.27 (d, *J* = 8.5 Hz, 1 H), 5.10-5.06 (m, 2 H), 4.98-4.95 (m, 2 H), 3.75 (d, *J* = 8.0 Hz, 1 H), 1.43 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 186.8, 159.2, 158.9, 152.2, 139.2, 135.6, 135.5, 134.9, 129.6, 129.2, 129.0, 129.0, 128.9, 128.6, 128.6, 128.5, 128.2, 127.6, 126.7, 124.9, 119.5, 118.6, 83.1, 78.4, 78.2, 53.3, 28.0.

HRMS (ESI): *m/z* calcd for $C_{37}H_{36}N_3O_7$: 634.25533; Found: 634.25580.

3.10. References

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CHAPTER 4

Hydro(hetero)arylation & Annulation Reactions

PART A

Palladium Catalyzed Hydroarylation of Urea Derived Bicyclic Olefins with Aryl Iodides

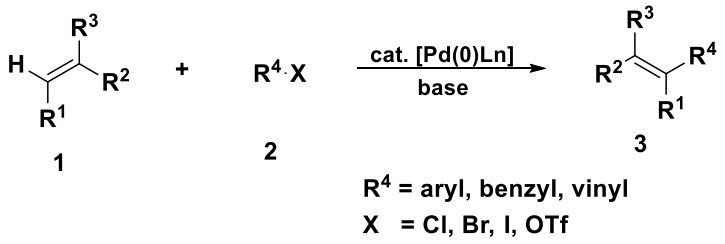
4A.1. Introduction

After the evolution of transition metal catalyzed reactions as an efficient and promising protocol for the synthesis of complex organic molecules omnipresent in many natural products and pharmaceuticals, organic chemistry enthusiasts have always been in a continued quest for developing new C-C bond forming reactions.[1] Transition metal-catalyzed reactions comprise a plethora of versatile carbon-carbon and carbon-heteroatom bond forming processes and asymmetric transformations. Transition metal catalysts provide an excellent tool for generating complex organic molecules in a single step from readily available starting substrates in a stereo, regio and chemo selective fashion, which is generally not possible using traditional organic synthesis.[2] Among the complexes of a variety of transition metals for carbon-carbon bond formation employed previously, palladium complexes have been most often used because they display wide reactivity and higher selectivity than other transition metal complexes.[3] They offer an abundance of possibility of C-C bond formations as the advantages of palladium catalysts include less sensitivity to oxygen and moisture, and the reactions can be carried out without protecting many of the functional groups. The discovery of palladium catalyzed carbon-carbon bond forming reactions *via* cross coupling between organometallic reagents and organic electrophiles marked the beginning of an era in synthetic organic chemistry. The most widely used Pd-catalyzed cross coupling reactions such as the Heck, Negishi, Suzuki, Stille and Sonogashira reactions played a remarkable role in the synthesis and manipulation of chemicals and pharmaceuticals.[3] Among them, the Heck reaction now stands as a remarkably robust and efficient method for carbon–carbon bond formation, particularly for intramolecular and intermolecular ring formation, in the generation of tertiary and quaternary stereo centers, and

in total synthesis.

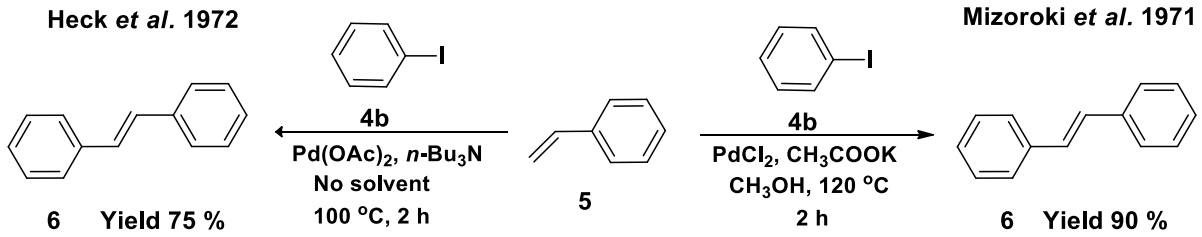
4A.2. Heck Coupling or Mizoroki Heck reaction

The Heck reaction, named after Tsutomu Mizoroki and Richard F Heck, can be broadly defined as the palladium-catalyzed coupling of alkenyl or aryl (sp^2) halides or triflates **2** with alkenes **1** to yield products which formally result from the substitution of a hydrogen atom in the alkene coupling partner (Scheme 4A.1).[4] This reaction is the first example of a C-C bond forming reaction that followed a Pd (0) to Pd (II) catalytic cycle and Heck was awarded the 2010 Nobel Prize in Chemistry for the discovery and development of the same. The outstanding *trans*-selectivity and the ability to do substitution reactions on planar sp^2 hybridized carbon centers prioritize this reaction.



Scheme 4A.1

The first example of this reaction was reported independently by Mizoroki in 1971 and, in an improved form, by Heck in 1972 (Scheme 4A.2).

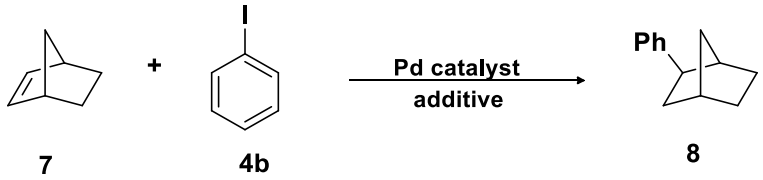


Scheme 4A.2

Thereafter, remarkable interest has been devoted to the development of novel strategies toward Heck coupling reactions such as dehydrogenative Heck, reductive Heck, Heck-oxyarylation, amino-Heck reactions and so on.[5–15] Hydroarylation reactions which can also be achieved *via* reductive Heck arylation have found useful applications in the synthesis of alkaloids like epibatidine.[16,17] The importance of these hydroarylated products necessitated the extension of the utility of these reactions to bicyclic alkenes that are useful precursors for the synthesis of a broad range of functional molecules.

4A.3. Hydroarylation Reaction on Bicyclic Olefins

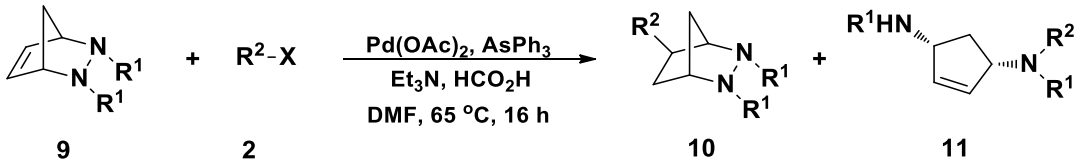
Any addition reaction in which a hydrogen atom and an aryl group are attached across a double bond or a triple bond is known as hydroarylation reaction. Pioneering works on the hydroarylation reactions of bicyclic alkenes was reported independently by Larock *et al.*[18] and Cacchi *et al.*[19] in which they presented the palladium-catalyzed intermolecular arylation and alkenylation of bicyclic substrates like norbornenes **7** (Scheme 4A.3).



Scheme 4A.3

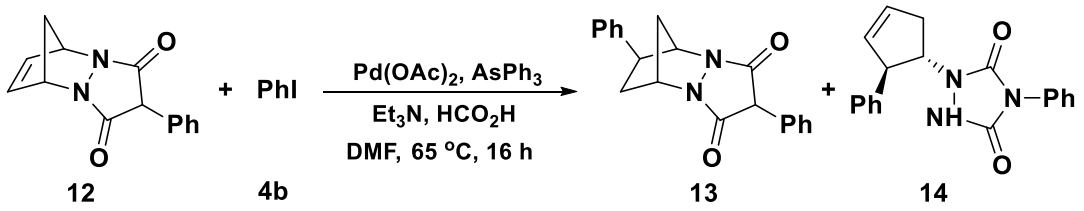
Later, the enantioselective hydroarylation of norbornene and norbornadiene with palladium(II)acetate/phosphine catalysts using aryl iodides were developed by Brunner and co-workers.[20]

Kaufmann *et al*. have carried out the hydroarylation reactions of diazabicyclic alkenes **9** with different aryl or *β*-styryl halides **2** in the presence of an in *situ* generated palladium catalyst, stabilized by triphenyl arsine, which afforded exclusively the *exo*-configurated hydroarylation **10** and hydrovinylation products in good yields (Scheme 4A.4).[21] They observed the formation of very small amount of 3,5-isomer **11** which was later confirmed as the 3,4-substituted cyclopentene by the same group in a different report.



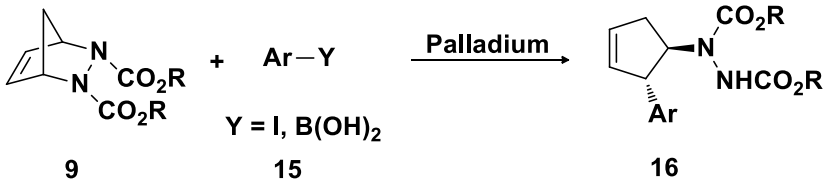
Scheme 4A.4

Later on Kaufmann *et al.* extended this reaction to sterically more hindered and more rigid tri- and tetracyclic substrates derived from 4-phenyl-1,2,4-triazoline-3,5-dione and 2,3-phthalazine-1,4-dione (Scheme 4A.5).[22] Under similar conditions applied to the bicyclic hydrazines, these tri- and tetracyclic substrates afforded the expected hydroarylated products **13** along with a minor product **14** formed *via* the C-N bond cleavage.



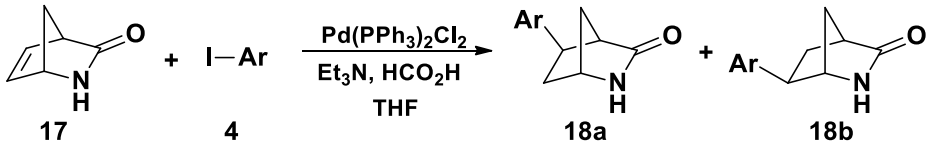
Scheme 4A.5

A simple and efficient method for the stereoselective ring opening of bicyclic hydrazines **9** with various aryl halides or aryl boronic acids **15** under palladium catalysis was elaborated by our group (Scheme 4A.6).[23]



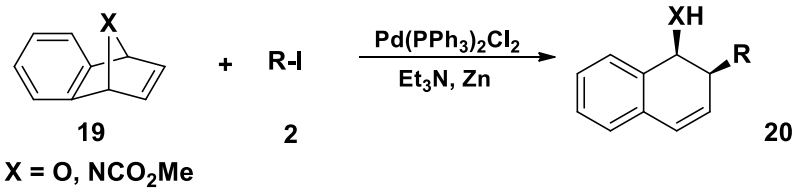
Scheme 4A.6

Different groups have tried a variety of transformations of Vince lactam, a bicyclic-*γ*-lactam, using the same strategies. Pietrowski and Polivkova have revealed the *C*−arylation of Vince lactam **17** in palladium mediated reaction system.[24] The reactions furnished the coupling products **18** in excellent yields with 5 mol% palladium catalyst loadings at 65 °C and the substrate scope of the reaction was explored with electron-rich as well as electron deficient aryl iodides (Scheme 4A.7).



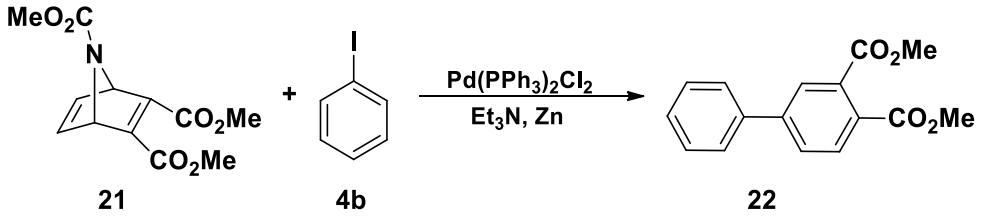
Scheme 4A.7

Cheng *et al*. explored the palladium-catalyzed stereoselective reductive coupling reactions of organic halides **2** with 7-heteroatom benzo norbornadienes **19** which resulted in the C-O bond cleavage to form dihydronaphthols **20** (Scheme 4A.8).[25]



Scheme 4A.8

Later the same group extended this strategy to 7-aza or oxa norbornadiene derivatives **21**, which gave biphenyl derivatives **22** (Scheme 4A.9).[26]

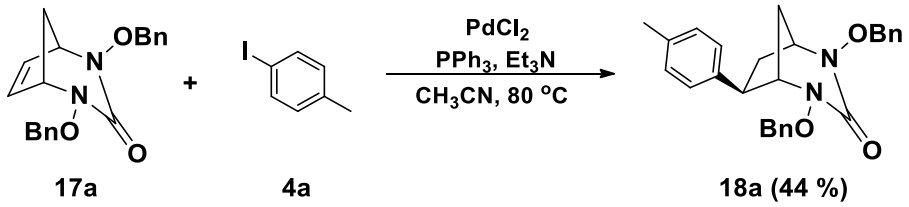


Scheme 4A.9

Since we were successful in exploring the transition metal mediated transformations of urea derived bicylic adducts to chromanone fused analogues, we have carried out the investigations on the reactivity of aryl iodides with the urea derived bicyclic olefins, the details of which are presented in the following sections.

4A.4. Results and Discussion

We initiated our experiments with the reaction of urea-derived bicyclic olefin **17a** with 4-iodotoluene **4a** in the presence of $PdCl_2$ as the catalyst, PPh_3 as ligand and Et_3N as the base in CH_3CN at 80 ^oC. The reaction afforded the expected hydroarylated product **18a** in 44 % yield (Scheme 4A.10). In this case, triethylamine is the plausible hydrogen source as previously reported by others.[27–30]



Scheme 4A.10. Hydroarylation of urea-derived bicyclic olefins

The structure of the product **18a** was confirmed using different spectroscopic techniques such as ^1H NMR, ^{13}C NMR, and HRMS-ESI analysis. The IR spectrum of **18a** showed characteristic carbonyl absorption of the urea at 1715 cm^{-1}.

In the ^1H NMR (Figure 4A.1), the aromatic protons were discernable in the region δ 7.48–6.93 ppm. The multiplets in the region δ 5.06-5.03 and δ 4.89-4.86 ppm were assigned to the methylene protons of the benzyloxy groups. The proton on the carbon bearing the phenyl ring appeared as a multiplet at δ 3.74-3.69 ppm. The proton on each carbon attached to nitrogen, *i.e.* the bridgehead protons, appeared at δ 3.74-3.69 and δ 3.50-3.49

ppm. The methylene protons near to the carbon bearing phenyl ring appeared as a multiplet at δ 2.70-2.65 and 1.87-1.76 ppm. The methyl group attached to aromatic ring resonated at δ 2.29 ppm. The bridge protons resonated as a multiplet in the region δ 2.07-2.05 and δ 1.87-1.76 ppm.

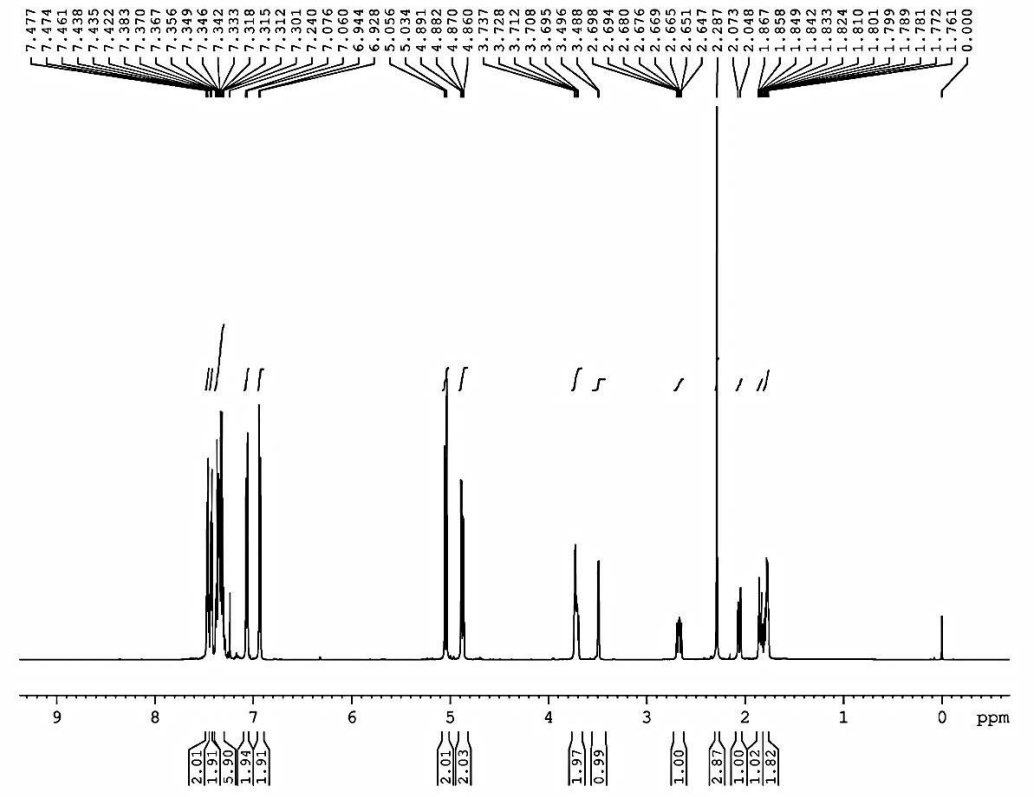


Figure 4A.1. ^{1}H NMR spectrum of compound **18a**

^{13}C NMR of **18a** (Figure 4A.2) displayed the carbonyl peak of the amide at δ 160.9 ppm. The methylene carbons of the benzyloxy groups were identified at δ 77.8 and 77.7 ppm. Each carbon bearing the nitrogen atom resonated at δ 69.0 and 63.1 ppm. The peak at δ 46.5 ppm was assigned to the carbon attached to the phenyl ring. The methylene carbon near to the carbon bearing phenyl ring appeared at δ 36.7 ppm. The methylene carbon at the bridge resonated at δ 32.2 ppm. The methyl groups attached to aromatic ring appeared at δ 20.9 ppm.

The mass spectrum of **18a** that showed $[M+H]^{+}$ peak at *m/z* = 429.21835 provided additional evidence for the structure assigned.

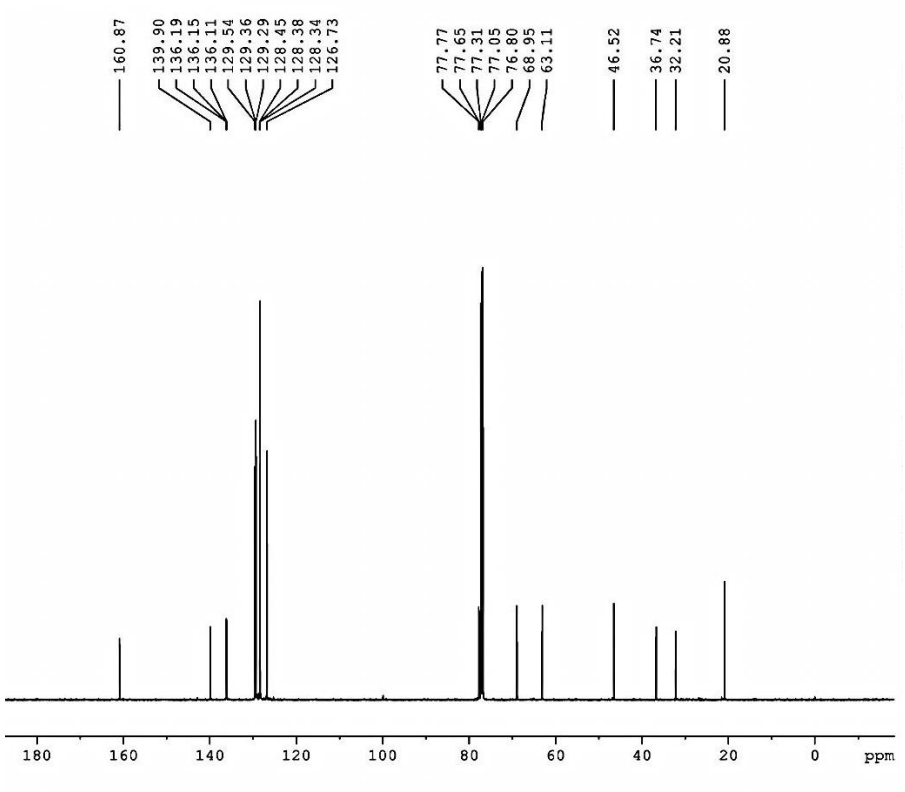
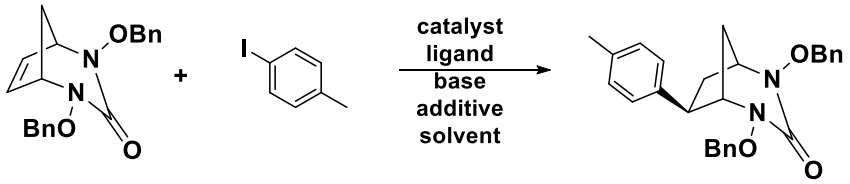


Figure 4A.2. ^{13}C NMR spectrum of compound **18a**

4A.4.1. Optimization Studies

Detailed optimization studies were carried out to find out the best conditions for this reaction (Table 4A.1). Among the various palladium catalysts screened, $[Pd(allyl)Cl]_2$ proved to be the best for this transformation (entry 3). The reaction was further tested with different bases and solvents and was found to be optimal with Et_3N and CH_3CN as the base and solvent respectively (entry 3). Lower yields were obtained in other solvents such as DCE, toluene and DMF (entry 6-8). To our delight, the yield of the product significantly increased to 65 % upon adding HCOOH as an additive (entry 10). Also, the reaction actually proceeded better without the ligand (entry 11). Other additives such as TFA and benzoic acid were shown to be ineffective for the present transformation (entry 12 & 13). Decreasing the temperature to 70 ^oC furnished the product in 80 % yield (entry 14). After the optimization studies, $[Pd(allyl)Cl]_2$ as the catalyst, Et_3N as the base and HCOOH as additive in CH_3CN at 80 ^oC were found to be the best conditions for this reaction, giving 93 % yield of **18a** (entry 11).

Table 4A.1. Optimization studies for the hydroarylation reaction [a]



Entry	Catalyst	Ligand	Base	Additive	Solvent	Yield (%)[b]
1	$PdCl_2$	PPh_3	Et_3N	-	CH_3CN	44
2	$Pd(OAc)_2$	PPh_3	Et_3N	-	CH_3CN	trace
3	$[Pd(allyl)Cl]_2$	PPh_3	Et_3N	-	CH_3CN	55
4	$[Pd(allyl)Cl]_2$	PPh_3	Cs_2CO_3	-	CH_3CN	24
5	$[Pd(allyl)Cl]_2$	PPh_3	NaOAc	-	CH_3CN	29
6	$[Pd(allyl)Cl]_2$	PPh_3	Et_3N	-	toluene	26
7	$[Pd(allyl)Cl]_2$	PPh_3	Et_3N	-	DCE	16
8	$[Pd(allyl)Cl]_2$	PPh_3	Et_3N	-	DMF	40
9	$[Pd(allyl)Cl]_2$	-	Et_3N	-	CH_3CN	nr
10	$[Pd(allyl)Cl]_2$	PPh_3	Et_3N	HCOOH	CH_3CN	65
11	**$[Pd(allyl)Cl]_2$**	**-**	**Et_3N**	**HCOOH**	**CH_3CN**	**93**
12	$[Pd(allyl)Cl]_2$	-	Et_3N	TFA	CH_3CN	nr
13	$[Pd(allyl)Cl]_2$	-	Et_3N	PhCOOH	CH_3CN	nr
14[c]	$[Pd(allyl)Cl]_2$	-	Et_3N	HCOOH	CH_3CN	80

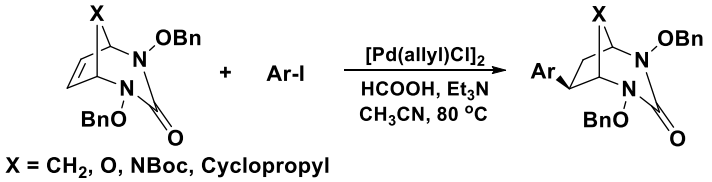
[a]**Reaction conditions:** adduct (1 equiv.), 4-iodotoluene (1.2 equiv.), catalyst (5 mol%), ligand (10 mol%), base (2 equiv.), additive (2 equiv.), solvent (2 mL), 80 ^oC, 8 h. nr = no reaction. [b] Isolated yield. [c]At 70 ^oC.

4A.4.2. Scope of the Reaction

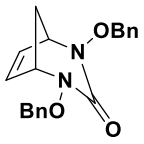
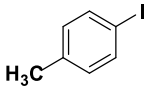
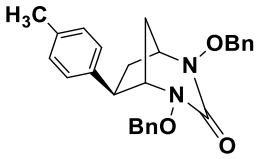
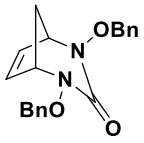
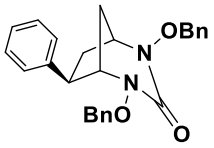
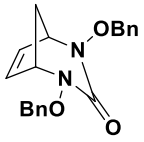
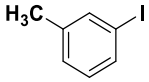
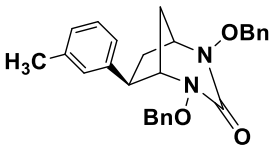
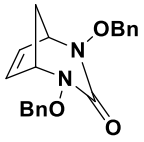
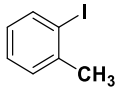
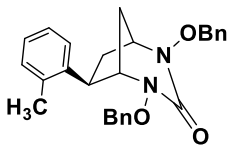
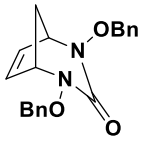
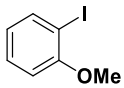
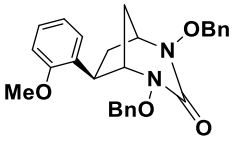
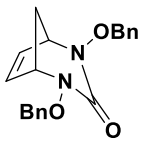
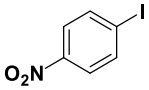
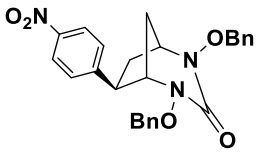
The scope of this methodology was examined with different iodoarenes under the optimized conditions (Table 4A.2). Aryl iodides with electron withdrawing and electron donating groups underwent the reaction and gave the corresponding hydroarylated products in good to excellent yields (**18c-j**). Substituents in the *ortho* position of aryl iodides showed no steric effect on the reaction and gave good yields (**18d-e**, **18i-j**). The reaction was found to be general with other bicyclic urea derivatives derived from spiro[2.4]hepta-4,6-diene, furan

and *N*-protected pyrrole. In all cases, the reaction afforded hydroarylated products (**18l-p**) in moderate to excellent yields.

Table 4A.2. Hydroarylation of urea derived bicyclic olefins with aryl iodides [a]



X = CH_2, O, NBoc, Cyclopropyl

Entry	Bicyclic Olefin	Iodoarene	Product	Yield (%)[b]
1	 **17a**	 **4a**	 **18a**	93
2	 **17a**	 **4b**	 **18b**	77
3	 **17a**	 **4c**	 **18c**	85
4	 **17a**	 **4d**	 **18d**	83
5	 **17a**	 **4e**	 **18e**	68
6	 **17a**	 **4f**	 **18f**	80

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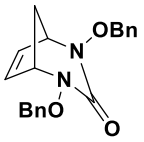
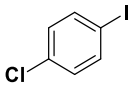
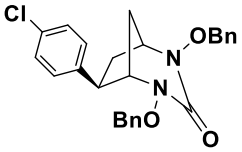
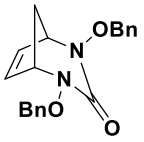
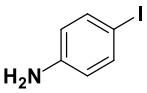
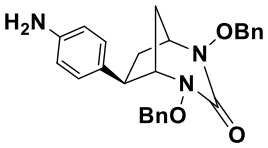
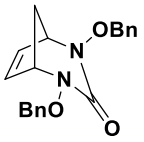
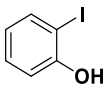
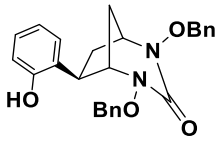
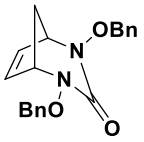
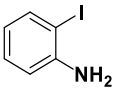
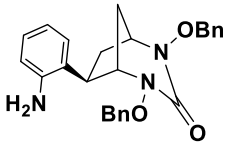
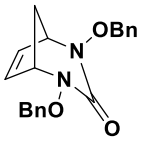
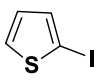
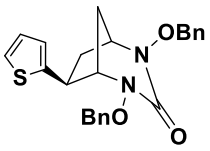
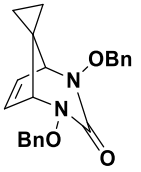
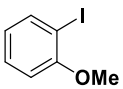
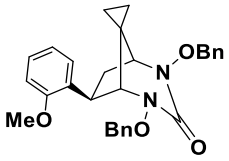
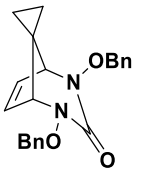
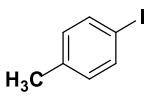
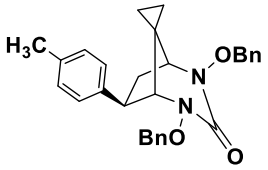
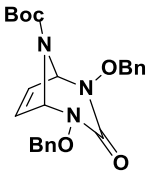
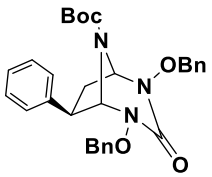
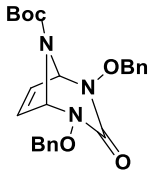
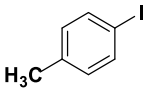
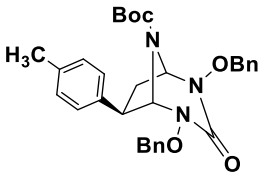
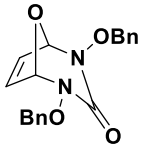
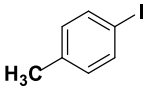
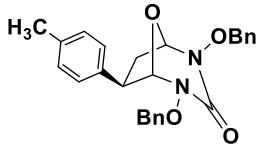
7	 **17a**	 **4g**	 **18g**	75
8	 **17a**	 **4h**	 **18h**	67
9	 **17a**	 **4i**	 **18i**	55
10	 **17a**	 **4j**	 **18j**	77
11	 **17a**	 **4k**	 **18k**	80
12	 **17b**	 **4e**	 **18l**	70
13	 **17b**	 **4a**	 **18m**	77
14	 **17c**	 **4b**	 **18n**	64

Continued..

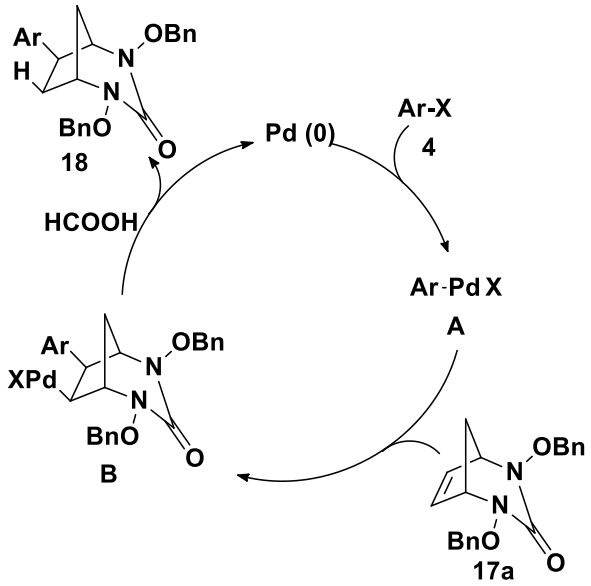
15	 **17c**	 **4a**	 **18o**	82
16	 **17d**	 **4a**	 **18p**	60

[a]**Reaction conditions:** adduct (1 equiv.), iodoarene (1.2 equiv.), $[Pd(allyl)Cl]_2$ (5 mol%), Et_3N (2 equiv.), HCOOH (2 equiv.), CH_3CN (2 mL), 80 ^oC, 8 h.

[b]Isolated yield.

4A.5. Plausible Mechanism

A plausible mechanism for this reaction is proposed in Scheme 4A.11 in accordance with the previous reports.[22] The reactive palladium (0) undergoes oxidative addition to the aryl-halogen bond (Ar-X) to form [ArPdX] species **A**, and the *syn*-addition of [ArPdX] species to the bicyclic olefin **17a** results in the formation of **B**. The intermediate **B** is then reduced by formic acid to furnish the product **18** and the active palladium species is regenerated in reaction medium.



Scheme 4A.11. Mechanistic pathway

4A.6. Conclusion

In conclusion, we have developed an efficient strategy for the palladium catalyzed hydroarylation of urea-derived bicyclic olefins. The present method offers an efficient approach for the preparation of a variety of biologically important functionalized urea derivatives that substantiates the current strategy. The evaluation of biological properties of the synthesized urea derivatives is underway in our laboratory.

4A.7. Experimental Section

4A.7.1. General Methods

General information about the experiments is given in Section 2.8.1 of Chapter 2.

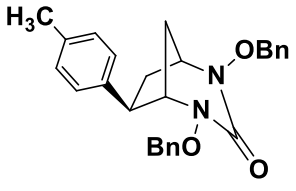
4A.7.2. General Procedure for the Hydroarylation Reaction

Bicyclic olefin **17** (1 equiv.), aryliodide **4** (1.2 equiv.), $[Pd(allyl)Cl]_2$ (5 mol%) and HCOOH (2 equiv.) were weighed into a Schlenk tube. The Schlenk tube was degassed for 10 minutes. To this, Et_3N (2 equiv.) followed by CH_3CN (2 mL) was added, and the reaction mixture was purged with argon, and allowed to stir at 80 ^oC for 8 hours. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel 100-200 mesh) using hexane-ethylacetate mixtures to yield the desired hydroarylated product **18**.

4A.7.3. Characterization of the Products

Compound 18a

Following the general procedure 4A.7.2, compound **18a** (59 mg, 93 %) was synthesised from bicyclic olefin **17a** (50 mg, 0.1486 mmol) and 4-iodotoluene **4a** (39 mg, 0.1784 mmol) using $[Pd(allyl)Cl]_2$ (2 mg, 0.0074 mmol), HCOOH (0.01 mL, 0.2972 mmol) and Et_3N (0.04 mL, 0.2972 mmol) as pale yellow viscous liquid.



R_f: 0.63 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3030, 2927, 2873, 1715, 1559, 1541, 1514, 1496, 1372, 1303, 1272, 1258, 1210, 1156, 1111, 1081, 1027, 995, 912, 879, 808, 750, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48-7.46 (m, 2 H), 7.44-7.42 (m, 2 H), 7.39-7.30 (m, 6 H), 7.08-7.06 (m, 2 H), 6.94-6.93 (m, 2 H), 5.06-5.03 (m, 2 H), 4.89-4.86 (m, 2 H), 3.74-3.69 (m, 2 H), 3.49 (d, *J* = 4.5 Hz, 1 H), 2.70-2.65 (m, 1 H), 2.29 (s, 3 H), 2.07-2.05 (m, 1 H), 1.87-1.82 (m, 1 H), 1.81-1.76 (m, 1 H).

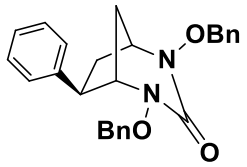
^{13}C NMR (125 MHz, $CDCl_3$): δ 160.9, 139.9, 136.2, 136.2, 136.1, 129.5, 129.4, 129.3,

128.5, 128.4, 128.3, 126.7, 77.8, 77.7, 68.9, 63.1, 46.5, 36.7, 32.2, 20.9.

HRMS (ESI): *m/z* calcd for $C_{27}H_{29}N_2O_3$: 429.21782; Found: 429.21835.

Compound 18b

Following the general procedure 4A.7.2, compound **18b** (47 mg, 77 %) was synthesised from bicyclic olefin **17a** (50 mg, 0.1486 mmol) and iodobenzene **4b** (36 mg, 0.1784 mmol) using $[Pd(allyl)Cl]_2$ (2 mg, 0.0074 mmol), HCOOH (0.01 mL, 0.2972 mmol) and Et_3N (0.04 mL, 0.2972 mmol) as light brown viscous liquid.



R_f: 0.66 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3030, 2943, 2874, 1710, 1602, 1495, 1453, 1371, 1262, 1210, 1156, 1106, 1074, 1025, 995, 914, 880, 830, 806, 750, 699, 620 cm^{-1}.

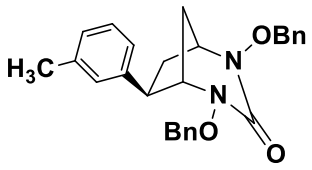
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.42 (m, 4 H), 7.38-7.30 (m, 7 H), 7.26-7.23 (m, 1 H), 7.18-7.14 (m, 1 H), 7.04-7.03 (m, 2 H), 5.06-5.03 (m, 2 H), 4.88-4.85 (m, 2 H), 3.76-3.71 (m, 2 H), 3.50 (d, *J* = 5.0 Hz, 1 H), 2.72-2.67 (m, 1 H), 2.08-2.06 (m, 1 H), 1.87-1.78 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.9, 142.9, 136.2, 136.2, 129.6, 129.4, 128.7, 128.4, 128.4, 128.3, 126.8, 126.5, 77.8, 77.7, 68.9, 63.2, 46.8, 36.7, 32.3.

HRMS (ESI): *m/z* calcd for $C_{26}H_{27}N_2O_3$: 415.20217; Found: 415.20258.

Compound 18c

Following the general procedure 4A.7.2, compound **18c** (54 mg, 85 %) was synthesised from bicyclic olefin **17a** (50 mg, 0.1486 mmol) and 3-iodotoluene **4c** (39 mg, 0.1784 mmol) using $[Pd(allyl)Cl]_2$ (2 mg, 0.0074 mmol), HCOOH (0.01 mL, 0.2972 mmol) and Et_3N (0.04 mL, 0.2972 mmol) as pale yellow viscous liquid.



R_f: 0.66 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3030, 2943, 2872, 1713, 1606, 1493, 1454, 1372, 1264, 1211, 1159, 1074, 1029, 920, 880, 826, 784, 748, 700, 620 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46-7.42 (m, 4 H), 7.37-7.27 (m, 6 H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1 H), 6.83-6.81 (m, 2 H), 5.05-5.02 (m, 2 H), 4.88-4.85 (m, 2 H), 3.70-3.68 (m, 2 H), 3.49 (d, *J* = 4.0 Hz, 1 H), 2.70-2.64 (m, 1 H), 2.29 (s, 3 H), 2.07-2.04 (m,

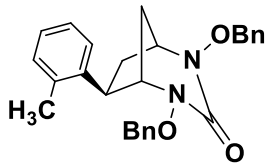
1 H), 1.87-1.82 (m, 1 H), 1.81-1.76 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.9, 142.9, 138.2, 136.3, 136.2, 129.6, 129.4, 128.6, 128.5, 128.4, 128.4, 127.7, 127.3, 123.8, 77.8, 77.7, 68.9, 63.2, 46.8, 36.7, 32.3, 21.5.

HRMS (ESI): *m/z* calcd for $C_{27}H_{29}N_2O_3$: 429.21782; Found: 429.21906.

Compound 18d

Following the general procedure 4A.7.2, compound **18d** (53 mg, 83 %) was synthesised from bicyclic olefin **17a** (50 mg, 0.1486 mmol) and 2-iodotoluene **4d** (39 mg, 0.1784 mmol) using $[Pd(allyl)Cl]_2$ (2 mg, 0.0074 mmol), HCOOH (0.01 mL, 0.2972 mmol) and Et_3N (0.04 mL, 0.2972 mmol) as pale yellow viscous liquid.



Yield: 83 % as pale yellow viscous liquid.

R_f: 0.55 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3061, 3030, 2931, 2872, 1713, 1492, 1455, 1372, 1263, 1213, 1159, 1076, 1026, 915, 829, 750, 700 cm^{-1}.

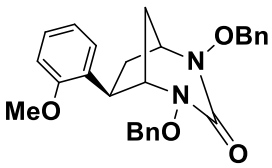
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.47 (m, 2 H), 7.41-7.31 (m, 8 H), 7.14-7.12 (m, 1 H), 7.11-7.09 (m, 2 H), 6.86-6.85 (m, 1 H), 5.07-5.03 (m, 2 H), 4.90-4.86 (m, 2 H), 3.90 (dd, J_1 = 9.0 Hz, J_2 = 6.0 Hz, 1 H), 3.76 (t, J = 4.5 Hz, 1 H), 3.51 (d, J = 4.5 Hz, 1 H), 2.76-2.70 (m, 1 H), 2.31 (s, 3 H), 2.11 (d, J = 12.5 Hz, 1 H), 1.97-1.92 (m, 1 H), 1.79-1.74 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 141.2, 136.7, 136.2, 135.9, 130.7, 129.6, 129.5, 128.5, 128.4, 128.4, 126.4, 126.0, 124.3, 77.9, 77.8, 67.9, 63.1, 43.2, 36.6, 32.3, 20.0.

HRMS (ESI): *m/z* calcd for $C_{27}H_{28}N_2O_3Na$: 451.19976; Found: 451.19840.

Compound 18e

Following the general procedure 4A.7.2, compound **18e** (45 mg, 68 %) was synthesised from bicyclic olefin **17a** (50 mg, 0.1486 mmol) and 2-iodoanisole **4e** (42 mg, 0.1784 mmol) using $[Pd(allyl)Cl]_2$ (2 mg, 0.0074 mmol), HCOOH (0.01 mL, 0.2972 mmol) and Et_3N (0.04 mL, 0.2972 mmol) as brownish viscous liquid.



R_f: 0.57 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3031, 2935, 2876, 1711, 1599, 1585, 1493, 1455, 1437, 1372, 1271, 1244, 1211, 1157, 1110, 1081, 1027, 995, 914, 884, 831, 809, 751, 699 cm^{-1}.

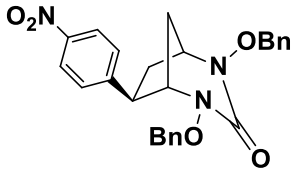
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.42 (m, 4 H), 7.37-7.30 (m, 6 H), 7.16-7.13 (m, 1 H), 6.85-6.79 (m, 3 H), 5.06-5.04 (m, 2 H), 4.89-4.87 (m, 2 H), 4.06-4.03 (m, 1 H), 3.74 (s, 3 H), 3.70 (t, *J* = 4.5 Hz, 1 H), 3.66 (d, *J* = 4.0 Hz, 1 H), 2.75-2.70 (m, 1 H), 2.09-2.07 (m, 1 H), 1.92-1.88 (m, 1 H), 1.68-1.63 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.7, 156.9, 136.3, 131.6, 129.5, 129.3, 128.4, 128.3, 128.2, 127.5, 125.4, 120.2, 110.4, 77.8, 77.6, 66.8, 63.0, 55.1, 41.0, 36.5, 32.6.

HRMS (ESI): *m/z* calcd for $C_{27}H_{29}N_2O_4$: 445.21273; Found: 445.21277.

Compound 18f

Following the general procedure 4A.7.2, compound **18f** (55 mg, 80 %) was synthesised from bicyclic olefin **17a** (50 mg, 0.1486 mmol) and 4-nitroiodobenzene **4f** (44 mg, 0.1784 mmol) using $[Pd(allyl)Cl]_2$ (2 mg, 0.0074 mmol), HCOOH (0.01 mL, 0.2972 mmol) and Et_3N (0.04 mL, 0.2972 mmol) as reddish brownish viscous liquid.



R_f: 0.66 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3032, 2944, 2875, 1709, 1600, 1517, 1454, 1347, 1265, 1210, 1157, 1110, 1079, 1028, 994, 913, 881, 853, 749, 699 cm^{-1}.

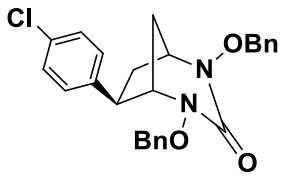
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12-8.09 (m, 2 H), 7.48-7.46 (m, 2 H), 7.43-7.42 (m, 2 H), 7.40-7.32 (m, 6 H), 7.19-7.17 (m, 2 H), 5.08-5.04 (m, 2 H), 4.90-4.87 (m, 2 H), 3.83-3.80 (m, 1 H), 3.77 (t, *J* = 4.0 Hz, 1 H), 3.48 (d, *J* = 4.5 Hz, 1 H), 2.78-2.72 (m, 1 H), 2.16-2.14 (m, 1 H), 1.84-1.75 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 150.2, 146.6, 136.1, 135.9, 129.6, 129.5, 128.6, 128.6, 128.5, 127.7, 123.9, 77.9, 77.9, 68.7, 63.0, 46.8, 36.9, 32.4.

HRMS (ESI): *m/z* calcd for $C_{26}H_{26}N_3O_5$: 460.18725; Found: 460.18823.

Compound 18g

Following the general procedure 4A.7.2, compound **18g** (50 mg, 75 %) was synthesised from bicyclic olefin **17a** (50 mg, 0.1486 mmol) and 4-chloroiodobenzene **4g** (43 mg, 0.1784 mmol) using $[Pd(allyl)Cl]_2$ (2 mg, 0.0074 mmol), HCOOH (0.01 mL, 0.2972 mmol) and Et_3N (0.04 mL, 0.2972 mmol) as yellow viscous liquid.



R_f: 0.37 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3031, 2942, 2875, 1712, 1493, 1454, 1373, 1269, 1210, 1157, 1091, 1028, 1013, 913, 881, 824, 749, 699 cm^{-1}.

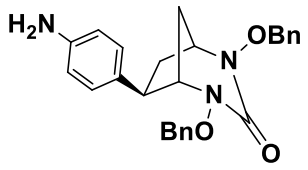
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.44 (m, 2 H), 7.41-7.40 (m, 2 H), 7.37-7.29 (m, 6 H), 7.20-7.18 (m, 2 H), 6.94-6.93 (m, 2 H), 5.05-5.01 (m, 2 H), 4.87-4.84 (m, 2 H), 3.71-3.66 (m, 2 H), 3.41 (d, *J* = 4.5 Hz, 1 H), 2.70-2.65 (m, 1 H), 2.07-2.05 (m, 1 H), 1.80-1.76 (m, 1 H), 1.74-1.69 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8, 141.3, 136.2, 136.1, 132.4, 129.6, 129.4, 128.8, 128.5, 128.4, 128.4, 128.2, 77.8, 77.8, 68.9, 63.1, 46.3, 36.8, 32.2.

HRMS (ESI): *m/z* calcd for $C_{26}H_{25}ClN_2NaO_3$: 471.14514; Found: 471.14346.

Compound 18h

Following the general procedure 4A.7.2, compound **18h** (43 mg, 67 %) was synthesised from bicyclic olefin **17a** (50 mg, 0.1486 mmol) and 4-iodoaniline **4h** (39 mg, 0.1784 mmol) using $[Pd(allyl)Cl]_2$ (2 mg, 0.0074 mmol), HCOOH (0.01 mL, 0.2972 mmol) and Et_3N (0.04 mL, 0.2972 mmol) as brownish viscous liquid.



R_f: 0.39 (hexane/ethyl acetate = 1:1).

IR (neat) ν_{max}: 3359, 3030, 2937, 2873, 1702, 1623, 1516, 1454, 1374, 1276, 1210, 1159, 1109, 1074, 1026, 994, 914, 880, 826, 747, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.40 (m, 4 H), 7.37-7.28 (m, 6 H), 6.80-6.79 (m, 2 H), 6.55-6.53 (m, 2 H), 5.03-5.01 (m, 2 H), 4.86-4.83 (m, 2 H), 3.68 (t, *J* = 4.0 Hz, 1 H), 3.63-3.60 (m, 1 H), 3.42 (d, *J* = 4.5 Hz, 1 H), 2.65-2.60 (m, 1 H), 2.04-2.00 (m, 1 H), 1.83-1.79 (m, 1 H), 1.75-1.70 (m, 1 H).

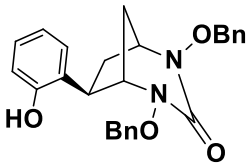
^{13}C NMR (125 MHz, $CDCl_3$): δ 160.9, 144.9, 136.3, 136.2, 132.8, 129.6, 129.4, 128.4, 128.4, 128.3, 127.7, 115.2, 77.7, 77.6, 69.2, 63.1, 46.2, 36.7, 32.1.

HRMS (ESI): *m/z* calcd for $C_{26}H_{28}N_3O_3$: 430.21307; Found: 430.21245.

Compound 18i

Following the general procedure 4A.7.2, compound **18i** (35 mg, 55 %) was synthesised from bicyclic olefin **17a** (50 mg, 0.1486 mmol) and 2-iodophenol **4i** (39 mg, 0.1784 mmol) using

[Pd(allyl)Cl]$_2$ (2 mg, 0.0074 mmol), HCOOH (0.01 mL, 0.2972 mmol) and Et_3N (0.04 mL, 0.2972 mmol) as orange viscous liquid.



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

IR (neat) ν_{max}: 3299, 3034, 2948, 2875, 1675, 1599, 1501, 1454, 1369, 1271, 1215, 1177, 1099, 1025, 991, 915, 883, 828, 749, 699 cm^{-1}.

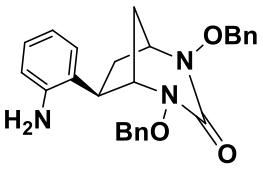
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.43 (m, 4 H), 7.36-7.24 (m, 6 H), 7.09-7.06 (m, 1 H), 6.88-6.83 (m, 2 H), 6.78-6.75 (m, 1 H), 6.51 (brs, 1 H), 5.09-5.07 (m, 1 H), 5.03-5.01 (m, 1 H), 4.94-4.92 (m, 1 H), 4.87-4.85 (m, 1 H), 3.83 (t, *J* = 7.0 Hz, 1 H), 3.72-3.71 (m, 1 H), 3.5 (s, 1 H), 2.64-2.59 (m, 1 H), 2.04-2.01 (m, 1 H), 1.97-1.94 (m, 1 H), 1.79-1.77 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 154.5, 136.0, 135.4, 129.7, 129.6, 128.6, 128.5, 128.4, 128.0, 125.1, 119.9, 116.3, 78.2, 77.8, 68.1, 63.1, 40.4, 34.4, 32.0.

HRMS (ESI): *m/z* calcd for $C_{26}H_{26}N_2NaO_4$: 453.17903; Found: 453.17781.

Compound 18j

Following the general procedure 4A.7.2, compound **18j** (49 mg, 77 %) was synthesised from bicyclic olefin **17a** (50 mg, 0.1486 mmol) and 2-iodoaniline **4j** (39 mg, 0.1784 mmol) using [Pd(allyl)Cl]$_2$ (2 mg, 0.0074 mmol), HCOOH (0.01 mL, 0.2972 mmol) and Et_3N (0.04 mL, 0.2972 mmol) as brown viscous liquid.



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

IR (neat) ν_{max}: 3374, 3031, 2948, 2876, 1710, 1631, 1496, 1454, 1370, 1301, 1258, 1213, 1159, 1107, 1066, 1026, 993, 915, 881, 826, 749, 700 cm^{-1}.

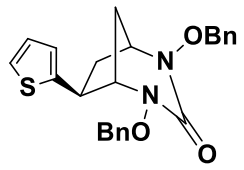
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.43 (m, 4 H), 7.37-7.33 (m, 6 H), 7.01-6.98 (m, 1 H), 6.82 (d, *J* = 7.5 Hz, 1 H), 6.64-6.58 (m, 2 H), 5.12-5.10 (m, 1 H), 5.05-5.02 (m, 1 H), 4.88-4.85 (m, 2 H), 3.75 (t, *J* = 4.0 Hz, 1 H), 3.65-3.62 (m, 1 H), 3.48 (d, *J* = 4.5 Hz, 1 H), 2.60-2.55 (m, 1 H), 2.10-2.03 (m, 2 H), 1.78-1.74 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.3, 144.8, 136.1, 135.6, 129.6, 128.6, 128.5, 128.5, 128.4, 117.6, 115.4, 78.2, 77.7, 67.8, 63.1, 40.9, 33.4, 31.6.

HRMS (ESI): *m/z* calcd for $C_{26}H_{28}N_3O_3$: 430.21307; Found: 430.21177.

Compound 18k

Following the general procedure 4A.7.2, compound **18k** (50 mg, 80 %) was synthesised from bicyclic olefin **17a** (50 mg, 0.1486 mmol) and 2-iodothiophene **4k** (37 mg, 0.1784 mmol) using $[Pd(allyl)Cl]_2$ (2 mg, 0.0074 mmol), HCOOH (0.01 mL, 0.2972 mmol) and Et_3N (0.04 mL, 0.2972 mmol) as orange viscous liquid.



R_f: 0.40 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3032, 2944, 2874, 1712, 1496, 1452, 1371, 1266, 1213, 1158, 1110, 1076, 1025, 992, 918, 883, 846, 826, 748, 699 cm^{-1}.

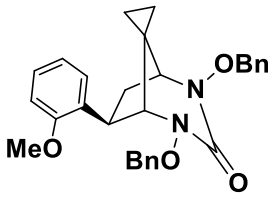
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44-7.43 (m, 4 H), 7.35-7.31 (m, 6 H), 7.07 (d, *J* = 4.5 Hz, 1 H), 6.86-6.84 (m, 1 H), 6.66 (d, *J* = 3.5 Hz, 1 H), 5.05-5.00 (m, 2 H), 4.87-4.84 (m, 2 H), 3.97-3.92 (m, 1 H), 3.68-3.67 (m, 1 H), 3.54 (d, *J* = 4.0 Hz, 1 H), 2.79-2.74 (m, 1 H), 2.05-2.03 (m, 1 H), 1.89-1.78 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 147.2, 136.2, 129.6, 129.4, 128.5, 128.4, 128.4, 126.9, 123.6, 123.5, 77.8, 77.8, 69.6, 62.7, 42.3, 38.6, 31.9.

HRMS (ESI): *m/z* calcd for $C_{24}H_{24}N_2NaO_3S$: 443.14053; Found: 443.13895.

Compound 18l

Following the general procedure 4A.7.2, compound **18l** (45 mg, 70 %) was synthesised from bicyclic olefin **17b** (50 mg, 0.1379 mmol) and 2-iodoanisole **4e** (39 mg, 0.1655 mmol) using $[Pd(allyl)Cl]_2$ (3 mg, 0.0069 mmol), HCOOH (0.01 mL, 0.2758 mmol) and Et_3N (0.04 mL, 0.2758 mmol) as pale yellow viscous liquid.



R_f: 0.63 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3032, 2938, 2875, 1707, 1599, 1492, 1457, 1369, 1290, 1241, 1202, 1162, 1108, 1025, 958, 913, 825, 790, 750, 699 cm^{-1}.

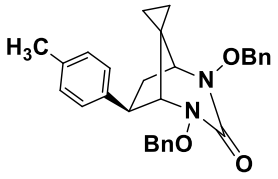
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.43 (m, 2 H), 7.41-7.40 (m, 2 H), 7.36-7.26 (m, 6 H), 7.15-7.12 (m, 1 H), 7.00-6.98 (m, 1 H), 6.83-6.78 (m, 2 H), 5.07-5.03 (m, 2 H), 4.89-4.85 (m, 2 H), 4.23 (dd, J_1 = 9.0 Hz, J_2 = 6.0 Hz, 1 H), 3.73 (s, 3 H), 2.81-2.80 (m, 1 H), 2.79-2.78 (m, 1 H), 2.75 (dd, J_1 = 13.5 Hz, J_2 = 9.0 Hz, 1 H), 2.03-1.98 (m, 1 H), 0.55-0.52 (m, 2 H), 0.50-0.47 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 157.0, 136.4, 136.4, 131.2, 129.8, 129.4, 128.4, 128.2, 128.2, 128.1, 127.4, 126.4, 119.9, 110.3, 77.7, 77.5, 72.7, 69.4, 55.1, 41.7, 36.2, 27.3, 11.7, 4.8.

HRMS (ESI): *m/z* calcd for $C_{29}H_{31}N_2O_4$: 471.22838; Found: 471.22858.

Compound 18m

Following the general procedure 4A.7.2, compound **18m** (48 mg, 77 %) was synthesised from bicyclic olefin **17b** (50 mg, 0.1379 mmol) and 4-iodotoluene **4a** (36 mg, 0.1655 mmol) using $[Pd(allyl)Cl]_2$ (3 mg, 0.0069 mmol), HCOOH (0.01 mL, 0.2758 mmol) and Et_3N (0.04 mL, 0.2758 mmol) as pale yellow viscous liquid.



R_f: 0.71 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3030, 2938, 2872, 1710, 1513, 1453, 1368, 1234, 1201, 1160, 1107, 1017, 959, 912, 837, 814, 780, 747, 699 cm^{-1}.

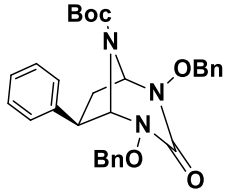
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44-7.42 (m, 2 H), 7.40-7.37 (m, 2 H), 7.36-7.25 (m, 6 H), 7.04-7.01 (m, 4 H), 5.04-5.01 (m, 2 H), 4.87-4.84 (m, 2 H), 3.77 (dd, J_1 = 9.0 Hz, J_2 = 6.5 Hz, 1 H), 2.81 (dd, J_1 = 4.0 Hz, J_2 = 1.5 Hz, 1 H), 2.72 (dd, J_1 = 14.0 Hz, J_2 = 9.0 Hz, 1 H), 2.6 (d, J = 1.5 Hz, 1 H), 2.28 (s, 3 H), 2.10-2.05 (m, 1 H), 2.03-1.98 (m, 1 H), 0.58-0.42 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4, 139.9, 136.4, 136.2, 135.9, 129.8, 129.6, 129.1, 128.4, 128.3, 128.2, 128.2, 127.4, 77.7, 77.6, 74.6, 69.6, 48.0, 37.0, 27.0, 20.9, 11.5, 4.8.

HRMS (ESI): *m/z* calcd for $C_{29}H_{31}N_2O_3$: 455.23347; Found: 455.23373.

Compound 18n

Following the general procedure 4A.7.2, compound **18n** (38 mg, 64 %) was synthesised from bicyclic olefin **17b** (50 mg, 0.1143 mmol) and iodobenzene **4b** (28 mg, 0.1372 mmol) using $[Pd(allyl)Cl]_2$ (2 mg, 0.0057 mmol), HCOOH (0.01 mL, 0.2286 mmol) and Et_3N (0.03 mL, 0.2286 mmol) as reddish brown viscous liquid.



R_f: 0.46 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3033, 2878, 1722, 1648, 1495, 1454, 1369, 1334, 1252, 1160, 1112, 1009, 945, 916, 854, 788, 750 cm^{-1}.

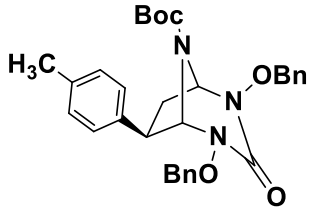
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46-7.45 (m, 2 H), 7.41-7.39 (m, 2 H), 7.37-7.27 (m, 8 H), 7.23-7.20 (m, 1 H), 7.15-7.13 (m, 2 H), 5.32 (brs, 1 H), 5.07-5.01 (m, 3 H), 4.88-4.83 (m, 2 H), 3.76-3.73 (m, 1 H), 2.88-2.84 (m, 1 H), 2.08-2.03 (m, 1 H), 1.48 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.7, 152.8, 128.9, 128.5, 128.4, 128.4, 127.2, 126.8, 82.1, 78.0, 77.8, 38.8, 28.2.

HRMS (ESI): *m/z* calcd for $C_{30}H_{33}N_3NaO_5$: 538.23179; Found: 538.23067.

Compound 18o

Following the general procedure 4A.7.2, compound **18o** (50 mg, 82 %) was synthesised from bicyclic olefin **17b** (50 mg, 0.1143 mmol) and 4-iodotoluene **4a** (30 mg, 0.1372 mmol) using $[Pd(allyl)Cl]_2$ (2 mg, 0.0057 mmol), HCOOH (0.01 mL, 0.2286 mmol) and Et_3N (0.03 mL, 0.2286 mmol) as brownish viscous liquid.



R_f: 0.74 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3031, 2976, 2931, 1704, 1453, 1368, 1284, 1255, 1214, 1162, 1077, 1012, 974, 912, 849, 745, 699 cm^{-1}.

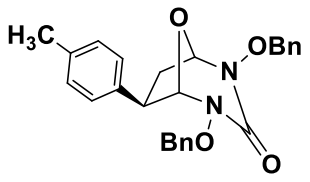
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46-7.44 (m, 2 H), 7.40-7.39 (m, 2 H), 7.37-7.29 (m, 6 H), 7.09-7.08 (m, 2 H), 7.04-7.02 (m, 2 H), 5.32 (brs, 1 H), 5.06-5.00 (m, 3 H), 4.88-4.82 (m, 2 H), 3.71 (dd, J_1 = 8.5 Hz, J_2 = 5.0 Hz, 1 H), 2.87-2.82 (m, 1 H), 2.31 (s, 3 H), 2.06 (brs, 1 H), 1.48 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8, 152.8, 137.2, 136.7, 135.0, 129.5, 128.5, 128.4, 128.4, 126.7, 82.0, 78.0, 77.8, 38.8, 28.2, 21.0.

HRMS (ESI): *m/z* calcd for $C_{31}H_{36}N_3O_5$: 530.26550; Found: 530.26672.

Compound 18p

Following the general procedure 4A.7.2, compound **18p** (38 mg, 60 %) was synthesised from bicyclic olefin **17d** (50 mg, 0.1478 mmol) and 4-iodotoluene **4a** (39 mg, 0.1774 mmol) using $[Pd(allyl)Cl]_2$ (3 mg, 0.0074 mmol), HCOOH (0.01 mL, 0.2956 mmol) and Et_3N (0.04 mL, 0.2956 mmol) as dark brownish viscous liquid.



R_f: 0.71 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3031, 2944, 2877, 1711, 1514, 1453, 1370, 1320, 1210, 1116, 1083, 1039, 1007, 918, 842, 820, 782, 741, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46-7.44 (m, 2 H), 7.39-7.34 (m, 5 H), 7.33-7.30 (m, 3 H), 7.04-7.03 (m, 2 H), 6.90-6.88 (m, 2 H), 5.12 (d, J = 5.5 Hz, 1 H), 5.06-5.04 (m, 2 H), 4.97-4.91 (m, 2 H), 4.86 (s, 1 H), 3.51 (dd, J_1 = 9.0 Hz, J_2 = 5.0 Hz, 1 H), 2.63 (dd, J_1 = 14.0 Hz, J_2 = 9.0 Hz, 1 H), 2.29 (s, 3 H), 1.88-1.83 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 139.1, 136.6, 135.8, 135.7, 129.7, 129.5, 129.4, 128.7, 128.6, 128.5, 128.5, 126.7, 96.7, 92.1, 78.5, 78.4, 47.8, 39.8, 21.0.

HRMS (ESI): *m/z* calcd for $C_{26}H_{27}N_2O_4$: 431.19708; Found: 431.19684.

4A.8. References

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CHAPTER 4

Hydro(hetero)arylation & Annulation Reactions

PART B

Palladium Catalyzed Annulation of Urea Derived Bicyclic Olefins Using Bi-functional Aryl Iodides

4B.1. Introduction

Ever since the discovery of palladium catalyzed Mizoroki-Heck reactions in 1971, a privileged space is occupied by them among the various transition metal catalyzed transformations.[1,2] The transition metal catalyzed reactions using aryl iodides resulted in the arylation reactions as discussed in the previous chapter. However, the use of reactive substrates that can trap the palladium species intramolecularly results in a cascade reaction and forms annulated products. The use of 2-iodophenols, 2-iodoanilines, 2-iodobenzylbromides, 2-iodobenzonitriles, 2-iodobenzyl alcohols, 2-iodophenyl malonates, 2-iodobenzoic acids, and 2-iodobenzamides *etc*. are deeply explored in the literature, which is discussed in the following sections.

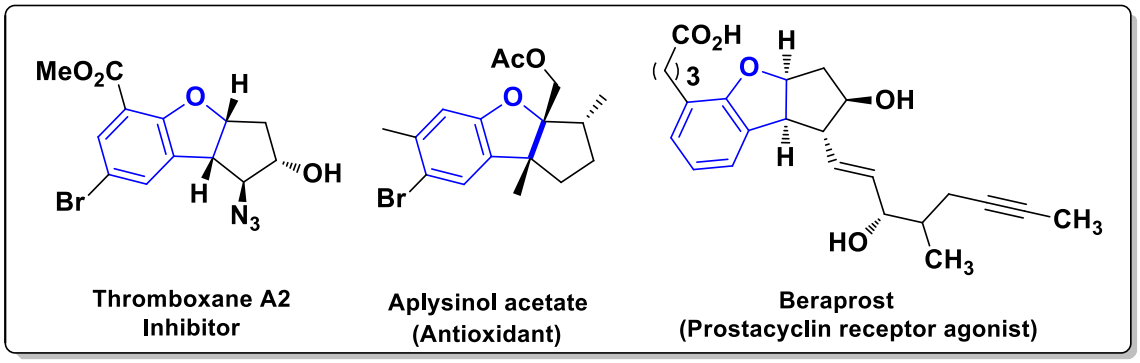
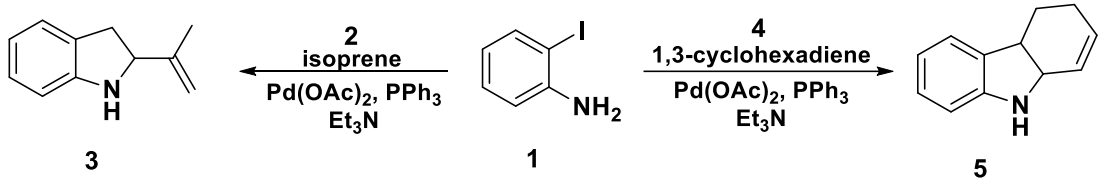


Figure 4B.1. Some biologically important benzofuran molecules

The use of 2-iodophenol in Heck reaction proceed *via* a cascade reaction to furnish benzofuran derivatives. Benzofurans, a class of important heterocyclics, are contained in the cores of a number of natural products and pharmaceuticals which exhibit many biological activities such as anti-inflammatory, anti-arrhythmic, haemostatic, anti-bacterial, fungicidal, anti-viral, anti-tumor, and anti-oxidant activities (Figure 4B.1).[3–13]

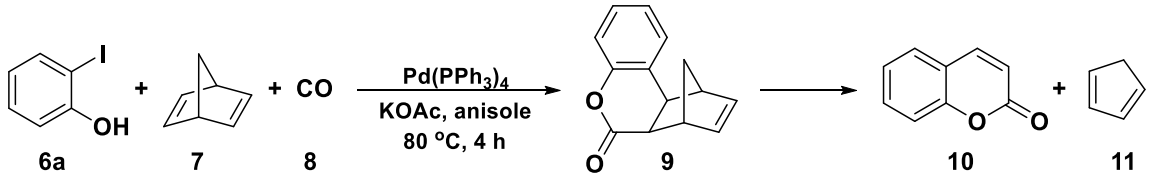
4B.2. Pioneering Reports on Palladium Catalyzed Annulation Reactions

Early 1980's marked the beginning of an era where in Dieck and coworkers were successful in extending the Heck reaction to the synthesis of heterocycles using *bi*-functional aryl iodides. They exemplified the potential of using these transformations in the construction of heterocyclic compounds by the reactions of *o*-iodoaniline **1** with isoprene **2** to yield dihydroindoles **3** in 72 % and with 1,3-cyclohexadiene **4** to yield tetrahydrocarbazoles **5** and 70 % yield, respectively (Scheme 4B.1).[14]



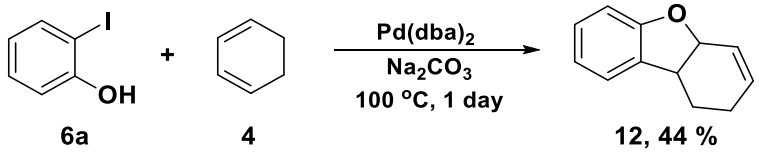
Scheme 4B.1

The utilization of carbon monoxide **8** in the synthesis of coumarin **10** involving ring formation from *o*-iodophenol **6a** and norbomadiene **7** followed by retro-Diels-Alder reaction to eliminate cyclopentadiene **11** was explored by Catellani *et al.* in 1989 (Scheme 4B.2).[15]

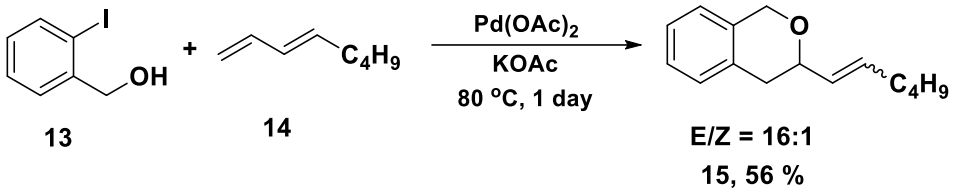


Scheme 4B.2

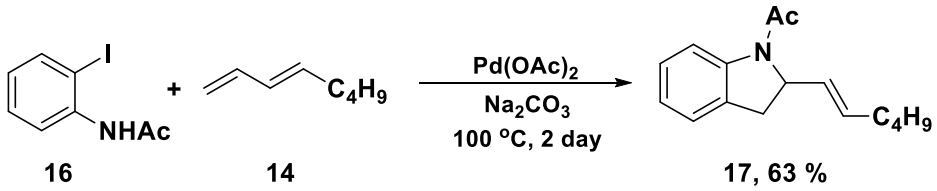
Later in 1990, Larock *et al*. extended this strategy to a number of different aryl iodides to synthesise dihydrobenzofuran derivatives **12** using 2-iodophenol **6a**, benzopyran derivatives **15** using 2-iodobenzyl alcohol **13**, indoline derivatives **17** using *N*-(2-iodophenyl)acetamide **16** and so on (Scheme 4B.3a-c).[16]



Scheme 4B.3a

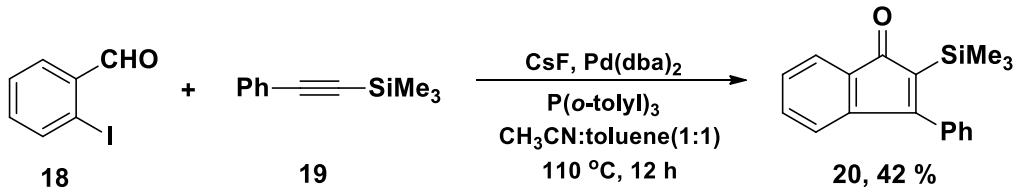


Scheme 4B.3b



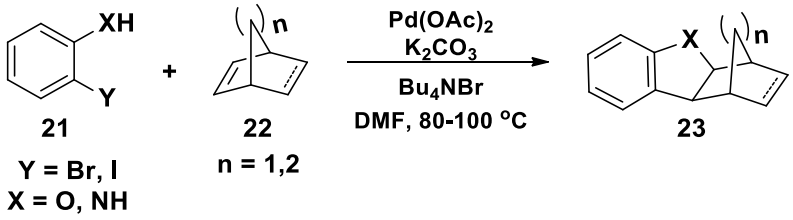
Scheme 4B.3c

Larock *et al.* explored an effective way to prepare a number of interesting indenones **20** by treating internal alkynes **19** with 2-iodo or 2-bromo benzaldehyde **18** in the presence of a palladium-catalyst (Scheme 4B.4).[17]



Scheme 4B.4

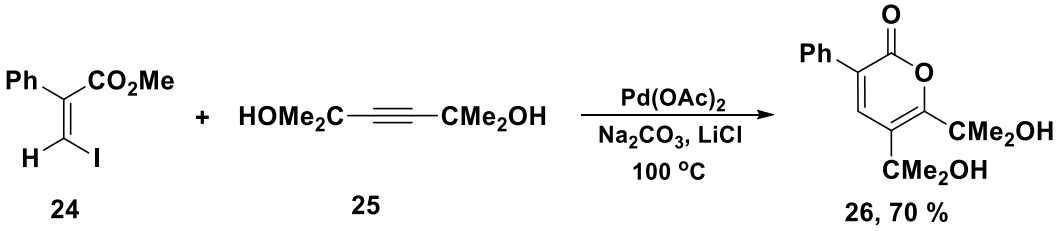
After elucidating the carbonylation reaction of norbornenes, Catellani and coworkers developed the heteroannulation reaction of norbornenes **22** *via* the palladium catalyzed coupling with *o*-iodophenol and *o*-iodoaniline (Scheme 4B.5).[18] This reaction with strained or rigid olefins proceeded under mild conditions in the absence of phosphine ligands and afforded fused dihydrofurans or pyrroles **23**.



Scheme 4B.5

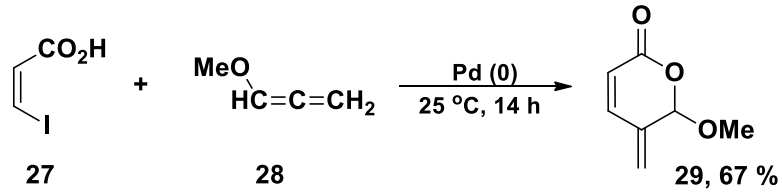
The synthesis of α-pyrones **26** *via* palladium catalysed annulation was reported by Larock *et al.*[19] The methodology provided a simple, convenient, and regioselective route to a number of 3,5,6-tri- and 3,4,5,6-tetrasubstituted α-pyrones containing aryl, silyl, *tert*-alkyl

and other hindered groups (Scheme 4B.6).

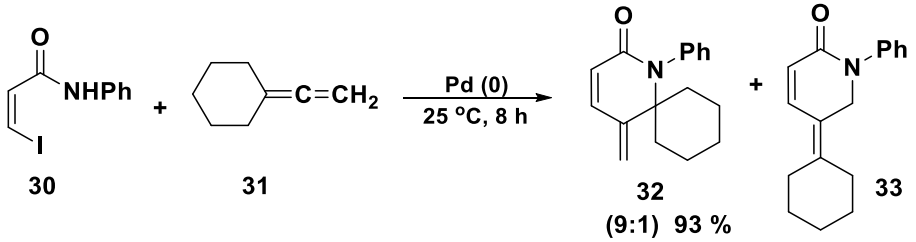


Scheme 4B.6

They also elucidated that the introduction of carbonyl functionality directly on the carbon-carbon double bond of the vinylic halide bearing functional groups such as alcohols, amines, sulfonamides, and even carboxylic acids **27** and amides **30** undergo annulation reaction (Scheme 4B.7a & Scheme 4B.7b).[20]

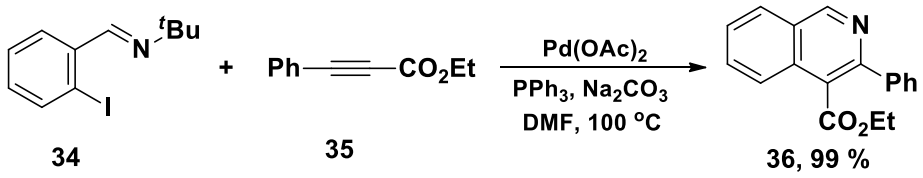


Scheme 4B.7a



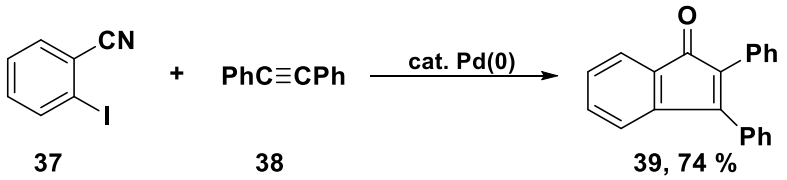
Scheme 4B.7b

The same group also discovered that the palladium-catalyzed iminoannulation of internal alkynes **35** by the *t*-butylimines **34** readily afforded isoquinolines **36**. The reaction of the *tert*-butylimines with 2 equiv. of an alkyne in the presence of 5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, and 1 equiv. of Na_2CO_3 in DMF as the solvent at 100 °C afforded the desired heterocyclic products in good to excellent yields in short reaction times (Scheme 4B.8).[21]



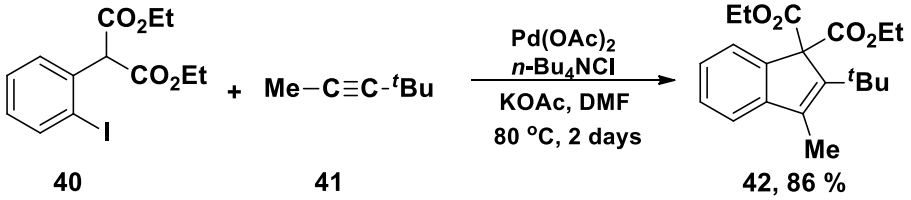
Scheme 4B.8

Organopalladium intermediates undergo various intramolecular reactions with functional groups that normally will not undergo if the reaction were intermolecular. The use of palladium salts with nitrile ligands in acetonitrile as solvent yields novel annulation products. The ketone products are presumably formed by the hydrolysis of resulting imines (Scheme 4B.9).[22]



Scheme 4B.9

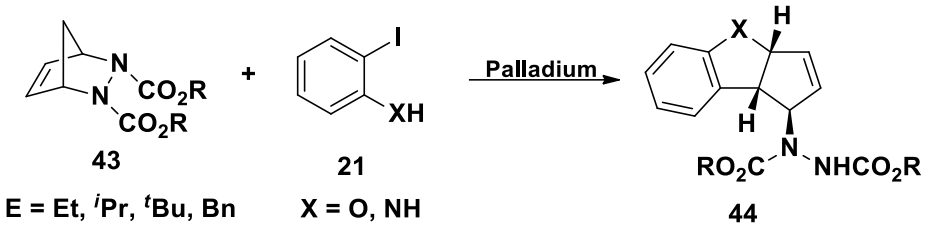
The synthesis of highly substituted indenes **42** which involves the palladium-catalyzed carboannulation of internal alkynes **41** was achieved by Larock *et al*. by three different transition metal-mediated methods (Scheme 4B.10). The first method is the palladium-catalyzed carboannulation of internal alkynes. A two-step approach is utilized in the second method which involves first the palladium/copper-catalyzed cross coupling of terminal alkynes with appropriately functionalized aryl halides, followed by copper-catalyzed intramolecular cyclization. The third method involves intermolecular palladium-catalyzed arylation of the arylalkynes formed in the first step of the second method. [23]



Scheme 4B.10

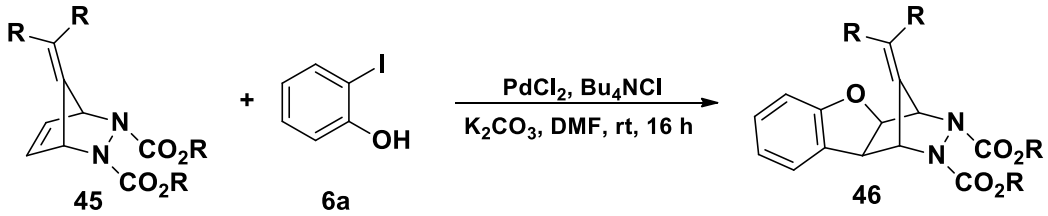
4B.3. Background to the Present Work

Diazabicyclic olefins, as discussed in Chapter 1, are versatile synthons for a variety of heterocycles of considerable biological potential. Our group reported the palladium catalyzed tandem ring opening and ring closing reaction of diazabicyclic olefins **43** with *o*-iodophenol and *o*-iodoaniline **21** that afforded cyclopentene fused benzofuran and indoles **44** (Scheme 4B.11).[24]



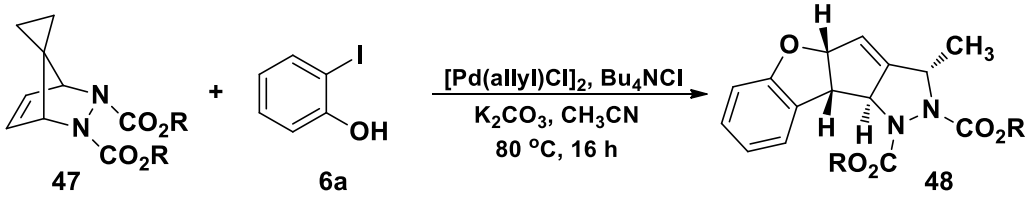
Scheme 4B.11

This reaction was shown to be general with the fulvene derived bicyclic olefins **45** even though the ring opened product was not observed in the reaction (Scheme 4B.12).[25]



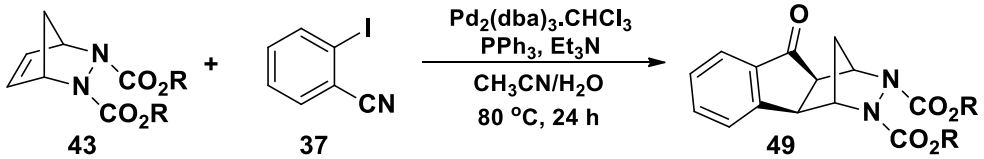
Scheme 4B.12

The extension of this strategy to spirotricyclic olefins **47** resulted in palladium-catalyzed skeletal rearrangement to synthesize novel motifs with cyclopentene fused to benzofuran and pyrazolidine **48** (Scheme 4B.13). The developed one-pot catalytic tandem reaction for the construction of tetracyclic skeletons was the first report on utilizing a cyclopropane bearing spirotricyclic olefin in palladium-catalyzed organic transformations wherein complexity is generated from two simple achiral molecules.[26]



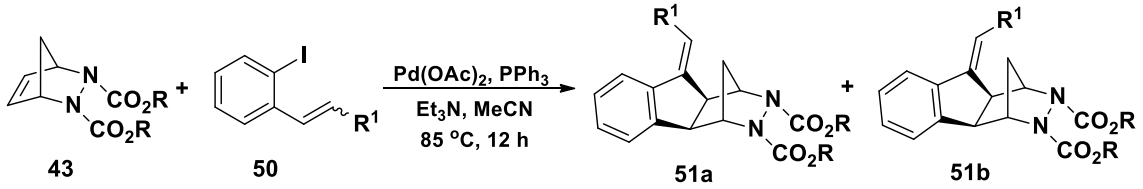
Scheme 4B.13

We also illustrated the preparation of functionalized indanones **49** by the palladium-catalyzed carboannulation of bicyclic hydrazines **43** with 2-iodobenzonitrile **37** (Scheme 4B.14).[27]



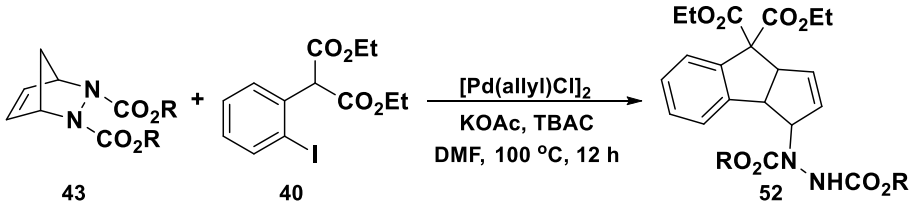
Scheme 4B.14

We had unravelled the coupling of various 2-iodostyrenes **50** with diazabicyclic olefins **43** which afforded functionalized indanes as two separable isomers **51a** and **51b** (Scheme 4B.15). The palladium-catalyzed carboannulation proceeded smoothly with tricyclic and spirotricyclic olefins and a variety of functional groups such as ester, ketone and nitrile, as substituents on the iodostyrenes were well tolerated.[28]



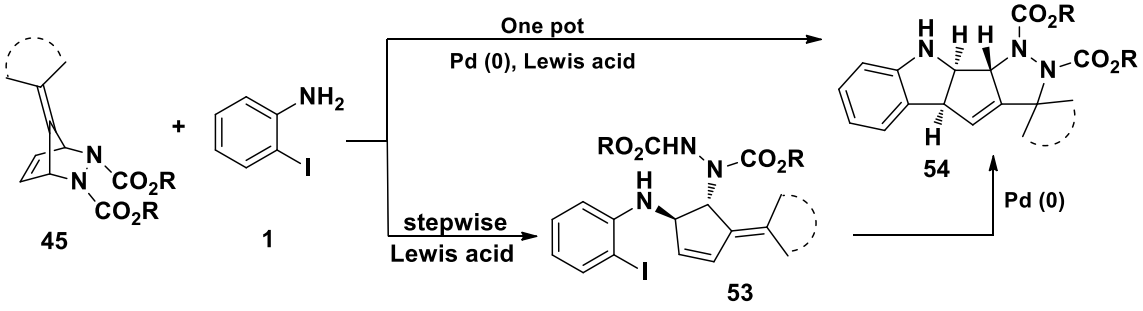
Scheme 4B.15

An efficient carboannulation reaction with diazabicyclic olefin **43** and diethyl(2-iodophenyl)malonate **40** for the synthesis of cyclopentene fused indanes **52** was developed by our group (Scheme 4B.16). The presence of indane ring systems as important structural motifs in many drug molecules such as Gnetuhainin E and Mirabiloside C makes this one pot strategy very significant.



Scheme 4B.16

The palladium/Lewis acid mediated stepwise and one-pot transformation of pentafulvene derived diazabicyclic olefins **45** offers a facile strategy for the synthesis of novel spiropentacyclic motifs with indoline and pyrazolidine fused to the cyclopentene core **54** (Scheme 4B.17).[29,30]



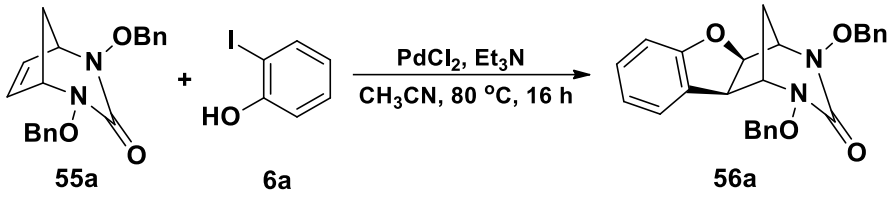
Scheme 4B.17

The Lewis acid catalyzed transformation *via* the nucleophilic attack of amine group furnished *trans*-3,4-disubstituted alkylidenecyclopentene **53** which was subsequently cyclised *via* Heck reaction to afford spiropentacyclic motifs **54**.

As part of our continued interest in the development of novel heterocycles and carbocycles utilizing the steric strain in urea derived bicycles, we have carried out the investigations on the reactivity of bi-functional aryl iodides with the urea derived bicyclic olefins. To the best of our knowledge, this is the first report on the palladium catalyzed heteroannulation of urea derived bicyclic olefins.

4B.4. Results and Discussion

After establishing a synthetic route towards the hydroarylated bicycles, the presence of *o*-hydroxyl and *o*-amino groups in products (Chapter 4, Part A, Table 4A.2, entry 9 & 10) encouraged us to check their reactivity in the absence of a hydrogen donor. As expected, the initial reaction conditions with 2-iodophenol **6a** and bicyclic olefin **55a** afforded the dihydrobenzofuran derivative **56a** in 20 % yield (Scheme 4B.18).



Scheme 4B.18

The structure of the product was confirmed *via* various spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR and HRMS (ESI) analysis. The IR spectrum of **56a** showed characteristic carbonyl absorption of the urea at 1718 cm^{-1}. In the ^{1}H NMR, the aromatic benzylic protons resonated in the region 7.50-7.34 ppm (Figure 4B.2). The aromatic protons of benzofuran were discernible as triplets and doublets at 7.07-6.63 ppm. The proton attached to carbon bearing oxygen atom was seen at 5.22 ppm. The multiplets in the region δ 5.10-5.04 and δ 4.92-4.89 ppm were assigned to the methylene protons of the benzyloxy groups. Proton attached to carbon bearing phenyl group of the benzofuran was discernible as a doublet at 4.15 ppm. The proton on each carbon attached to nitrogen atom of the urea group appeared as doublet at δ 3.71 and δ 3.43 ppm. The bridge protons resonated as a multiplet in the region δ 1.94-1.92 and δ 1.67-1.61 ppm.

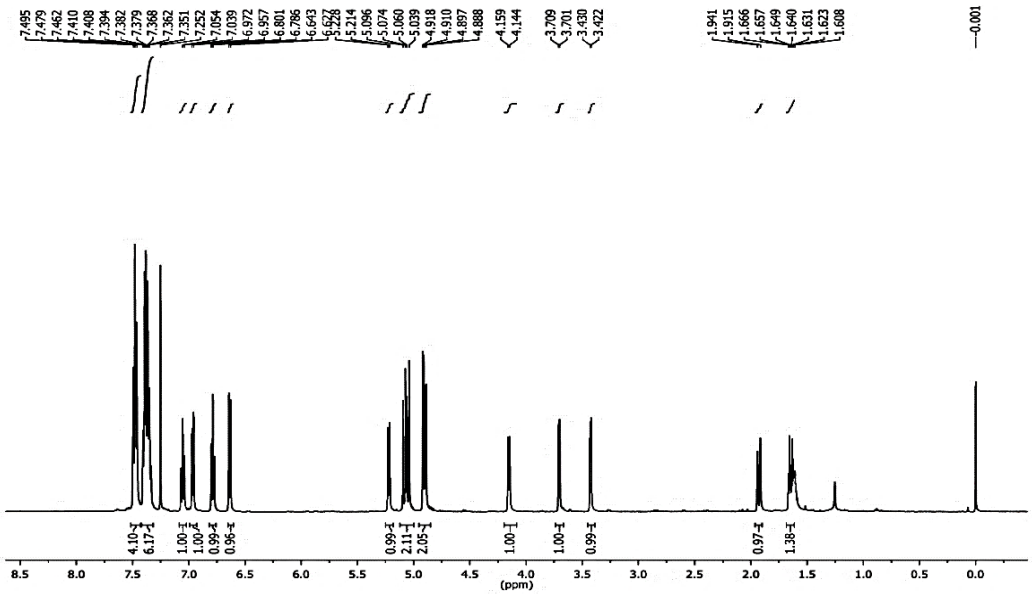


Figure 4B.2. ^{1}H NMR spectrum of compound **56a**

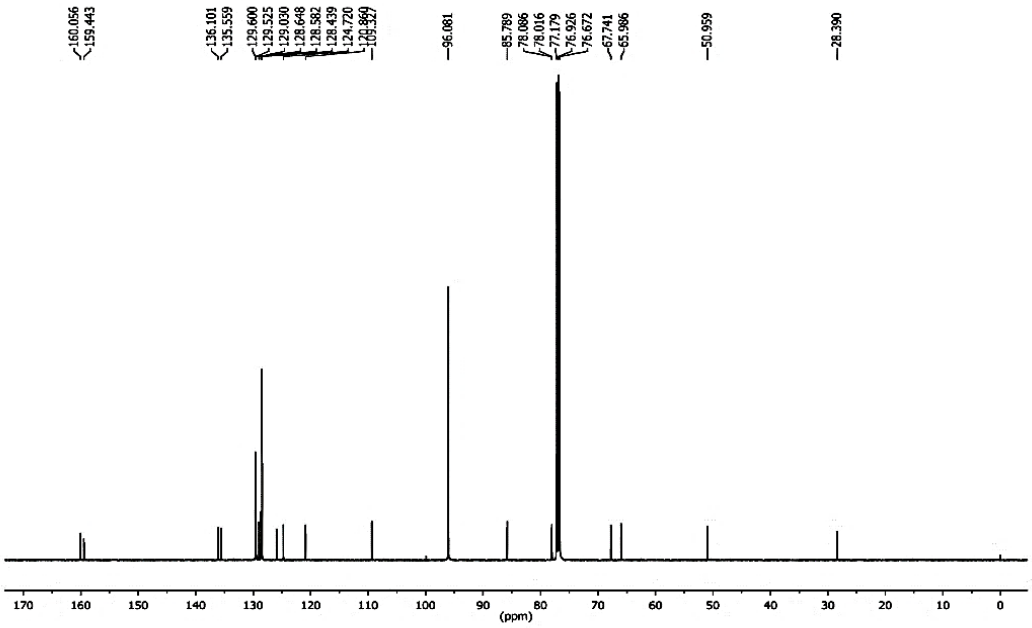


Figure 4B.3. ^{13}C NMR spectrum of compound **56a**

^{13}C NMR of **56a** displayed the carbonyl peak of the urea at δ 160.1 ppm (Figure 4B.3). The peak at δ 85.8 ppm was assigned to the carbon attached to the oxygen atom of the dihydrobenzofuran. The methylene carbons of the benzyloxy groups were identified at δ 78.1 and 78.0 ppm. Each carbon bearing the nitrogen atom resonated at δ 67.7 and 66.0 ppm. The

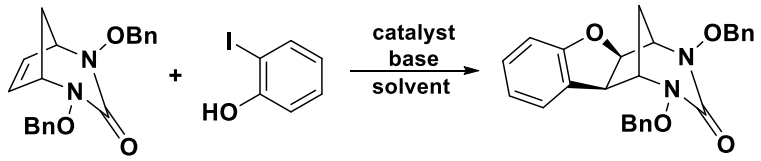
carbon bearing the phenyl group of dihydrobenzofuran appeared at δ 51.0 ppm. The methylene carbons resonated at δ 28.4 ppm.

Further confirmation was obtained from HRMS-ESI analysis that showed $[M+Na]^+$ peak at 451.16376.

4B.4.1. Optimization Studies

After confirming the structure of the product *via* various spectroscopic techniques, we performed detailed studies to optimize the reaction conditions (Table 4B.1). The reaction was optimal with K_2CO_3 as the base. Among the various palladium catalysts screened, $PdCl_2$ proved to be the best for this transformation. Finally, the best reaction conditions were found to be 5 mol% of $PdCl_2$ as the catalyst, 2 equiv. of K_2CO_3 as the base in CH_3CN solvent at 80 ^oC for 8 h, which gave 70 % yield (Table 4B.1, entry 5). It is worth mentioning that adding 1 equiv. of Bu_4NCl as the additive reduced the yield of the reaction to 60 % (Table 4B.1, entry 15).

Table 4B.1. Optimization studies for heteroannulation reaction[a]



Entry	Catalyst	Base	Solvent	Yield (%) [b]
1	$PdCl_2$	Et_3N	CH_3CN	20
2	$PdCl_2$	NaOAc	CH_3CN	55
3	$PdCl_2$	KOAc	CH_3CN	34
4	$PdCl_2$	KO^tBu	CH_3CN	nr
5	**$PdCl_2$**	**K_2CO_3**	**CH_3CN**	**70**
6	$PdCl_2$	Cs_2CO_3	CH_3CN	15
7	$Pd_2(dba)_3.CHCl_3$	K_2CO_3	CH_3CN	trace
8	$Pd(OAc)_2$	K_2CO_3	CH_3CN	40
9	$Pd(PPh_3)_2Cl_2$	K_2CO_3	CH_3CN	trace
10	$[Pd(allyl)Cl]_2$	K_2CO_3	CH_3CN	25
11	$Pd(PPh_3)_4$	K_2CO_3	CH_3CN	trace

Continued..

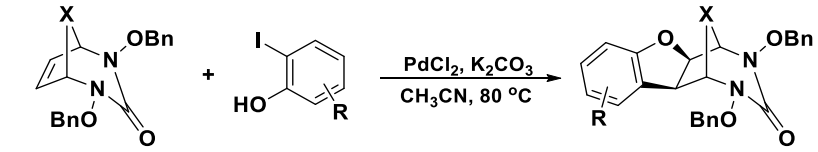
12	$PdCl_2$	K_2CO_3	Toluene	trace
13	$PdCl_2$	K_2CO_3	DMF	30
14	$PdCl_2$	K_2CO_3	DCE	trace
15	$PdCl_2$	K_2CO_3	CH_3CN	60[c]

[a]**Reaction conditions:** adduct (1 equiv.), 2-iodophenol (1.2 equiv.), catalyst (5 mol%), base (2 equiv.), solvent (2 mL), 12 h. [b]Isolated yield. [c]In presence of 1 equiv. Bu_4NCl as additive.

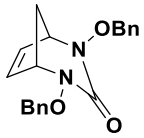
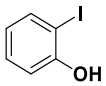
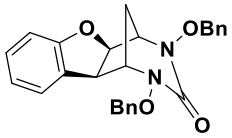
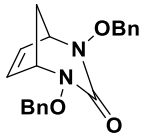
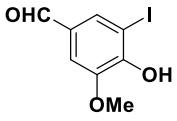
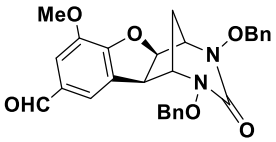
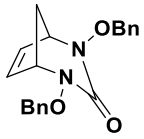
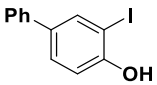
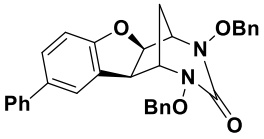
4B.4.2. Scope of the Reaction

The generality of this reaction was demonstrated using different substituted *o*-iodophenols. Iodophenols bearing electron donating groups such as methoxy group and electron withdrawing groups such as -COOMe reacted smoothly to furnish the corresponding benzofuran derivatives in moderate to good yields (Table 4B.2). The scope of the reaction was also tested with adducts derived from furan and Boc-protected pyrrole.

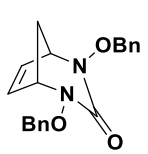
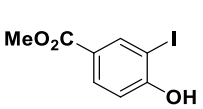
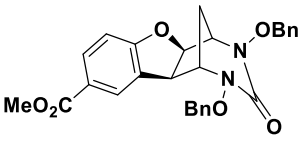
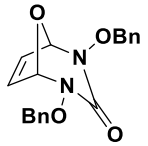
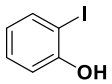
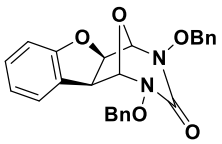
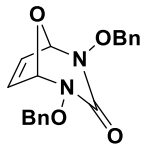
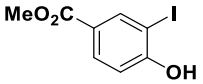
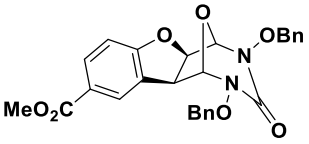
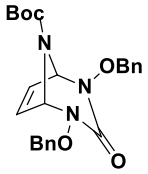
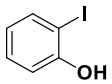
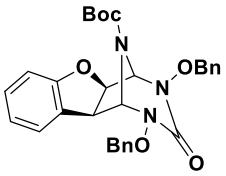
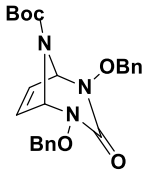
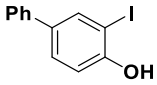
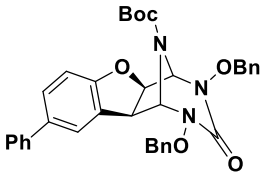
Table 4B.2. Heteroannulation of urea derived bicyclic olefins[a]



X = CH_2, O, NBoc

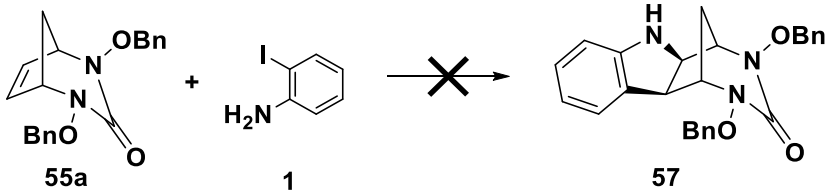
Entry	Bicyclic Olefin	Iodopehnols	Product	Yield (%)[b]
1	 **55a**	 **6a**	 **56a**	70
2	 **55a**	 **6b**	 **56b**	48
3	 **55a**	 **6c**	 **56c**	61

Continued..

4	 **55a**	 **6d**	 **56d**	57
5	 **55b**	 **6a**	 **56e**	55
6	 **55b**	 **6d**	 **56f**	45
7	 **55c**	 **6a**	 **56g**	63
8	 **55c**	 **6c**	 **56h**	60

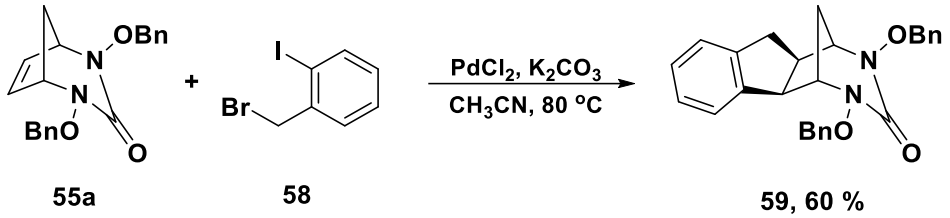
[a]Reaction conditions: adduct (1 equiv.), 2-iodophenol (1.2 equiv.), $PdCl_2$ (5 mol%), K_2CO_3 (2 equiv.), CH_3CN (2 mL), 80 ^oC, 12 h. [b]Isolated yield.

Next, we examined the scope of 2-iodo aniline with urea derived bicyclic olefins. To our dismay, the reaction didn't proceed as expected to furnish the indoline fused bicyclic urea derivative **57** (Scheme 4B.19).



Scheme 4B.19. Reaction with 2-iodoaniline

Finally, to check the scope of other bi-functional aryl iodides, we performed the reaction of urea derived bicyclic adduct **55a** with 2-iodobenzyl bromide **58**. Interestingly, the reaction proceeded well to furnish the indane fused bicycle **59** in 60 % yield (Scheme 4B.20).

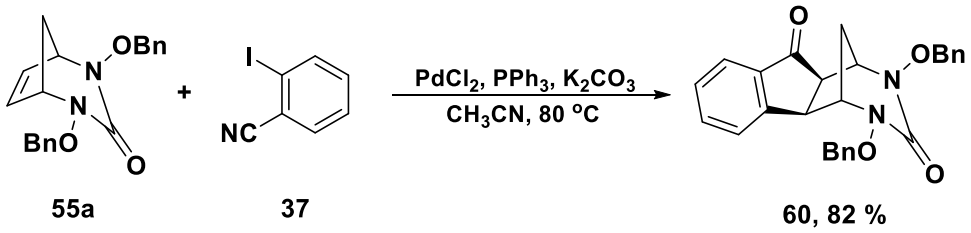


55a **58** **59, 60 %**

Scheme 4B.20. Reaction with 2-iodobenzyl bromide

Reaction conditions: adduct (1 equiv.), iodobenzyl bromide (1.2 equiv.), $PdCl_2$ (5 mol%), K_2CO_3 (2 equiv.), CH_3CN (2 mL), 80 ^oC, 12 h.

We also checked the reactivity of 2-iodobenzonitrile **37** with bicyclic olefin **55a** and were delighted to observe the indanone derivative **60** in 82 % yield using PPh_3 as the ligand (Scheme 4B.21).



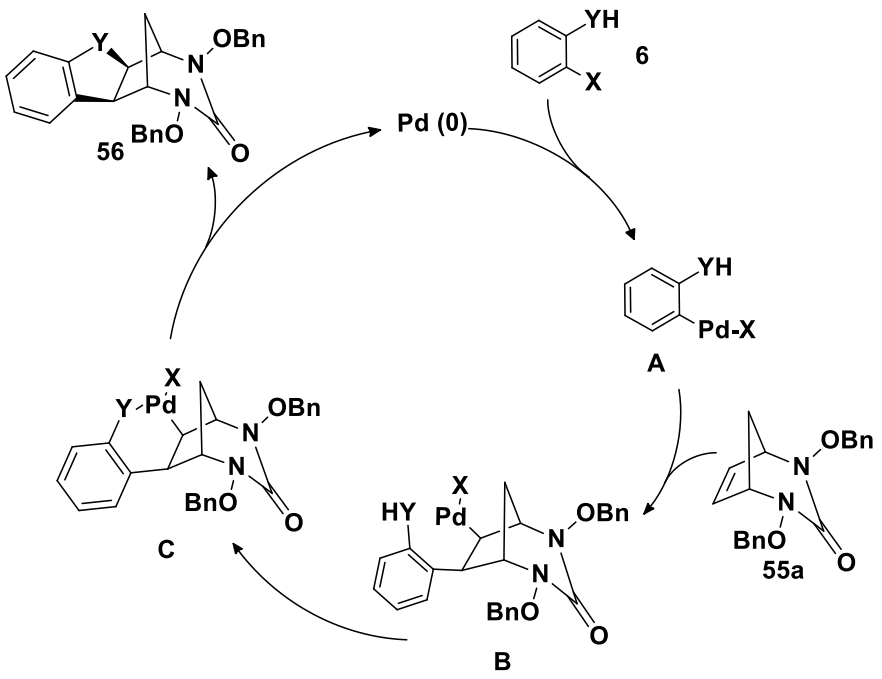
55a **37** **60, 82 %**

Scheme 4B.21. Reaction with 2-iodobenzonitrile

Reaction conditions: adduct (1 equiv.), iodobenzonitrile (1.2 equiv.), $PdCl_2$ (5 mol%), PPh_3 (10 mol%), K_2CO_3 (2 equiv.), CH_3CN (2 mL), 80 ^oC, 12 h.

4B.5. Plausible Mechanism

A plausible mechanism for this reaction is proposed in Scheme 4B.22 in accordance with the previous reports.[31] The reactive palladium (0) undergoes oxidative addition to the aryl-halogen bond (Ar-X) to form [ArPdX] species **A**, and the *syn*-addition of [ArPdX] species to the bicyclic olefin **55a** results in the formation of **B**. Subsequently, the functional group Y coordinates to palladium and forms the intermediate **C**. Intermediate **C** undergoes reductive elimination to give the heteroannulated product **56** and the active palladium species is regenerated in reaction medium.



Scheme 4B.22. Plausible mechanistic pathway

4B.6. Conclusion

In conclusion, we have developed an efficient strategy for the palladium-catalyzed annulation of urea-derived bicyclic olefins. 2-Iodophenols, 2-iodobenzonitrile and 2-iodobenzyl bromide were effective in generating the annulated products such as benzofuran, indanone and indane derivatives. The biological significance of the urea derivatives substantiates the current strategy.

4B.7. Experimental Section

4B.7.1. General Methods

General information about the experiments is given in Section 2.8.1 of Chapter 2.

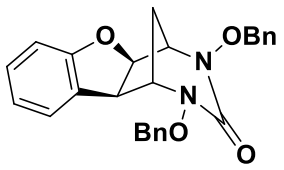
4B.7.2. General Procedure for the Annulation Reaction

Bicyclic olefin **55** (1 equiv.), *bi*-functional aryliodide **6** (1.2 equiv.), $PdCl_2$ (5 mol%) and K_2CO_3 (2 equiv.) were weighed into a Schlenk tube (10 mol% of PPh_3 was also added for **60**). The tube was closed with a rubber septa and was purged with argon using vacuum/fill cycles for 10 minutes. To this, CH_3CN (2 mL) was added, and the reaction mixture was purged with argon, and allowed to stir at 80 ^oC for 12 hours. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (silica gel 100-200 mesh) using hexane-ethylacetate mixtures to yield the desired annulated product.

4B.7.3. Characterization of the Products

Compound 56a

Following the general procedure 4B.7.2, compound **56a** (45 mg, 70 %) was synthesised from bicyclic olefin **55a** (50 mg, 0.1486 mmol) and 2-iodophenol **6a** (39 mg, 0.1784 mmol) using $PdCl_2$ (1 mg, 0.0074 mmol), and K_2CO_3 (41 mg, 0.2972 mmol) as brown viscous liquid.



R_f: 0.57 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3061, 3032, 2954, 2877, 1718, 1595, 1479, 1459, 1370, 1320, 1278, 1245, 1206, 1180, 1154, 1102, 1082, 995, 921, 862, 826, 751, 700 cm^{-1}.

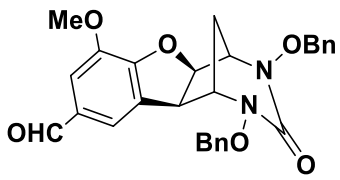
^{1}H NMR (500 MHz, $CDCl_3$): δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.46 (m, 4 H), 7.41-7.34 (m, 6 H), 7.05 (t, *J* = 7.5 Hz, 1 H), 6.96 (d, *J* = 7.5 Hz, 1 H), 6.79 (t, *J* = 7.5 Hz, 1 H), 6.63 (d, *J* = 8.0 Hz, 1 H), 5.22 (d, *J* = 7.0 Hz, 1 H), 5.10-5.04 (m, 2 H), 4.92-4.89 (m, 2 H), 4.15 (d, *J* = 7.5 Hz, 1 H), 3.71 (d, *J* = 4.0 Hz, 1 H), 3.43 (d, *J* = 4.0 Hz, 1 H), 1.93 (d, *J* = 13.0 Hz, 1 H), 1.67-1.61 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 159.4, 136.1, 135.6, 129.6, 129.5, 129.0, 128.7, 128.6, 128.4, 125.9, 124.7, 120.9, 109.3, 85.8, 78.1, 78.0, 67.7, 66.0, 51.0, 28.4.

HRMS (ESI): *m/z* calcd for $C_{26}H_{24}O_4N_2Na$: 451.16338; Found: 451.16376.

Compound 56b

Following the general procedure 4B.7.2, compound **56b** (35 mg, 48 %) was synthesised from bicyclic olefin **55a** (50 mg, 0.1486 mmol) and 5-iodovanillin **6b** (50 mg, 0.1784 mmol) using $PdCl_2$ (1 mg, 0.0074 mmol), and K_2CO_3 (41 mg, 0.2972 mmol) as reddish brown viscous liquid.



R_f: 0.26 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3062, 3032, 2942, 2877, 1710, 1687, 1611, 1591, 1493, 1454, 1371, 1323, 1296, 1257, 1135, 1097, 1026, 979, 923, 867, 826, 752, 700 cm^{-1}.

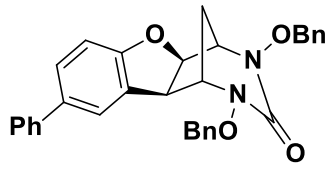
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.75 (s, 1 H), 7.50-7.49 (m, 2 H), 7.45-7.33 (m, 8 H), 7.24 (s, 1 H), 7.14 (s, 1 H), 5.41 (d, *J* = 7.5 Hz, 1 H), 5.10-5.02 (m, 2 H), 4.91-4.88 (m, 2 H), 4.22 (d, *J* = 7.5 Hz, 1 H), 3.87 (s, 3 H), 3.78 (d, *J* = 4.0 Hz, 1 H), 3.48 (d, *J* = 4.0 Hz, 1 H), 1.98 (d, *J* = 13.5 Hz, 1 H), 1.67-1.63 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 189.7, 159.3, 154.0, 144.8, 136.0, 135.5, 131.8, 129.7, 129.6, 128.7, 128.5, 128.5, 127.7, 120.9, 111.9, 88.0, 78.2, 78.1, 67.5, 65.8, 56.0, 50.8, 28.4.

HRMS (ESI): *m/z* calcd for $C_{28}H_{26}O_6N_2Na$: 509.16886; Found: 509.16858.

Compound 56c

Following the general procedure 4B.7.2, compound **56c** (46 mg, 61 %) was synthesised from bicyclic olefin **55a** (50 mg, 0.1486 mmol) and 4-hydroxy-3-iodobiphenyl **6c** (53 mg, 0.1784 mmol) using $PdCl_2$ (1 mg, 0.0074 mmol), and K_2CO_3 (41 mg, 0.2972 mmol) as brown viscous liquid.



R_f: 0.54 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3062, 3033, 2955, 2877, 1716, 1607, 1478, 1454, 1371, 1308, 1279, 1246, 1208, 1162, 1115, 1081, 995, 921, 888, 825, 757 cm^{-1}.

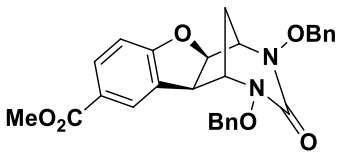
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.47 (m, 4 H), 7.44-7.35 (m, 10 H), 7.30-7.26 (m, 2 H), 7.14 (s, 1 H), 6.69 (d, *J* = 8.0 Hz, 1 H), 5.27 (d, *J* = 7.0 Hz, 1 H), 5.10-5.05 (m, 2 H), 4.93-4.90 (m, 2 H), 4.18 (d, *J* = 7.0 Hz, 1 H), 3.72 (d, *J* = 3.5 Hz, 1 H), 3.48 (d, *J* = 4.5 Hz, 1 H), 1.95 (d, *J* = 13.0 Hz, 1 H), 1.73-1.68 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 159.4, 140.8, 136.2, 135.7, 134.7, 129.7, 129.6, 128.7, 128.7, 128.5, 128.5, 128.2, 126.8, 126.8, 126.7, 123.6, 109.5, 86.4, 78.2, 78.1, 67.9, 66.1, 51.1, 28.5.

HRMS (ESI): *m/z* calcd for $C_{32}H_{28}O_4N_2Na$: 527.19468; Found: 527.19456.

Compound 56d

Following the general procedure 4B.7.2, compound **56d** (41 mg, 57 %) was synthesised from bicyclic olefin **55a** (50 mg, 0.1486 mmol) and methyl 4-hydroxy-3-iodobenzoate **6d** (50 mg, 0.1784 mmol) using $PdCl_2$ (1 mg, 0.0074 mmol), and K_2CO_3 (41 mg, 0.2972 mmol) as pale yellow viscous liquid.



R_f: 0.57 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3063, 3032, 2951, 2878, 1715, 1610, 1489, 1442, 1371, 1326, 1290, 1258, 1176, 1114, 1086, 1025, 990, 926, 871, 828, 769, 750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1 H), 7.66 (s, 1 H), 7.52 –

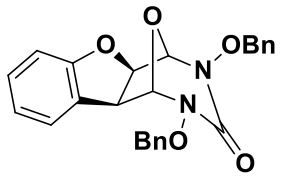
7.49 (m, 2 H), 7.48-7.47 (m, 2 H), 7.43 – 7.35 (m, 6 H), 6.65 (d, *J* = 8.5 Hz, 1 H), 5.29 (d, *J* = 6.5 Hz, 1 H), 5.10-5.04 (m, 2 H), 4.92-4.90 (m, 2 H), 4.16 (d, *J* = 7.0 Hz, 1 H), 3.87 (s, 3 H), 3.69 (d, *J* = 4.0 Hz, 1 H), 3.48 (d, *J* = 4.0 Hz, 1 H), 1.95 (d, *J* = 13.0 Hz, 1 H), 1.61-1.57 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 164.0, 159.2, 136.0, 135.6, 132.0, 129.7, 129.6, 128.7, 128.5, 128.5, 126.8, 126.6, 123.4, 109.1, 87.0, 78.2, 78.1, 67.7, 65.9, 51.9, 50.5, 28.4.

HRMS (ESI): *m/z* calcd for $C_{28}H_{27}O_6N_2$: 487.18691; Found: 487.18689.

Compound 56e

Following the general procedure 4B.7.2, compound **56e** (35 mg, 55 %) was synthesised from bicyclic olefin **55b** (50 mg, 0.1478 mmol) and 2-iodophenol **6a** (39 mg, 0.1774 mmol) using $PdCl_2$ (1 mg, 0.0074 mmol), and K_2CO_3 (41 mg, 0.2956 mmol) as reddish brown viscous liquid.



R_f: 0.51 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3062, 3032, 2940, 2880, 1721, 1597, 1481, 1459, 1371, 1322, 1277, 1226, 1209, 1101, 1000, 920, 848, 750, 700 cm^{-1}.

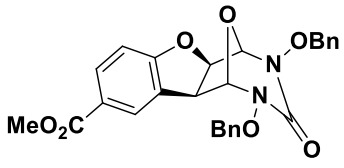
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.46 (m, 4 H), 7.44-7.35 (m, 6 H), 7.09-7.06 (m, 1 H), 6.79 (d, *J* = 4.0 Hz, 2 H), 6.65 (d, *J* = 8.0 Hz, 1 H), 5.09-5.06 (m, 3 H), 5.02-4.98 (m, 3 H), 4.77 (s, 1 H), 3.90 (d, *J* = 7.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.2, 156.6, 136.1, 135.2, 129.8, 129.7, 129.5, 129.1, 129.0, 128.8, 128.7, 124.5, 124.3, 124.1, 121.2, 109.5, 96.7, 94.3, 85.8, 78.9, 78.7, 52.3.

HRMS (ESI): *m/z* calcd for $C_{25}H_{22}O_5N_2Na$: 453.14264; Found: 453.14369.

Compound 56f

Following the general procedure 4B.7.2, compound **56f** (32 mg, 45 %) was synthesised from bicyclic olefin **55b** (50 mg, 0.1478 mmol) and methyl 4-hydroxy-3-iodobenzoate **6d** (49 mg, 0.1774 mmol) using $PdCl_2$ (1 mg, 0.0074 mmol), and K_2CO_3 (41 mg, 0.2956 mmol) as yellow viscous liquid.



R_f: 0.51 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3064, 3032, 2951, 2882, 1715, 1610, 1491, 1444, 1357, 1326, 1291, 1262, 1203, 1167, 1115, 1089, 999,

917, 885, 846, 771, 739, 700 cm^{-1}.

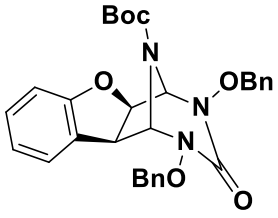
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (dd, J_1 = 8.5 Hz, J_2 = 1.7 Hz, 1 H), 7.53-7.46 (m, 8 H), 7.43-7.38 (m, 3 H), 6.66 (d, *J* = 8.5 Hz, 1 H), 5.09-5.01 (m, 6 H), 4.78 (s, 1 H), 3.89 (s, 3 H), 3.83 (d, *J* = 7.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 163.9, 136.0, 135.2, 132.3, 129.9, 129.8, 129.3, 129.1, 128.9, 128.7, 126.7, 124.8, 123.7, 109.2, 96.9, 93.9, 86.9, 79.1, 78.8, 51.9, 51.7.

HRMS (ESI): *m/z* calcd for $C_{27}H_{24}O_7N_2Na$: 511.14812; Found: 511.14902.

Compound 56g

Following the general procedure 4B.7.2, compound **56g** (38 mg, 63 %) was synthesised from bicyclic olefin **55c** (50 mg, 0.1143 mmol) and 2-iodophenol **6a** (30 mg, 0.1372 mmol) using $PdCl_2$ (1 mg, 0.0057 mmol), and K_2CO_3 (32 mg, 0.2286 mmol) as colourless solid.



M. P. : 155-157 ^oC.

R_f: 0.54 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3027, 2980, 2936, 2877, 1723, 1595, 1480, 1457, 1368, 1326, 1246, 1172, 1106, 1013, 939, 915, 840, 791,751 cm^{-1}.

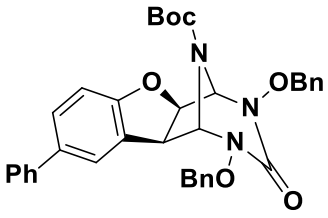
^{1}H NMR (500 MHz, $CDCl_3$): δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.46 (m, 4 H), 7.42-7.33 (m, 6 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 7.06 (d, *J* = 7.0 Hz, 1 H), 6.85 (t, *J* = 7.5 Hz, 1 H), 6.72 (d, *J* = 8.0 Hz, 1 H), 5.28-5.27 (m, 2 H), 5.10-5.06 (m, 3 H), 4.92-4.91 (m, 2 H), 4.27 (d, *J* = 7.5 Hz, 1 H), 1.40 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.5, 159.3, 152.8, 152.7, 151.8, 129.6, 128.7, 128.7, 128.5, 125.5, 124.2, 122.5, 121.2, 113.1, 109.6, 82.5, 78.4, 28.0.

HRMS (ESI): *m/z* calcd for $C_{30}H_{31}O_6N_3Na$: 552.21106; Found: 552.21131.

Compound 56h

Following the general procedure 4B.7.2, compound **56h** (41 mg, 60 %) was synthesised from bicyclic olefin **55c** (50 mg, 0.1143 mmol) and 4-hydroxy-3-iodobiphenyl **6c** (41 mg, 0.1372 mmol) using $PdCl_2$ (1 mg, 0.0057 mmol), and K_2CO_3 (32 mg, 0.2286 mmol) as pale yellow solid.



M. P. : 171-173 ^{o}C.

R_f: 0.51 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3063, 3033, 2977, 2933, 2880, 1726, 1611, 1498, 1479, 1455, 1369, 1349, 1326, 1284, 1241, 1158, 1115, 1013, 943, 917, 880, 836, 793, 749 cm^{-1}.

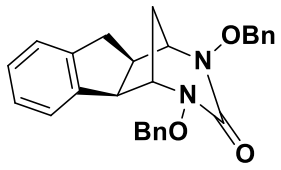
^{1}H NMR (500 MHz, $CDCl_3$): δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.47 (m, 6 H), 7.41-7.34 (m, 9 H), 7.29 (t, *J* = 7.0 Hz, 1 H), 7.23 (s, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 5.32-5.27 (m, 2 H), 5.14 – 5.04 (m, 3 H), 4.92-4.91 (m, 2 H), 4.29 (d, *J* = 7.5 Hz, 1 H), 1.42 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.1, 152.7, 140.7, 137.4, 135.0, 129.0, 128.8, 128.7, 128.7, 128.6, 128.5, 126.9, 126.8, 124.9, 123.6, 109.8, 82.6, 78.4, 28.0.

HRMS (ESI): *m/z* calcd for $C_{36}H_{35}O_6N_3Na$: 628.24236; Found: 628.24340.

Compound 59

Following the general procedure 4B.7.2, compound **59** (38 mg, 60 %) was synthesised from bicyclic olefin **55a** (50 mg, 0.1486 mmol) and 2-iodobenzylbromide **58** (53 mg, 0.1784 mmol) using $PdCl_2$ (1 mg, 0.0074 mmol), and K_2CO_3 (41 mg, 0.2972 mmol) as pale yellow viscous liquid.



R_f: 0.56 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3063, 3031, 2953, 2875, 1714, 1587, 1495, 1480, 1454, 1372, 1310, 1258, 1204, 1160, 1080, 1028, 916, 828, 750, 700 cm^{-1}.

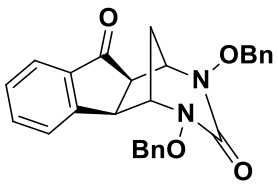
^{1}H NMR (500 MHz, $CDCl_3$): δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53-7.48 (m, 4 H), 7.41-7.33 (m, 6 H), 7.13-7.10 (m, 2 H), 7.08-7.07 (m, 1 H), 7.01 (d, *J* = 5.5 Hz, 1 H), 5.12-5.06 (m, 2 H), 4.93-4.88 (m, 2 H), 4.05 (d, *J* = 7.5 Hz, 1 H), 3.45 (d, *J* = 4.0 Hz, 1 H), 3.39 (d, *J* = 4.0 Hz, 1 H), 3.34-3.30 (m, 1 H), 3.27-3.21 (m, 1 H), 2.42-2.38 (m, 1 H), 1.87 (d, *J* = 12.5 Hz, 1 H), 1.44-1.40 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 143.0, 142.5, 136.5, 136.1, 129.6, 129.5, 129.5, 129.5, 128.5, 128.5, 128.5, 128.4, 128.4, 128.4, 127.4, 126.9, 124.6, 78.0, 77.9, 68.5, 68.4, 54.3, 44.2, 37.3, 29.2.

HRMS (ESI): *m/z* calcd for $C_{27}H_{27}N_2O_3$: 427.20217; Found: 427.20259.

Compound 60

Following the general procedure 4B.7.2, compound **60** (54 mg, 82 %) was synthesised from bicyclic olefin **55a** (50 mg, 0.1486 mmol) and 2-iodobenzonitrile **37** (41 mg, 0.1784 mmol) using $PdCl_2$ (1 mg, 0.0074 mmol), PPh_3 (4 mg, 0.0149) and K_2CO_3 (41 mg, 0.2972 mmol) as reddish brown viscous liquid.



R_f: 0.41 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3062, 3032, 2941, 2877, 1710, 1604, 1496, 1457, 1372, 1328, 1274, 1215, 1157, 1098, 1026, 920, 884, 865, 830, 797, 753, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 1 H), 7.60 (t, *J* = 7.5 Hz, 1 H), 7.54-7.51 (m, 4 H), 7.43-7.35 (m, 8 H), 5.15-5.08 (m, 2 H), 4.96-4.93 (m, 2 H), 4.11 (d, *J* = 6.0 Hz, 1 H), 3.85 (d, *J* = 4.0 Hz, 1 H), 3.56 (d, *J* = 4.0 Hz, 1 H), 3.54 (d, *J* = 6.0 Hz, 1 H), 1.84 (d, *J* = 13.0 Hz, 1 H), 1.25-1.21 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 204.1, 160.4, 153.6, 137.5, 136.2, 135.8, 135.5, 129.6, 129.6, 128.7, 128.6, 128.5, 128.5, 126.1, 124.1, 78.1, 78.0, 66.6, 64.5, 55.5, 47.2, 29.0.

HRMS (ESI): *m/z* calcd for $C_{27}H_{24}O_4N_2Na$: 463.16338; Found: 463.16345.

4B.8. References

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CHAPTER 4

Hydro(hetero)arylation & Annulation Reactions

PART C

Iridium Catalyzed Hydroheteroarylation of Urea Derived Bicyclic Olefins *via* C-2 Activation of Indoles

4C.1. Introduction

The synthesis and functionalization of indoles is of great significance in synthetic organic chemistry ever since its discovery in 1866.[1] The ubiquitous presence of this heterocyclic core in numerous natural products and compounds of pharmaceutical importance is the prime reason for this (Figure 4C.1).[2–4]

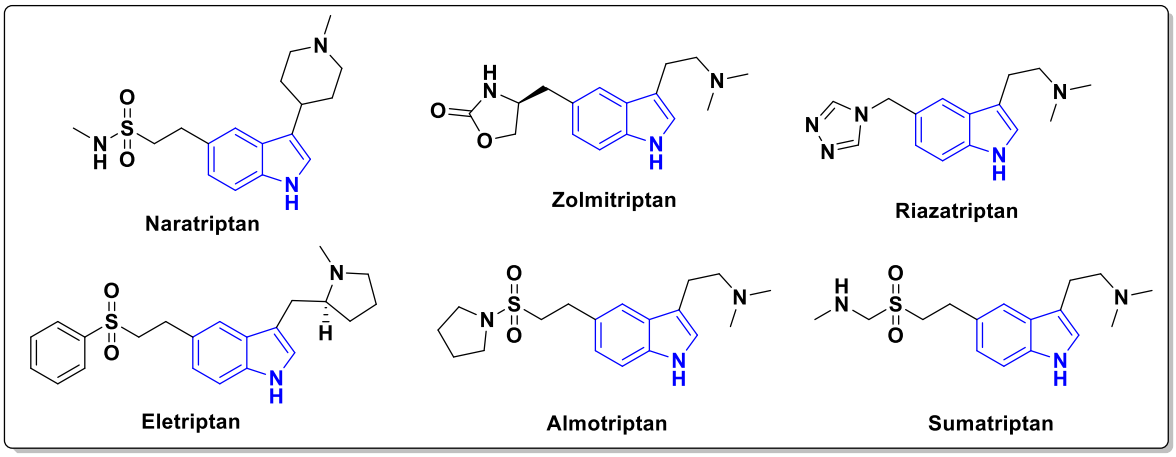


Figure 4C.1. Biologically significant indole derivatives

The major issue confronted in the functionalization of indole core is the regioselectivity. Transition metal catalyzed aromatic C-H activation reactions have revolutionized the field of organic synthesis by opening efficient methodologies for a variety of site-selective C-C bond formations.[5–9] These C-H activation reactions include selective functionalization of the C-2, C-3 and C-7 positions of the indole nucleus *via* various transition metals such as Pd, Rh, Ru, Cu, Ir *etc*.[10–25] However, as the indole ring tends to undergo metalation and subsequent C-C bond formation at the C-3 position, activation of the comparatively inert C-2 position is still a great challenge. Directing group assisted, as well as

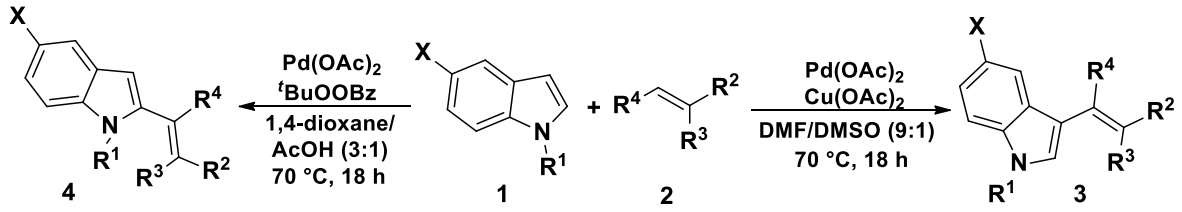
non-directed methodologies were reported in this category wherein different catalysts decide the reactivity pattern.[26–33]

4C.2. C-2 Selective Functionalization of Indoles

Various groups have developed different promising synthetic protocols for the C-2 selective functionalization of indoles and among them, some selected reports are discussed in the following sections.

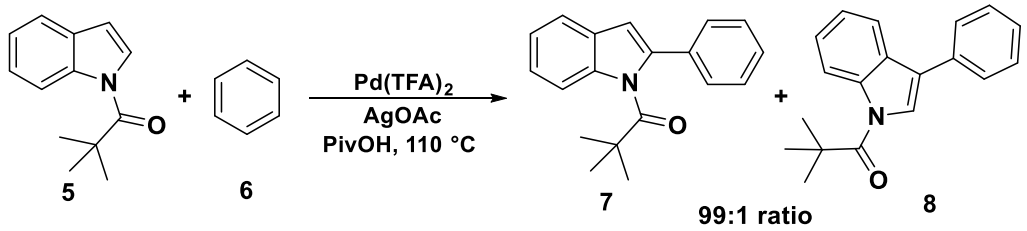
4C.2.1. Using Palladium

Gaunt and co-workers reported unexpected palladium-catalyzed site selectivity between C-2 and C-3 position of indole determined by the nature of solvent. The selective intermolecular alkenylation of indoles through the C-H functionalization reaction can be directed to either the 2- or the 3-position of free (NH) indoles **1** (Scheme 4C.1).[26]



Scheme 4C.1

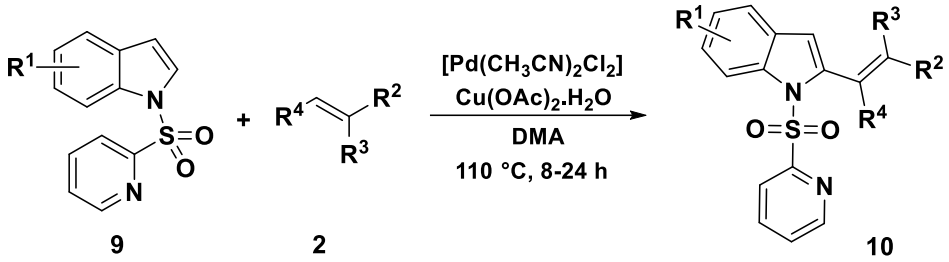
Regioselective oxidative arene cross-coupling of indoles was developed by Fagnou and co-workers wherein they exploited $Pd(TFA)_2$ as catalyst in combination with AgOAc as oxidant (Scheme 4C.2). They elucidated that AgOAc favored C-2 activation of indoles whereas $Cu(OAc)_2$ favored the C-3 position.[27] The use of *N*-pivaloyl indole **5** resulted in 100 % conversion.



Scheme 4C.2

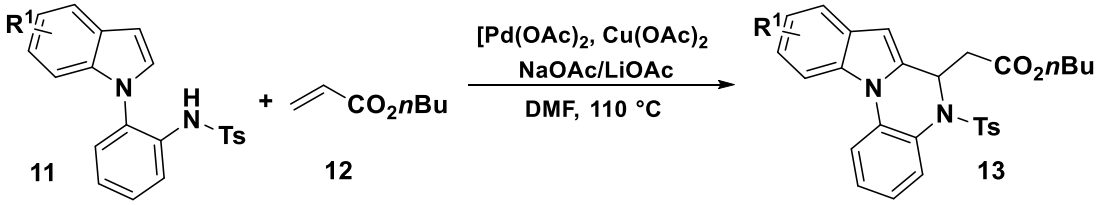
Carretero and co-workers divulged the use of 2-pyridylsulfonyl as directing group to alkenylate indoles and the method provided access to corresponding 2-alkenylindoles **10** in moderate to excellent yields with high functional group tolerance (Scheme 4C.3).[11] The auxiliary group can be reductively removed by using either Zn or Mg and thus demonstrating

the synthetic versatility of the process. This procedure was modified using O_2 as oxidant and $Pd(TFA)_2$ as catalyst by Wang *et al*.[34]



Scheme 4C.3

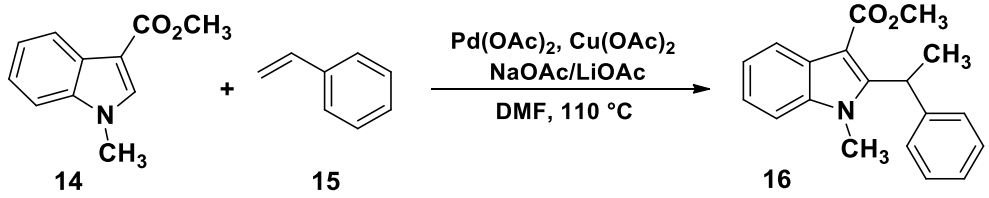
Xiao *et al*. developed a highly efficient Pd-catalyzed regioselective approach through a C-H olefination/cyclization sequence to furnish indolo[1,2-*a*]quinoxaline derivatives **13** (Scheme 4C.4). The reaction was applicable to a wide range of *N*-aryl-substituted indoles **11** and electron-withdrawing olefins **12** affording the corresponding indole/ pyrrole-fused quinoxaline derivatives **13** in moderate to good yields.[35]



Scheme 4C.4

4C.2.2. Using Nickel

Hiyama and co-workers demonstrated that the coupling of indoles **14** and vinyl arenes **15** catalyzed by a Ni-NHC catalyst could selectively yield branched 2-alkylindoles **16** (Scheme 4C.5).[36] The nickel-catalyzed hydroheteroarylation of vinylarenes exclusively gave a variety of 1,1-diarylethanes that contain heteroaryl motifs.

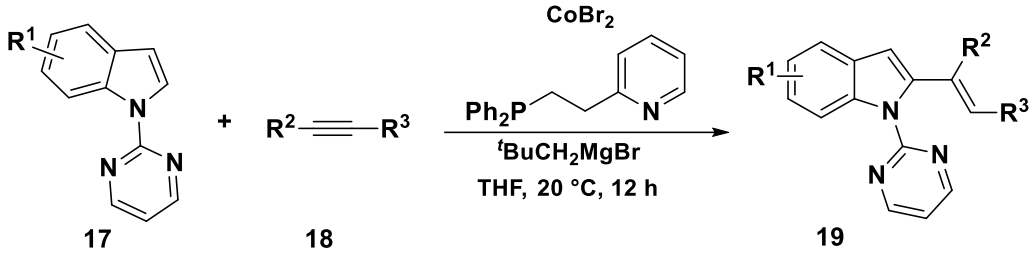


Scheme 4C.5

4C.2.3. Using Cobalt

Yoshikai and co-workers developed a highly efficient, mild, and stereoselective C2-alkenylation reaction of indoles **17** with alkynes **18** catalyzed by a Co–pyphos catalyst

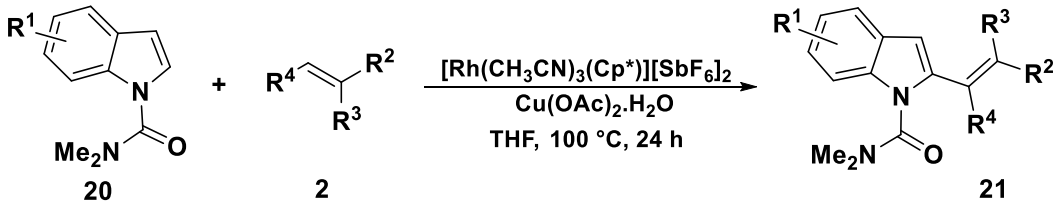
(Scheme 4C.6). The desired indoles **19** were obtained in mostly good to excellent yields.[37] The same strategy using pyrimidyl group as directing group under Rh (III) catalysis was developed by Huang *et al*.[38]



Scheme 4C.6

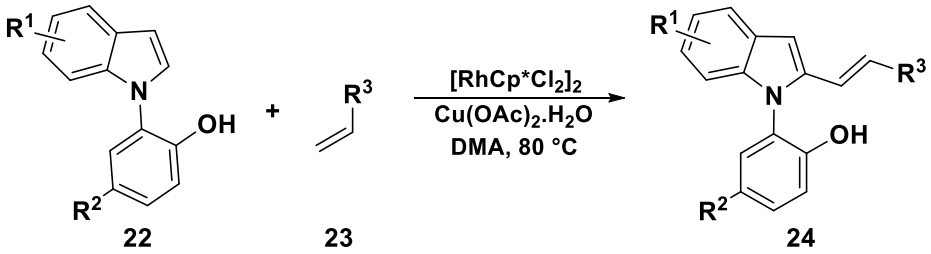
4C.2.4. Using Rhodium

An efficient rhodium (III) catalyzed oxidative olefination of indoles **20** and pyrroles assisted by the *N*,*N*-dimethylcarbamoyl protecting group with broad substrate scope tolerance was explored by Li-Wang and co-workers (Scheme 4C.7). The reaction was even extended to strained olefins such as norbornenes.[39]



Scheme 4C.7

Year 2014 witnessed the utilization of simple phenolic OH and aniline NH_2 groups as the directing group to provide the direct C-2 olefination of unactivated indoles under Rh (III) catalysis by Sha and co-workers (Scheme 4C.8).[40]

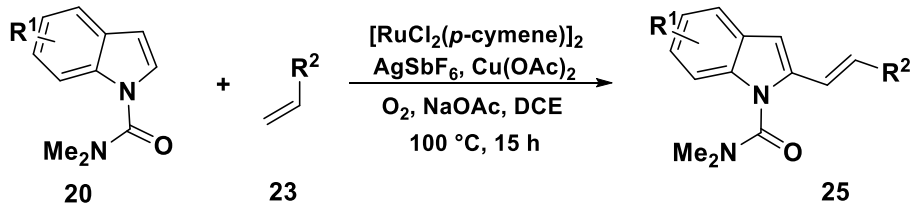


Scheme 4C.8

They acted as effective chelating groups to activate the aryl C-H bond to furnish 2-vinylindoles/2-vinylpyrroles **24** in good yields with excellent selectivity and high functional group tolerance.

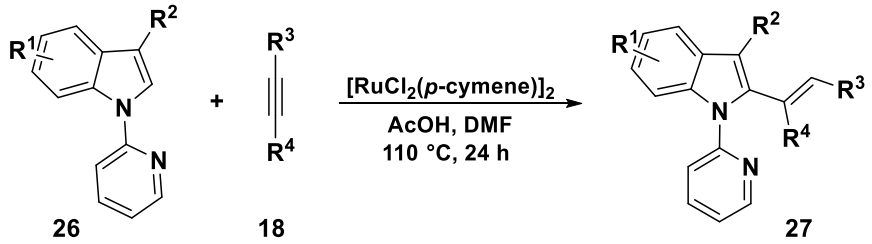
4C.2.5. Using Ruthenium

A highly efficient and selective aerobic ruthenium catalyzed direct C-2 olefination of *N*-heteroarenes such as indoles **20**, pyrroles, and carbazoles with alkenes **23** directed by a removable *N*-dimethylcarbamoyl group by using O_2 as the terminal oxidant was elucidated by Song *et al.* (Scheme 4C.9).[41] In the same year, Wang & Li *et al*. reported the same strategy using $Cu(OAc)_2.H_2O$ as oxidant.[42]



Scheme 4C.9

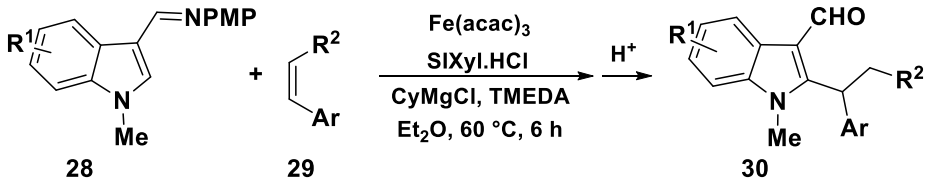
Ruthenium-catalyzed C2-hydroindolation of alkynes **18** provided access to various 2-alkenyl-substituted *N*-(2-pyridyl)indoles **27** in which the pyridyl moiety can be easily removed to afford free (N−H) indoles under mild conditions (Scheme 4C.10).[18]



Scheme 4C.10

4C.2.6. Using Iron

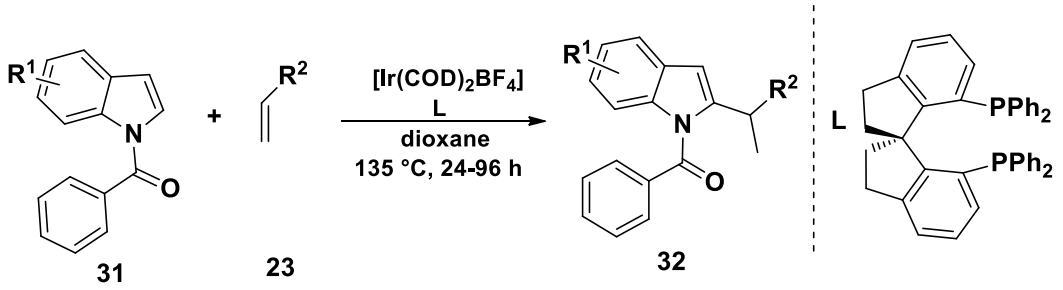
Iron−*N*-heterocyclic carbene catalysts have also been used in the C-2 activation of indoles and an example include alkylation and alkenylation reactions with vinylarenes and internal alkynes which was reported Yoshikai *et al.* (Scheme 4C.11).[43] The iron-*N*-heterocyclic carbene catalyst was generated from an iron (III) salt, an imidazolinium salt, and Grignard reagent.



Scheme 4C.11

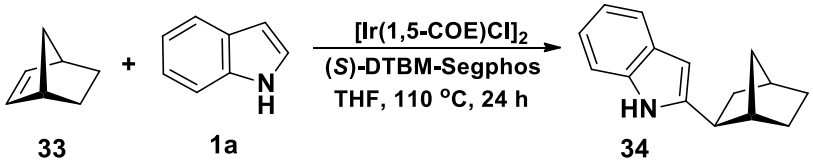
4C.2.7. Using Iridium

Iridium (I)-catalysed C−H bond alkylation of C2-position of indoles **31** with alkenes **23** towards the selective synthesis of linear or branched 2-alkylindoles **32** depending on the directing auxiliary present on the *N*-1 position of the indole ring was divulged by Shibata *et al.* (Scheme 4C.12).[14] They also elucidated that using acetyl group as auxiliary yielded unbranched 2-alkylindoles whereas the benzoyl groups as auxiliary favored the formation of branched 2-alkylindoles.



Scheme 4C.12

The asymmetric hydroheteroarylation of bicycloalkenes such as norbornenes **33** was reported by Hartwig and co-workers (Scheme 4C.13). Enantioselective alkylation at the C-2 positon of indole **1a**, thiophenes, pyrroles, and furans occurred in high yields with high *ee*.[44]

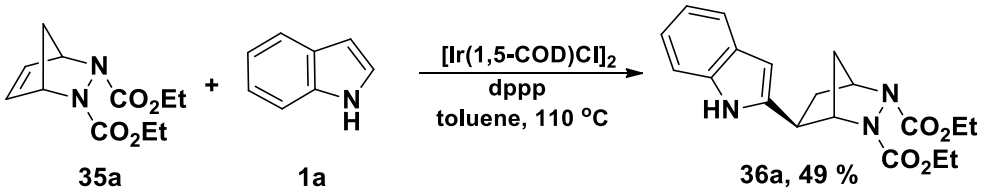


Scheme 4C.13

In this chapter, we disclose our preliminary results on the iridium catalyzed regioselective C-H activation of indoles with diazabicyclic as well as urea derived bicyclic olefins.

4C.3. Results and Discussion

We commenced our studies with the reaction of indole **1a** with the diazabicyclic olefin **35a** using $[Ir(1,5\text{-}COD)Cl]_2$ as the catalyst and dppp as the ligand in toluene at 110 ^{o}C for 16 h (Scheme 4C.14). Instead of the expected cyclopentenylated product, the heterohydroarylated product **36a** was obtained in 49 % yield.



Scheme 4C.14

Various spectroscopic analyses like ^{1}H NMR, ^{13}C NMR and HRMS-ESI provided confirmation for the structure of the product.

The IR spectrum of **36a** showed the –NH peak at 3333 cm^{-1} and the characteristic carbonyl absorption of the ester group at 1713 cm^{-1} respectively.

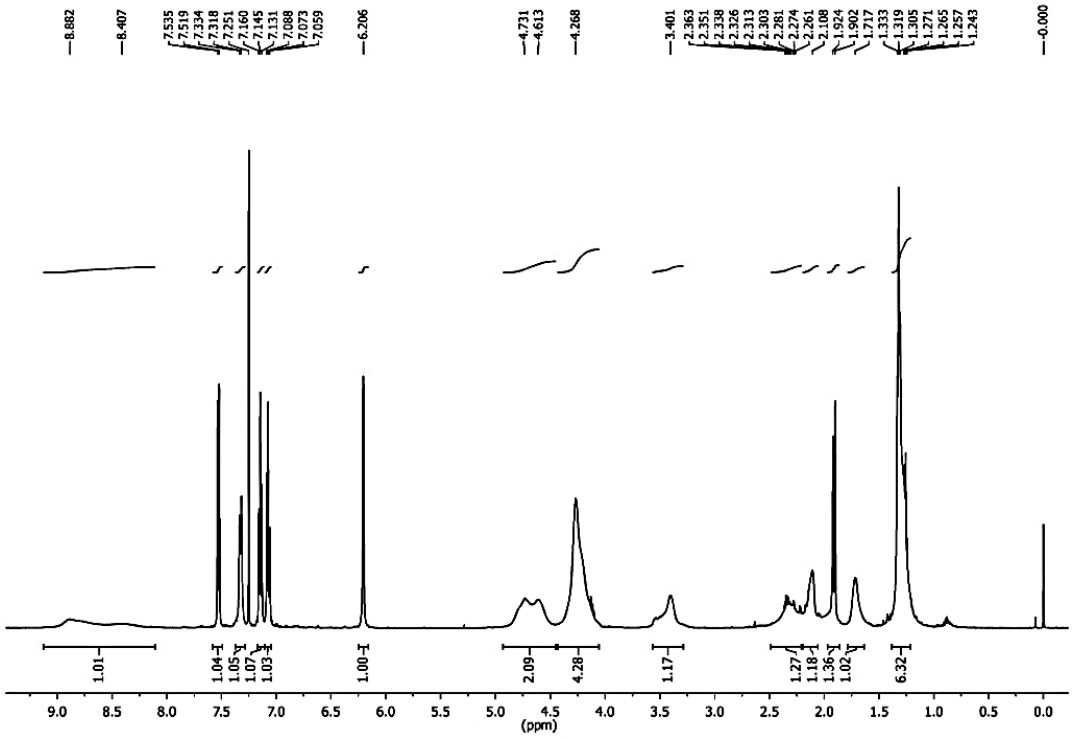


Figure 4C.2. ^{1}H NMR spectrum of compound **36a**

In ^{1}H NMR (Figure 4C.2), the aromatic protons were discernible in the range 7.54-7.06 ppm. The proton at the C-3 position of indole resonated at 6.21 ppm. NH- proton resonated at 8.88-8.41 ppm. The protons attached to carbon bearing the nitogen atom of hydrazines was seen at 4.73-4.61 ppm. Methylene protons of the ethoxy group were visible at 4.27 ppm and methyl protons resonated at 1.33-1.24 ppm. Proton attached to carbon bearing the indole moiety appeared as a broad singlet at 3.40 ppm. The methylene protons appeared

at 2.36-2.26 ppm and as a doublet at 1.91 ppm. The bridge protons were discernible as two separate singlets at 2.11 and 1.72 ppm.

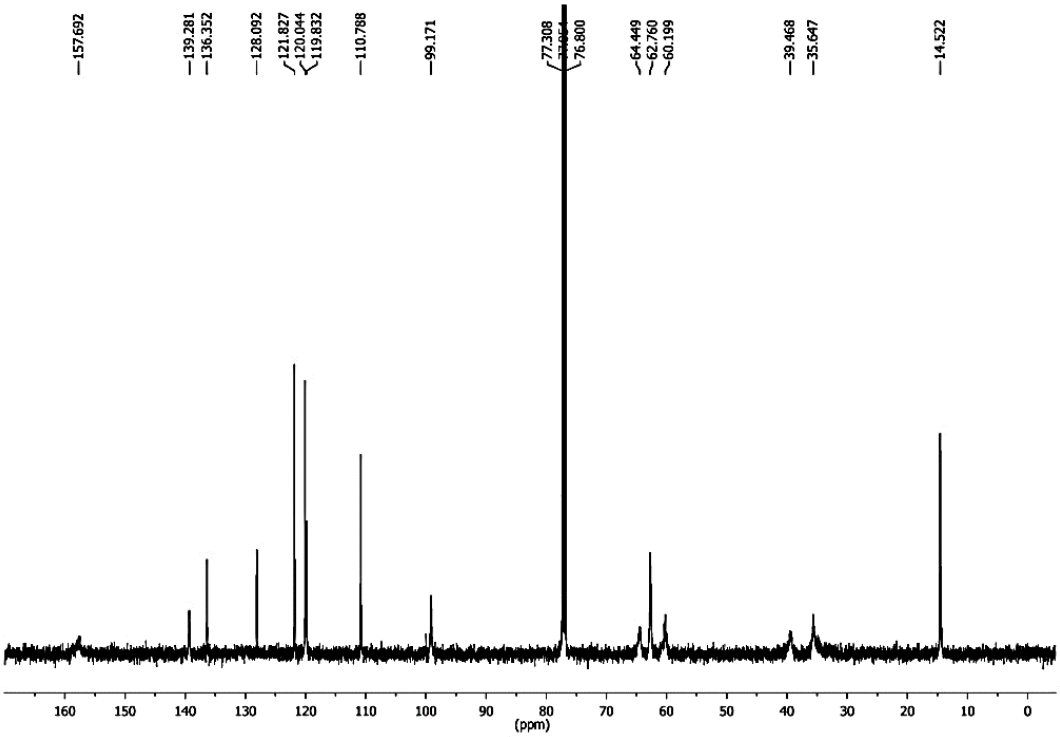


Figure 4C.3. ^{13}C NMR spectrum of compound **36a**

In ^{13}C NMR spectrum (Figure 4C.3), the carbonyl group was seen at 157.7 ppm. The carbons attached to the nitrogen atom of the hydrazine moiety was discernible at 64.4 and 60.2 ppm. The carbon attached to oxygen atom of the ethoxy group was visible at 62.8 ppm. The carbon bearing indole moiety appeared at 39.5 ppm. The methylene carbon was seen at 35.6 ppm. In addition, the methyl carbons resonated at 14.5 ppm.

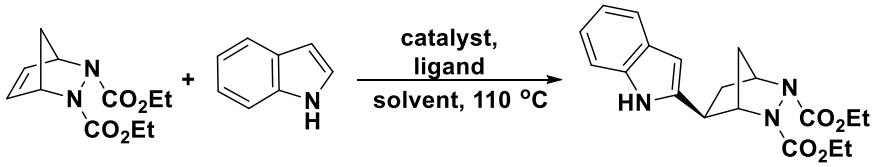
The structure was further confirmed by the HRMS-ESI analysis that showed $[M+Na]^+$ peak at 380.16012.

4C.3.1. Optimization Studies

Later, in a search for optimized reaction conditions, we observed that the reaction did not proceed well with other catalysts like $[Ir(OMe)(1,5\text{-}COD)]_2$ and $[IrCl(CO)(PPh_3)_2]$ (Table 4C.1, entry 2 & 3). Among the ligands screened, dppe gave a better yield of 64 % (entry 4). Best solvent for this transformation was found to be toluene, and the reaction was

futile with other solvents like DMF, DMSO and CH_3CN (entry 8-10). The reaction with carboxamide protected indole didn't give any satisfactory results (entry 11). Detailed optimization studies revealed that the reaction was optimal with $[Ir(1,5\text{-}COD)Cl]_2$ (5 mol%) as the catalyst and dppe (10 mol%) as the ligand in toluene at 110 ^oC for 16 h furnishing **36a** in 64 % yield (entry 4).

Table 4C.1. Optimization studies for the hydroheteroarylation reaction[a]



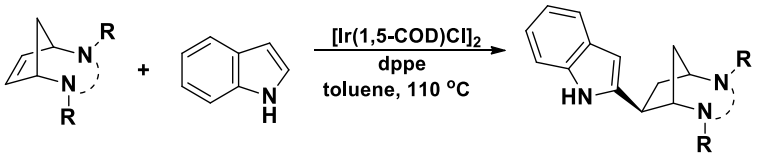
Entry	Catalyst	Ligand	Solvent	Yield (%)[b]
1	$[Ir(1,5\text{-}COD)Cl]_2$	dppp	toluene	54
2	$[Ir(OMe)(1,5\text{-}COD)]_2$	dppp	toluene	trace
3	$[IrCl(CO)(PPh_3)_2]$	dppp	toluene	nr
4	**$[Ir(1,5\text{-}COD)Cl]_2$**	**dppe**	**toluene**	**64**
5	$[Ir(1,5\text{-}COD)Cl]_2$	dppf	toluene	trace
6	$[Ir(1,5\text{-}COD)Cl]_2$	(*rac*)-BINAP	toluene	20
7	$[Ir(1,5\text{-}COD)Cl]_2$	PPh_3	toluene	nr
8	$[Ir(1,5\text{-}COD)Cl]_2$	dppe	DMF	nr
9	$[Ir(1,5\text{-}COD)Cl]_2$	dppe	CH_3CN	nr
10	$[Ir(1,5\text{-}COD)Cl]_2$	dppe	DMSO	nr
11[c]	$[Ir(1,5\text{-}COD)Cl]_2$	dppe	toluene	nr

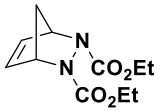
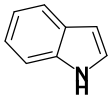
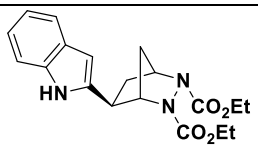
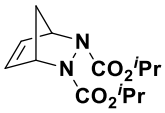
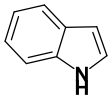
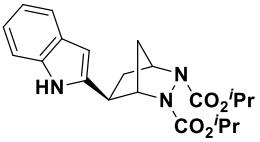
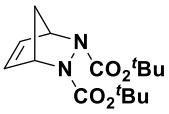
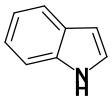
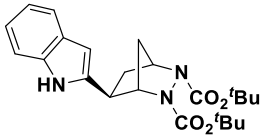
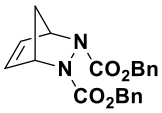
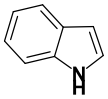
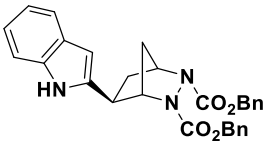
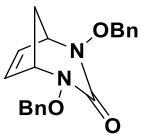
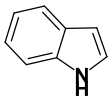
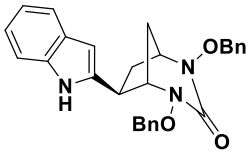
[a]**Reaction conditions:** adduct (1 equiv.), indole (0.9 equiv.), catalyst (5 mol%), ligand (10 mol%), solvent (2 mL), 110 ^oC, 16 h. [b]Isolated yield. [c]With carboxamide protected indole.

4C.3.2. Scope of the Reaction

Further, the generality of this transformation was checked with different bicyclic olefins (Table 4C.2). The diazabicyclic olefins **35a-35d** derived from various dialkyl azadicarboxylates reacted smoothly to furnish the hydroheteroarylated products **36a-36d** in good yields. We were successful in obtaining **36e** in 80 % yield by extending this strategy to urea derived bicyclic olefins also.

Table 4C.2. Reactivity of different bicyclic olefins[a]

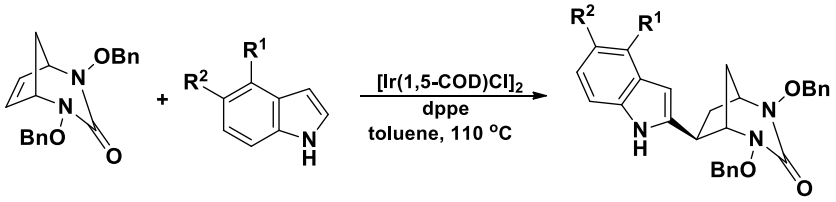


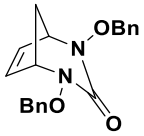
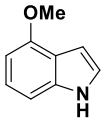
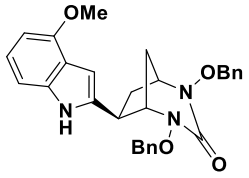
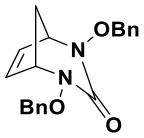
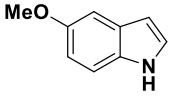
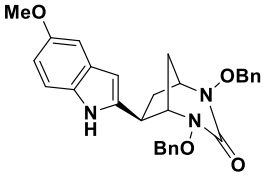
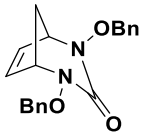
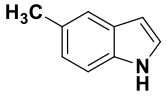
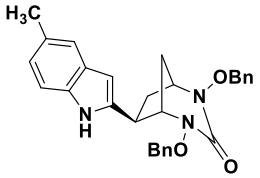
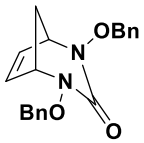
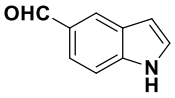
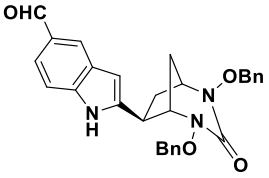
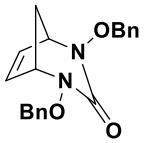
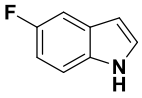
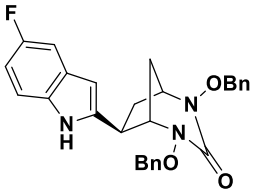
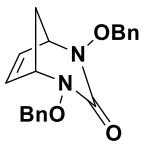
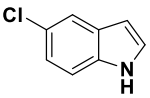
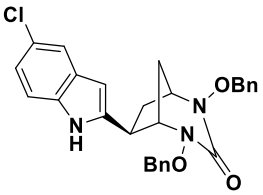
Entry	Bicyclic Olefin	Indole	Product	Yield (%)[b]
1				64
	35a	**1a**	**36a**	
2				58
	35b	**1a**	**36b**	
3				51
	35c	**1a**	**36c**	
4				49
	35d	**1a**	**36d**	
5				80
	35e	**1a**	**36e**	

[a]**Reaction conditions:** adduct (1 equiv.), indole (0.9 equiv.), $[Ir(1,5\text{-}COD)Cl]_2$ (5 mol%), dppe (10 mol%), toluene (2 mL), 110 °C, 16 h. [b]Isolated yield.

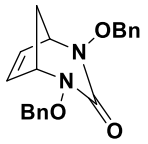
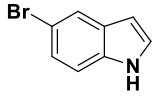
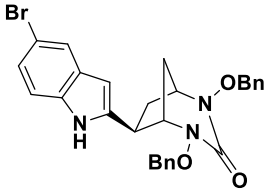
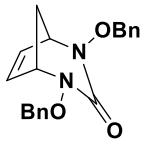
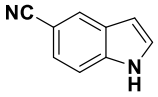
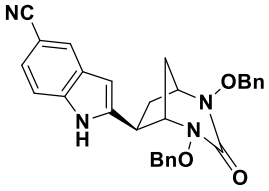
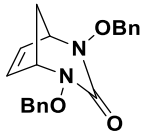
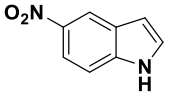
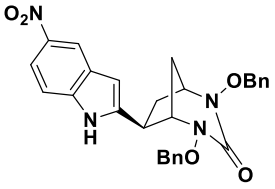
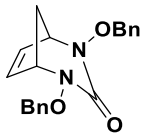
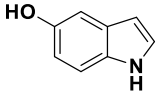
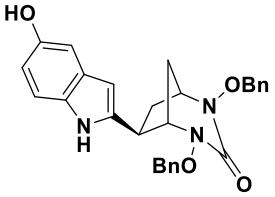
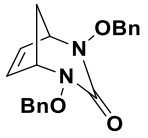
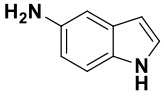
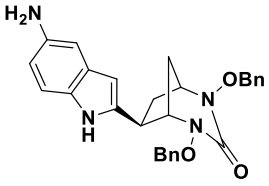
Later, the scope of various substituted indoles was tested for the reaction. Indoles with electron donating substituents such as OMe, Me, OH and NH_2 at the 4th or 5th position underwent the hydroheteroarylation reaction and gave moderate to good yields (Table 4C.3, **36f**-**36h**, **36o**-**36p**). Also, the reaction was shown to be general with electron withdrawing substituents such as CHO, F, Cl, Br, CN, NO_2 at the 5th position of indoles (Table 4C.3, **36i**-**36n**).

Table 4C.3. Reactivity of various substituted indoles[a]



Entry	Bicyclic Olefin	Indoles	Product	Yield (%)[b]
1				57
	35e	**1b**	**36f**	
2				66
	35e	**1c**	**36g**	
3				71
	35e	**1d**	**36h**	
4				68
	35e	**35e**	**36i**	
5				70
	35e	**1f**	**36j**	
6				74
	35e	**1g**	**36k**	

Continued..

7	 **35e**	 **1h**	 **36l**	78
8	 **35e**	 **1i**	 **36m**	68
9	 **35e**	 **1j**	 **36n**	75
10	 **35e**	 **1k**	 **36o**	40
11	 **35e**	 **1l**	 **36p**	55

[a]**Reaction conditions:** adduct (1 equiv.), indole (0.9 equiv.), $[Ir(1,5\text{-COD})Cl]_2$ (5 mol%), dppe (10 mol%), toluene (2 mL), 110 ^{o}C, 16 h. [b]Isolated yield.

The single crystal X-ray of the compound **36n** obtained while checking the generality of the reaction provided additional structural confirmation for the product (CCDC 1449575) (Figure 4C.4).

The biological significance of heteroarenes and their predominance in various natural products prompted us to expand the scope of this method to other heteroarenes like benzofuran **37** and pyrrole **39**. The reaction was performed with these heterocycles to furnish the products **38** and **40** in moderate yields (Scheme 4C.15 and 4C.16).

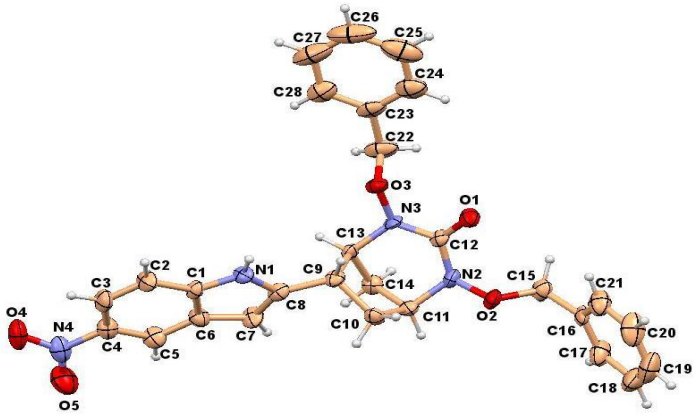
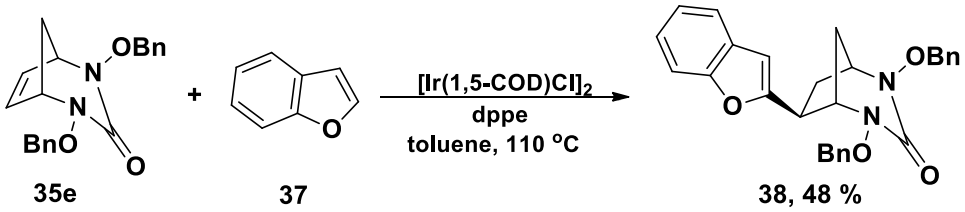
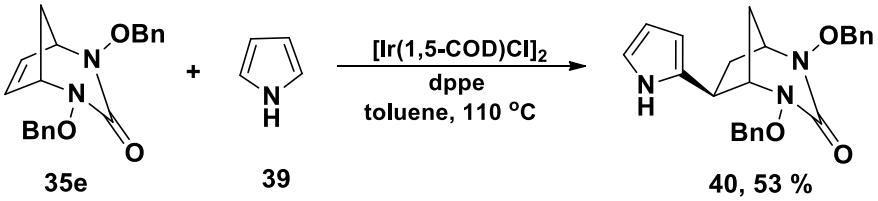


Figure 4C.4. Single crystal X-ray structure of compound **36n**



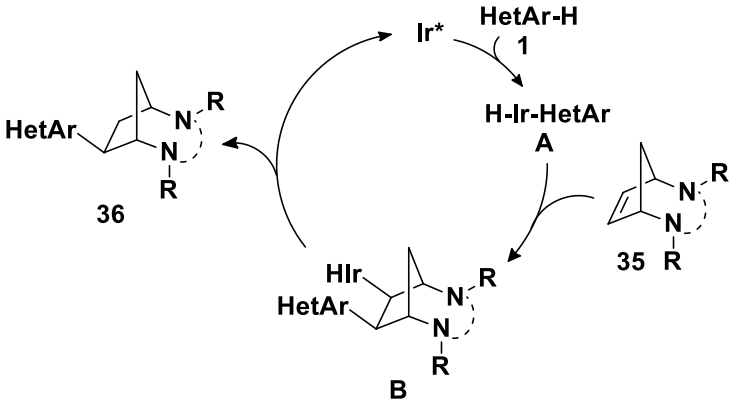
Scheme 4C.15



Scheme 4C.16

4C.4. Mechanistic Pathway

The proposed mechanism for this transformation is shown in Scheme 4C.17.



Scheme 4C.17. Proposed mechanistic pathway

The active iridium species cleaves the aromatic C-H bond of the heteroarene **1** to form aryl iridium intermediate **A**, which adds to the olefinic bond of **35** to form intermediate **B**. The formed intermediate **B** undergoes reductive elimination to furnish the product **36** and regenerates the active iridium catalyst for the next catalytic cycle.

4C.5. Conclusion

In conclusion, we have disclosed an efficient strategy for the iridium catalyzed regioselective C-H bond activation of free indoles with bicyclic olefins. The reaction resulted in the hydroheteroarylation of bicyclic olefins *via* the C-2 activation of *N*-free indoles. Further, the developed strategy was extended to other heterocycles like benzofuran and pyrrole.

4C.6. Experimental Section

4C.6.1. General Methods

General information about the experiments is given in Section 2.8.1 of Chapter 2.

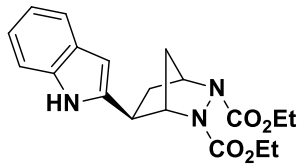
4C.6.2. General Procedure for Iridium-catalyzed Hydroheteroarylation

A mixture of bicyclic alkene **35** (1.0 equiv.), indole **1** (0.9 equiv.), $[Ir(1,5\text{-COD})Cl]_2$ (5 mol%) and dppe (10 mol%) were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 110 ^{o}C for 16 hours. The crude reaction mixture on alumina column chromatography using ethyl acetate/hexane mixture yielded hydroheteroarylated bicycles **36**.

4C.6.3. Characterization of the Products

Compound 36a

Following the general procedure 4C.6.2, compound **36a** (76 mg, 64 %) was synthesised from bicyclic olefin **35a** (80 mg, 0.3329 mmol) and indole **1a** (35 mg, 0.2996 mmol) using $[Ir(1,5\text{-COD})Cl]_2$ (11 mg, 0.0166 mmol) and dppe (13 mg, 0.0333 mmol) as reddish brown viscous liquid.



R_f: 0.28 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3333, 3054, 2982, 2911, 1713, 1618, 1459, 1402, 1374, 1323, 1171 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.88-8.41 (m, 1 H), 7.53 (d, *J* = 8.0 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.15 (t, *J* = 7.0 Hz, 1 H), 7.07 (t, *J* = 7.0 Hz, 1 H), 6.21 (s, 1 H), 4.73-4.61 (m,

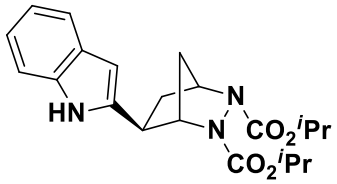
2 H), 4.27 (m, 4 H), 3.40 (brs, 1 H), 2.36-2.26 (m, 1 H), 2.11 (brs, 1 H), 1.92-1.90 (m, 1 H), 1.72 (brs, 1 H), 1.33-1.24 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.7, 139.3, 136.4, 128.1, 121.8, 120.0, 119.8, 110.8, 99.2, 64.4, 62.8, 60.2, 39.5, 35.6, 14.5.

HRMS (ESI): *m/z* calcd for $C_{19}H_{23}N_3O_4Na$: 380.15863; Found: 380.16012.

Compound 36b

Following the general procedure 4C.6.2, compound **36b** (67 mg, 58 %) was synthesised from bicyclic olefin **35b** (80 mg, 0.2982 mmol) and indole **1a** (31 mg, 0.2683 mmol) using $[Ir(1,5\text{-}COD)Cl]_2$ (10 mg, 0.0149 mmol) and dppe (12 mg, 0.0298 mmol) as pale brown viscous liquid.



R_f: 0.42 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3329, 3056, 2982, 1710, 1619, 1458, 1315, 1098 cm^{-1}.

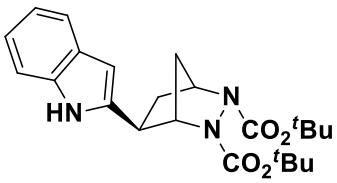
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.30-8.75 (m, 1 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 7.30 (s, 1 H), 7.10 (t, *J* = 7.5 Hz, 1 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 6.15 (s, 1 H), 5.03 (brs, 2 H), 4.72 (brs, 1 H), 4.56 (brs, 1 H), 3.52-3.39 (m, 1 H), 2.34-2.14 (m, 2 H), 1.90-1.88 (m, 1 H), 1.67-1.60 (m, 1 H), 1.31-1.17 (m, 12 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.3, 139.6, 136.5, 128.1, 121.6, 119.9, 119.7, 111.0, 98.7, 70.5, 64.9, 64.3, 59.9, 39.1, 35.6, 22.1, 21.9.

HRMS (ESI): *m/z* calcd for $C_{21}H_{27}N_3O_4Na$: 408.18993; Found: 408.18894.

Compound 36c

Following the general procedure 4C.6.2, compound **36c** (57 mg, 51 %) was synthesised from bicyclic olefin **35c** (80 mg, 0.2699 mmol) and indole **1a** (28 mg, 0.2429 mmol) using $[Ir(1,5\text{-}COD)Cl]_2$ (9 mg, 0.0135 mmol) and dppe (11 mg, 0.0270 mmol) as pale brown viscous liquid.



R_f: 0.50 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3317, 2978, 2932, 1713, 1457, 1367, 1345, 1290, 1256, 1144, 1107, 1050 cm^{-1}.

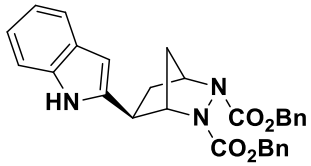
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.37-8.27 (m, 1 H), 7.49 (d, *J* = 7.5 Hz, 1 H), 7.34-7.28 (m, 1 H), 7.11 (t, *J* = 7.5 Hz, 1 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 6.16 (s, 1 H), 4.72-4.66 (m, 1 H), 4.51 (brs, 1 H), 3.53-3.44 (m, 1 H), 2.39-2.16 (m, 2 H), 1.85 (brs, 1 H), 1.64 (brs, 1 H), 1.55-1.47 (m, 15 H), 1.29-1.26 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.8, 139.7, 136.5, 129.0, 128.2, 125.3, 121.7, 120.0, 119.7, 110.7, 99.7, 81.6, 64.8, 64.1, 60.0, 39.2, 35.4, 28.4, 28.2.

HRMS (ESI): *m/z* calcd for $C_{23}H_{31}N_3O_4Na$: 436.22123; Found: 436.22126.

Compound 36d

Following the general procedure 4C.6.2, compound **36d** (52 mg, 49 %) was synthesised from bicyclic olefin **35d** (80 mg, 0.2195 mmol) and indole **1a** (23 mg, 0.1976 mmol) using $[Ir(1,5\text{-}COD)Cl]_2$ (7 mg, 0.0109 mmol) and dppe (9 mg, 0.0220 mmol) as pale yellow viscous liquid.



R_f: 0.39 (hexane/ethyl acetate = 7:3).

IR (neat) ν_{max}: 3340, 3033, 2956, 1714, 1456, 1391, 1322, 1294, 1264, 1165, 1106 cm^{-1}.

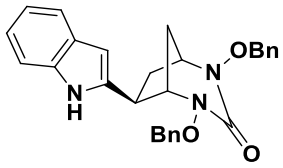
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.81-8.36 (m, 1 H), 7.47 (d, *J* = 7.5 Hz, 1 H), 7.30 (m, 11 H), 7.09 (t, *J* = 7.0 Hz, 1 H), 7.03 (t, *J* = 7.0 Hz, 1 H), 6.11 (s, 1 H), 5.18-5.07 (m, 4 H), 4.69-4.59 (m, 2 H), 3.47-3.29 (m, 1 H), 2.26-2.21 (m, 1 H), 2.03 (brs, 1 H), 1.86-1.84 (m, 1 H), 1.66 (brs, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.5, 138.9, 135.8, 128.6, 128.3, 128.1, 121.8, 120.0, 119.8, 110.8, 99.1, 68.2, 65.1, 60.3, 39.4, 35.6.

HRMS (ESI): *m/z* calcd for $C_{29}H_{27}N_3O_4Na$: 504.18993; Found: 504.18909.

Compound 36e

Following the general procedure 4C.6.2, compound **36e** (86 mg, 80 %) was synthesised from bicyclic olefin **35e** (80 mg, 0.2378 mmol) and indole **1a** (25 mg, 0.2140 mmol) using $[Ir(1,5\text{-}COD)Cl]_2$ (8 mg, 0.0119 mmol) and dppe (10 mg, 0.0238 mmol) as colourless viscous liquid.



R_f: 0.42 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3296, 3032, 2979, 2945, 1699, 1545, 1495, 1456, 1371, 1274, 1214, 1170, 1078, 1029, 990, 911, 786, 749 cm^{-1}.

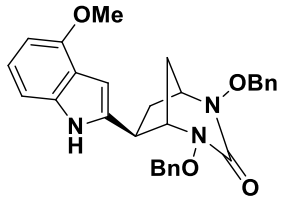
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70-8.65 (m, 1 H), 7.44-7.38 (m, 5 H), 7.33-7.30 (m, 7 H), 7.11-7.08 (m, 1 H), 7.02 (t, *J* = 7.5 Hz, 1 H), 5.95 (s, 1 H), 5.02-5.00 (m, 2 H), 4.89-4.84 (m, 2 H), 3.77 (s, 1 H), 3.70 (t, *J* = 4.0 Hz, 1 H), 3.57 (d, *J* = 4.0 Hz, 1 H), 2.72-2.67 (m, 1 H), 2.06-2.03 (m, 1 H), 1.89-1.86 (m, 1 H), 1.84-1.79 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8, 140.8, 136.2, 136.1, 136.0, 129.7, 129.6, 128.4, 121.5, 119.8, 119.6, 110.8, 97.6, 77.9, 77.8, 67.9, 62.6, 40.9, 36.4, 32.0.

HRMS (ESI): *m/z* calcd for $C_{28}H_{27}N_3O_3Na$: 476.19501; Found: 476.19604.

Compound 36f

Following the general procedure 4C.6.2, compound **36f** (66 mg, 57 %) was synthesised from bicyclic olefin **35e** (80 mg, 0.2378 mmol) and indole **1b** (31 mg, 0.2140 mmol) using $[Ir(1,5\text{-}COD)Cl]_2$ (8 mg, 0.0119 mmol) and dppe (10 mg, 0.0238 mmol) as colourless solid.



M. P. = 192-194 °C.

R_f: 0.36 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3389, 1649, 1453, 1428, 1391, 1360, 1268, 1241, 1168, 1093, 997, 910, 738, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (s, 1 H), 7.44-7.40 (m, 4 H), 7.34-7.32 (m, 6 H), 7.02 (t, *J* = 8.0 Hz, 1 H), 6.93 (d, *J* = 8.5 Hz, 1 H), 6.45 (d, *J* = 8.0 Hz, 1 H), 6.08 (d, *J* = 2.0 Hz, 1 H), 5.03-5.01 (m, 2 H), 4.89-4.84 (m, 2 H), 3.90 (s, 3 H), 3.73-3.69 (m, 2 H), 3.55 (d, *J* = 4.5 Hz, 1 H), 2.71-2.66 (m, 1 H), 2.04-2.01 (m, 1 H), 1.92-1.82 (m, 2 H).

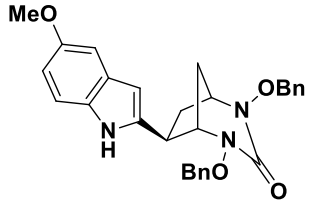
^{13}C NMR (125 MHz, $CDCl_3$): δ 160.7, 152.7, 139.2, 137.4, 136.3, 136.0, 129.7, 129.6, 128.6, 128.5, 128.4, 122.3, 118.6, 104.3, 99.4, 95.0, 77.9, 77.8, 68.0, 62.6, 55.1, 40.9, 36.3, 31.9.

HRMS (ESI): *m/z* calcd for $C_{29}H_{30}N_3O_4$: 484.22363; Found: 484.22456.

Compound 36g

Following the general procedure 4C.6.2, compound **36g** (76 mg, 66 %) was synthesised from bicyclic olefin **35e** (80 mg, 0.2378 mmol) and indole **1c** (31 mg, 0.2140 mmol) using

$[Ir(1,5\text{-COD})Cl]_2$ (8 mg, 0.0119 mmol) and dppe (10 mg, 0.0238 mmol) as yellow viscous liquid.



R_f: 0.37 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3303, 3063, 3033, 2944, 1697, 1589, 1488, 1455, 1372, 1326, 1268, 1209, 1169, 1030, 912, 739, 700 cm^{-1}.

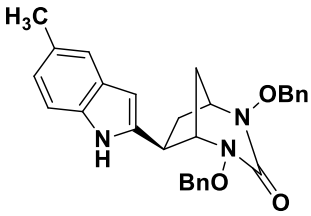
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.36 (brs, 1 H), 7.36-7.32 (m, 4 H), 7.27-7.24 (m, 6 H), 7.12 (d, *J* = 9.0 Hz, 1 H), 6.86 (d, *J* = 2.5 Hz, 1 H), 6.70 (dd, J_1 = 8.5 Hz, J_2 = 7.5 Hz, 1 H), 5.84 (t, *J* = 1.0 Hz, 1 H), 4.95-4.93 (m, 2 H), 4.82-4.77 (m, 2 H), 3.72 (s, 3 H), 3.66-3.63 (m, 2 H), 3.49 (d, *J* = 4.0 Hz, 1 H), 2.63-2.58 (m, 1 H), 1.98-1.96 (m, 1 H), 1.82-1.72 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.7, 153.1, 140.5, 135.2, 134.9, 130.2, 128.6, 128.5, 127.5, 127.5, 127.4, 110.5, 100.9, 96.5, 76.9, 76.8, 66.9, 61.5, 54.9, 40.0, 35.3, 31.0.

HRMS (ESI): *m/z* calcd for $C_{29}H_{30}N_3O_4$: 484.22363; Found: 484.22291.

Compound 36h

Following the general procedure 4C.6.2, compound **36h** (79 mg, 71 %) was synthesised from bicyclic olefin **35e** (80 mg, 0.2378 mmol) and indole **1d** (28 mg, 0.2140 mmol) using $[Ir(1,5\text{-COD})Cl]_2$ (8 mg, 0.0119 mmol) and dppe (10 mg, 0.0238 mmol) as brownish viscous liquid.



R_f: 0.45 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3391, 2929, 2864, 1691, 1455, 1372, 1319, 1267, 1213, 1170, 1028, 992, 911, 784, 740, 700 cm^{-1}.

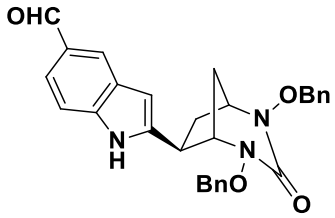
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.48 (brs, 1 H), 7.34-7.30 (m, 4 H), 7.25-7.22 (m, 6 H), 7.14-7.11 (m, 2 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 5.79-5.78 (m, 1 H), 4.93-4.91 (m, 2 H), 4.80-4.75 (m, 2 H), 3.68-3.65 (m, 1 H), 3.60 (t, *J* = 4.0 Hz, 1 H), 3.47 (d, *J* = 4.0 Hz, 1 H), 2.62-2.57 (m, 1 H), 2.32 (s, 3 H), 1.96-1.94 (m, 1 H), 1.81-1.76 (m, 1 H), 1.74-1.69 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.9, 141.0, 136.3, 136.0, 134.5, 129.7, 129.6, 128.6, 128.5, 128.5, 128.5, 128.4, 123.0, 119.5, 110.5, 97.1, 77.9, 77.8, 67.9, 62.7, 41.0, 36.5, 32.1, 21.5.

HRMS (ESI): *m/z* calcd for $C_{29}H_{30}N_3O_3$: 468.22872; Found: 468.22867.

Compound 36i

Following the general procedure 4C.6.2, compound **36i** (78 mg, 68 %) was synthesised from bicyclic olefin **35e** (80 mg, 0.2378 mmol) and indole **1e** (31 mg, 0.2140 mmol) using $[Ir(1,5\text{-}COD)Cl]_2$ (8 mg, 0.0119 mmol) and dppe (10 mg, 0.0238 mmol) as reddish brown viscous liquid.



R_f: 0.34 (hexane/ethyl acetate = 1:1).

IR (neat) ν_{max}: 3409, 1677, 1615, 1549, 1488, 1455, 1428, 1374, 1331, 1306, 1267, 1221, 1163, 1114, 1078, 1029, 998, 909, 786, 741, 701 cm^{-1}.

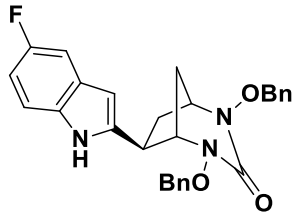
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.30 (s, 1 H), 9.97 (s, 1 H), 7.97 (s, 1 H), 6.80 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1 H), 7.47 (d, J = 8.5 Hz, 1 H), 7.37-7.35 (m, 2 H), 7.31-7.29 (m, 3 H), 7.28-7.26 (m, 2 H), 7.23-7.17 (m, 3 H), 6.04-6.03 (m, 1 H), 4.98-4.96 (m, 1 H), 4.92-4.87 (m, 2 H), 4.82-4.80 (m, 1 H), 3.90 (dd, J_1 = 9.0 Hz, J_2 = 6.0 Hz, 1 H), 3.73 (t, J = 4.0 Hz, 1 H), 3.62 (d, J = 4.5 Hz, 1 H), 2.74-2.69 (m, 1 H), 2.15-2.12 (m, 1 H), 1.97-1.93 (m, 1 H), 1.77-1.72 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 192.5, 161.4, 143.5, 140.0, 135.7, 129.5, 129.5, 129.4, 128.6, 128.5, 128.4, 128.4, 128.2, 124.8, 122.2, 111.7, 98.5, 77.8, 77.8, 67.4, 62.8, 40.8, 37.2, 32.4.

HRMS (ESI): *m/z* calcd for $C_{29}H_{27}N_3NaO_4$: 504.18993; Found: 504.19184.

Compound 36j

Following the general procedure 4C.6.2, compound **36j** (78 mg, 70 %) was synthesised from bicyclic olefin **35e** (80 mg, 0.2378 mmol) and indole **1f** (29 mg, 0.2140 mmol) using $[Ir(1,5\text{-}COD)Cl]_2$ (8 mg, 0.0119 mmol) and dppe (10 mg, 0.0238 mmol) as reddish brown viscous liquid.



R_f: 0.39 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3433, 1650, 1490, 1454, 1375, 1326, 1269, 1211, 1176, 1113, 1029, 995, 959, 911, 852, 747, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.24 (brs, 1 H), 7.39-7.37 (m, 2 H), 7.33-7.31 (m, 5 H), 7.26-7.23 (m, 4 H), 7.08-7.06 (m, 1 H), 6.84 (td, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1 H), 5.88 (t, J =

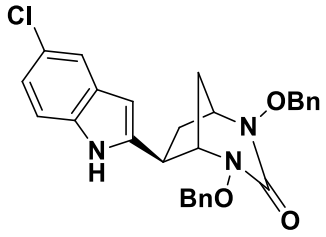
1.0 Hz, 1 H), 4.99-4.93 (m, 2 H), 4.88-4.80 (m, 2 H), 3.79 (s, 1 H), 3.70 (t, *J* = 4.0 Hz, 1 H), 5.80 (d, *J* = 4.0 Hz, 1 H), 2.70-2.65 (m, 1 H), 2.09-2.06 (m, 1 H), 1.92-1.88 (m, 1 H), 1.78-1.73 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2, 158.8, 156.9, 142.9, 135.9, 135.8, 132.7, 129.6, 129.5, 128.6, 128.5, 128.4, 128.4, 111.6, 111.5, 109.6, 109.4, 104.6, 104.5, 97.3, 77.8, 67.7, 62.7, 40.9, 36.9, 32.3.

HRMS (ESI): *m/z* calcd for $C_{28}H_{26}FN_3NaO_3$: 494.18559; Found: 494.18571.

Compound 36k

Following the general procedure 4C.6.2, compound **36k** (86 mg, 74 %) was synthesised from bicyclic olefin **35e** (80 mg, 0.2378 mmol) and indole **1g** (32 mg, 0.2140 mmol) using $[Ir(1,5\text{-COD})Cl]_2$ (8 mg, 0.0119 mmol) and dppe (10 mg, 0.0238 mmol) as brownish viscous liquid.



R_f: 0.45 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3301, 1696, 1580, 1542, 1496, 1453, 1368, 1315, 1267, 1218, 1169, 1062, 1029, 992, 915, 867, 779, 740, 699 cm^{-1}.

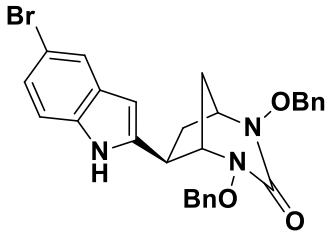
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.30 (s, 1 H), 7.41-7.38 (m, 3 H), 7.33-7.31 (m, 5 H), 7.28-7.23 (m, 4 H), 7.06 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1 H), 5.88-5.87 (m, 1 H), 4.99-4.93 (m, 2 H), 4.89-4.80 (m, 2 H), 3.80 (dd, J_1 = 8.5 Hz, J_2 = 6.0 Hz, 1H), 3.72 (t, *J* = 4.0 Hz, 1 H), 3.57 (d, *J* = 4.5 Hz, 1 H), 2.70-2.65 (m, 1 H), 2.10-2.07 (m, 1H), 1.91-1.87 (m, 1 H), 1.78-1.73 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.1, 142.7, 135.9, 134.5, 129.6, 129.5, 129.3, 128.6, 128.6, 128.5, 128.5, 112.0, 97.0, 77.9, 77.8, 67.7, 62.7, 40.9, 36.9, 32.2.

HRMS (ESI): *m/z* calcd for $C_{28}H_{27}ClN_3O_3$: 488.17409; Found: 488.17340.

Compound 36l

Following the general procedure 4C.6.2, compound **36l** (99 mg, 78 %) was synthesised from bicyclic olefin **35e** (80 mg, 0.2378 mmol) and indole **1h** (42 mg, 0.2140 mmol) using $[Ir(1,5\text{-COD})Cl]_2$ (8 mg, 0.0119 mmol) and dppe (10 mg, 0.0238 mmol) as brownish viscous liquid.



R_f: 0.37 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3279, 3032, 2979, 2944, 1696, 1577, 1540, 1495, 1456, 1373, 1313, 1268, 1214, 1169, 1111, 1078, 1029, 991, 905, 827, 780, 738, 699 cm^{-1}.

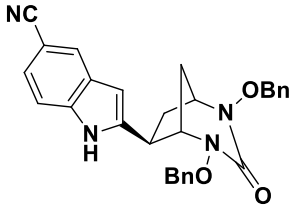
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.35 (s, 1 H), 7.49 (d, *J* = 2.0 Hz, 1 H), 7.31-7.29 (m, 2 H), 7.27-7.22 (m, 5 H), 7.19-7.15 (m, 4 H), 7.11-7.09 (m, 1 H), 5.79 (t, *J* = 1.0 Hz, 1 H), 4.91-4.84 (m, 2 H), 4.80-4.72 (m, 2 H), 3.72 (dd, J_1 = 9.0 Hz, J_2 = 6.0 Hz, 1 H), 3.63 (t, *J* = 4.0 Hz, 1 H), 3.49 (d, *J* = 4.0 Hz, 1 H), 2.62-2.57 (m, 1 H), 2.02-1.99 (m, 1 H), 1.83-1.77 (m, 1 H), 1.68-1.64 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.1, 142.6, 135.9, 134.8, 130.0, 129.6, 129.5, 128.6, 128.6, 128.5, 128.5, 122.2, 112.6, 112.5, 96.8, 77.9, 77.8, 67.6, 62.7, 40.9, 36.9, 32.3.

HRMS (ESI): *m/z* calcd for $C_{28}H_{26}BrN_3O_3Na$: 554.10552; Found: 554.10531.

Compound 36m

Following the general procedure 4C.6.2, compound **36m** (77 mg, 68 %) was synthesised from bicyclic olefin **35e** (80 mg, 0.2378 mmol) and indole **1i** (30 mg, 0.2140 mmol) using $[Ir(1,5\text{-}COD)Cl]_2$ (8 mg, 0.0119 mmol) and dppe (10 mg, 0.0238 mmol) as pale yellow viscous liquid.



R_f: 0.39 (hexane/ethyl acetate = 1:1).

IR (neat) ν_{max}: 3303, 1645, 1455, 1372, 1321, 1268, 1214, 1025, 754 cm^{-1}.

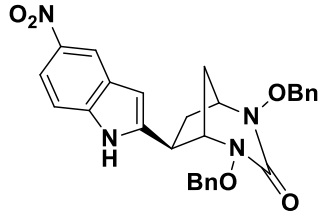
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.04 (brs, 1 H), 7.71 (s, 1 H), 7.36-7.34 (m, 1 H), 7.30-7.22 (m, 6 H), 7.21-7.19 (m, 2 H), 7.17-7.12 (m, 3 H), 5.90 (s, 1 H), 4.91-4.89 (m, 1 H), 4.85-4.80 (m, 2 H), 4.75-4.72 (m, 1 H), 3.80 (dd, J_1 = 8.5 Hz, J_2 = 6.0 Hz, 1 H), 3.67 (t, *J* = 4.0 Hz, 1 H), 3.52 (d, *J* = 4.5 Hz, 1 H), 2.67-2.61 (m, 1 H), 2.08-2.06 (m, 1 H), 1.88-1.84 (m, 1 H), 1.69-1.64 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 142.7, 137.0, 134.5, 128.4, 128.3, 127.6, 127.5, 127.4, 127.0, 124.1, 123.3, 119.8, 110.9, 101.4, 96.5, 76.8, 66.3, 61.6, 39.7, 36.2, 31.3.

HRMS (ESI): *m/z* calcd for $C_{29}H_{26}N_4NaO_3$: 501.19026; Found: 501.19153.

Compound 36n

Following the general procedure 4C.6.2, compound **36n** (89 mg, 75 %) was synthesised from bicyclic olefin **35e** (80 mg, 0.2378 mmol) and indole **1j** (35 mg, 0.2140 mmol) using $[Ir(1,5\text{-COD})Cl]_2$ (8 mg, 0.0119 mmol) and dppe (10 mg, 0.0238 mmol) as pale yellow solid.



M. P. = 185-187 ^{o}C.

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

IR (neat) ν_{max}: 3409, 1687, 1556, 1518, 1470, 1374, 1331, 1270, 1215, 1172, 1070, 1029, 994, 892, 815, 783, 740 cm^{-1}.

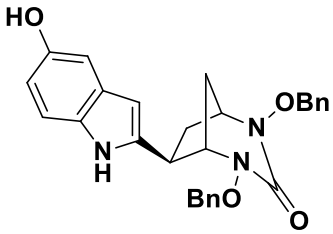
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.70 (s, 1 H), 8.39 (d, *J* = 2.0 Hz, 1 H), 8.02 (dd, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1 H), 7.41 (d, *J* = 9.0 Hz, 1 H), 7.35-7.33 (m, 2 H), 7.32-7.29 (m, 3 H), 7.23-7.19 (m, 3 H), 7.17-7.14 (m, 2 H), 6.04 (t, *J* = 0.5 Hz, 1 H), 4.97-4.95 (m, 1 H), 4.89-4.87 (m, 2 H), 4.81-4.79 (m, 1 H), 3.92 (dd, J_1 = 8.5 Hz, J_2 = 6.0 Hz, 1 H), 3.76 (t, *J* = 4.0 Hz, 1 H), 3.63 (d, *J* = 4.5 Hz, 1 H), 2.74-2.69 (m, 1 H), 2.19-2.17 (m, 1 H), 2.00-1.95 (m, 1 H), 1.74-1.69 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4, 144.7, 141.6, 139.4, 135.5, 135.5, 129.5, 129.4, 128.7, 128.6, 128.4, 127.6, 117.1, 116.9, 110.9, 99.0, 77.9, 77.8, 67.3, 62.7, 40.8, 37.3, 32.4.

HRMS (ESI): *m/z* calcd for $C_{28}H_{26}N_4O_5Na$: 521.18009; Found: 521.18112.

Compound 36o

Following the general procedure 4C.6.2, compound **36o** (45 mg, 40 %) was synthesised from bicyclic olefin **35e** (80 mg, 0.2378 mmol) and indole **1k** (28 mg, 0.2140 mmol) using $[Ir(1,5\text{-COD})Cl]_2$ (8 mg, 0.0119 mmol) and dppe (10 mg, 0.0238 mmol) as light brown viscous liquid.



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

IR (neat) ν_{max}: 3396, 3367, 3034, 2955, 2876, 1668, 1543, 1493, 1456, 1370, 1268, 1211, 1181, 1126, 1029, 924, 844, 750, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (brs, 1 H), 7.44-7.43 (m, 4 H), 7.37-7.34 (m, 6 H), 7.08 (d, *J* = 8.5 Hz, 1 H), 6.85 (d, *J* = 2.5 Hz, 1 H), 6.67 (dd, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1 H), 5.85

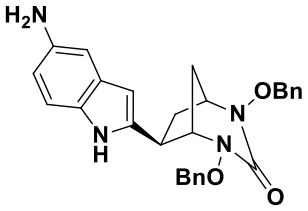
(s, 1 H), 5.07-5.01 (m, 2 H), 4.89-4.86 (m, 2 H), 3.69 (t, J = 4.0 Hz, 1 H), 3.65 (dd, J_1 = 9.0 Hz, J_2 = 6.0 Hz, 1 H), 3.54 (d, J = 4.5 Hz, 1 H), 2.70-2.64 (m, 1 H), 2.04-2.01 (m, 1 H), 1.86-1.80 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 149.7, 141.4, 136.3, 136.0, 131.2, 129.7, 129.6, 128.6, 128.5, 128.4, 111.3, 111.1, 104.5, 97.6, 77.9, 77.8, 68.0, 62.5, 41.1, 36.0, 31.9.

HRMS (ESI): *m/z* calcd for $C_{28}H_{27}N_3O_4Na$: 492.18993; Found: 492.19013.

Compound 36p

Following the general procedure 4C.6.2, compound **36p** (61 mg, 55 %) was synthesised from bicyclic olefin **35e** (80 mg, 0.2378 mmol) and indole **1l** (28 mg, 0.2140 mmol) using $[Ir(1,5\text{-}COD)Cl]_2$ (8 mg, 0.0119 mmol) and dppe (10 mg, 0.0238 mmol) as brownish viscous liquid.



R_f: 0.29 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3617, 3248, 1651, 1425, 1266, 1027, 781, 732 cm^{-1}.

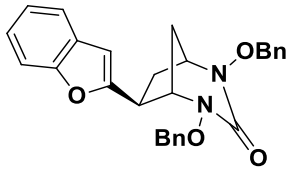
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (s, 1 H), 7.45-7.43 (m, 4 H), 7.36-7.34 (m, 6 H), 7.06 (d, J = 8.5 Hz, 1 H), 6.79 (d, J = 2.0 Hz, 1 H), 5.80 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1 H), 5.82 (t, J = 1.0 Hz, 1 H), 5.06-5.01 (m, 2 H), 4.89-4.86 (m, 2 H), 3.71 (t, J = 4.0 Hz, 1 H), 3.66 (dd, J_1 = 8.5 Hz, J_2 = 5.5 Hz, 1 H), 3.55 (d, J = 9.0 Hz, 1 H), 3.25 (brs, 2 H), 2.69-2.63 (m, 1 H), 2.04-2.02 (m, 1 H), 1.87-1.80 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 150.4, 141.2, 138.7, 136.3, 136.0, 131.0, 129.7, 129.6, 129.0, 128.6, 128.6, 128.4, 112.6, 111.2, 105.5, 97.2, 78.0, 77.9, 68.0, 62.5, 41.1, 36.1, 32.0.

HRMS (ESI): *m/z* calcd for $C_{28}H_{29}N_4O_3$: 469.22397; Found: 469.22344.

Compound 38

Following the general procedure 4C.6.2, compound **38** (52 mg, 48 %) was synthesised from bicyclic olefin **35e** (80 mg, 0.2378 mmol) and benzofuran **37** (25 mg, 0.2140 mmol) using $[Ir(1,5\text{-}COD)Cl]_2$ (8 mg, 0.0119 mmol) and dppe (10 mg, 0.0238 mmol) as pale yellow viscous liquid.



R_f: 0.50 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 2923, 2851, 1643, 1457, 1364, 1266, 1210, 1166, 1026, 914, 749, 702 cm^{-1}.

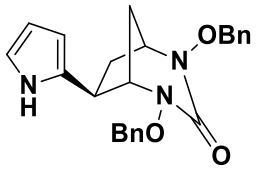
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.42 (m, 5 H), 7.38-7.31 (m, 7 H), 7.21-7.13 (m, 2 H), 6.31 (s, 1 H), 5.08-5.03 (m, 2 H), 4.90-4.86 (m, 2 H), 3.87 (dd, J_1 = 9.0 Hz, J_2 = 5.5 Hz, 1 H), 3.72-3.70 (m, 2 H), 2.71-2.66 (m, 1 H), 2.12-2.09 (m, 1 H), 2.04-1.99 (m, 1 H), 1.94-1.89 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.6, 158.6, 154.7, 136.2, 136.1, 129.6, 129.4, 128.4, 128.4, 123.8, 122.7, 120.5, 110.9, 102.2, 77.8, 77.8, 67.0, 62.7, 40.9, 34.9, 32.6.

HRMS (ESI): *m/z* calcd for $C_{28}H_{26}N_2NaO_4$: 477.17903; Found: 477.17776.

Compound 40

Following the general procedure 4C.6.2, compound **40** (51 mg, 53 %) was synthesised from bicyclic olefin **35e** (80 mg, 0.2378 mmol) and pyrrole **39** (14 mg, 0.2140 mmol) using $[Ir(1,5\text{-}COD)Cl]_2$ (8 mg, 0.0119 mmol) and dppe (10 mg, 0.0238 mmol) as light brown viscous liquid.



R_f: 0.39 (hexane/ethyl acetate = 3:2).

IR (neat) ν_{max}: 3272, 1653, 1498, 1454, 1374, 1264, 1214, 1166, 1028, 784, 728 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (brs, 1 H), 7.35-7.34 (m, 4 H), 7.29-7.23 (m, 6 H), 6.53-6.52 (m, 1 H), 5.93 (q, J = 3.0 Hz, 1 H), 5.59 (s, 1 H), 4.95-4.91 (m, 2 H), 4.79-4.75 (m, 2 H), 3.59 (t, J = 4.0 Hz, 1 H), 3.55-3.52 (m, 1 H), 3.39 (d, J = 4.5 Hz, 1 H), 2.59-2.54 (m, 1 H), 1.93-1.91 (m, 1 H), 1.78-1.74 (m, 1 H), 1.69-1.64 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.7, 136.3, 136.1, 133.7, 129.6, 129.5, 128.5, 128.4, 117.1, 108.0, 103.6, 77.8, 77.8, 68.2, 62.5, 40.5, 36.4, 31.8.

HRMS (ESI): *m/z* calcd for $C_{24}H_{25}N_3NaO_3$: 426.17936; Found: 426.17895.

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CHAPTER 5

Rh(III) Catalyzed Synthesis of Azaheterocycles

PART A

Rhodium Catalyzed C-H Activation of *O*-acetylketoximes towards the Synthesis of Isoquinoline Fused Bicycles

5A.1. Introduction

Isoquinolines constitute an important class of heterocycles, ubiquitous in a variety of natural products, biologically active molecules, and synthetic pharmaceutical compounds (Figure 5A.1).[1–3] Over the past decade much effort has been directed towards the development of efficient synthetic methodologies to obtain these heterocycles. Recent advances in transition metal catalyzed reactions have paved a way to the facile syntheses of these heterocycles *via* the functionalization of omnipresent carbon–hydrogen bonds.[4–8] The formation of these heterocycles largely depends upon the directing groups present in the starting materials. Among these attempts, transition metal-catalyzed reactions involving oximes have emerged as a promising synthetic protocol.[9]

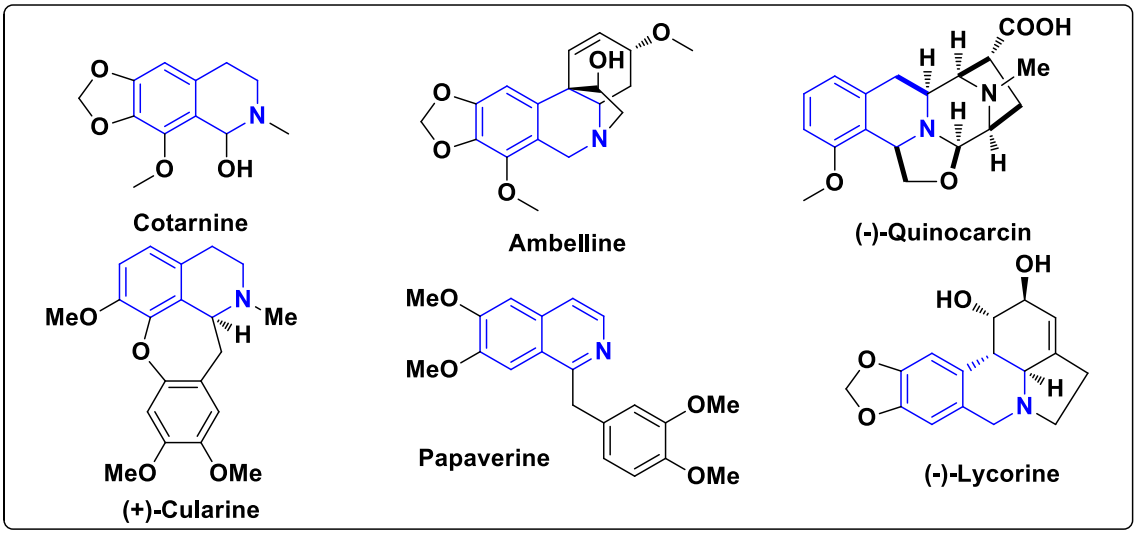


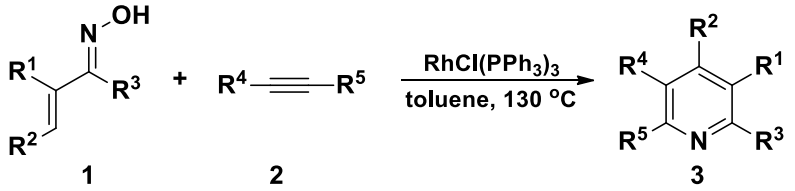
Figure 5A.1. Biologically relevant isoquinoline derivatives

5A.2. C-H Activation of Oximes

Oximes can be generated by the reaction of hydroxylamine derivatives with aldehydes or ketones and are further classified as hydroxy oximes, oxime ethers and oxime esters. Different strategies by the transition metal catalyzed reactions using Rh, Ru, Pd, Co, Ni and so forth have been reported for the C-H activation of oximes. Of these, some selected reports are mentioned in the following sections.

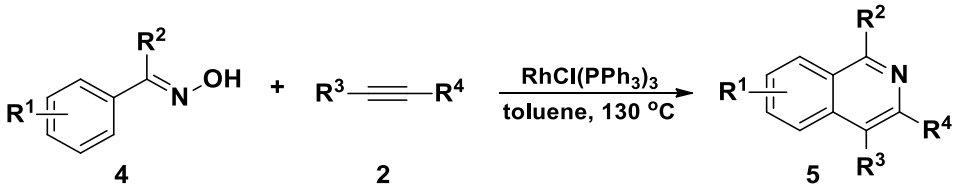
5A.2.1. Using Rhodium

The strategy of using oximes as directing groups in the synthesis of heterocycles came to lame light in 2008 when Cheng *et al*. reported the rhodium-catalyzed coupling reaction of α,β-unsaturated ketoximes **1** with alkynes **2** to synthesize highly substituted pyridine derivatives **3** (Scheme 5A.1). Even though styryl methyl ketoxime did not underwent the reaction, α- and β-substituted alkyl vinyl ketoximes reacted with diphenylacetylene or aliphatic alkynes smoothly.[10]



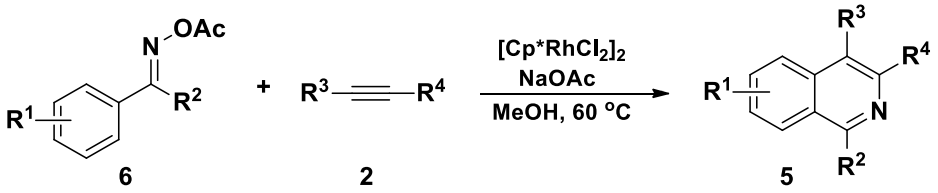
Scheme 5A.1

The similar strategy was extended by Cheng and coworkers in 2009 to synthesize isoquinoline **5** and tetrahydroquinoline derivatives by rhodium catalyzed C–H activation using aromatic ketoximes **4** and alkynes **2** (Scheme 5A.2).[11] Wilkinson's catalyst ($Rh(PPh_3)_3Cl$) proved to be the most effective one for this transformation.



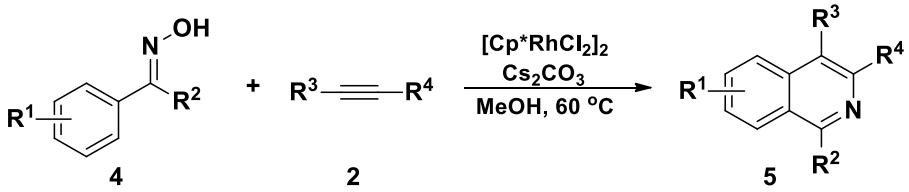
Scheme 5A.2

In 2010, Chiba *et al*. reported the synthesis of isoquinolines **5** using *O*-acetyl aryl ketoxime derivatives **6** with internal alkynes **2** using $[Cp^*RhCl_2]_2$ as the catalyst (Scheme 5A.3). Here the N-O bond of oxime derivatives worked as an internal oxidant to maintain the catalytic cycle.[12]



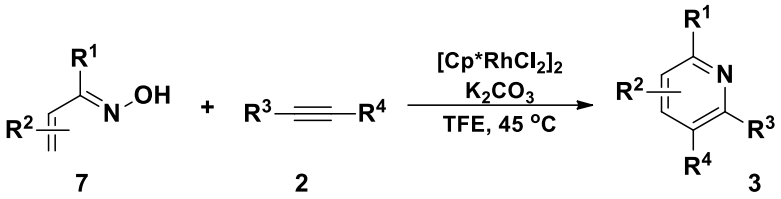
Scheme 5A.3

Rh(III)-catalyzed dehydrative C–C and C–N coupling reaction of oximines and internal alkynes was explored by Zhao, Jia and Li *et al*. in 2011 (Scheme 5A.4). Substituted aromatic oximes **4** and asymmetric alkynes **2** containing phenyl and alkyl groups reacted smoothly to afford isoquinoline products **5** in moderate to good yields.[13]



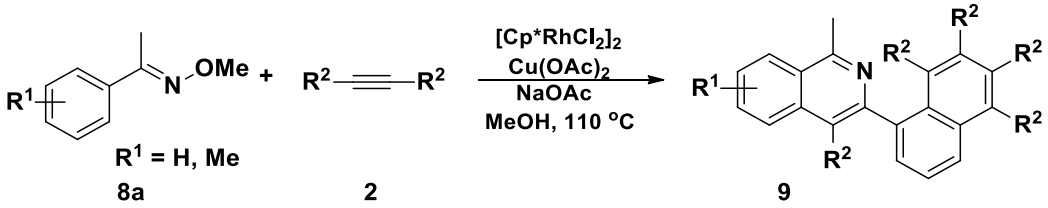
Scheme 5A.4

A variety of substituted α,β-unsaturated oximes **7** and alkynes **2** underwent coupling reaction under mild conditions to synthesize pyridine derivatives **3** (Scheme 5A.5). The report by Rovis *et al*. also elucidated the synthesis of isoquinolines with ketoximes.[14]



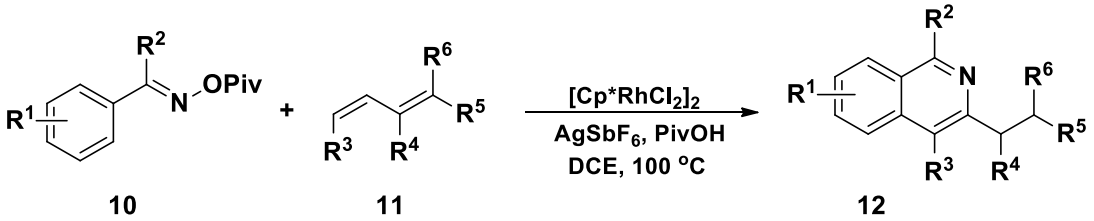
Scheme 5A.5

Rhodium(III)-catalyzed cascade oxidative annulation of aryl ketoximes **8a** with diphenylacetylene **2** by sequential cleavage of multiple C-H bonds with $Cu(OAc)_2$ as oxidant to construct highly congested isoquinolines **9** in moderate to good yields was explored by Shi *et al.* (Scheme 5A.6).[15]



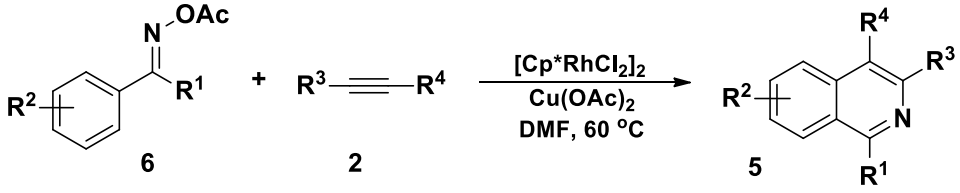
Scheme 5A.6

Glorius *et al*. described the reaction of *O*-pivaloyl aryl ketoximes **10** and 1,3-dienes **11** through redox-neutral C–H activation/aromatization cascade catalyzed by Rh(III) to achieve the synthesis of isoquinolines **12** (Scheme 5A.7). The use of α,β-unsaturated oxime esters in the reaction provided access to pyridine derivatives.[16]



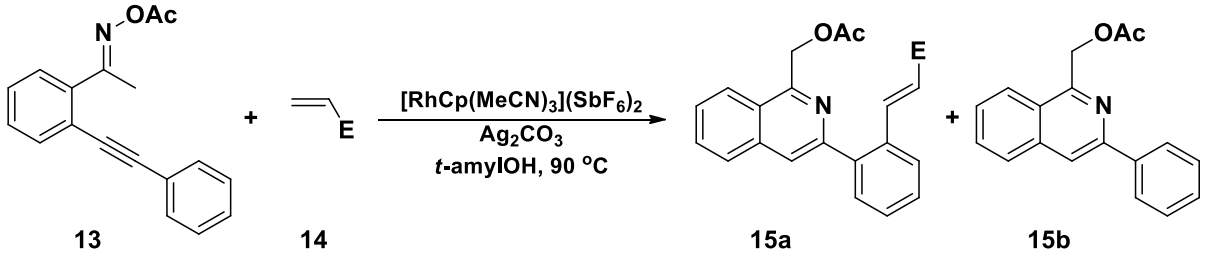
Scheme 5A.7

In 2011, a Cu–Rh-catalyzed aza-heterocycle synthesis using aryl *O*-acetyl ketoximes **6** and internal alkynes **2** was described by Chiba *et al.* (Scheme 5A.8).[17]



Scheme 5A.8

Rhodium(III)-catalyzed cyclization and olefination of *N*-acetoxy ketoimines with alkynes **13** developed by Li *et al*. afforded (2-acetoxymethyl)isoquinolines **15a** bearing an *ortho*-olefinated aryl group (Scheme 5A.9). This reaction sequence involved Rh(III)-catalyzed alkyne cyclization with intramolecular 1,3-acetoxyl migration and isoquinoline directed *ortho*- C-H olefination.[18] The use of Ag_2CO_3 as external oxidant was essential for the olefination step.

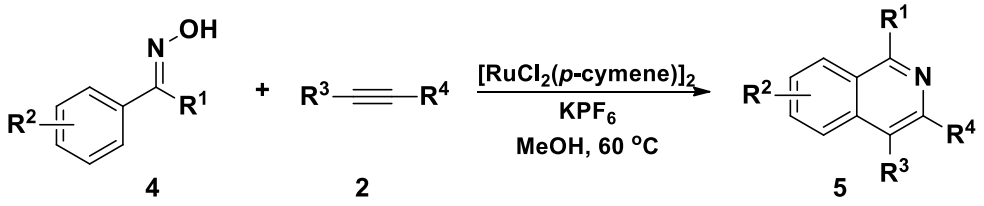


Scheme 5A.9

5A.2.2. Using Ruthenium

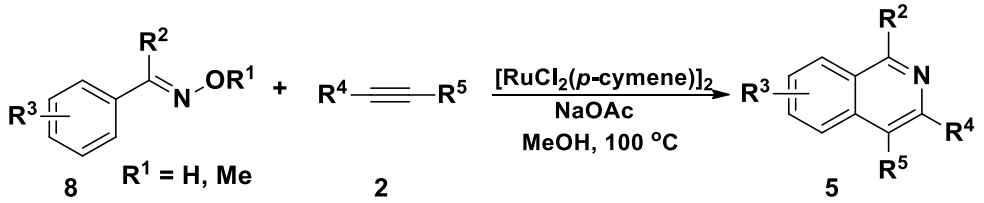
Cationic ruthenium-catalyzed cyclization of aromatic oximes **4** through catalytic dehydrative C−H/N−O bond functionalization was developed by Ackermann *et al*. in 2012

(Scheme 5A.10). The cationic ruthenium (II) species was derived from $[RuCl_2(p\text{-cymene})]_2$ and KPF_6 in situ.[19]



Scheme 5A.10

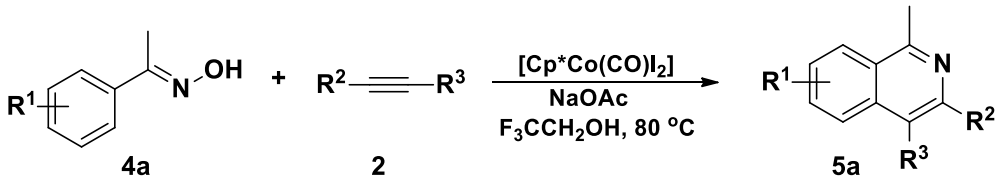
Ruthenium catalyzed highly regioselective cyclization of aromatic ketoximes **8** with alkynes **2** to synthesize substituted isoquinoline derivatives **5** by C-H bond activation were unraveled by Jeganmohan *et al.* (Scheme 5A.11). The reaction was compatible with both aromatic or heteroaromatic ketoximes and oxime ethers.[20]



Scheme 5A.11

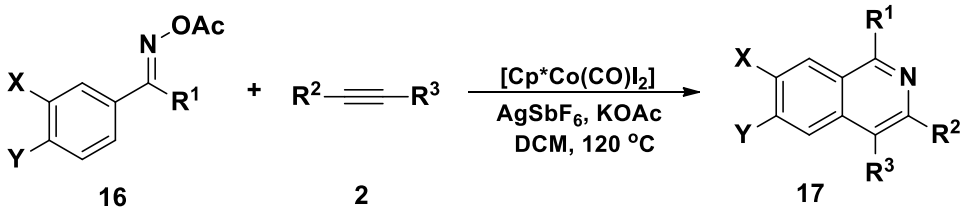
5A.2.3. Using Cobalt

Co(III)-catalyzed redox-neutral dehydrative [4 + 2] annulation of oximes **4a** with alkyne **2** by C-H and N-OH activation to furnish polysubstituted isoquinoline derivatives **5a** without an external oxidant was reported by Sundararaju *et al*. in 2015 (Scheme 5A.12).[21]



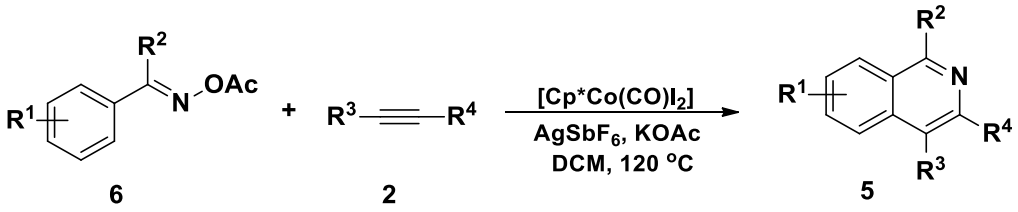
Scheme 5A.12

The same strategy *via* site selective C–H activation of unsymmetrical *O*-acyl oximes **16** and subsequent coupling with terminal/internal alkynes **2** was illustrated by Kanai and Matsunaga *et al.* (Scheme 5A.13).[22] Compared to Rh(III) catalysts, the Cp*Co(III) catalyst showed higher site selectivity and reactivity affording multi-substituted isoquinolines in good to excellent yields with numerous unsymmetrical *O*-acyl oximes.



Scheme 5A.13

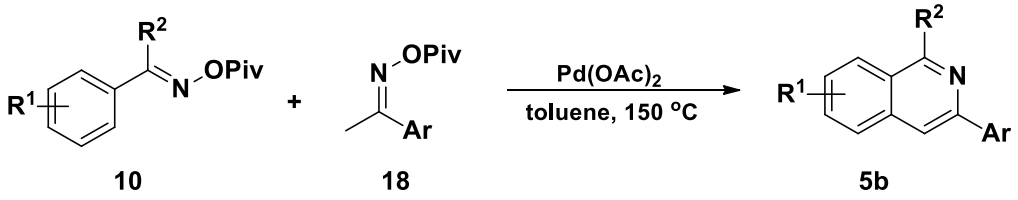
Ackermann *et al*. investigated the Co (III)-catalyzed reaction of *O*-acetyl oximes **6** and alkynes **2** through isohypsic annulations to synthesize isoquinolines **5** (Scheme 5A.14).[23] Competitive experiments proved that electron rich substrates were more reactive indicating a base assisted intramolecular electrophilic-type substitution mechanism.



Scheme 5A.14

5A.2.4. Using Palladium

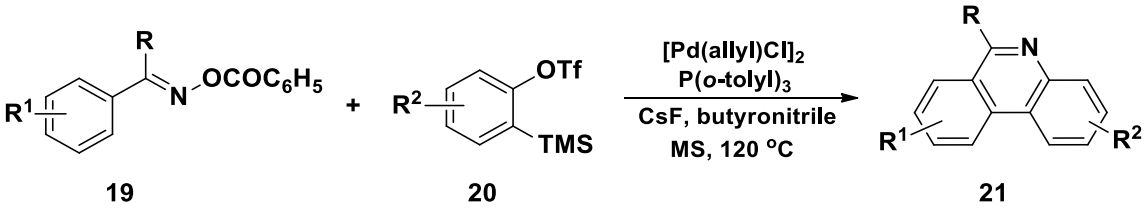
The Pd(II)-catalyzed coupling reaction of methyl ketone oxime esters with aryl oxime esters to synthesize substituted isoquinolines *via* aromatic C–H alkylation was developed by Yang *et al.* (Scheme 5A.15).[24] Various substituted methyl/non-methyl aryl oxime pivalates **10** with methyl ketone oxime pivalates **18** delivered the corresponding isoquinolines **5b** in moderate to good yields.



Scheme 5A.15

Novel palladium-catalyzed synthesis of isoquinolines and phenanthridines **21** *via* C-H functionalization and sequential annulation of aryl ketoxime *O*-pentafluorobenzoates and acetophenone-type acyl oximes **19** with *o*-(trimethylsilyl)phenyl triflate **20** was demonstrated by Neuville and Zhu (Scheme 5A.16). This report represented the first example wherein a $\{R^1R^2C{=}N\text{-}Pd\}$ species generated by oxidative addition of acyloxime to Pd (0) underwent

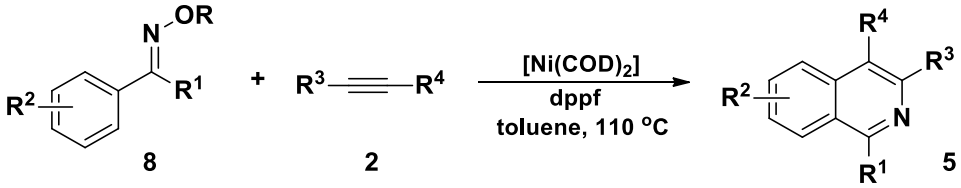
intermolecular aminopalladation reaction of alkynes.[25]



Scheme 5A.16

5A.2.5. Using Nickel

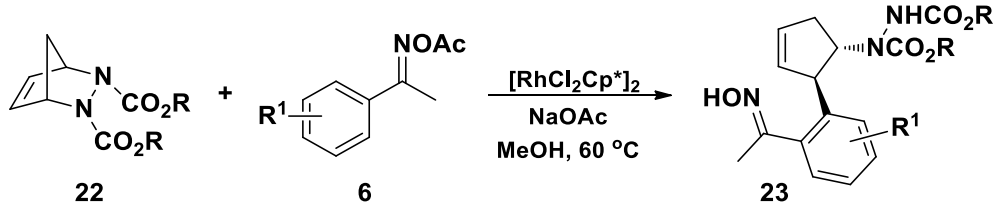
Kurahashi and Matsubara *et al*. explored the nickel-catalyzed cycloaddition of aromatic ketoxime ethers **8** with alkynes **2** to synthesize 3,4-disubstituted isoquinoline derivatives **5** in moderate to good yields (Scheme 5A.17). 3,4-disubstituted isoquinoline *N*-oxides were also synthesized *via* a similar reaction using ketoximes instead of *O*-benzyl ketoximes.[26]



Scheme 5A.17

5A.3. Statement of the Problem

The rhodium-catalyzed desymmetrization of diazabicyclic olefins **22** *via* the *ortho* functionalization of oximes **6** was reported independently by Cui *et al.* and our group (Scheme 5A.18).[27,28] The present strategy provides an efficient access to biologically important *trans*-functionalized cyclopentenes **23** and spiro[2.4]heptenes without using pre-functionalized starting materials.



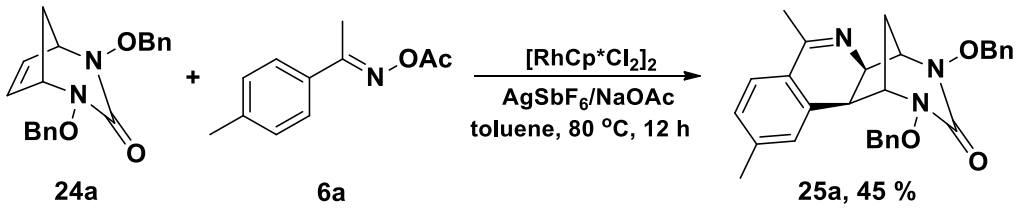
Scheme 5A.18

Our continued interest in the functionalization of bicyclic systems together with the aim of developing biologically relevant molecules prompted us to expand the scope of these reactions to more biologically potent urea derivatives. Enthralled by the biological

significance of urea derivatives, we envisaged that the coupling of biologically important isoquinolines with urea derivatives could significantly increase their biological activity. With this idea in mind, we started our investigations with the reaction of urea-derived bicyclic olefins and *O*-acetylketoximes, the results of which are presented in the following sections. To the best of our knowledge, this is the first report on the rhodium catalyzed ring annulation *via* C-H activation on urea-derived bicycles.

5A.4. Results and Discussion

We started our investigations with the reaction of urea-derived bicyclic olefin **24a** with the *O*-acetyl ketoxime **6a** using $[RhCp^*Cl_2]_2$ as the catalyst and NaOAc as additive in accordance with our previous report.[28] To our dismay, the reaction didn't furnish any fruitful result. Surprisingly, the use of $[RhCp^*Cl_2]_2/AgSbF_6$ as the catalyst system and increasing the temperature to 80 ^oC, furnished the annulated product **25a** in 45 % yield (Scheme 5A.19).



Scheme 5A.19. Reaction of *O*-acylketoxime with urea-derived bicyclic olefin

The structure of the product was confirmed using various spectroscopic techniques such as ^1H NMR, ^{13}C NMR and HRMS analyses. The IR spectrum of **25a** showed characteristic carbonyl absorption of the urea at 1715 cm^{-1}.

In the ^1H NMR (Figure 5A.2), the aromatic protons were discernable in the region δ 7.51-6.87 ppm. The multiplets in the region δ 5.15-5.05 and δ 4.98-4.91 ppm were assigned to the methylene protons of the benzyloxy groups. The proton on the carbon attached to the nitrogen atom of the isoquinoline appeared as a doublet at δ 4.77 ppm. The proton on each carbon attached to nitrogen atom of the urea group appeared as doublets at δ 3.93 and δ 3.35 ppm. The proton attached to the carbon bearing the phenyl ring of isoquinoline appeared as a doublet at δ 3.72 ppm. The methyl protons were discernible at δ 2.33 and δ 2.28 ppm. The bridge protons resonated as a multiplet in the region δ 1.99-1.97 and δ 1.58-1.53 ppm.

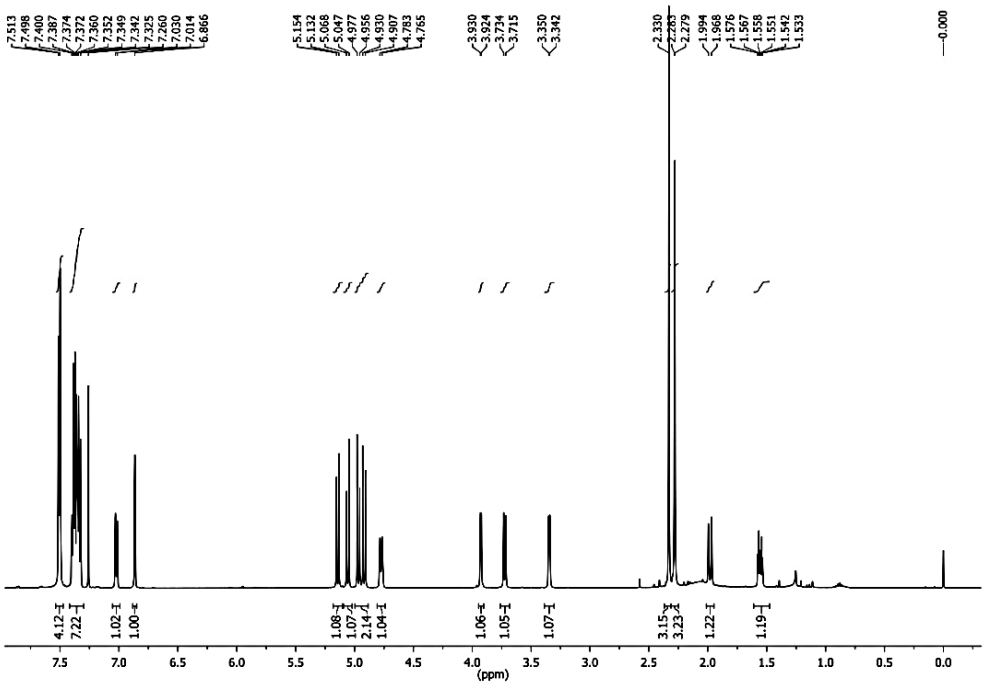


Figure 5A.2. ^{1}H NMR spectrum of compound **25a**

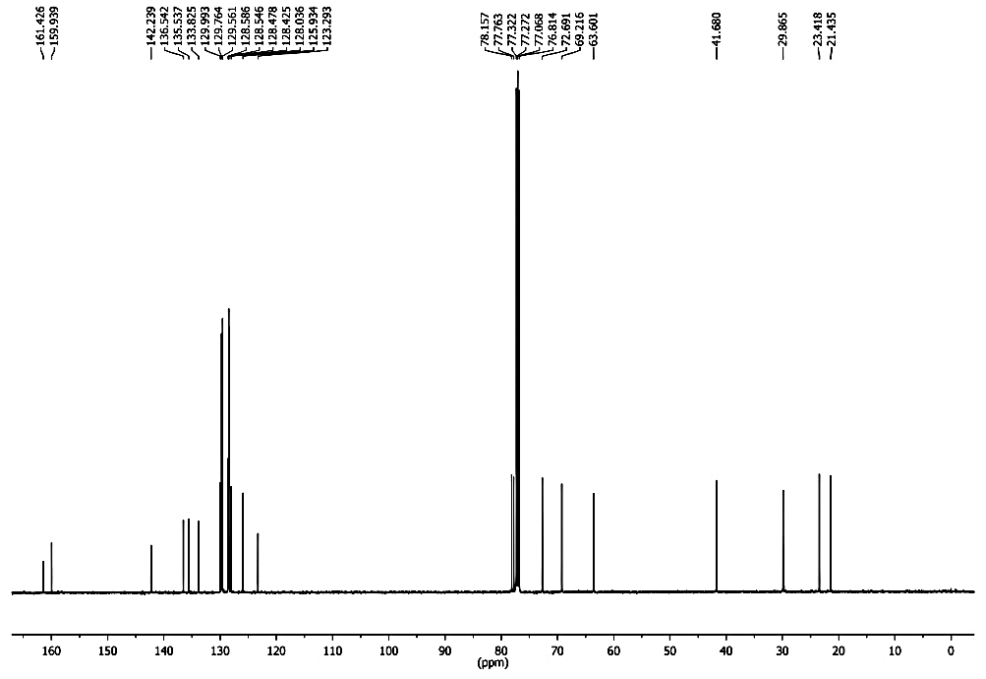


Figure 5A.3. ^{13}C NMR spectrum of compound **25a**

^{13}C NMR of **25a** (Figure 5A.3) displayed the carbonyl peak of the urea at 161.4 ppm. The methylene carbons of the benzyloxy groups were identified at δ 78.2 and 77.8 ppm. Each

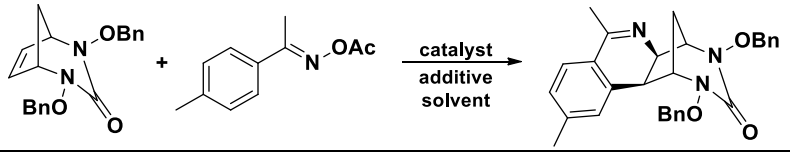
carbon bearing the nitrogen atom resonated at δ 72.7 and 69.2 ppm. The peak at δ 63.6 ppm was assigned to the carbon attached to the nitrogen atom of the isoquinoline. The carbon bearing the phenyl group of isoquinoline appeared at δ 41.7 ppm. The methylene carbon resonated at δ 29.9 ppm. The methyl carbons were discernible at δ 23.4 and δ 21.4 ppm.

Further confirmation was obtained from HRMS-ESI analysis that showed $[M+H]^+$ peak at 468.22974.

5A.4.1. Optimization Studies

Detailed optimization studies performed revealed that other solvents such as CH_3CN and DMF were futile for this transformation (Table 5A.1, entry 4 and 5). The reaction was found to be optimal using toluene as the solvent (entry 7). Ru(II)/Ag(I) catalyst system was found to be ineffective for the present transformation (entry 8). Finally, the best reaction condition that gave a maximum yield of 91 % was found to be 5 mol% of $[RhCp^*Cl_2]_2$ as the catalyst, 10 mol% of $AgSbF_6$ and 2 equiv. of $Cu(OAc)_2$ as the additive in toluene at 80 ^oC for 12 h (entry 7).

Table 5A.1. Optimization studies for the synthesis of isoquinoline derivatives[a]



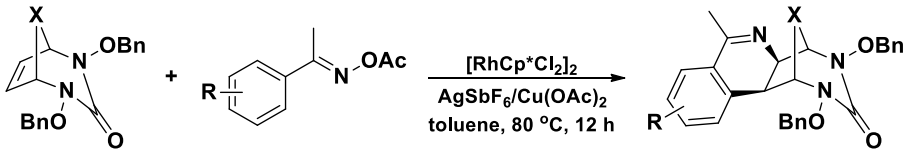
Entry	Catalyst	Additive	Solvent	Yield (%)[b]
1	$[RhCp^*Cl_2]_2$	NaOAc	MeOH	nr
2	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	toluene	nr
3	$[RhCp^*Cl_2]_2$	$AgSbF_6$/NaOAc	toluene	45
4	$[RhCp^*Cl_2]_2$	$AgSbF_6/Cu(OAc)_2$	CH_3CN	trace
5	$[RhCp^*Cl_2]_2$	$AgSbF_6/Cu(OAc)_2$	DMF	nr
6	$[RhCp^*Cl_2]_2$	$AgSbF_6/Cu(OAc)_2$	xylene	60
7	**$[RhCp^*Cl_2]_2$**	**$AgSbF_6/Cu(OAc)_2$**	**toluene**	**91**
8	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6/Cu(OAc)_2$	toluene	nr

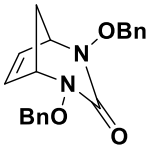
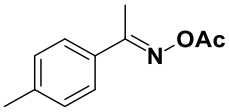
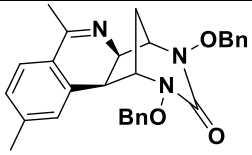
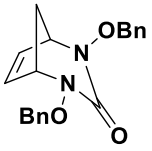
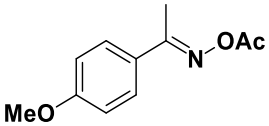
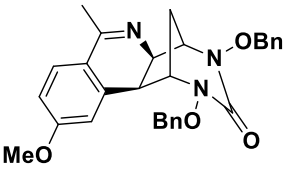
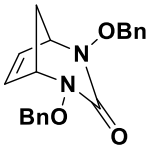
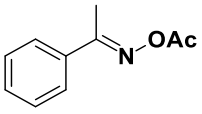
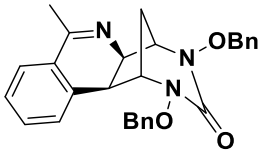
[a]**Reaction conditions:** adduct (1 equiv.), *O*-acetyl ketoxime (1 equiv.), catalyst (5 mol%), $AgSbF_6$ (10 mol%), additive (2 equiv.), solvent (2 mL), 80 ^oC, 12 h. nr = no reaction. [b]Isolated yield.

5A.4.2. Scope of the Reaction

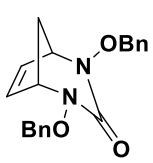
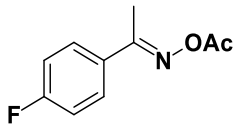
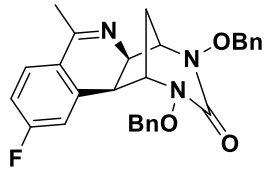
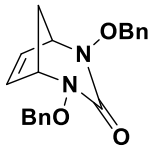
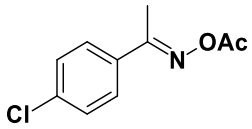
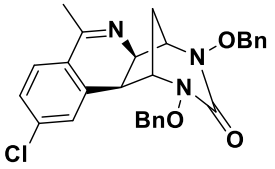
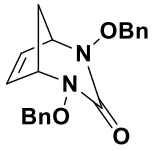
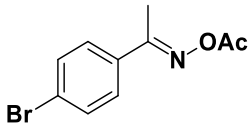
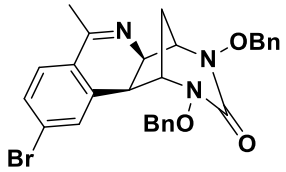
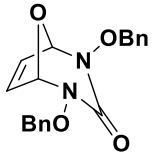
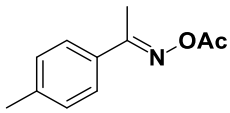
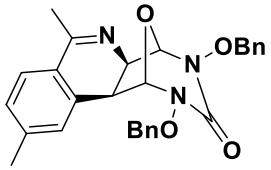
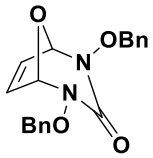
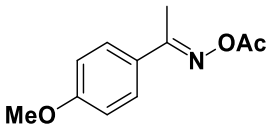
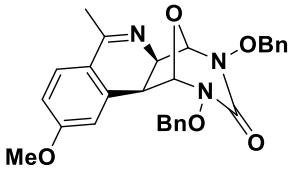
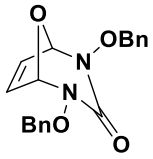
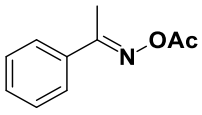
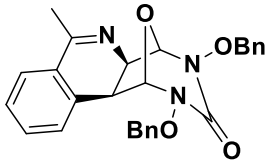
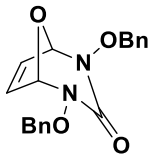
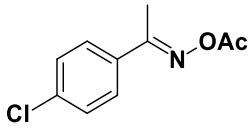
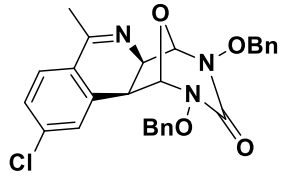
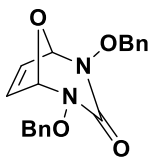
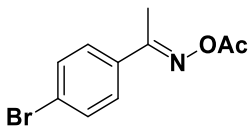
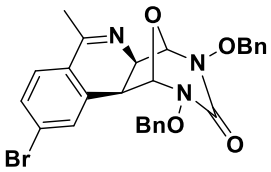
The scope of this reaction was checked with different substituted ketoximes and bicylic olefins derived from furan and Boc-protected pyrrole (Table 5A.2). Ketoximes bearing substituents such as OMe, F, Cl and Br groups furnished the isoquinoline derivatives in moderate to good yields (**25b**, **25d-25f**). Compared to other bicyclic olefins (**25a-25k**), yields with pyrrole derived bicyles were moderate (**25l-25n**). No product was formed when the reaction of NO_2 substituted oxime was conducted with **24a** (**25r**). Also, *ortho*- and *meta*-substituted ketoximes were not siutable for this transformation as the reactions of 2-chloro and 2-trifluoromethyl *O*-acetyl ketoximes with the bicyclic olefins were futile (**25s** & **25t**). In our previous report, the reaction of ketoximes with diazabicyclic olefins generated the ring opened 3,4-disubstituted cyclopentene derivatives without the presence of $AgSbF_6$ as the additive.[28] We were curious to check the reactivity of diazabicyclic olefins under this optimized conditions, and interestingly, the annulated isoquinoline derivatives **25o**-**25q** were formed in this reaction instead of the ring opened product.

Table 5A.2. Reaction of oximes with bicyclic olefins [a]



Entry	Bicyclic Olefin	Oximes	Product	Yield (%)[b]
1	 **24a**	 **6a**	 **25a**	91
2	 **24a**	 **6b**	 **25b**	76
3	 **24a**	 **6c**	 **25c**	84

Continued..

4	 **24a**	 **6d**	 **25d**	52
5	 **24a**	 **6e**	 **25e**	55
6	 **24a**	 **6f**	 **25f**	56
7	 **24b**	 **6a**	 **25g**	75
8	 **24b**	 **6b**	 **25h**	64
9	 **24b**	 **6c**	 **25i**	70
10	 **24b**	 **6e**	 **25j**	47
11	 **24b**	 **6f**	 **25k**	50

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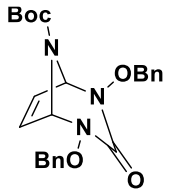
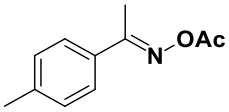
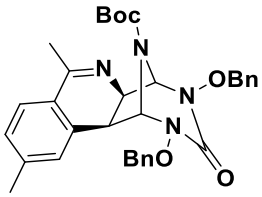
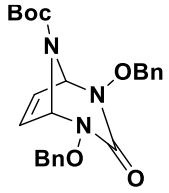
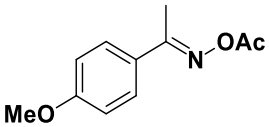
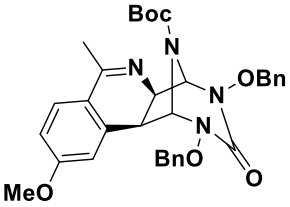
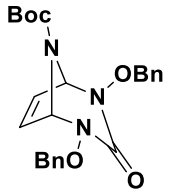
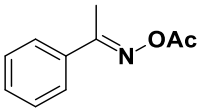
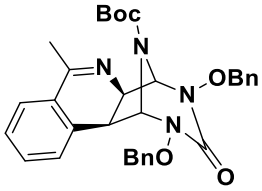
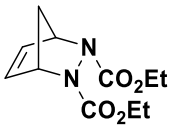
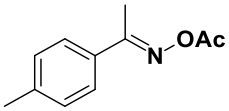
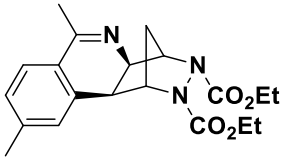
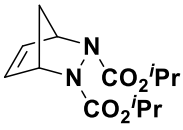
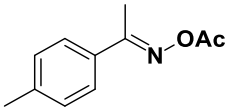
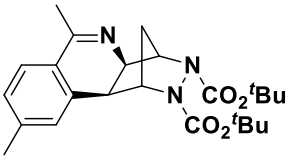
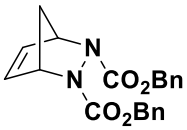
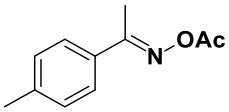
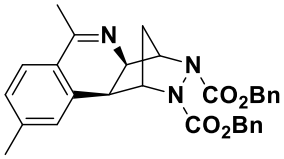
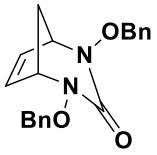
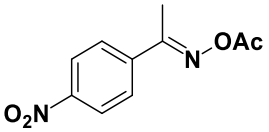
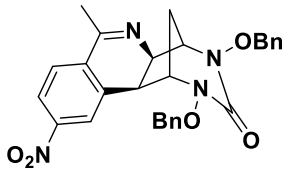
12	 **24c**	 **6a**	 **25l**	62
13	 **24c**	 **6b**	 **25m**	51
14	 **24c**	 **6c**	 **25n**	56
15	 **24d**	 **6a**	 **25o**	66
16	 **24e**	 **6a**	 **25p**	51
17	 **24f**	 **6a**	 **25q**	58
18	 **24a**	 **6g**	 **25r**	0

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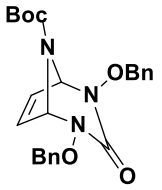
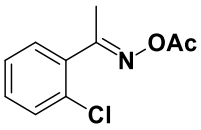
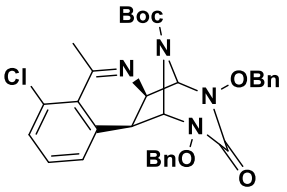
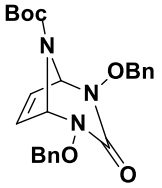
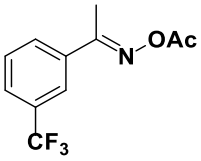
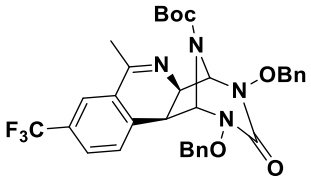
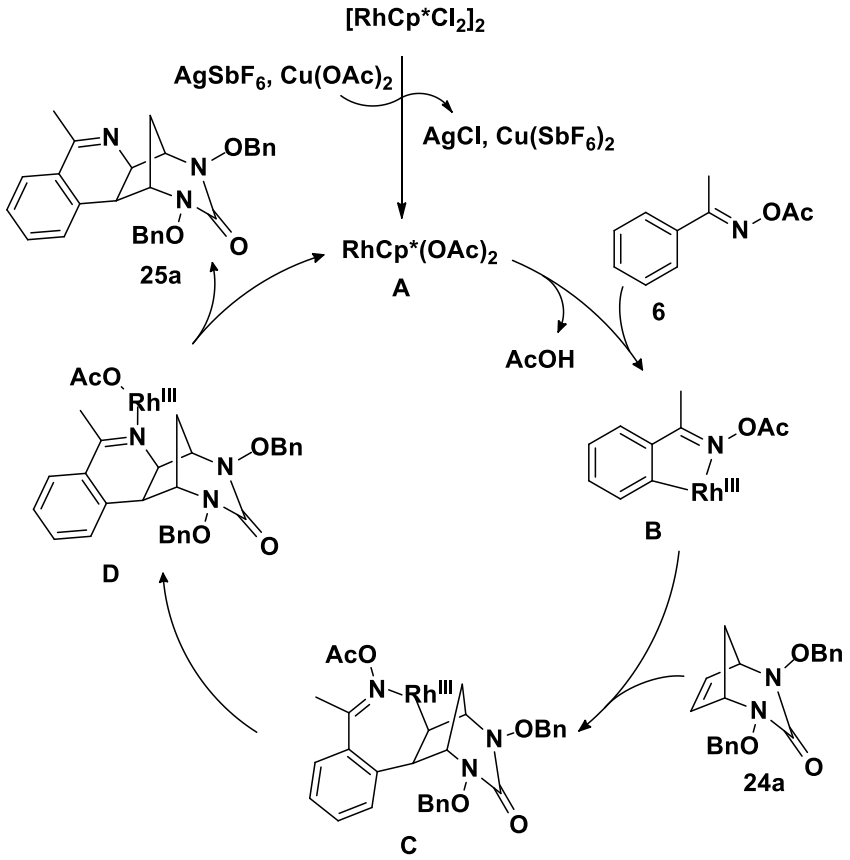
19	 **24c**	 **6h**	 **25s**	0
20	 **24c**	 **6i**	 **25t**	0

[a]**Reaction conditions:** adduct (1 equiv.), ketoxime (1 equiv.), $[RhCp^*Cl_2]_2$ (5 mol%), $AgSbF_6$ (10 mol%), $Cu(OAc)_2$ (2 equiv.), toluene (2 mL), 80 °C, 12 h. [b]Isolated yield.

5A.5. Mechanistic Pathway

A plausible mechanistic pathway for the synthesis of isoquinoline derivatives is illustrated in Scheme 5A.20 in accordance with the literature reports.[12,29]



Scheme 5A.20. Proposed reaction mechanism

The active Rh(III) complex **A** is formed by the removal of chloride using $AgSbF_6$. Subsequently, the formation of the rhodacycle **B** occurs *via* the cleavage of C-H bond and coordination to the nitrogen atom. The intermediate **B** then adds to the olefinic bond in **24a** to form the seven membered intermediate **C**. The intermediate **C** then undergoes N–O bond cleavage and oxidative addition of rhodium species to the N-O bond occurs to form the intermediate **D**. Intermediate **D** undergoes reductive elimination to form the product **25a** and regenerates the active rhodium species.

5A.6. Conclusion

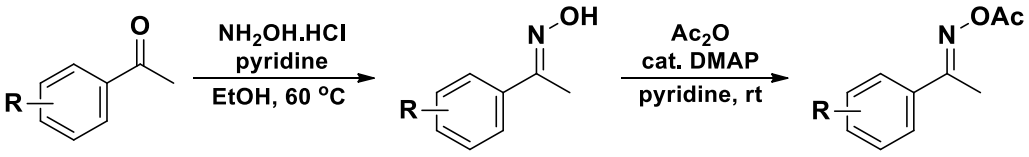
In conclusion, we have developed an efficient strategy for the construction of isoquinoline fused urea-derived bicyclic olefins. The rhodium-catalyzed reaction of *O*-acetylketoximes furnished the isoquinoline derivatives. Considering the biological significance of the urea derivatives and these heterocycles, the synthesized products are expected to show good biological activity. The evaluation of biological properties of the synthesized urea derivatives are in progress in our laboratory.

5A.7. Experimental Section

5A.7.1. General Methods

General information about the experiments is given in Section 2.8.1 of Chapter 2.

5A.7.2. General Procedure for the Preparation of Aryl Ketone *O*-Acetyloximes[30]



Scheme 5A.21

To a solution of aryl ketone (1 equiv.) and pyridine (2.8 equiv.) in EtOH (10 mL) was added $NH_2OH.HCl$ (1.5 equiv.) in one portion and the reaction mixture was stirred at 60 ^oC for 1 h. The reaction was quenched by adding water and the organic materials were extracted twice with ethyl acetate. The combined extracts were washed with 1N aqueous HCl and brine, and dried over Na_2SO_4. Volatile materials were removed in *vacuo* to give aryl ketone oxime, which was used for the next acetylation without further purification.

The crude residue of aryl ketone oxime obtained above was treated with Ac_2O (2 equiv.) and a catalytic amount of 4-dimethylaminopyridine (5 mg) in pyridine (10 mL) and the reaction mixture was stirred at room temperature for 1 h. After volatile materials were

evaporated, the resulting residue was treated with water, and organic materials were extracted twice with ethyl acetate. The combined extracts were washed with 1N aqueous HCl and brine, and dried over Na_2SO_4. The solvents were removed under reduced pressure, giving white solid of crude aryl ketone *O*-acetyloximes. Further recrystallization was conducted from ethyl acetate-hexane to provide pure products.

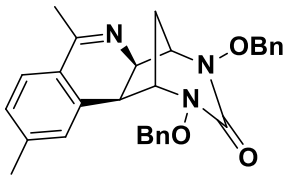
5A.7.3. General Procedure for the Synthesis of Isoquinoline Derivatives

A mixture of urea derived bicyclic olefin **24** (1 equiv.), *O*-acetylketoxime **6** (1 equiv.), $[RhCl_2Cp^*]_2$ (5 mol%), $AgSbF_6$ (10 mol%) and $Cu(OAc)_2$ (2 equiv.) were weighed into a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 80 ^oC for 12 hours. The solvent was evaporated *in vacuo* and the residue on silica column chromatography (100-200 mesh) with hexane-ethylacetate mixtures yielded isoquinoline fused bicycle **25**.

5A.7.4. Characterization of the Products

Compound 25a

Following the general procedure 5A.7.3, compound **25a** (76 mg, 91 %) was synthesised from bicyclic olefin **24a** (60 mg, 0.1784 mmol) and *O*-acetylketoxime **6a** (34 mg, 0.1784 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol), $AgSbF_6$ (6 mg, 0.0178 mmol) and $Cu(OAc)_2$ (65 mg, 0.3568 mmol) as off white solid.



M. P. : 145-147 ^oC.

R_f: 0.44 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3031, 2925, 2875, 1715, 1643, 1610, 1573, 1498, 1448, 1372, 1289, 1245, 1212, 1156, 1113, 1079, 1026, 994, 920, 823, 749 cm^{-1}.

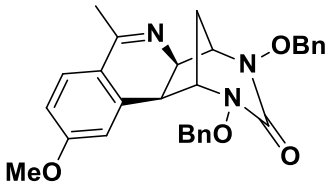
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.50 (m, 4 H), 7.40-7.33 (m, 7 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 6.87 (s, 1 H), 5.14 (d, *J* = 11.0 Hz, 1 H), 5.06 (d, *J* = 10.5 Hz, 1 H), 4.98-4.91 (m, 2 H), 4.77 (d, *J* = 9.0 Hz, 1 H), 3.92 (d, *J* = 3.0 Hz, 1 H), 3.72 (d, *J* = 9.5 Hz, 1 H), 3.34 (d, *J* = 4.0 Hz, 1 H), 2.33 (s, 3 H), 2.28 (d, *J* = 2.0 Hz, 3 H), 1.98 (d, *J* = 13.0 Hz, 1 H), 1.58-1.53 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4, 159.9, 142.2, 136.5, 135.5, 133.8, 130.0, 129.8, 129.6, 128.6, 128.6, 128.5, 128.4, 128.0, 125.9, 123.3, 78.2, 77.8, 72.7, 69.2, 63.6, 41.7, 29.9, 23.4, 21.4.

HRMS (ESI): *m/z* calcd for $C_{29}H_{30}N_3O_3$: 468.22872; Found: 468.22974.

Compound 25b

Following the general procedure 5A.7.3, compound **25b** (66 mg, 76 %) was synthesised from bicyclic olefin **24a** (60 mg, 0.1784 mmol) and *O*-acetylketoxime **6b** (37 mg, 0.1784 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol), $AgSbF_6$ (6 mg, 0.0178 mmol) and $Cu(OAc)_2$ (65 mg, 0.3568 mmol) as brownish viscous liquid.



R_f: 0.36 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3031, 2937, 2877, 1713, 1646, 1604, 1571, 1501, 1453, 1374, 1282, 1253, 1215, 1149, 1080, 1026, 992, 921, 875, 826, 749 cm^{-1}.

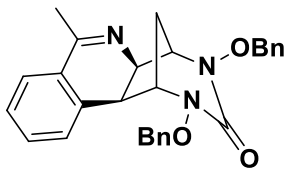
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.44 (m, 5 H), 7.38-7.32 (m, 6 H), 6.75 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1 H), 6.62 (d, *J* = 2.5 Hz, 1 H), 5.12 (d, *J* = 11.0 Hz, 1 H), 5.04 (d, *J* = 10.0 Hz, 1 H), 4.97-4.89 (m, 2 H), 4.74 (d, *J* = 9.5 Hz, 1 H), 4.06 (s, 1 H), 3.82 (d, *J* = 10.0 Hz, 1 H), 3.80 (s, 3 H), 3.39 (d, *J* = 4.0 Hz, 1 H), 2.33 (d, *J* = 1.5 Hz, 3 H), 2.06-2.03 (m, 1 H), 1.67-1.62 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.0, 159.9, 136.4, 136.3, 135.4, 129.7, 129.5, 128.9, 128.6, 128.6, 128.5, 128.4, 118.5, 113.9, 113.5, 78.2, 77.8, 72.7, 68.7, 62.4, 55.5, 42.4, 29.9, 22.5.

HRMS (ESI): *m/z* calcd for $C_{29}H_{30}N_3O_4$: 484.22363; Found: 484.22232.

Compound 25c

Following the general procedure 5A.7.3, compound **25c** (68 mg, 84 %) was synthesised from bicyclic olefin **24a** (60 mg, 0.1784 mmol) and *O*-acetylketoxime **6c** (32 mg, 0.1784 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol), $AgSbF_6$ (6 mg, 0.0178 mmol) and $Cu(OAc)_2$ (65 mg, 0.3568 mmol) as light yellow solid.



M. P. : 100-102 ^oC.

R_f: 0.50 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3062, 3032, 2933, 2875, 1713, 1645, 1494, 1448, 1374, 1288, 1212, 1159, 1112, 1081, 1024, 994, 922, 834, 749 cm^{-1}.

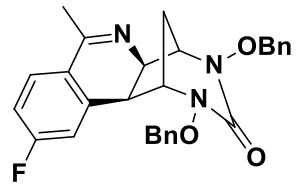
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.45 (m, 5 H), 7.40-7.32 (m, 7 H), 7.23 (t, *J* = 7.5 Hz, 1 H), 7.07 (d, *J* = 7.5 Hz, 1 H), 5.13-5.05 (m, 2 H), 4.98-4.91 (m, 2 H), 4.81 (d, *J* = 9.0 Hz, 1 H), 3.98 (s, 1 H), 3.79 (d, *J* = 9.5 Hz, 1 H), 3.37 (d, *J* = 4.0 Hz, 1 H), 2.32 (d, *J* = 1.5 Hz, 3 H), 2.00 (d, *J* = 13.0 Hz, 1 H), 1.60-1.56 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0, 159.9, 136.4, 135.6, 133.8, 132.1, 129.7, 129.5, 129.5, 128.6, 128.5, 128.4, 127.4, 126.1, 78.1, 77.8, 72.7, 69.0, 63.3, 41.7, 29.9, 23.1.

HRMS (ESI): *m/z* calcd for $C_{28}H_{28}N_3O_3$: 454.21307; Found: 454.21317.

Compound 25d

Following the general procedure 5A.7.3, compound **25d** (44 mg, 52 %) was synthesised from bicyclic olefin **24a** (60 mg, 0.1784 mmol) and *O*-acetylketoxime **6d** (35 mg, 0.1784 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol), $AgSbF_6$ (6 mg, 0.0178 mmol) and $Cu(OAc)_2$ (65 mg, 0.3568 mmol) as brownish viscous liquid.



R_f: 0.46 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3035, 2933, 2875, 1715, 1647, 1592, 1498, 1445, 1373, 1282, 1248, 1215, 1159, 1123, 1081, 985, 921, 879, 824, 745 cm^{-1}.

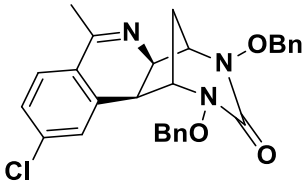
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.49 (m, 4 H), 7.44 (dd, J_1 = 8.6 Hz, J_2 = 5.6 Hz, 1 H), 7.41-7.34 (m, 6 H), 6.90 (td, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1 H), 6.72 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1 H), 5.14-5.05 (m, 2 H), 4.97-4.91 (m, 2 H), 4.77 (d, *J* = 9.5 Hz, 1 H), 3.92 (s, 1 H), 3.73 (d, *J* = 9.5 Hz, 1 H), 3.32 (d, *J* = 4.5 Hz, 1 H), 2.28 (d, *J* = 2.0 Hz, 3 H), 2.00 (d, *J* = 12.5 Hz, 1 H), 1.56-1.52 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.3, 163.3, 160.3, 159.8, 137.1, 137.1, 136.4, 135.5, 129.7, 129.6, 128.6, 128.6, 128.6, 128.4, 128.3, 128.3, 122.3, 122.3, 116.1, 115.9, 114.5, 114.3, 78.2, 77.8, 72.6, 69.1, 63.4, 41.9, 29.9, 23.5.

HRMS (ESI): *m/z* calcd for $C_{28}H_{27}N_3O_3F$: 472.20364; Found: 472.20606.

Compound 25e

Following the general procedure 5A.7.3, compound **25e** (48 mg, 55 %) was synthesised from bicyclic olefin **24a** (60 mg, 0.1784 mmol) and *O*-acetylketoxime **6e** (38 mg, 0.1784 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol), $AgSbF_6$ (6 mg, 0.0178 mmol) and $Cu(OAc)_2$ (65 mg, 0.3568 mmol) as off white solid.



M. P. : 125-127 ^{o}C.

R_f: 0.52 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3033, 2936, 2876, 1714, 1644, 1591, 1490, 1447, 1372, 1287, 1211, 1157, 1104, 993, 919, 886, 826, 747 cm^{-1}.

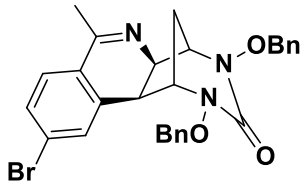
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.49 (m, 4 H), 7.42-7.34 (m, 7 H), 7.19 (d, *J* = 8.5 Hz, 1 H), 7.02 (s, 1 H), 5.14 (d, *J* = 11.5 Hz, 1 H), 5.06 (d, *J* = 10.5 Hz, 1 H), 4.97-4.90 (m, 2 H), 4.78 (d, *J* = 9.5 Hz, 1 H), 3.91 (s, 1 H), 3.71 (d, *J* = 9.5 Hz, 1 H), 3.29 (d, *J* = 4.0 Hz, 1 H), 2.28 (s, 3 H), 1.99 (d, *J* = 12.5 Hz, 1 H), 1.53-1.49 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.3, 159.7, 137.4, 136.4, 135.9, 135.5, 129.7, 129.6, 129.4, 128.7, 128.6, 128.4, 127.6, 127.3, 124.1, 78.3, 77.8, 72.7, 69.1, 63.7, 41.4, 29.9, 23.5.

HRMS (ESI): *m/z* calcd for $C_{28}H_{27}N_3O_3Cl$: 488.17409; Found: 488.17311.

Compound 25f

Following the general procedure 5A.7.3, compound **25f** (53 mg, 56 %) was synthesised from bicyclic olefin **24a** (60 mg, 0.1784 mmol) and *O*-acetylketoxime **6f** (46 mg, 0.1784 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol), $AgSbF_6$ (6 mg, 0.0178 mmol) and $Cu(OAc)_2$ (65 mg, 0.3568 mmol) as pale brown solid.



M. P. : 140-142 ^{o}C.

R_f: 0.52 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3032, 2934, 2875, 1716, 1645, 1581, 1488, 1446, 1372, 1285, 1211, 1157, 1088, 993, 917, 824, 746 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.49 (m, 4 H), 7.43-7.34 (m, 7 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 7.20 (s, 1 H), 5.14 (d, *J* = 11.0 Hz, 1 H), 5.06 (d, *J* = 10.0 Hz, 1 H), 4.97-4.89 (m, 2 H), 4.78 (d, *J* = 9.5 Hz, 1 H), 3.92 (s, 1 H), 3.71 (d, *J* = 9.5 Hz, 1 H), 3.28 (d, *J* = 4.0 Hz, 1 H), 2.28 (d, *J* = 2.0 Hz, 3 H), 1.99 (d, *J* = 13.0 Hz, 1 H), 1.53-1.49 (m, 1 H).

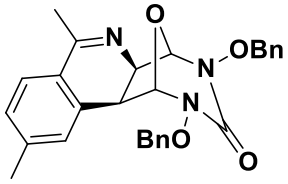
^{13}C NMR (125 MHz, $CDCl_3$): δ 160.7, 159.8, 136.3, 136.1, 135.5, 132.4, 130.6, 129.8, 129.6, 128.7, 128.7, 128.5, 127.5, 125.9, 124.4, 78.3, 77.8, 72.7, 69.0, 63.6, 41.2, 29.8, 23.4.

HRMS (ESI): *m/z* calcd for $C_{28}H_{27}N_3O_3Br$: 532.12358; Found: 532.12607.

Compound 25g

Following the general procedure 5A.7.3, compound **25g** (62 mg, 75 %) was synthesised

from bicyclic olefin **24b** (60 mg, 0.1773 mmol) and *O*-acetylketoxime **6a** (34 mg, 0.1773 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol), $AgSbF_6$ (6 mg, 0.0177 mmol) and $Cu(OAc)_2$ (65 mg, 0.3546 mmol) as light orange viscous liquid.



R_f: 0.58 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3032, 2939, 2880, 1719, 1647, 1612, 1576, 1498, 1451, 1372, 1294, 1212, 1131, 1084, 999, 852, 745 cm^{-1}.

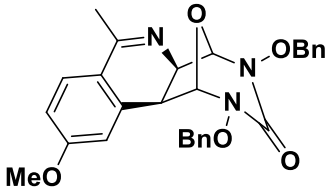
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.49 (m, 4 H), 7.43-7.36 (m, 7 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.54 (s, 1 H), 5.33 (s, 1 H), 5.18-5.12 (m, 2 H), 5.05-4.98 (m, 2 H), 4.75 (s, 1 H), 4.71 (dd, J_1 = 9.0 Hz, J_2 = 1.5 Hz, 1 H), 3.62 (d, *J* = 9.0 Hz, 1 H), 2.32 (s, 3 H), 2.30 (d, *J* = 2.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3, 157.7, 142.6, 136.2, 135.0, 131.7, 129.8, 129.8, 129.5, 128.9, 128.9, 128.7, 128.7, 128.6, 126.3, 122.9, 100.5, 96.5, 78.9, 78.5, 64.5, 42.2, 23.2, 21.4.

HRMS (ESI): *m/z* calcd for $C_{28}H_{28}N_3O_4$: 470.20798; Found: 470.20797.

Compound 25h

Following the general procedure 5A.7.3, compound **25h** (55 mg, 64 %) was synthesised from bicyclic olefin **24b** (60 mg, 0.1773 mmol) and *O*-acetylketoxime **6b** (37 mg, 0.1773 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol), $AgSbF_6$ (6 mg, 0.0177 mmol) and $Cu(OAc)_2$ (65 mg, 0.3546 mmol) as pale yellow viscous liquid.



R_f: 0.48 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3031, 3001, 2939, 2881, 1724, 1645, 1605, 1574, 1503, 1455, 1372, 1325, 1286, 1257, 1215, 1151, 1081, 1026, 852, 813, 747 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.38 (m, 4 H), 7.35-7.25 (m, 7 H), 6.67 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1 H), 6.34 (d, *J* = 2.5 Hz, 1 H), 5.23 (s, 1 H), 5.09-5.01 (m, 2 H), 4.95-4.88 (m, 2 H), 4.70 (s, 1 H), 4.65 (d, *J* = 9.0 Hz, 1 H), 3.69 (s, 3 H), 3.60 (d, *J* = 9.0 Hz, 1 H), 2.20 (d, *J* = 1.0 Hz, 3 H).

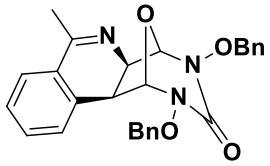
^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2, 160.8, 157.2, 134.8, 133.9, 132.8, 128.7, 128.6, 127.9, 127.8, 127.6, 127.5, 127.2, 117.9, 112.9, 112.2, 98.8, 95.9, 77.8, 77.4, 63.3, 54.4,

41.7, 22.1.

HRMS (ESI): *m/z* calcd for $C_{28}H_{28}N_3O_5$: 486.20290; Found: 486.20209.

Compound 25i

Following the general procedure 5A.7.3, compound **25i** (57 mg, 70 %) was synthesised from bicyclic olefin **24b** (60 mg, 0.1773 mmol) and *O*-acetylketoxime **6c** (31 mg, 0.1773 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol), $AgSbF_6$ (6 mg, 0.0177 mmol) and $Cu(OAc)_2$ (65 mg, 0.3546 mmol) as light brown viscous liquid.



R_f: 0.63 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3032, 2934, 2880, 1719, 1648, 1495, 1453, 1373, 1293, 1211, 1133, 997, 918, 852, 747 cm^{-1}.

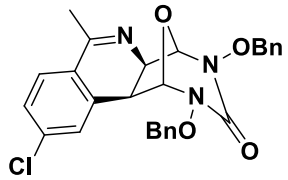
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.48 (m, 5 H), 7.42-7.35 (m, 6 H), 7.33 (t, *J* = 7.0 Hz, 1 H), 7.27 (d, *J* = 7.5 Hz, 1 H), 6.67 (d, *J* = 7.5 Hz, 1 H), 5.35 (s, 1 H), 5.15-5.12 (m, 2 H), 5.06-4.99 (m, 2 H), 4.77 (s, 1 H), 4.73 (d, *J* = 8.5 Hz, 1 H), 3.65 (d, *J* = 9.0 Hz, 1 H), 2.33 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.4, 157.6, 136.1, 135.0, 132.0, 131.6, 129.8, 129.1, 129.1, 128.9, 128.8, 128.8, 128.6, 128.2, 128.0, 126.2, 100.5, 96.4, 78.9, 78.5, 64.6, 42.2, 23.2.

HRMS (ESI): *m/z* calcd for $C_{27}H_{26}N_3O_4$: 456.19233; Found: 456.18732.

Compound 25j

Following the general procedure 5A.7.3, compound **25j** (41 mg, 47 %) was synthesised from bicyclic olefin **24b** (60 mg, 0.1773 mmol) and *O*-acetylketoxime **6e** (38 mg, 0.1773 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol), $AgSbF_6$ (6 mg, 0.0177 mmol) and $Cu(OAc)_2$ (65 mg, 0.3546 mmol) as reddish brown viscous liquid.



R_f: 0.60 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3032, 2936, 2879, 1722, 1648, 1592, 1491, 1451, 1372, 1293, 1212, 1103, 997, 920, 849, 744 cm^{-1}.

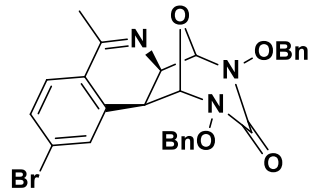
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.50 (m, 4 H), 7.48-7.35 (m, 7 H), 7.23 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1 H), 6.65 (s, 1 H), 5.29 (s, 1 H), 5.17-5.12 (m, 2 H), 5.05-4.98 (m, 2 H), 4.71-4.68 (m, 2 H), 3.58 (d, *J* = 9.0 Hz, 1 H), 2.31 (d, *J* = 1.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2, 157.4, 137.8, 136.0, 134.9, 133.7, 129.9, 129.8, 129.3, 129.0, 128.9, 128.9, 128.6, 128.3, 127.6, 123.7, 100.3, 96.3, 79.0, 78.5, 64.6, 41.9, 23.3.

HRMS (ESI): *m/z* calcd for $C_{27}H_{25}N_3O_4Cl$: 490.15336; Found: 490.15673.

Compound 25k

Following the general procedure 5A.7.3, compound **25k** (47 mg, 50 %) was synthesised from bicyclic olefin **24b** (60 mg, 0.1773 mmol) and *O*-acetylketoxime **6f** (45 mg, 0.1773 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol), $AgSbF_6$ (6 mg, 0.0177 mmol) and $Cu(OAc)_2$ (65 mg, 0.3546 mmol) as reddish viscous liquid.



R_f: 0.60 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3063, 3033, 2935, 2880, 1719, 1649, 1585, 1489, 1452, 1370, 1292, 1212, 1130, 1091, 997, 961, 918, 850, 742 cm^{-1}.

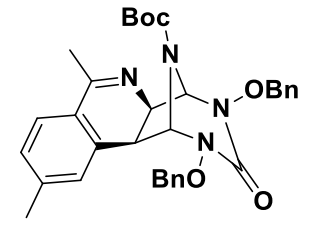
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.49 (m, 4 H), 7.47-7.32 (m, 8 H), 6.87 (s, 1 H), 5.27 (s, 1 H), 5.18-5.11 (m, 2 H), 5.05-4.97 (m, 2 H), 4.70 (d, *J* = 9.0 Hz, 1 H), 4.67 (s, 1 H), 3.59 (d, *J* = 9.0 Hz, 1 H), 2.30 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2, 157.5, 135.9, 134.9, 133.9, 131.9, 131.3, 129.9, 129.8, 129.3, 129.0, 128.9, 128.6, 127.7, 126.1, 124.1, 100.2, 96.4, 79.0, 78.5, 64.7, 41.8, 23.3.

HRMS (ESI): *m/z* calcd for $C_{27}H_{25}N_3O_4Br$: 534.10284; Found: 534.10316.

Compound 25l

Following the general procedure 5A.7.3, compound **25l** (48 mg, 62 %) was synthesised from bicyclic olefin **6c** (60 mg, 0.1371 mmol) and *O*-acetylketoxime **6a** (26 mg, 0.1371 mmol) using $[RhCp^*Cl_2]_2$ (4 mg, 0.0069 mmol), $AgSbF_6$ (5 mg, 0.0137 mmol) and $Cu(OAc)_2$ (50 mg, 0.2743 mmol) as brownish viscous liquid.



R_f: 0.65 (hexane/ethyl acetate = 3:7).

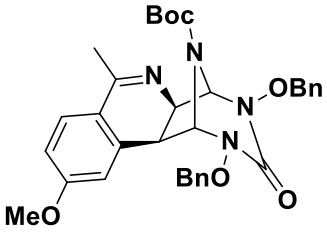
IR (neat) ν_{max}: 3030, 2976, 2930, 2878, 1725, 1648, 1611, 1576, 1452, 1372, 1331, 1250, 1160, 1002, 943, 838, 789, 746 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.50 (m, 4 H), 7.40-7.33 (m, 7 H), 7.07 (d, *J* = 7.0 Hz, 1 H), 6.84 (s, 1 H), 5.43 (s, 1 H), 5.14 (d, *J* = 10.5 Hz, 1 H), 5.06 (d, *J* = 10.0 Hz, 1 H), 4.97-4.88 (m, 4 H), 3.83 (d, *J* = 9.0 Hz, 1 H), 2.34 (d, *J* = 2.0 Hz, 3 H), 2.32 (s, 3 H), 1.45 (s, 9 H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 162.3, 160.0, 153.0, 142.6, 135.8, 135.1, 131.8, 129.8, 129.5, 129.0, 128.7, 128.6, 128.5, 128.4, 128.2, 126.2, 123.2, 82.4, 79.9, 78.4, 78.0, 63.2, 41.8, 28.1, 23.3, 21.4.

HRMS (ESI): *m/z* calcd for $C_{33}H_{37}N_4O_5$: 569.27640; Found: 569.27647.

Compound 25m

Following the general procedure 5A.7.3, compound **25m** (mg, 51 %) was synthesised from bicyclic olefin **24c** (60 mg, 0.1371 mmol) and *O*-acetylketoxime **6b** (28 mg, 0.1371 mmol) using $[RhCp^*Cl_2]_2$ (4 mg, 0.0069 mmol), $AgSbF_6$ (5 mg, 0.0137 mmol) and $Cu(OAc)_2$ (50 mg, 0.2743 mmol) as reddish viscous liquid.



R_f: 0.60 (hexane/ethyl acetate = 3:7).

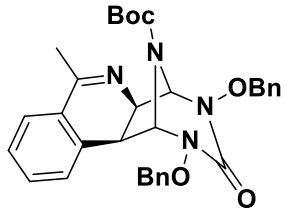
IR (neat) ν_{max}: 2974, 2933, 1725, 1647, 1606, 1504, 1456, 1372, 1329, 1257, 1159, 1082, 1021, 944, 840, 746 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51-7.44 (m, 5 H), 7.40-7.34 (m, 6 H), 6.77 (d, *J* = 7.0 Hz, 1 H), 6.60 (s, 1 H), 5.41 (s, 1 H), 5.14 (d, *J* = 10.5 Hz, 1 H), 5.05 (d, *J* = 10.0 Hz, 1 H), 4.97-4.86 (m, 4 H), 3.85 (d, *J* = 9.0 Hz, 1 H), 3.74 (s, 3 H), 2.32 (d, *J* = 2.0 Hz, 3 H), 1.45 (s, 9 H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 162.2, 161.4, 160.2, 153.0, 135.7, 135.0, 134.3, 134.0, 129.5, 128.6, 128.5, 128.4, 128.1, 119.2, 113.7, 82.4, 81.9, 80.2, 78.3, 78.0, 63.2, 55.3, 42.3, 28.1, 23.4.

HRMS (ESI): *m/z* calcd for $C_{33}H_{37}N_4O_6$: 585.27131; Found: 585.27031.

Compound 25n

Following the general procedure 5A.7.3, compound **25n** (43 mg, 56 %) was synthesised from bicyclic olefin **24c** (60 mg, 0.1371 mmol) and *O*-acetylketoxime **6c** (24 mg, 0.1371 mmol) using $[RhCp^*Cl_2]_2$ (4 mg, 0.0069 mmol), $AgSbF_6$ (5 mg, 0.0137 mmol) and $Cu(OAc)_2$ (50 mg, 0.2743 mmol) as yellow viscous liquid.



R_f: 0.58 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3032, 2977, 2932, 2879, 1956, 1725, 1650, 1489, 1452, 1373, 1331, 1256, 1214, 1160, 1000, 946, 842, 798, 748 cm^{-1}.

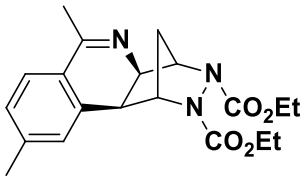
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.49 (m, 5 H), 7.42-7.29 (m, 8 H), 7.06 (d, *J* = 7.5 Hz, 1 H), 5.47 (s, 1 H), 5.13-5.05 (m, 2 H), 4.98-4.92 (m, 4 H), 3.90 (d, *J* = 9.0 Hz, 1 H), 2.40 (s, 3 H), 1.44 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 153.0, 135.7, 135.0, 131.9, 129.4, 128.7, 128.6, 128.6, 128.5, 128.1, 126.4, 82.6, 80.5, 79.8, 78.3, 78.1, 62.9, 42.0, 28.1, 23.3.

HRMS (ESI): *m/z* calcd for $C_{32}H_{35}N_4O_5$: 555.26075; Found: 555.25867.

Compound 25o

Following the general procedure 5A.7.3, compound **25o** (61 mg, 66 %) was synthesised from bicyclic olefin **24d** (60 mg, 0.2497 mmol) and *O*-acetylketoxime **6a** (48 mg, 0.2497 mmol) using $[RhCp^*Cl_2]_2$ (8 mg, 0.0125 mmol), $AgSbF_6$ (9 mg, 0.0249 mmol) and $Cu(OAc)_2$ (91 mg, 0.4994 mmol) as reddish viscous liquid.



R_f: 0.29 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3056, 2985, 2929, 1744, 1704, 1646, 1613, 1574, 1451, 1377, 1321, 1174, 1134, 1102, 1040, 823, 768 cm^{-1}.

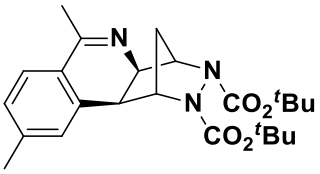
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.0 Hz, 1 H), 7.16-7.14 (m, 2 H), 5.09-4.80 (m, 2 H), 4.50 (s, 1 H), 4.27 (s, 4 H), 3.52 (s, 1 H), 2.48 (s, 3 H), 2.41 (s, 3 H), 1.76-1.69 (m, 2 H), 1.33-1.31 (m, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.7, 144.8, 132.9, 129.9, 128.9, 127.9, 122.7, 67.8, 62.8, 60.4, 40.9, 33.1, 22.7, 21.7, 14.5, 14.5.

HRMS (ESI): *m/z* calcd for $C_{20}H_{26}N_3O_4$: 372.19233; Found: 372.19186.

Compound 25p

Following the general procedure 5A.7.3, compound **25p** (44 mg, 51 %) was synthesised from bicyclic olefin **24e** (60 mg, 0.2025 mmol) and *O*-acetylketoxime **6a** (39 mg, 0.2025 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0101 mmol), $AgSbF_6$ (7 mg, 0.0203 mmol) and $Cu(OAc)_2$ (74 mg, 0.4050 mmol) as orange viscous liquid.



R_f: 0.42 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 2978, 2929, 2578, 1704, 1645, 1610, 1572, 1451, 1365, 1254, 1142, 1104, 1045, 1005, 968, 857, 766 cm^{-1}.

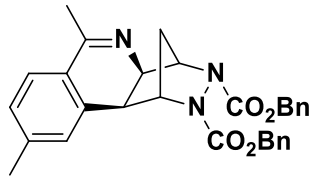
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.0 Hz, 1 H), 7.18-7.12 (m, 2 H), 4.95-4.73 (m, 1 H), 4.52-4.38 (m, 2 H), 3.58-3.46 (m, 1 H), 2.48 (s, 3 H), 2.39 (s, 3 H), 1.69 (s, 2 H), 1.53 (s, 18 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.6, 146.6, 133.2, 130.3, 129.7, 128.6, 127.1, 123.1, 82.0, 69.5, 67.9, 66.7, 65.3, 61.0, 40.8, 33.1, 32.6, 28.2, 22.8, 21.6.

HRMS (ESI): *m/z* calcd for $C_{24}H_{34}N_3O_4$: 428.25493; Found: 428.25693.

Compound 25q

Following the general procedure 5A.7.3, compound **25q** (47 mg, 58 %) was synthesised from bicyclic olefin **24f** (60 mg, 0.1647 mmol) and *O*-acetylketoxime **6a** (32 mg, 0.1647 mmol) using $[RhCp^*Cl_2]_2$ (5 mg, 0.0082 mmol), $AgSbF_6$ (6 mg, 0.0165 mmol) and $Cu(OAc)_2$ (mg, 0. mmol) as reddish viscous liquid.



R_f: 0.48 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3062, 2957, 1706, 1649, 1612, 1498, 1451, 1390, 1317, 1135, 1021, 947, 908, 822, 742 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47-7.29 (m, 11 H), 7.18-7.12 (m, 2 H), 5.29-5.19 (m, 4 H), 4.92 (s, 1 H), 4.49 (s, 2 H), 3.42 (s, 1 H), 2.48-2.35 (m, 6 H), 1.71-1.64 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.8, 135.8, 132.7, 129.0, 128.8, 128.6, 128.6, 128.3, 126.5, 125.3, 122.8, 68.3, 60.7, 41.5, 33.1, 22.7, 21.6.

HRMS (ESI): *m/z* calcd for $C_{30}H_{30}N_3O_4$: 496.22363; Found: 496.22324.

5A.8. References

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CHAPTER 5

Rh(III) Catalyzed Synthesis of Azaheterocycles

PART B

Rhodium Catalyzed C-H Activation of *N*-methoxybenzamides towards the Synthesis of Isoquinolone Fused Bicycles

5B.1. Introduction

Isoquinolones constitute an important class of heterocycles, ubiquitous in various natural products, biologically active molecules, and synthetic pharmaceutical compounds (Figure 5B.1).[1–4] Transition-metal-catalyzed cleavage and functionalization of the C–H bonds have attracted significant interest because these approaches allow the use of cheaper and more readily available starting materials in an atom economic way with less generation of toxic waste.[5]

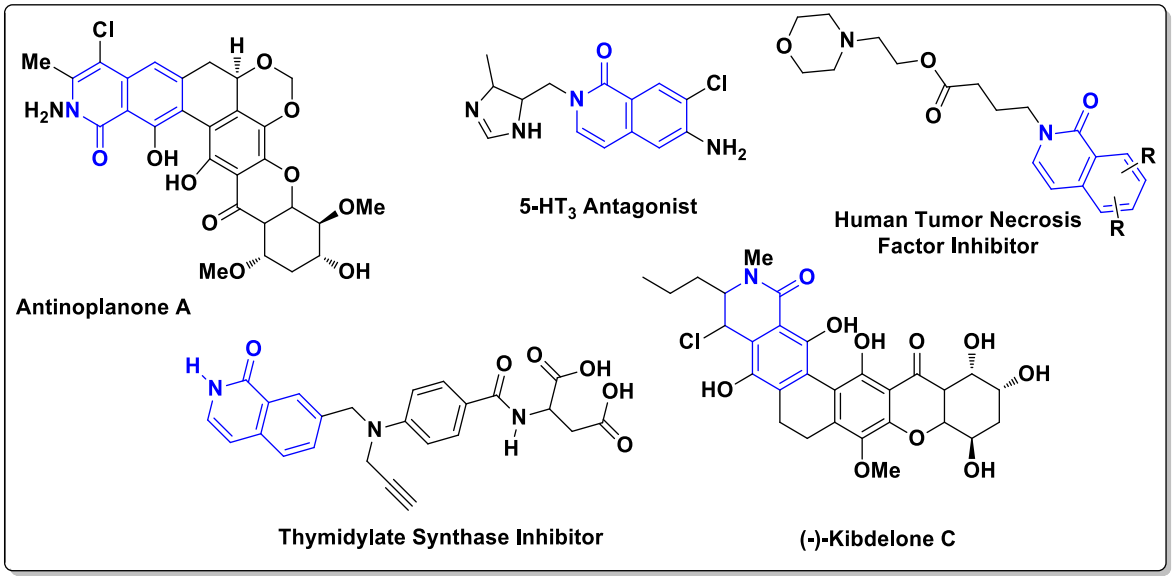


Figure 5B.1. Biologically relevant isoquinolone scaffolds

Among the various aromatic substrates containing the nitrogen based functional groups as a directing group, benzamide derivatives represents a highly valuable method to azaheterocycle synthesis. Oxidative coupling reactions are usually carried out in the presence of an external oxidant, which also helps in the regeneration of the active catalyst. However, the waste by-product formation *via* the reduction of the oxidant is often problematic. An

alternative to this strategy is the use of an internal oxidant as the directing group that both offers directing effect and regenerates the catalyst.[6]

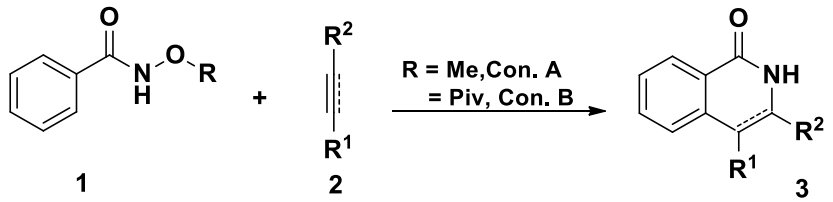
In the present chapter, the results of our studies on the annulation reaction of various urea derived bicyclic olefins *via* the C-H activation of *N*-methoxybenzamides toward the synthesis of isoquinolone fused bicycles are discussed in detail. A brief discussion on the transition metal catalyzed C-H activation of *N*-alkoxybenzamides is illustrated in the following sections.

5B.2. *N*-alkyloxy benzamides as Directing Groups

Directing groups that perform as internal oxidants are highly beneficial in transition metal-catalyzed C-H activation reactions.

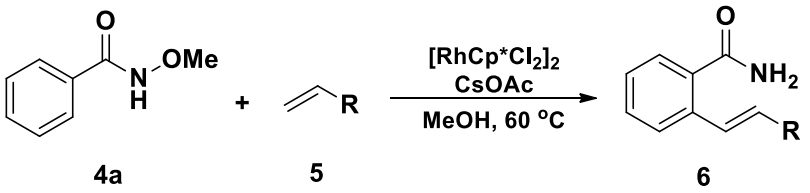
5B.2.1. Using Rhodium

The pioneering report on the synthesis of isoquinolines **3** *via ortho* C–H activation of *N*-methoxybenzamides **1** with an alkyne **2** catalyzed by rhodium(III) was developed by Guimond *et al*. in 2010 (Scheme 5B.1).[7] N-O bond acted as a handle for C-N bond formation and subsequently is cleaved in the reaction to afford NH-isoquinolones. The same group extended this reaction to alkenes, terminal alkynes and highly strained olefins such as norbornenes utilizing *N*-pivaloyl group as the directing group.[8] In the same year, Rovis *et al*. also reported the same reaction using *N*-methyl benzamides.[9]



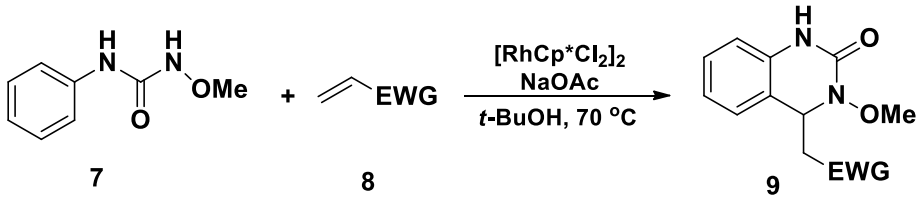
Scheme 5B.1

An efficient Rh(III)-catalyzed oxidative olefination by directed C-H bond activation of *N*-methoxybenzamides **4a** was demonstrated by Glorius *et al*. under slightly different conditions. Depending up on the effect of substituents on the directing group, they obtained either *ortho*-olefinated primary benzamides **6** or cyclized tetrahydroisoquinolones as products (Scheme 5B.2).[10]



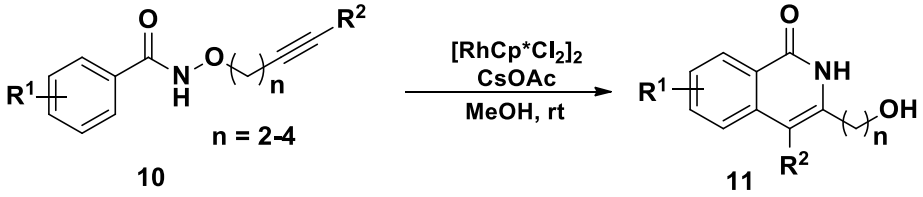
Scheme 5B.2

The same group also elucidated the use of *N*-methoxy-*N'*-aryl ureas **7** instead of *N*-methoxybenzamides as internal oxidants (Scheme 5B.3). The reported olefination–Michael addition tandem process with acrylates furnished dihydroquinazolinone products **9** in high yields.[11]



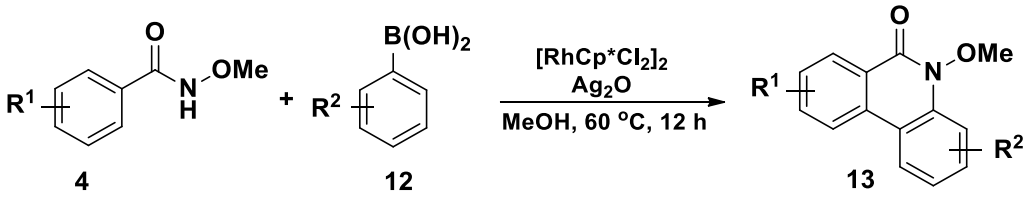
Scheme 5B.3

Park *et al.* illustrated an efficient and practical rhodium(III)-catalyzed intramolecular annulation of alkyne-tethered hydroxamic esters **10** for the synthesis of 3-hydroxy-alkyl isoquinolines **11** and 6-hydroxyalkyl-2-pyridones (Scheme 5B.4). Furthermore, the highly efficient total synthesis of (+/-)antofine, (+/-)septicine, (+/-)tylophorine, and rosettacin involving rhodium(III)-catalyzed C-H bond functionalization as a key step, was also accomplished.[12]



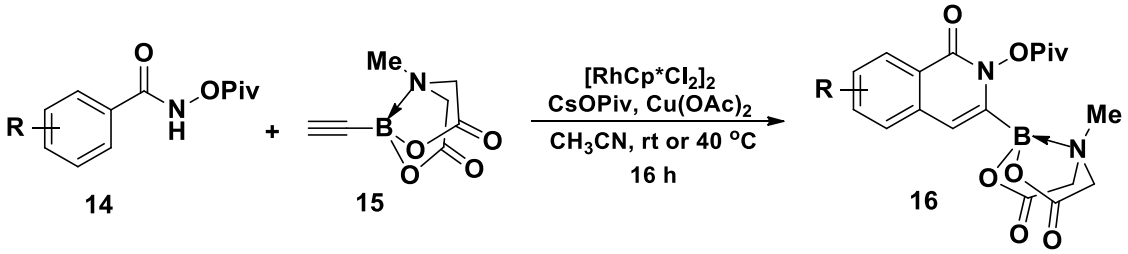
Scheme 5B.4

A rhodium (III) catalyzed regioselective synthesis of phenanthridinones **13** from *N*-methoxybenzamides **4** and aryl boronic acids **12** through one-pot C-C/C-N bond formation under mild conditions was explored by Cheng *et al.* (Scheme 5B.5).[13]



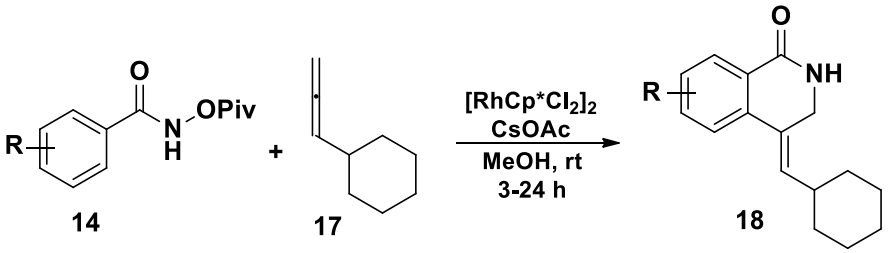
Scheme 5B.5

Glorius *et al.* achieved mild, short and efficient synthesis of heterocyclic boronic acid derivatives **16** *via* Rh(III)-catalyzed C−H activation and annulation with alkyne MIDA boronates **15** (Scheme 5B.6). The methodology provided straightforward access to four important classes of 2-heterocyclic MIDA boronates such as isoquinolone, isoquinoline, pyrrole, and indole.[14]



Scheme 5B.6

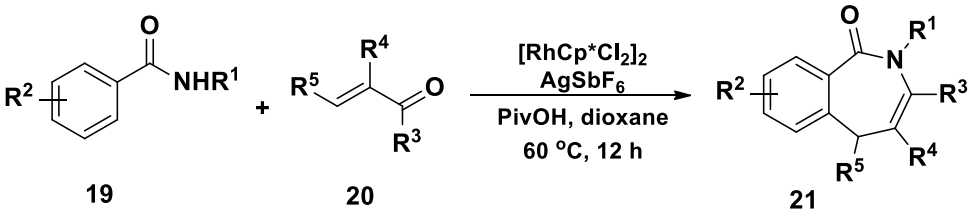
The same group reported a novel and efficient Rh(III)-catalyzed intermolecular annulation of benzamide derivatives **14** with allenes **17** towards the synthesis of 3,4-dihydroisoquinolin-1(*2H*)-ones **18** (Scheme 5B.7). This reaction features high regio- and stereoselectivity, impressive substrate scope for both coupling partners and excellent functional group tolerance.[15]



Scheme 5B.7

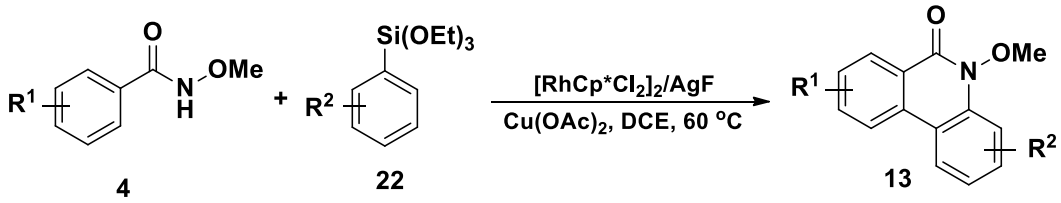
They also explored a novel and efficient method for the synthesis of azepinones **21** utilizing benzamides **19** and α,β-unsaturated aldehydes and ketones **20** as starting materials (Scheme 5B.8). This Rh(III)-catalyzed intermolecular annulation procedure involving tandem C-H activation, cyclization and condensation steps, proceeds under mild conditions,

releases H_2O as the only by-product and displays a broad substrate scope with respect to the substituents.[16]



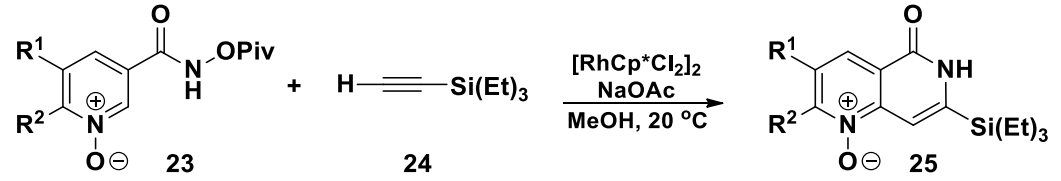
Scheme 5B.8

An efficient method for the one-pot synthesis of substituted phenanthridinone derivatives **13** from *N*-methoxybenzamides **4** and aryl tri-ethoxysilanes **22** through rhodium-catalyzed dual C-H bond activation and annulation reactions was described by Cheng *et al.* (Scheme 5B.9). The aryl group of aryl tri-alkoxysilane acted like a benzyne equivalent and underwent cyclization with *N*-methoxybenzamide to give the expected phenanthridinone product.[17]



Scheme 5B.9

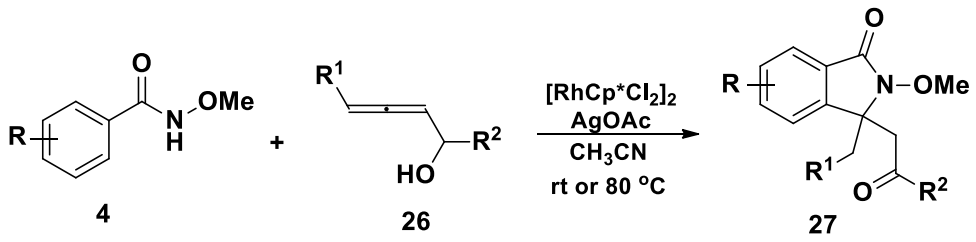
Huckins and Bercot *et al*. were successful in developing Rh(III)-catalyzed C−H activation and double directing group strategy for the regioselective synthesis of naphthyridinones **25** using nicotinamide *N*-oxides **23** as substrates in the presence of alkenes or alkynes or terminal alkynes **24** (Scheme 5B.10).[18]



Scheme 5B.10

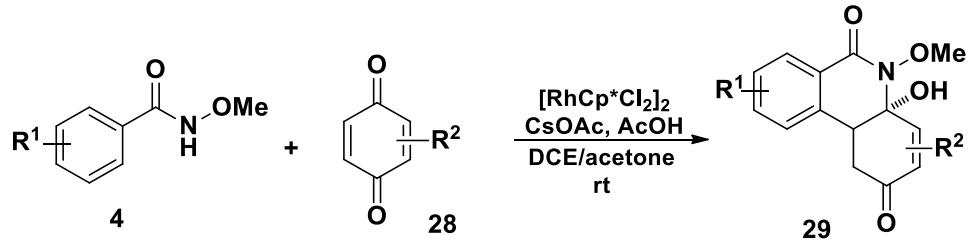
A mild, region-controlled coupling of aromatic and vinylic amides **4** with *α*-allenols **26** to form *γ*-lactams **27** *via* rhodium(III)-catalyzed C−H activation has been demonstrated by Liu and Lu *et al.* (Scheme 5B.11). This [4 + 1] annulation reaction provides an efficient

method for the synthesis of isoindolinones and 1,5-dihydro-pyrrol-2-ones bearing a tetra-substituted carbon atom α to the nitrogen atom with good functional group tolerance.[19]



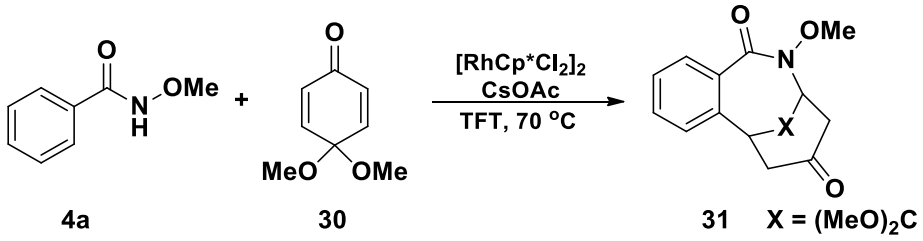
Scheme 5B.11

Xu *et al*. developed a temperature dependent redox neutral Rh-(III)-catalyzed C-H bond annulation of *N*-methoxybenzamides **4** with quinones **28** for the chemoselective synthesis of hydrophenanthridinones **29** and phenanthridinones (Scheme 5B.12).[20]



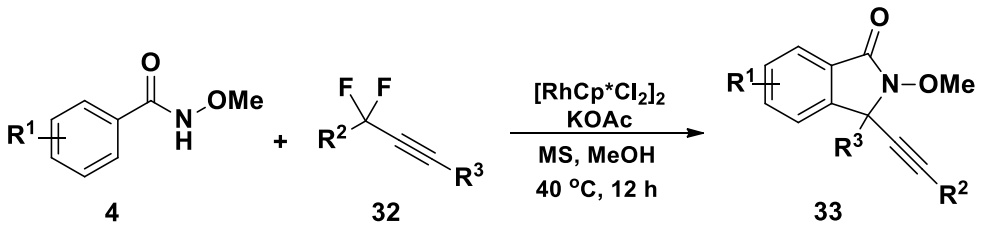
Scheme 5B.12

Xy *et al*. developed Rh(III)-catalyzed annulation of various benzamides **4a** and acrylamides with quinone monoacetals **30** for the facile and efficient one-pot synthesis of bridged nine-membered benzo[c]azonine-1,5(2H)-diones and 2-azabicyclo[4.3.1]dec-4-ene-3,8-diones **31** (Scheme 5B.13). This was the first example of synthesis of nine-membered heterocycles through Rh(III)-catalyzed C−H bond functionalization wherein both aryl and vinyl C−H bonds showed tolerance in this reaction.[21]



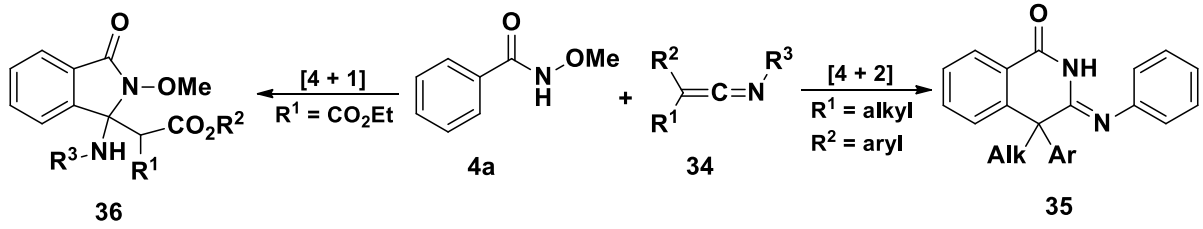
Scheme 5B.13

The use of *α,α*-difluoromethylene alkyne **32** as a non-traditional one-carbon reaction partner for the synthesis of isoindolin-1-one derivatives **33** *via* Rh(III)-catalyzed [4 + 1] annulation reaction was explored by Loh *et al.* (Scheme 5B.14).[22]



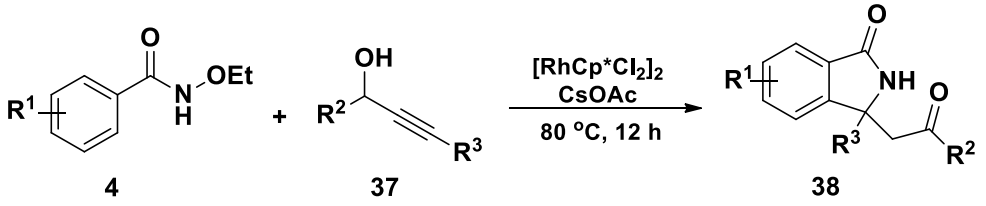
Scheme 5B.14

The use of ketenimines as substrates for the rhodium-catalyzed C−H activation or annulation reactions with *N*-methoxybenzamides **4a** toward the synthesis of isoquinolinones and isoindolinones were reported by Wang-Lu and coworkers (Scheme 5B.15). The *β*-alkyl-substituted ketenimines **34** furnish 3-iminoisoquinolin-1(2H)-ones **35** in a formal [4 + 2] annulation manner, while the *β*-ester substituted ketenimines afford 3-aminoisoindolin-1-ones **36** in a formal [4 + 1] annulation manner.[23]



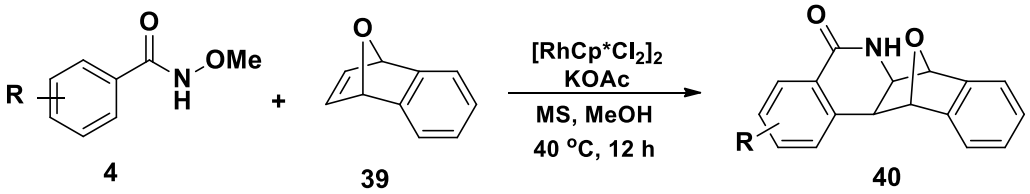
Scheme 5B.15

Liu and coworkers developed the rhodium(III)-catalyzed C−H activation followed by subsequent [4 + 1] cyclization reactions between benzamides **4** and propargyl alcohols **37** for the synthesis of isoindolinones **38** bearing a quaternary carbon (Scheme 5B.16). The propargyl alcohols served as unusual one carbon units in this reaction.[24]



Scheme 5B.16

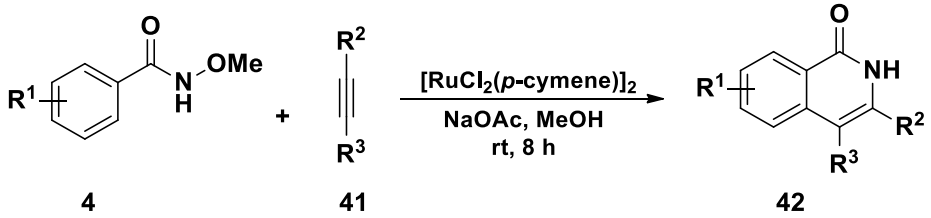
Bolm *et al*. extended the rhodium(III)-catalyzed annulation of *N*-methoxybenzamides **4** with 7-oxa/azabenzonorbornadienes **39** by C–H functionalization to construct benzo[*b*]phenanthridinones **40** (Scheme 5B.17).[25] This method provided polycyclic products containing oxygen/nitrogen bridged core structures in excellent yields.



Scheme 5B.17

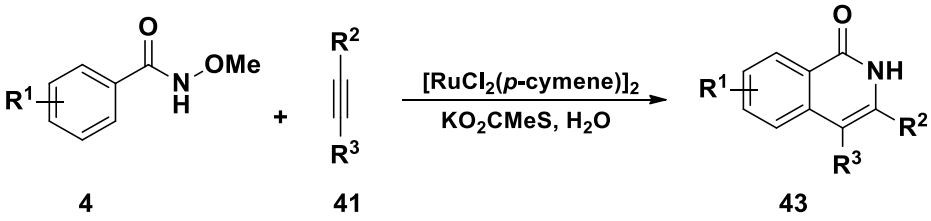
5B.2.2. Using Ruthenium

Wang and Li *et al*. developed a mild, practical, efficient, and regioselective Ru-catalyzed isoquinolone **42** synthesis *via* the annulation reaction of alkynes **41** with *N*-methoxy benzamides **4** (Scheme 5B.18).[26] This redox neutral strategy circumvents the use of wasteful metal oxidants and leads to a clean process.



Scheme 5B.18

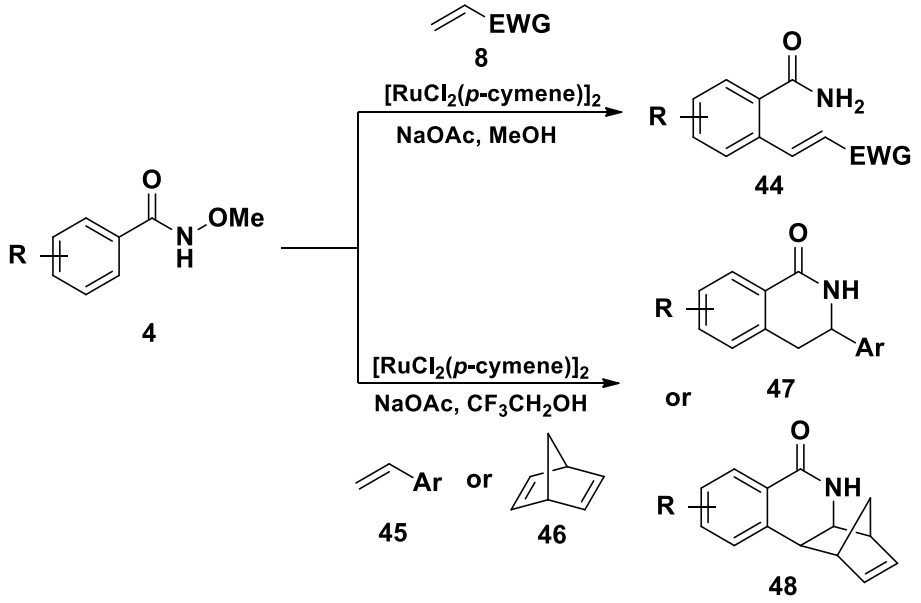
The first ruthenium catalyzed annulation reaction of alkynes **41** with benzamides **4** through C-H bond cleavage using water as a green reaction medium was employed by Ackermann and co-workers (Scheme 5B.19).[27] The carboxylate assisted ruthenium-catalyzed isoquinolone synthesis from *N*-methoxybenzamides allowed the direct use of free hydroxamic acids in annulations of alkynes with extraordinary chemoselectivity.



Scheme 5B.19

The ruthenium-catalyzed oxidative C-H bond olefination of *N*-methoxybenzamides **4** as an oxidizing directing group with a broad substrate scope was achieved by Wang *et al.* (Scheme 5B.20).[28] The catalytic reaction was exclusively *ortho*- and mono-olefination selective. Intriguingly, the reactions with acrylate esters in MeOH afford olefinated

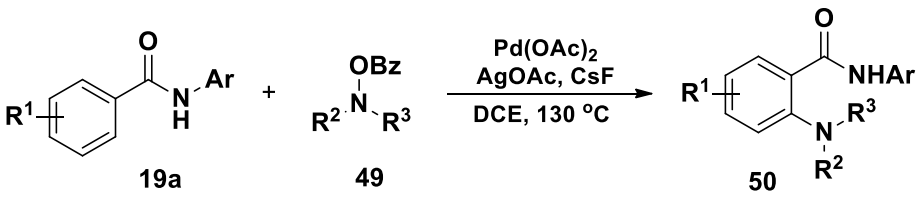
benzamides **44**, whereas with styrenes or norbornadiene in TFE provide 3,4-dihydroisoquinolinone derivatives (**47** or **48**) as products.



Scheme 5B.20

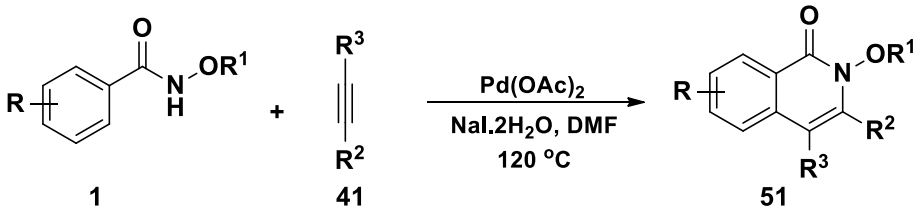
5B.2.3. Using Palladium

In 2011, Yu *et al*. developed the C-H amination of *N*-aryl benzamides **19a** with *O*-benzoyl hydroxylamines **49** with either Pd(II) or Pd(0) catalysts (Scheme 5B.21). They also demonstrated that secondary amines can be directly used with benzoyl peroxide in a one-pot procedure that proceeds *via* the *in situ* generation of the appropriate *O*-benzoyl hydroxylamines.[29]



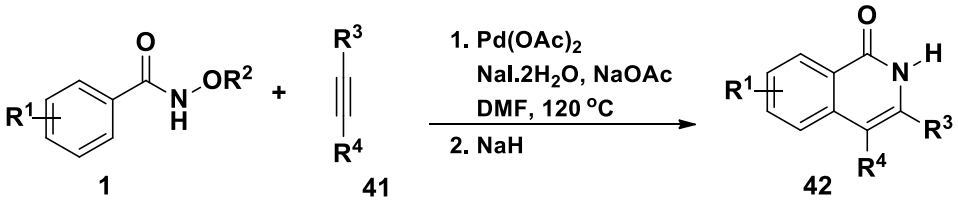
Scheme 5B.21

An atom economical synthesis of isoquinolinones and analogues *via* ligand-free Pd-catalysed C–H and N–H double activation was reported by Huang *et al.* (Scheme 5B.22). A wide range of isoquinolinones **51** were successfully constructed in moderate to good yields with good regioselectivity for unsymmetrical alkynes **41**. They also described a novel one pot synthesis of N–H isoquinolinones *via* activation reaction followed by NaH dealkoxylation.[30]



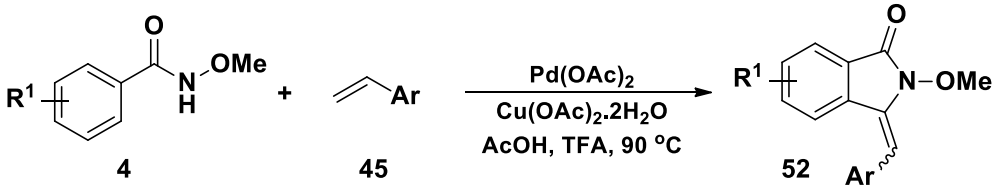
Scheme 5B.22

Later, a practical one-pot procedure for the preparation of N–H isoquinolines was reported by the same group. This 2-step process *via* C–H activation of *N*-alkoxylbenzamides **1** and NaH-mediated dealkoxylation reaction has been demonstrated to be a high yielding alternative methodology for the efficient synthesis of a wide range of representative N–H isoquinolones **42** (Scheme 5B.23).[31]



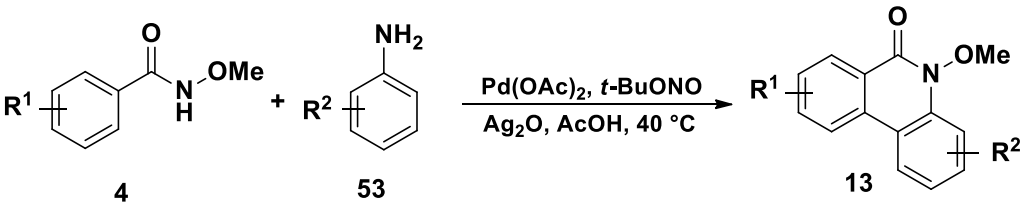
Scheme 5B.23

An atom-economical protocol for a tandem process involving Fujiwara-Moritani-aza-Wacker reactions has been developed by Hii and coworkers for the Pd-catalyzed coupling between *N*-methoxy benzamide **4** and styrene derivatives **45** towards the synthesis of 3-benzyl substituted isoindolinones **52** (Scheme 5B.24).[32]



Scheme 5B.24

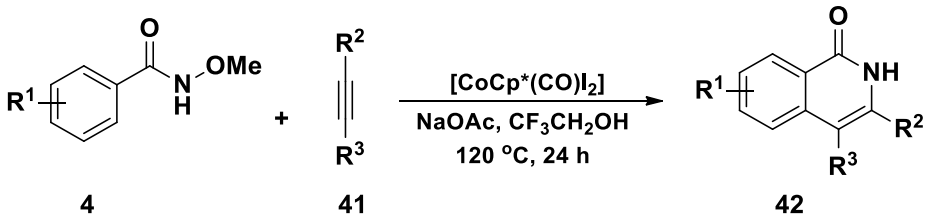
The palladium-catalyzed phenanthridinone synthesis using the coupling of aniline **53** and amide **4** by formation of C−C and C−N bonds *via* dual C−H bond activation was developed by Bhanage *et al.* (Scheme 5B.25).[33] The reported protocol is ligand-free and takes place under mild reaction conditions, which involve simultaneous cleavage of four bonds and the formation of two new bonds.



Scheme 5B.25

5B.2.4. Using Cobalt

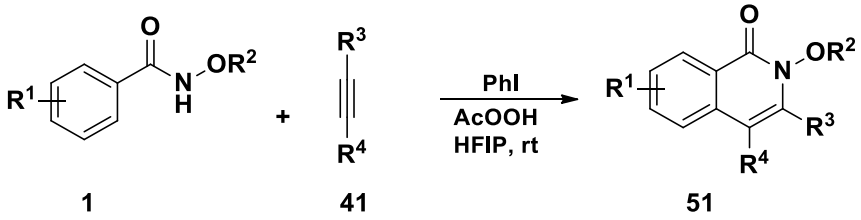
In a report by Jeganmohan *et al*., the cyclization of substituted *N*-methoxy benzamides **4** with alkynes **41** in the presence of cobalt complex [$Co^{III}Cp^*(OR)_2$] (R = Me or Ac) and NaOAc through C-H/N-O bond activation provided isoquinolone derivatives **42** in good to excellent yields (Scheme 5B.26).[34]



Scheme 5B.26

5B.2.5. Using Organocatalyst

Organocatalytic annulation by functionalization of benzamide derivatives **1** with alkynes **41** was developed by Antonchick and coworkers (Scheme 5B.27). This new approach of cycloaddition under mild reaction conditions using simple catalysts, such as iodobenzene and peracetic acid, as oxidant provided straightforward access to isoquinolines **51** with fast reaction rate.[35]

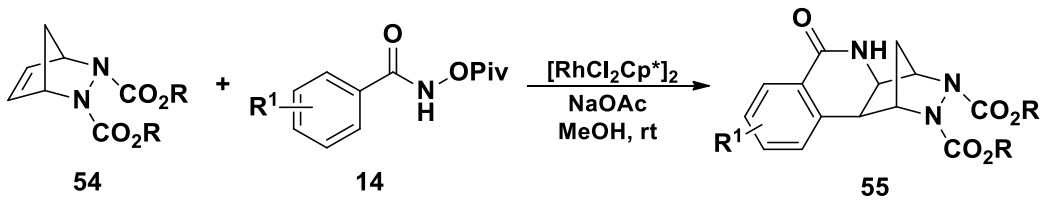


Scheme 5B.27

5B.3. Statement of the Problem

We were successful in developing the rhodium catalyzed synthesis of isoquinolone fused azabicycles **55** utilizing *N*-pivaloyloxy benzamides **14** and diazabicyclic olefins **54**

(Scheme 5B.28).[36] N–N bond cleavage of synthesized compounds makes them effective precursors for the preparation of diaminocyclopentane fused isoquinolones.

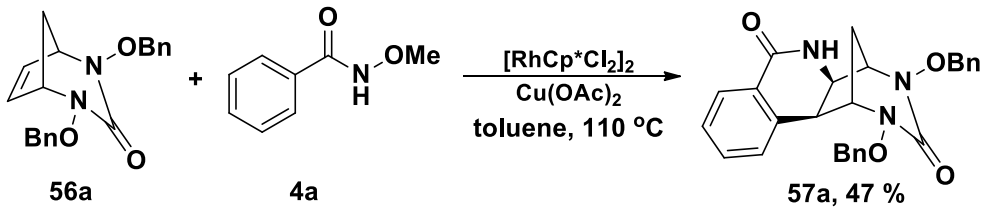


Scheme 5B.28

After investigating the reactivity of benzamides with these diazabicyclic olefins, we were interested to check their reactivity with urea derived bicycles because of their tremendous biological potential.

5B.4. Results and Discussion

We initiated our investigations with the reaction of urea-derived bicyclic olefin **56a** with *N*-methoxybenzamide **4a**. Under the optimized conditions that we had performed for diazabicyclic olefins, only a trace amount of the expected product was formed with urea-derived bicyclic olefin.[36] Later, by changing the solvent to toluene, and increasing the temperature to 110 ^{o}C, the fused isoquinolone **57a** was obtained in 47 % yield.



Scheme 5B.29

Various spectroscopic techniques such as ^{1}H, ^{13}C and HRMS analyses provided structural confirmation for the product. The IR spectrum of **57a** showed the –NH peak at 3434 cm^{-1} and characteristic carbonyl absorption of amide as well as the urea group as a broad peak at 1672 cm^{-1}. In the ^{1}H NMR (Figure 5B.2), the aromatic protons were discernable in the region δ 8.06-7.06 ppm. The NH proton of the amide resonated as a singlet at δ 7.01 ppm. The multiplets in the region δ 5.14-5.06 and δ 4.95-4.92 ppm were assigned to the methylene protons of the benzyloxy groups. The proton on the carbon attached to the nitrogen atom of the isoquinolone appeared as a doublet at δ 4.45 ppm. The proton attached to the carbon bearing the phenyl ring of isoquinolone appeared as a doublet at δ 4.01 ppm. The proton on each carbon attached to nitrogen atom of the urea group appeared as doublets

at δ 3.57 and δ 3.45 ppm. The bridge methylene protons resonated as a multiplet in the region δ 1.98-1.95 and δ 1.91-1.87 ppm.

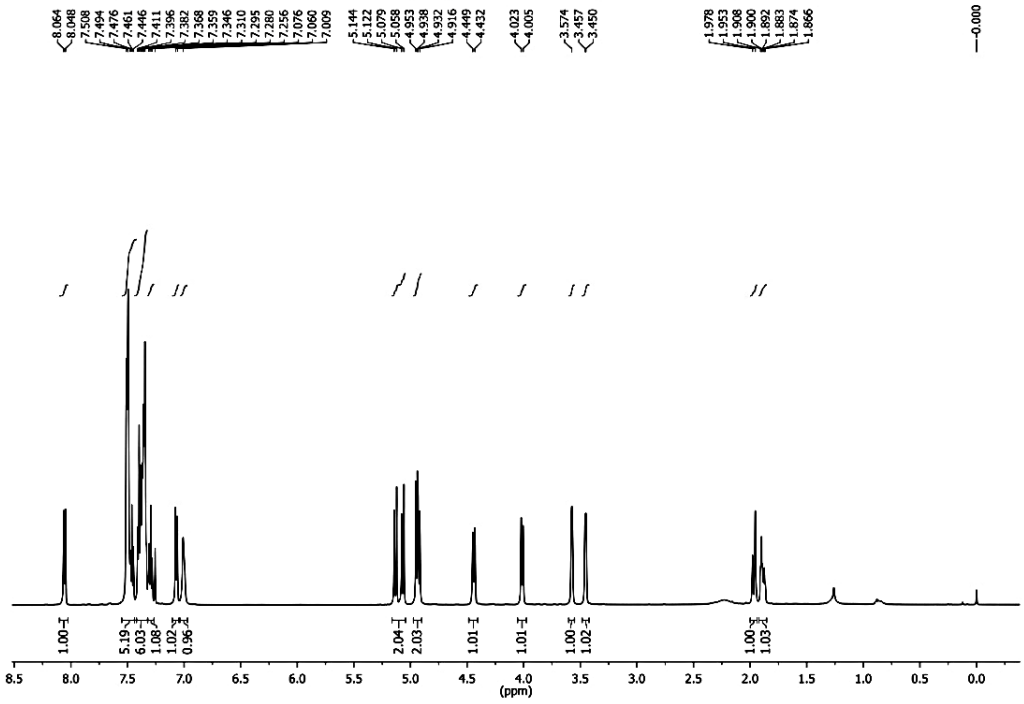


Figure 5B.2. ^{1}H NMR spectrum of compound **57a**

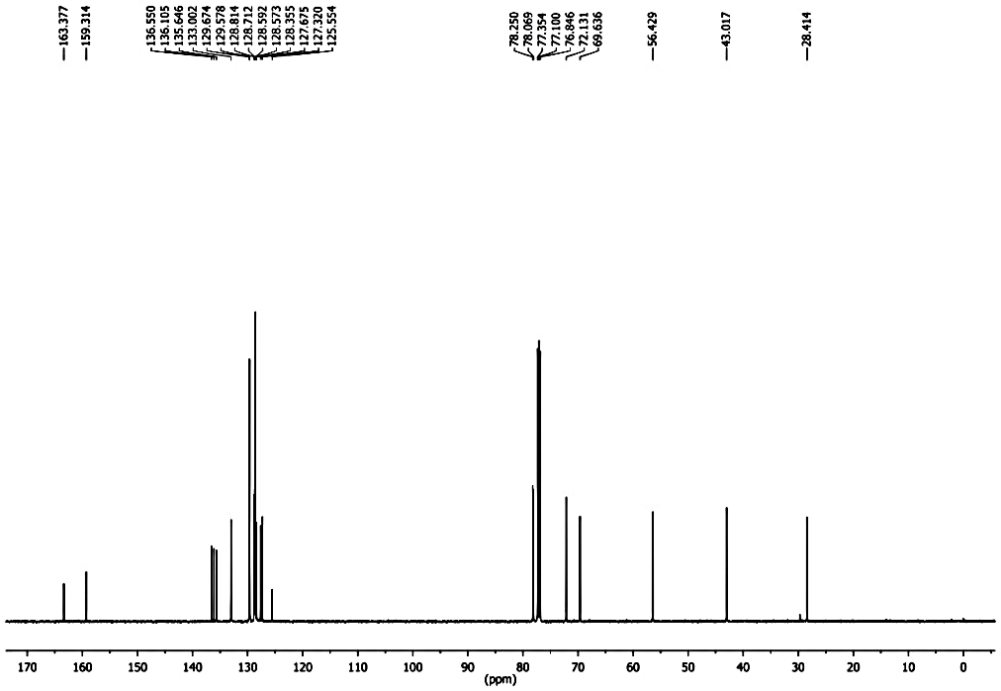


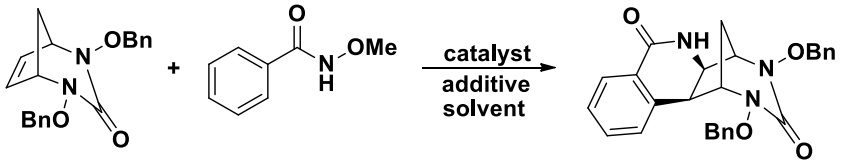
Figure 5B.3. ^{13}C NMR spectrum of compound **57a**

^{13}C NMR of **57a** (Figure 5B.3) displayed the carbonyl peak of the urea and amide at δ 163.4 and 159.3 ppm. The methylene carbons of the benzyloxy groups were identified at δ 78.2 and 78.1 ppm. Each carbon bearing the nitrogen atom resonated at δ 72.1 and 69.6 ppm. The peak at δ 56.4 ppm was assigned to the carbon attached to the nitrogen atom of the isoquinolone. The carbon bearing the phenyl group of isoquinolone appeared at δ 43.0 ppm. The methylene carbon resonated at δ 28.4 ppm. Further confirmation was obtained from HRMS-ESI analysis that showed $[M+H]^+$ peak at 456.19114.

5B.4.1. Optimization Studies

Detailed optimization studies were performed to reveal the best condition for this reaction. Solvents such as CH_3CN, DMF and xylene were not effective for the transformation. Finally, increasing the temperature to 130 ^oC furnished a maximum yield of 75 % for the reaction (Table 5B.1, entry 5). Adding $AgSbF_6$ as additive also reduced the yield of the reaction (entry 8).

Table 5B.1. Optimization studies for heteroannulation reaction[a]



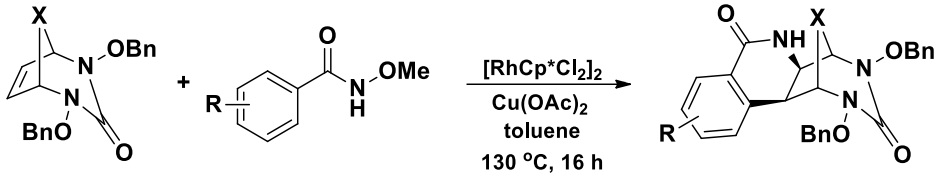
Entry	Catalyst	Additive	Solvent	Temp	Yield (%)[b]
1	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	MeOH	60 ^oC	trace
2	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	CH_3CN	80 ^oC	nr
3	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	toluene	110 ^oC	47
4	$[RhCp^*Cl_2]_2$	NaOAc	toluene	110 ^oC	nr
5	**$[RhCp^*Cl_2]_2$**	**$Cu(OAc)_2$**	**toluene**	**130 ^oC**	**75**
6	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	DMF	130 ^oC	40
7	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	xylene	130 ^oC	58
8	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	toluene	130 ^oC	65[c]
9	$[Ru(p\text{-cymene})Cl_2]_2$	$Cu(OAc)_2$	toluene	130 ^oC	nr

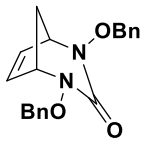
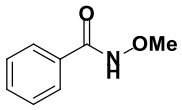
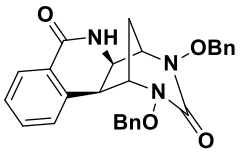
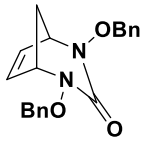
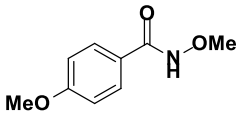
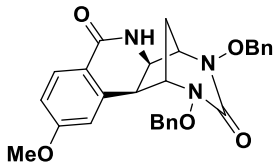
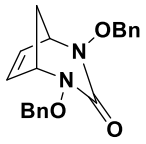
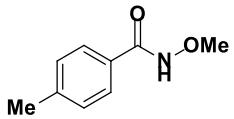
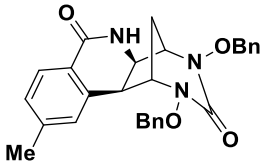
[a]**Reaction conditions:** adduct (1 equiv.), benzamide (1.2 equiv.), catalyst (5 mol%), additive (2 equiv.), solvent (2 mL), 16 h. [b]Isolated yield. [c]With 10 mol% $AgSbF_6$. nr = no reaction.

5B.4.2. Scope of the Reaction

The reactivity of various substituted benzamides was checked with different bicylic olefins to prove the generality of this reaction (Table 5B.2). Benzamides with substituents such as Me, OMe, F, Cl and Br groups reacted to give the isoquinolone derivatives in moderate yields (**57b-57f**). The scope of the reaction was further tested with bicylic olefins derived from furan and Boc-protected pyrrole. All of them reacted smoothly to furnish the corresponding fused isoquinolone derivatives in moderate yields (**57g-57o**). However, only a trace amount of product was formed with benzamide bearing NO_2 group as the substituent (**57p**). Eventhough the reaction with *ortho*-trifluoromethyl substituted benzamide did not furnish any product (**57q**), *meta*-bromo substituted *N*-methoxybenzamide gave trace amount of the corresponding isoquinolone derivative (**57r**).

Table 5B.2. Heteroannulation of urea derived bicyclic olefins[a]



Entry	Bicyclic Olefin	Benzamides	Product	Yield (%)[b]
1				75
	56a	**4a**	**57a**	
2				63
	56a	**4b**	**57b**	
3				70
	56a	**4c**	**57c**	

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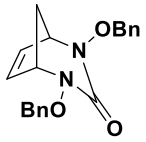
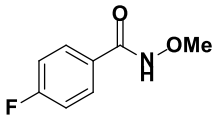
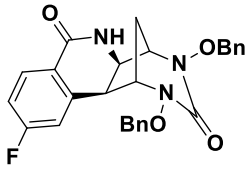
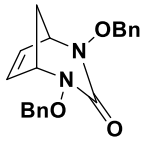
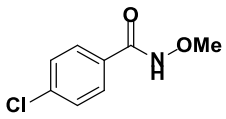
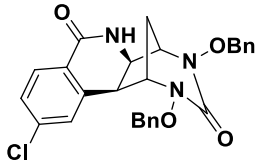
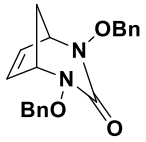
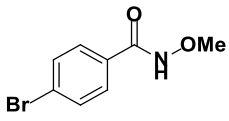
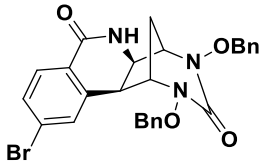
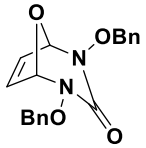
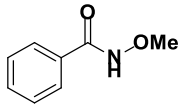
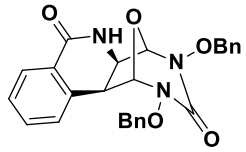
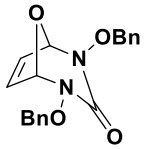
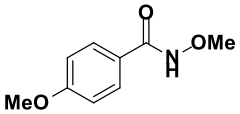
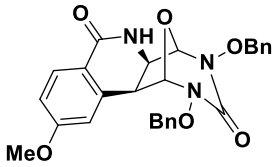
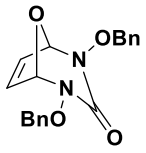
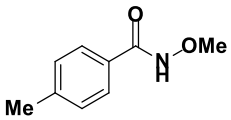
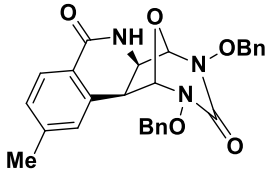
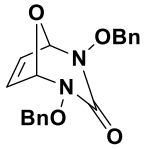
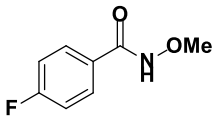
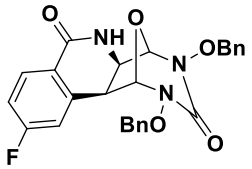
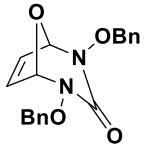
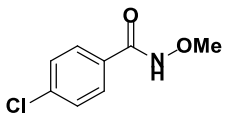
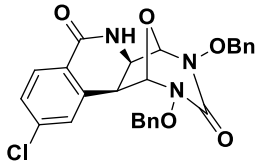
4	 **56a**	 **4d**	 **57d**	50
5	 **56a**	 **4e**	 **57e**	54
6	 **56a**	 **4f**	 **57f**	60
7	 **56b**	 **4a**	 **57g**	65
8	 **56b**	 **4b**	 **57h**	59
9	 **56b**	 **4c**	 **57i**	64
10	 **56b**	 **4d**	 **57j**	42
11	 **56b**	 **4e**	 **57k**	48

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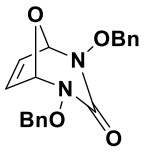
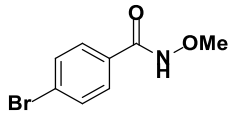
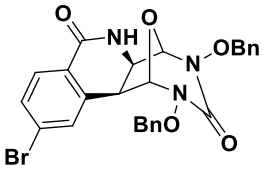
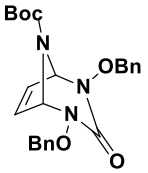
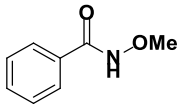
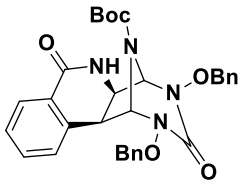
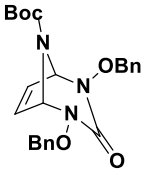
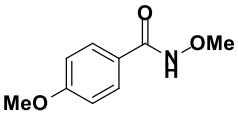
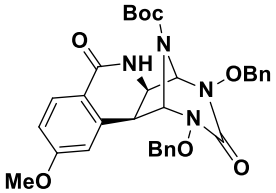
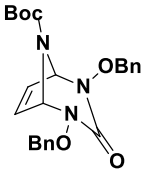
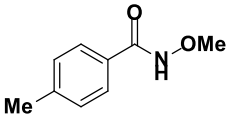
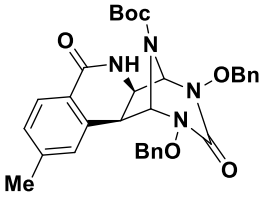
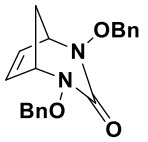
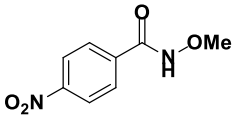
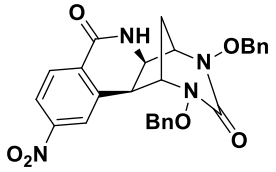
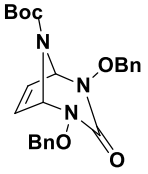
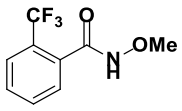
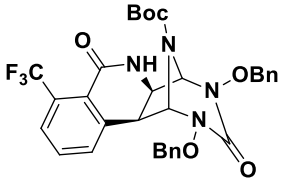
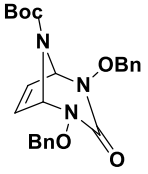
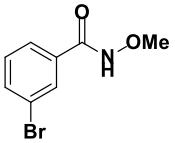
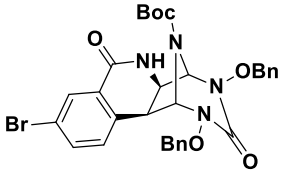
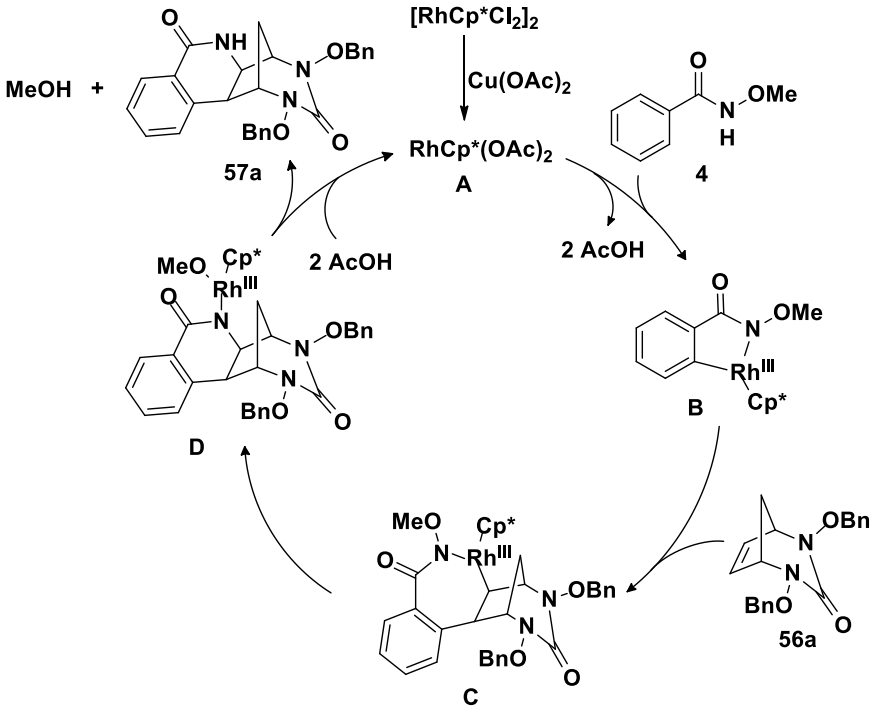
12	 **56b**	 **4f**	 **57l**	50
13	 **56c**	 **4a**	 **57m**	59
14	 **56c**	 **4b**	 **57n**	51
15	 **56c**	 **4c**	 **57o**	58
16	 **56a**	 **4g**	 **57p**	2
17	 **56c**	 **4h**	 **57q**	0
18	 **56c**	 **4i**	 **57r**	4

[a]**Reaction conditions:** adduct (1 equiv.), benzamide (1.2 equiv.), $[RhCp^*Cl_2]_2$ (5 mol%), $Cu(OAc)_2$ (2 equiv.), toluene (2 mL), 16 h. [b]Isolated yield.

5B.5. Plausible Mechanism

In the case of isoquinolone synthesis, we have proposed a plausible mechanism based on the previous reports as described in Scheme 5B.30. The catalytic cycle begins with the anion exchange between Rh(III) catalyst and $Cu(OAc)_2$ to form the complex **A**. The N-H and C-H bond cleavage by the Rh(III) species furnishes the pentacyclic intermediate **B** which then undergoes insertion to the alkene **56a** to afford seven membered intermediate **C**. Reductive elimination followed by the oxidative addition to the N–O bond forms intermediate **D** which subsequently undergoes protonolysis to form **57a** regenerating the active catalyst.



Scheme 5B.30. Proposed reaction mechanism

5B.6. Conclusion

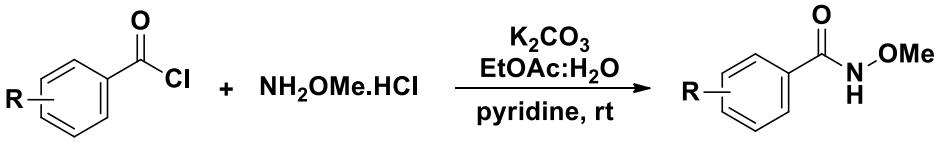
In conclusion, we have developed an efficient strategy for the construction of isoquinolone fused urea-derived bicyclic olefins. The reaction with *N*-methoxybenzamides generated isoquinolone fused urea derived bicyclic motifs. Considering the biological significance of the urea derivatives and these heterocycles, the synthesized products are expected to show good biological activity.

5B.7. Experimental Section

5B.7.1. General Methods

General information about the experiments is given in Section 2.8.1 of Chapter 2.

5B.7.2. General Procedure for the Synthesis of *N*-methoxy benzamides[37]



O-methylhydroxylamine hydrochloride (1 equiv.) was dissolved in water (12 mL) and EtOAc (25 mL) and cooled to 0 °C in an ice bath. K_2CO_3 (2 equiv.) followed by acid chloride (0.9 equiv.) were added to the reaction mixture. After stirring at room temperature for 16 h, the aqueous layer was removed and the organic layer was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to get the pure product.

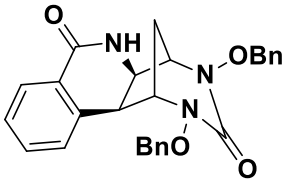
5B.7.3. General Procedure for the Synthesis of Isoquinolone Derivatives

A mixture of urea derived bicyclic olefin **56** (1 equiv.), *N*-methoxy benzamide **4** (1.2 equiv.), $[RhCl_2Cp^*]_2$ (5 mol%) and $Cu(OAc)_2$ (2 equiv.) were weighed into a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 130 ^oC for 16 hours. The solvent was evaporated *in vacuo* and the residue on silica column chromatography (100-200 mesh) with hexane-ethylacetate mixtures yielded isoquinolone derivative **57**.

5B.7.4. Characterization of the Products

Compound 57a

Following the general procedure 5.9.2, compound **57a** (61 mg, 75 %) was synthesised from bicyclic olefin **56a** (60 mg, 0.1784 mmol) and *N*-methoxybenzamide **4a** (32 mg, 0.2141 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol) and $Cu(OAc)_2$ (65 mg, 0.3568 mmol) as pale yellow solid.



MP: 138-140 ^oC

R_f: 0.40 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3434, 3062, 2938, 2879, 1672, 1603, 1582, 1494, 1473, 1457, 1411, 1373, 1337, 1311, 1285, 1267, 1247,

1212, 1159, 1124, 1083, 1026, 994, 918, 750 cm^{-1}.

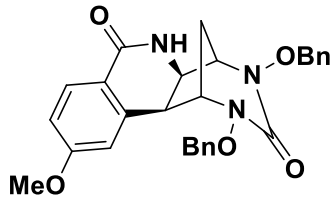
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.0 Hz, 1 H), 7.51-7.45 (m, 5 H), 7.41-7.35 (m, 6 H), 7.29 (t, *J* = 7.5 Hz, 1 H), 7.07 (d, *J* = 8.0 Hz, 1 H), 7.01 (bs, 1 H), 5.14-5.06 (m, 2 H), 4.95-4.92 (m, 2 H), 4.44 (d, *J* = 8.5 Hz, 1 H), 4.01 (d, *J* = 9.0 Hz, 1 H), 3.57 (s, 1 H), 3.45 (d, *J* = 3.5 Hz, 1 H), 1.96 (d, *J* = 12.5 Hz, 1 H), 1.91-1.87 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.4, 159.3, 136.6, 136.1, 135.7, 133.0, 129.7, 129.6, 128.8, 128.7, 128.6, 128.6, 128.4, 127.7, 127.3, 125.6, 78.3, 78.1, 72.1, 69.6, 56.4, 43.0, 28.4.

HRMS (ESI): *m/z* calcd for $C_{27}H_{26}N_3O_4$: 456.19233; Found: 456.19114.

Compound 57b

Following the general procedure 5.9.2, compound **57b** (55 mg, 63 %) was synthesised from bicyclic olefin **56a** (60 mg, 0.1784 mmol) and *N*-methoxybenzamide **4b** (39 mg, 0.2141 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol) and $Cu(OAc)_2$ (65 mg, 0.3568 mmol) as off white solid.



MP: 175-177 ^oC

R_f: 0.26 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3254, 3062, 3033, 2938, 1707, 1667, 1606, 1460, 1403, 1373, 1328, 1255, 1217, 1157, 1130, 1085, 1027, 995, 921, 879, 836, 780, 750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.5 Hz, 1 H), 7.50-7.47 (m, 4 H), 7.40-7.36 (m, 6 H), 6.80 (dd, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1 H), 6.57 (d, *J* = 2.0 Hz, 1 H), 6.21 (bs, 1 H), 5.14 (d, *J* = 11.5 Hz, 1 H), 5.06 (d, *J* = 11.0 Hz, 1 H), 4.92 (dd, J_1 = 11.0 Hz, J_2 = 9.0 Hz, 2 H), 4.40 (d, *J* = 9.0 Hz, 1 H), 3.98 (d, *J* = 9.0 Hz, 1 H), 3.80 (s, 3 H), 3.46 (d, *J* = 4.0 Hz, 2 H), 1.97 (d, *J* = 13.0 Hz, 1 H), 1.93-1.88 (m, 1 H).

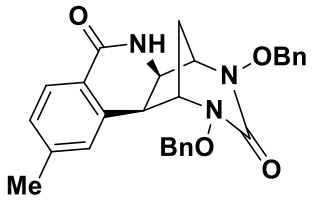
^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2, 159.5, 138.6, 136.0, 135.6, 129.9, 129.7, 129.5, 129.3, 128.9, 128.8, 128.6. 128.6, 113.8, 113.8, 112.4, 78.3, 78.1, 77.4, 72.1, 69.9, 56.6, 55.4, 43.3, 28.5.

HRMS (ESI): *m/z* calcd for $C_{28}H_{27}N_3O_5Na$: 508.18484; Found: 508.18583.

Compound 57c

Following the general procedure 5.9.2, compound **57c** (59 mg, 70 %) was synthesised from

bicyclic olefin **56a** (60 mg, 0.1784 mmol) and *N*-methoxybenzamide **4c** (35 mg, 0.2141 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol) and $Cu(OAc)_2$ (65 mg, 0.3568 mmol) as light brown solid.



MP: 185-187 ^oC

R_f: 0.48 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3350, 3036, 2926, 2858, 1667, 1614, 1572, 1462, 1390, 1333, 1287, 1217, 1184, 1084, 1027, 994, 838, 749 cm^{-1}.

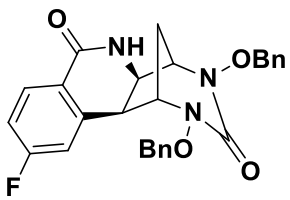
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.0 Hz, 1 H), 7.53-7.48 (m, 4 H), 7.43-7.35 (m, 6 H), 7.09 (d, *J* = 8.0 Hz, 1 H), 6.84 (s, 1 H), 6.45 (bs, 1 H), 5.15 (d, *J* = 11.0 Hz, 1 H), 5.06 (d, *J* = 11.0 Hz, 1 H), 4.95-4.91 (m, 2 H), 4.39 (d, *J* = 8.5 Hz, 1 H), 3.97 (d, *J* = 9.0 Hz, 1 H), 3.46 (d, *J* = 3.0 Hz, 1 H), 3.41 (d, *J* = 4.0 Hz, 1 H), 2.36 (s, 3 H), 1.95 (d, *J* = 13.0 Hz, 1 H), 1.88-1.84 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.6, 159.3, 143.7, 136.5, 136.2, 135.6, 129.7, 129.6, 128.9, 128.8, 128.7, 128.6, 128.6, 128.4, 127.8, 127.4, 78.4, 78.1, 72.2, 69.8, 56.4, 42.9, 29.7, 28.4, 21.6.

HRMS (ESI): *m/z* calcd for $C_{28}H_{28}N_3O_4$: 470.20798; Found: 470.20721.

Compound 57d

Following the general procedure 5.9.2, compound **57d** (42 mg, 50 %) was synthesised from bicyclic olefin **56a** (60 mg, 0.1784 mmol) and *N*-methoxybenzamide **4d** (36 mg, 0.2141 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol) and $Cu(OAc)_2$ (65 mg, 0.3568 mmol) as pale yellow solid.



MP: 177-179 ^oC.

R_f: 0.41 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3265, 3062, 2929, 1710, 1673, 1612, 1476, 1406, 1368, 1327, 1253, 1155, 1084, 1026, 922, 881, 747 cm^{-1}.

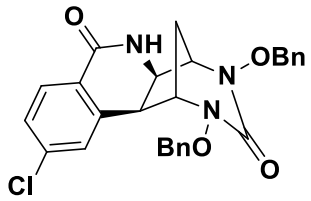
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (dd, J_1 = 8.5 Hz, J_2 = 6.0 Hz, 1 H), 7.52-7.47 (m, 4 H), 7.44-7.36 (m, 6 H), 6.97 (td, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1 H), 6.69 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1 H), 5.88 (bs, 1 H), 5.15-5.06 (m, 2 H), 4.95-4.90 (m, 2 H), 4.39 (d, *J* = 9.0 Hz, 1 H), 3.98 (d, *J* = 8.5 Hz, 1 H), 3.42-3.39 (m, 2 H), 1.98 (d, *J* = 13.0 Hz, 1 H), 1.88-1.83 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.5, 164.5, 162.1, 159.1, 139.4, 139.3, 135.9, 135.6, 130.9, 130.8, 129.7, 129.7, 129.0, 128.9, 128.7, 128.7, 115.2, 115.0, 114.8, 114.6, 78.5, 78.2, 72.0, 69.9, 56.6, 43.2, 28.4.

HRMS (ESI): *m/z* calcd for $C_{27}H_{24}N_3O_4FNa$: 496.16485; Found: 496.16444.

Compound 57e

Following the general procedure 5.9.2, compound **57e** (47 mg, 54 %) was synthesised from bicyclic olefin **56a** (60 mg, 0.1784 mmol) and *N*-methoxybenzamide **4e** (40 mg, 0.2141 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol) and $Cu(OAc)_2$ (65 mg, 0.3568 mmol) as pale yellow solid.



MP: 194-196 ^oC

R_f: 0.43 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3268, 2109, 1672, 1597, 1464, 1400, 1366, 1329, 1287, 1213, 1165, 1128, 1088, 1025, 995, 833, 746 cm^{-1}.

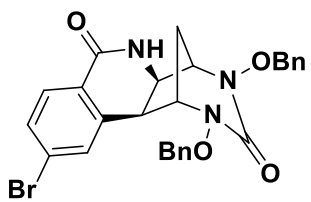
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.5 Hz, 1 H), 7.52-7.47 (m, 4 H), 7.44-7.41 (m, 2 H), 7.39-7.36 (m, 4 H), 7.26-7.24 (m, 1 H), 7.01 (d, *J* = 1.0 Hz, 1 H), 6.72 (bs, 1 H), 5.15 (d, *J* = 11.0 Hz, 1 H), 5.06 (d, *J* = 10.5 Hz, 1 H), 4.94-4.91 (m, 2 H), 4.39 (d, *J* = 9.0 Hz, 1 H), 3.95 (d, *J* = 9.0 Hz, 1 H), 3.51 (s, 1 H), 3.35 (d, *J* = 4.0 Hz, 1 H), 1.97 (d, *J* = 13.0 Hz, 1 H), 1.85-1.81 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5, 159.1, 139.2, 138.3, 136.0, 135.5, 129.7, 129.4, 129.0, 128.9, 128.7, 128.6, 128.2, 127.8, 124.0, 78.5, 78.1, 72.1, 69.5, 56.5, 42.7, 28.4.

HRMS (ESI): *m/z* calcd for $C_{27}H_{25}N_3O_4Cl$: 490.15336; Found: 490.15268.

Compound 57f

Following the general procedure 5.9.2, compound **57f** (57 mg, 60 %) was synthesised from bicyclic olefin **56a** (60 mg, 0.1784 mmol) and *N*-methoxybenzamide **4f** (49 mg, 0.2141 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol) and $Cu(OAc)_2$ (65 mg, 0.3568 mmol) as off white solid.



MP: 201-203 ^oC

R_f: 0.45 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3244, 3037, 2931, 1957, 1671, 1590, 1462, 1366, 1328, 1276, 1212, 1165, 1082, 995, 923, 749 cm^{-1}.

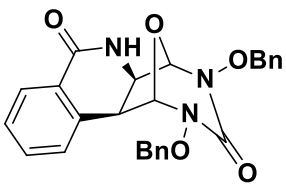
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.0 Hz, 1 H), 7.52-7.47 (m, 4 H), 7.45-7.35 (m, 7 H), 7.20 (d, *J* = 1.0 Hz, 1 H), 6.64 (s, 1 H), 5.15 (d, *J* = 11.0 Hz, 1 H), 5.06 (d, *J* = 11.0 Hz, 1 H), 4.94-4.90 (m, 2 H), 4.39 (d, *J* = 9.0 Hz, 1 H), 3.95 (d, *J* = 9.0 Hz, 1 H), 3.50 (d, *J* = 2.5 Hz, 1 H), 3.34 (d, *J* = 4.0 Hz, 1 H), 1.97 (d, *J* = 13.0 Hz, 1 H), 1.84-1.80 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5, 159.2, 138.4, 136.0, 135.6, 131.2, 130.8, 129.7, 129.7, 129.5, 129.0, 128.9, 128.8, 128.6, 127.8, 124.4, 78.5, 78.1, 72.2, 69.6, 56.6, 42.5, 28.4.

HRMS (ESI): *m/z* calcd for $C_{27}H_{25}N_3O_4Br$: 534.10284; Found: 534.10210.

Compound 57g

Following the general procedure 5.9.2, compound **57g** (53 mg, 65 %) was synthesised from bicyclic olefin **56b** (60 mg, 0.1773 mmol) and *N*-methoxybenzamide **4a** (32 mg, 0.2128 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol) and $Cu(OAc)_2$ (65 mg, 0.3546 mmol) as light yellow solid.



MP: 198-200 ^oC

R_f: 0.46 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3341, 2945, 2094, 1726, 1673, 1484, 1411, 1349, 1205, 995, 918, 854, 789, 745 cm^{-1}.

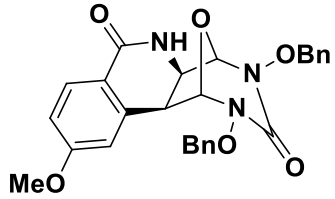
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.0 Hz, 1 H), 7.50 (d, *J* = 7.0 Hz, 4 H), 7.43-7.37 (m, 7 H), 7.31 (t, *J* = 7.5 Hz, 1 H), 7.12 (s, 1 H), 6.66 (d, *J* = 8.0 Hz, 1 H), 5.15-5.08 (m, 2 H), 5.04 (s, 1 H), 5.01-5.0 (m, 2 H), 4.82 (s, 1 H), 4.17 (d, *J* = 9.0 Hz, 1 H), 3.83 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.1, 156.8, 135.9, 135.4, 134.6, 133.1, 129.9, 129.8, 129.2, 129.0, 128.9, 128.8, 128.0, 127.9, 127.8, 125.6, 99.7, 97.3, 79.1, 78.7, 57.5, 43.8.

HRMS (ESI): *m/z* calcd for $C_{26}H_{23}N_3O_5Na$: 480.15354; Found: 480.15221.

Compound 57h

Following the general procedure 5.9.2, compound **57h** (51 mg, 59 %) was synthesised from bicyclic olefin **56b** (60 mg, 0.1773 mmol) and *N*-methoxybenzamide **4b** (39 mg, 0.2128 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol) and $Cu(OAc)_2$ (65 mg, 0.3546 mmol) as light yellow solid.



MP: 215-217 ^{o}C

R_f: 0.35 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3256, 3032, 2922, 2850, 1960, 1715, 1669, 1606, 1459, 1413, 1355, 1257, 1173, 1092, 1028, 1000, 921, 889, 848, 752 cm^{-1}.

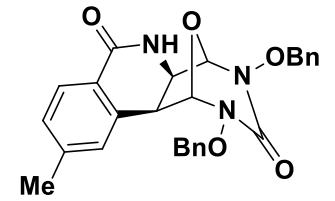
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.5 Hz, 1 H), 7.50-7.49 (m, 4 H), 7.43-7.38 (m, 6 H), 6.82 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1 H), 6.36 (d, *J* = 2.5 Hz, 1 H), 6.17 (bs, 1 H), 5.16 (d, *J* = 11.5 Hz, 1 H), 5.08 (d, *J* = 11.5 Hz, 1 H), 5.01 (d, *J* = 11.5 Hz, 2 H), 4.87 (s, 1 H), 4.83 (s, 1 H), 4.16 (d, *J* = 7.5 Hz, 1 H), 3.85 (d, *J* = 9.0 Hz, 1 H), 3.80 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.3, 157.2, 135.6, 135.5, 130.2, 129.8, 129.7, 129.2, 129.2, 128.9, 128.8, 113.7, 112.6, 99.1, 97.9, 79.0, 78.8, 57.5, 55.5, 44.1.

HRMS (ESI): *m/z* calcd for $C_{27}H_{25}N_3O_6Na$: 510.16411; Found: 510.16607.

Compound 57i

Following the general procedure 5.9.2, compound **57i** (54 mg, 64 %) was synthesised from bicyclic olefin **56b** (60 mg, 0.1773 mmol) and *N*-methoxybenzamide **4c** (35 mg, 0.2128 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol) and $Cu(OAc)_2$ (65 mg, 0.3546 mmol) as white solid.



MP: 215-218 ^{o}C.

R_f: 0.56 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3439, 2921, 2098, 1740, 1679, 1647, 1614, 1508, 1489, 1452, 1429, 1350, 1325, 1206, 1031, 997, 963, 919, 854, 834, 791, 753 cm^{-1}.

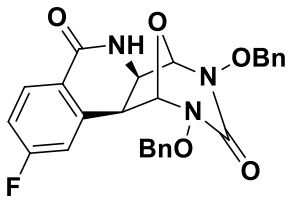
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.0 Hz, 1 H), 7.52-7.49 (m, 4 H), 7.45-7.37 (m, 6 H), 7.11 (d, *J* = 8.0 Hz, 1 H), 6.98 (bs, 1 H), 6.51 (s, 1 H), 5.16 (d, *J* = 11.5 Hz, 1 H), 5.08 (d, *J* = 11.0 Hz, 1 H), 5.03-4.97 (m, 3 H), 4.79 (s, 1 H), 4.17 (d, *J* = 8.5 Hz, 1 H), 3.80 (d, *J* = 8.5 Hz, 1 H), 2.34 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2, 156.9, 143.8, 135.9, 135.4, 134.5, 129.9, 129.8, 129.2, 129.1, 128.8, 128.8, 128.2, 127.9, 123.1, 99.7, 97.4, 79.1, 78.7, 57.5, 43.8, 29.7, 21.6.

HRMS (ESI): *m/z* calcd for $C_{27}H_{25}N_3O_5Na$: 494.16919; Found: 494.16875.

Compound 57j

Following the general procedure 5.9.2, compound **57j** (35 mg, 42 %) was synthesised from bicyclic olefin **56b** (60 mg, 0.1773 mmol) and *N*-methoxybenzamide **4d** (36 mg, 0.2128 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol) and $Cu(OAc)_2$ (65 mg, 0.3546 mmol) as white solid.



MP: 208-210 ^oC

R_f: 0.47 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3385, 3187, 3040, 2916, 2850, 2100, 1735, 1676, 1601, 1484, 1447, 1411, 1354, 1252, 1204, 1035, 992, 920, 889, 842, 753 cm^{-1}.

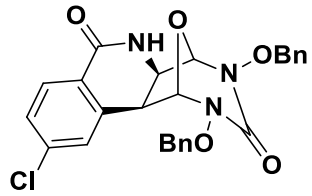
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (dd, J_1 = 9.0 Hz, J_2 = 6.0 Hz, 1 H), 7.52-7.49 (m, 4 H), 7.47-7.40 (m, 6 H), 6.98(td, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1 H), 6.40 (bs, 1 H), 6.25 (d, J = 7.0 Hz, 1 H), 5.15-5.02 (m, 4 H), 4.91 (s, 1 H), 4.76 (s, 1 H), 4.10 (d, J = 8.5 Hz, 1 H), 3.76 (d, J = 8.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.5, 164.4, 161.9, 156.4, 137.3, 137.2, 135.8, 135.5, 130.9, 130.9, 129.9, 129.8, 129.4, 129.3, 129.0, 128.9, 115.7, 115.5, 114.5, 114.3, 99.6, 97.5, 79.2, 78.8, 57.6, 44.0.

HRMS (ESI): *m/z* calcd for $C_{26}H_{22}N_3O_5FNa$: 498.14412; Found: 498.14353.

Compound 57k

Following the general procedure 5.9.2, compound **57k** (42 mg, 48 %) was synthesised from bicyclic olefin **56b** (60 mg, 0.1773 mmol) and *N*-methoxybenzamide **4e** (39 mg, 0.2128 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol) and $Cu(OAc)_2$ (65 mg, 0.3546 mmol) as pale yellow solid.



MP: 115-117 ^oC.

R_f: 0.53 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3416, 2924, 2097, 1734, 1677, 1594, 1482, 1432, 1352, 1208, 1095, 994, 956, 843, 750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, J = 8.5 Hz, 1 H), 7.54-7.41 (m, 10 H), 7.29 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1 H), 6.93 (s, 1 H), 6.65 (s, 1 H), 5.16 (d, J = 11.5 Hz, 1 H), 5.10 (d, J = 11.0 Hz, 1 H), 5.06-5.02 (m, 2 H), 4.94 (s, 1 H), 4.73 (s, 1 H), 4.13 (d, J = 8.0 Hz, 1 H), 3.78

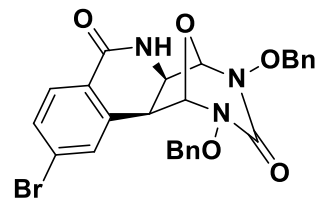
(d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.4, 156.6, 139.7,139.5, 136.2, 135.7, 135.4, 131.4, 129.9, 129.8, 129.6, 129.5, 129.3, 129.1, 128.9, 128.8, 128.5, 127.7, 123.9, 99.5, 97.4, 79.2, 78.8, 57.6, 43.6.

HRMS (ESI): *m/z* calcd for $C_{26}H_{22}N_3O_5ClNa$: 514.11457; Found: 514.11412.

Compound 57l

Following the general procedure 5.9.2, compound **57l** (48 mg, 50 %) was synthesised from bicyclic olefin **56b** (60 mg, 0.1773 mmol) and *N*-methoxybenzamide **4f** (49 mg, 0.2128 mmol) using $[RhCp^*Cl_2]_2$ (6 mg, 0.0089 mmol) and $Cu(OAc)_2$ (65 mg, 0.3546 mmol) as white solid.



MP: 218-220 ^oC.

R_f: 0.60 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3437, 2921, 2095, 1736, 1648, 1590, 1498, 1477, 1454, 1431, 1397, 1348, 1321, 1209, 1137, 1088, 1053, 1029, 1000, 963, 944, 922, 893, 840, 785, 754 cm^{-1}.

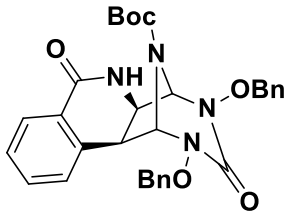
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.0 Hz, 1 H), 7.53-7.43 (m, 11 H), 6.86 (s, 1 H), 6.00 (s, 1 H), 5.15 (d, *J* = 11.5 Hz, 1 H), 5.09-5.00 (m, 3 H), 4.84 (s, 1 H), 4.69 (s, 1 H), 4.08 (d, *J* = 8.0 Hz, 1 H), 3.77 (d, *J* = 9.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.1, 156.6, 136.3, 135.7, 135.5, 131.4, 130.7, 129.9, 129.9, 129.6, 129.5, 129.3, 129.1, 128.9, 127.9, 124.4, 99.4, 97.6, 79.2, 78.8, 57.6, 43.5, 29.7.

HRMS (ESI): *m/z* calcd for $C_{26}H_{23}N_3O_5Br$: 536.08211; Found: 536.08169.

Compound 57m

Following the general procedure 5.9.2, compound **57m** (45 mg, 59 %) was synthesised from bicyclic olefin **56c** (60 mg, 0.1371 mmol) and *N*-methoxybenzamide **4a** (25 mg, 0.1645 mmol) using $[RhCp^*Cl_2]_2$ (4 mg, 0.0069 mmol) and $Cu(OAc)_2$ (50 mg, 0.2743 mmol) as off white solid.



MP: 170-172 ^{o}C

R_f: 0.54 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3321, 3065, 2974, 2932, 1723, 1675, 1473, 1369, 1325, 1255, 1159, 1006, 844, 747 cm^{-1}.

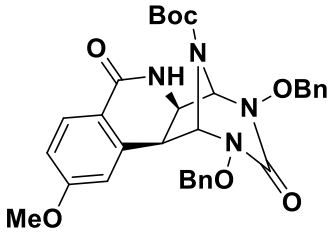
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.5 Hz, 1 H), 7.52-7.48 (m, 5 H), 7.44-7.35 (m, 7 H), 7.06 (d, *J* = 8.0 Hz, 1 H), 6.02 (s, 1 H), 5.15-5.08 (m, 3 H), 5.01-4.91 (m, 3 H), 4.51 (d, *J* = 9.0 Hz, 1 H), 4.14 (d, *J* = 9.0 Hz, 1 H), 1.42 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.9, 159.2, 152.5, 135.4, 134.7, 133.3, 129.5, 128.9, 128.8, 128.7, 128.7, 128.1, 127.9, 83.1, 81.7, 78.6, 78.5, 56.6, 43.3, 27.9.

HRMS (ESI): *m/z* calcd for $C_{31}H_{32}N_4O_6Na$: 579.22195; Found: 579.22156.

Compound 57n

Following the general procedure 5.9.2, compound **57n** (41 mg, 51 %) was synthesised from bicyclic olefin **56c** (60 mg, 0.1371 mmol) and *N*-methoxybenzamide **4b** (30 mg, 0.1645 mmol) using $[RhCp^*Cl_2]_2$ (4 mg, 0.0069 mmol) and $Cu(OAc)_2$ (50 mg, 0.2743 mmol) as light brown solid.



MP: 157-159 ^{o}C

R_f: 0.43 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3428, 2977, 2933, 1722, 1667, 1609, 1465, 1370, 1326, 1256, 1160, 1024, 943, 844, 780, 743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 9.0 Hz, 1 H), 7.50-7.48 (m, 4 H), 7.42-7.37 (m, 6 H), 6.85 (d, *J* = 7.5 Hz, 1 H), 6.56 (s, 1 H), 6.01-5.94 (m, 1 H), 5.15 (d, *J* = 10.5 Hz, 1 H), 5.09-4.99 (m, 3 H), 4.96-4.90 (m, 2 H), 4.50 (d, *J* = 9.0 Hz, 1 H), 4.09 (d, *J* = 8.5 Hz, 1 H), 3.77 (s, 3 H), 1.42 (s, 9 H).

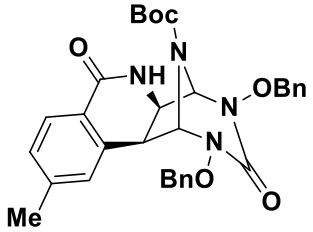
^{13}C NMR (125 MHz, $CDCl_3$): δ 163.4, 162.9, 159.4, 152.5, 136.8, 135.4, 130.1, 129.4, 128.9, 128.9, 128.7, 128.7, 129.3, 118.5, 114.2, 112.4, 83.1, 81.6, 78.6, 78.5, 56.7, 55.4, 43.5, 28.0.

HRMS (ESI): *m/z* calcd for $C_{32}H_{34}N_4O_7Na$: 609.23252; Found: 609.23170.

Compound 57o

Following the general procedure 5.9.2, compound **57o** (45 mg, 58 %) was synthesised from

bicyclic olefin **56c** (60 mg, 0.1371 mmol) and *N*-methoxybenzamide **4c** (27 mg, 0.1645 mmol) using $[RhCp^*Cl_2]_2$ (4 mg, 0.0069 mmol) and $Cu(OAc)_2$ (50 mg, 0.2743 mmol) as light brown solid.



MP: 193-195 ^oC

R_f: 0.53 (hexane/ethyl acetate = 3:7).

IR (neat) ν_{max}: 3269, 2927, 1724, 1674, 1614, 1471, 1369, 1327, 1257, 1159, 1005, 843, 749 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.0 Hz, 1 H), 7.53-7.48 (m, 4 H), 7.44-7.38 (m, 6 H), 7.14 (d, *J* = 7.5 Hz, 1 H), 6.83 (s, 1 H), 6.18 (bs, 1 H), 5.15 (d, *J* = 10.5 Hz, 1 H), 5.10-4.91 (m, 5 H), 4.49 (d, *J* = 9.0 Hz, 1 H), 4.08 (d, *J* = 9.0 Hz, 1 H), 2.35 (s, 3 H), 1.42 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.1, 159.2, 152.6, 143.9, 135.6, 135.2, 134.7, 129.6, 129.4, 128.9, 128.9, 128.9, 128.7, 128.7, 128.5, 127.9, 123.1, 83.0, 81.7, 80.5, 78.7, 78.5, 56.6, 43.2, 28.0, 21.6.

HRMS (ESI): *m/z* calcd for $C_{32}H_{34}N_4O_6Na$: 593.23760; Found: 593.23663.

5B.8. References

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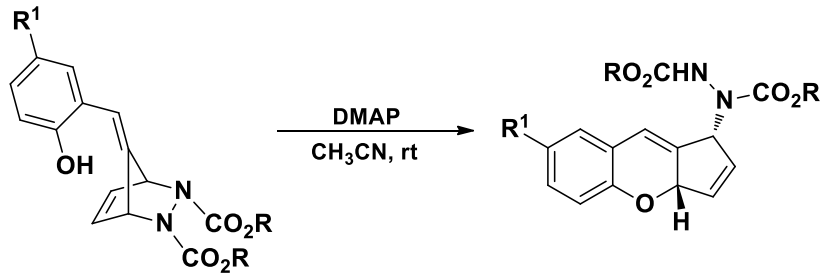
Summary

The thesis entitled "**Construction of Carbocycles and Heterocycles Utilizing the Steric Strain in Heterobicyclic Olefins**" embodies the results of our investigations on the transition metal mediated as well as metal free synthetic transformations of strained diazanorbornenes and urea-derived bicyclic olefins toward the synthesis of functionalized carbocycles and heterocycles. The thesis is divided into five chapters, which deal with detailed discussion on DMAP, rhodium, palladium and iridium catalyzed transformations of these bicyclic olefins.

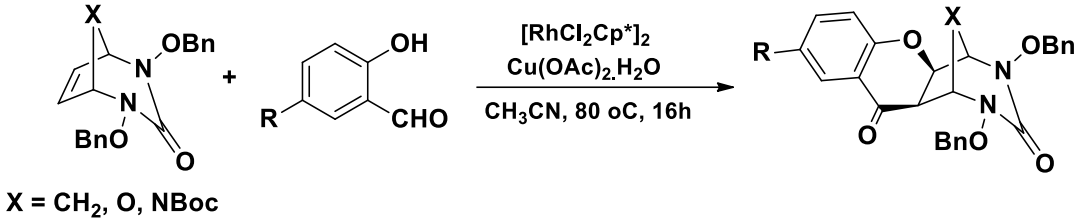
Transition metal catalyzed reactions have revolutionized the area of synthetic organic chemistry by providing an easy, facile and efficient route toward the construction of carbocycles and heterocycles. In this regard, the discovery of novel synthons and their useful synthetic transformations have been an interesting prospect for many synthetic chemists. Among the different synthons utilized so far, heterobicyclic alkenes achieved considerable attention and of these, majority of the investigations have been made on oxa/aza norbornadiene derivatives, oxazabicycles, Vince lactams, diazabicyclic olefins and urea derived bicyclic olefins. The transition metal catalyzed reactions of these heterobicyclic olefins are described in chapter one.

The desymmetrization of diazabicyclic olefins provides an easy route towards the synthesis of carbocycles and heterocycles that are of both synthetic and biological interest, and thus they have been widely exploited. Even though there are limited reports on the palladium/Lewis acid mediated desymmetrization of fulvene derived azabicyclic olefins, the synthetic transformations of phenol-substituted fulvene derived azabicyclic olefins have not been investigated so far. A detailed investigation on the base mediated intramolecular reactions of various phenol substituted fulvene derived bicyclic hydrazines was carried out and the results of these studies are presented in Chapter 2 (Scheme 1).



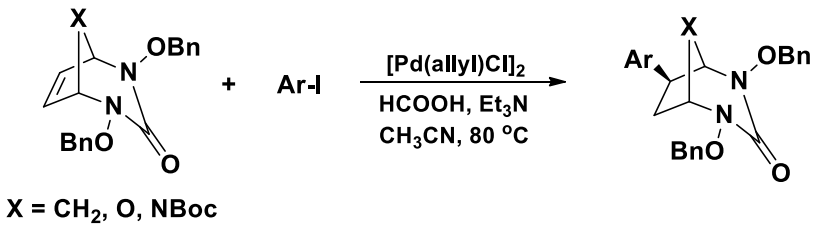
Scheme 1

Urea and its cyclic derivatives represent a class of biologically relevant molecules, widely occurring in natural products and have been studied for various biological activities. In this perspective, the urea derived bicycles synthesized by Jeffrey *et al*. grabbed our attention because of their tremendous synthetic potential. Our continued interest in the chemistry of transition metal catalyzed synthetic transformations of strained bicyclic systems prompted us to investigate the reactivity of bicyclic urea adduct with salicylaldehydes under rhodium catalysis, which is discussed in Chapter 3 (Scheme 2).



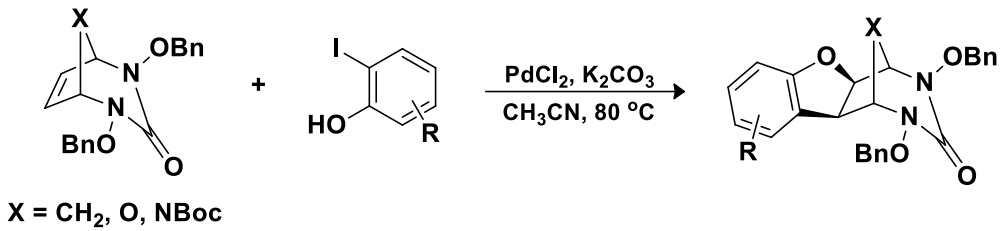
Scheme 2

Among the complexes of a variety of transition metals for carbon-carbon bond formation employed previously, palladium complexes have been most often used as they display wide reactivity and higher selectivity than other transition metal complexes. The most widely used palladium-catalyzed cross coupling reactions such as the Heck, Negishi, Suzuki, Stille and Sonogashira reactions played a remarkable role in the synthesis and manipulation of chemicals and pharmaceuticals. Among them, the Heck reaction now stands as a remarkably robust and efficient method for carbon–carbon bond formation, particularly for intramolecular and intermolecular ring formation, in the generation of tertiary and quaternary stereo centers, and in total synthesis. As we were successful in exploring the transition metal mediated transformations of urea derived bicyclic adducts to chromanone fused analogues, we have carried out the investigations on the reactivity of aryl iodides with the urea derived bicyclic olefins, which is presented in Part A of Chapter 4 (Scheme 3).



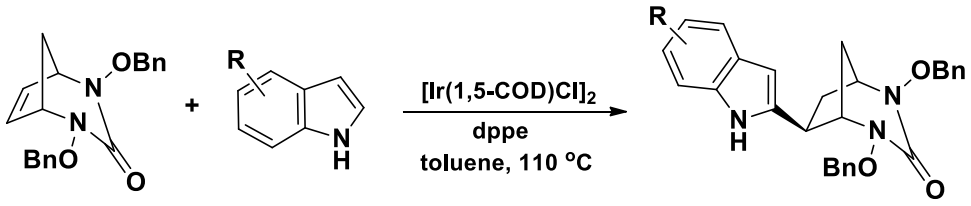
Scheme 3

The transition metal catalyzed reactions using aryl iodides resulted in the arylation reactions as discussed in the previous chapter. Based on the previous reports, the use of reactive substrates that can trap the palladium species intramolecularly results in a cascade reaction and forms annulated products. In this regard, 2-iodophenols, 2-iodoanilines, 2-iodobenzylbromides, 2-iodobenzonitriles, 2-iodobenzyl alcohols, 2-iodophenyl malonates, 2-iodobenzoic acids, and 2-iodobenzamides *etc*. are deeply explored in the literature. Enthralled by these reports, we have carried out the investigations on the reactivity of bi-functional aryl iodides with the urea derived bicyclic olefins. To the best of our knowledge, this is the first report on the palladium-catalyzed heteroannulation of urea derived bicyclic olefins and is summarized in Part B of Chapter 4 (Scheme 4).



Scheme 4

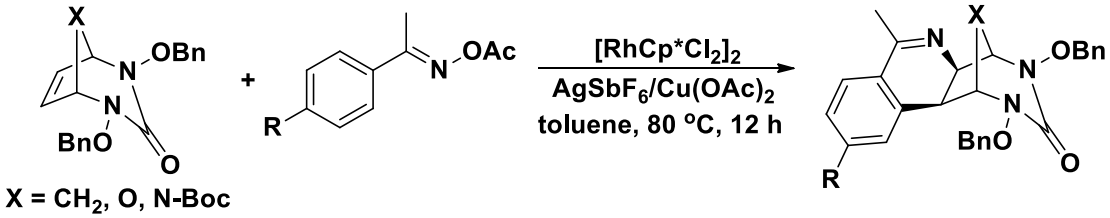
The synthesis and functionalization of indoles is of great significance in synthetic organic chemistry ever since its discovery in 1866. The major issue confronted in the functionalization of indole core is the regioselectivity. Part C of Chapter 4 deals with iridium catalysed the C-2 activation of indoles, which resulted in the hydroheteroarylation of urea derived bicyclic olefins (Scheme 5). Moreover, the reaction was extended to benzofurans and pyrroles.



Scheme 5

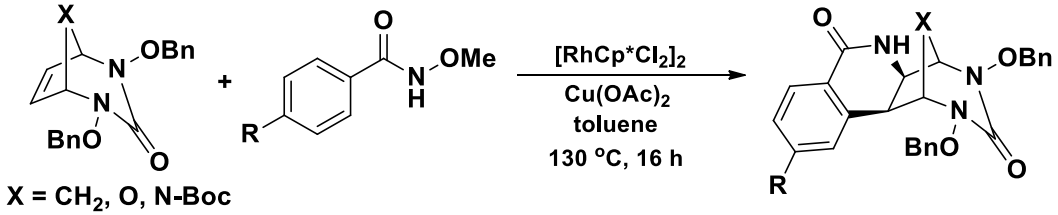
Recent advances in transition metal catalyzed reactions have paved a way to the facile syntheses of azaheterocycles such as isoquinolines and isoquinolones *via* the functionalization of omnipresent carbon–hydrogen bonds. The formation of these heterocycles largely depends upon the directing groups present in the starting materials.

Among these attempts, transition metal-catalyzed reactions involving oximes have emerged as a promising synthetic protocol. We have performed investigations with the reaction of urea-derived bicyclic olefins and *O*-acetyl ketoximes using Rh(III) as the catalyst and the results are detailed in Part A of Chapter 5 (Scheme 6). To the best of our knowledge, this is the first report on the rhodium catalyzed ring annulation *via* C-H activation on urea-derived bicycles.



Scheme 6

Among the various aromatic substrates containing the nitrogen based functional groups as a directing group, benzamide derivatives represents a highly valuable method to azaheterocycle synthesis. In Part B of Chapter 5, the results of our studies on the annulation reaction of various urea derived bicyclic olefins *via* the C-H activation of *N*-methoxybenzamides toward the synthesis of isoquinolone fused bicycles are discussed in detail (Scheme 7).



Scheme 7

In conclusion, we have developed facile and efficient strategies for the synthesis of highly functionalized carbocycles and heterocycles using base mediated and transition metal catalyzed approaches. Considering the biological significance of the urea derivatives and these heterocycles, the synthesized products are expected to show good biological activity.

List of Publications

1) T. V. Baiju, **Ajesh Vijayan**, Nayana Joseph, Preethanuj Preethalayam, K. V. Radhakrishnan*, E. Suresh and Yoshinori Yamamoto, Bis-functionalization of 1,3-dienes *via* 1,4-conjugate addition of amphiphilic bis-π-allyl and related palladium intermediates, *Synlett*, **2014**, *25* (3), 359.
2) **Ajesh Vijayan**, T. V. Baiju, Sunil Varughese and K. V. Radhakrishnan*, Transition metal free intramolecular approach for the synthesis of cyclopenta[*b*]chromene derivatives from phenol substituted fulvene derived azabicyclic olefins, *Tetrahedron Lett.*, **2016**, *57* (27), 2965.
3) **Ajesh Vijayan**, T. V. Baiju, E. Jijy, Praveen Prakash, M. Shimi, Nayana Joseph, Petri M. Pihko, Sunil Varughese and K.V. Radhakrishnan*, An easy access to fused chromanones *via* rhodium catalyzed oxidative coupling of salicylaldehydes with heterobicyclic olefins, *Tetrahedron*, **2016**, *72* (27), 4007.
4) P. Preethanuj, V. Jijitha, **Ajesh Vijayan**, Jubi John and K. V. Radhakrishnan*, Sequential Tandem Transformations of Functionalized Diazanorbornenes: Facile Strategy towards Pentacyclic Framework with Multiple Stereocenters, *Synthesis*, **2017**, *49* (08), 1816.
5) Aparna P. S.[‡], **Ajesh Vijayan**[‡], Saran P. Raveendran, E. Suresh, R. Luxmi Varma and K. V. Radhakrishnan*, Ruthenium/Iridium-catalyzed C-2 activation of indoles with bicyclic olefins: An easy access to functionalized heterocyclic motifs, *Synlett*, **2017**, *28* (05), 572.
6) **Ajesh Vijayan**, C. P. Ummu Jumaila, T. V. Baiju and K. V. Radhakrishnan*, Palladium-catalyzed cross-coupling of aryl iodides with heterobicyclic olefins: Access to hydroarylated and heteroannulated motifs, *ChemistrySelect* **2017**, *2* (21), 5913.
7) **Ajesh Vijayan**, C. P. Ummu Jumaila and K. V. Radhakrishnan*, Rhodium(III)-catalyzed C–H activation of *O*-acetyl ketoximes/*N*-methoxy benzamides toward the synthesis of isoquinoline/isoquinolone-fused bicycles, *Asian J. Org. Chem.* **2017**, *6* (11), 1561.

Posters Presented at Conferences

1) **Ajesh Vijayan**, T. V. Baiju, K. V. Radhakrishnan, Bis-functionalization of 1,3-dienes *via* 1,4-conjugate addition of amphiphilic bis-π-allyl and related palladium intermediates, paper presented at National Symposium for Transcending Frontiers in Organic Chemistry (TFOC-2014), held at CSIR-NIIST, Trivandrum in October 2014.
2) **Ajesh Vijayan**, T. V. Baiju, K. V. Radhakrishnan, Bis-functionalization of 1,3-dienes *via* 1,4-conjugate addition of amphiphilic bis-π-allyl and related palladium intermediates, paper presented at International conference on Nascent Developments in Chemical Sciences: Opportunities for Academia Industry Collaboration (NDCS-2015), held at Birla Institute of Technology and Science, Rajasthan in October 2015.
3) **Ajesh Vijayan**, T. V. Baiju, K. V. Radhakrishnan, Base catalyzed synthesis of cyclopenta[b]chromene derivatives from phenol substituted fulvene derived azabicyclic olefins, paper presented at CRSI-National Symposium In Chemistry (CRSI NSC-19), held at University of North Bengal, West Bengal in July 2016.

Oral Presentation

1) **Ajesh Vijayan**, K. V. Radhakrishnan, Urea-derived Bicyclic Olefins: Novel Synthons for Biologically Significant Motifs Using Transition Metal Catalyzed Synthetic Transformations, presented at Prof. R. H. Sahasrabudhey Birth Centenary Symposium (CYHOC-2017) at Hotel Residency Towers, Trivandrum in December 2017.