Desymmetrization of Diazabicyclic Olefins *via* Transition Metal Catalyzed sp^2 C-H Activation: Access to Functionalized Cyclopentenes

Thesis Submitted to AcSIR for the Award of Degree of

DOCTOR OF PHILOSOPHY

in Chemical Sciences

By

APARNA P S

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Under the Combined Supervision of

Dr. K. V. Radhakrishnan & Dr. R. Luxmi Varma

Organic Chemistry Section

CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST)

Thiruvananthapuram

March 2018

To my parents,

V. K. Sureshan & C. Pankajakshi

7th March, 2018

Declaration

I hereby declare that the Ph.D. thesis entitled "***Desymmetrization Of Diazabicyclic Olefins Via Transition Metal Catalyzed sp^2 C-H Activation: Access To Functionalized Cyclopentenes***" is an independent work carried out by me and it has not been submitted anywhere else for any other degree, diploma or title.

Aparna P. S.

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CERTIFICATE

*This is to certify that the work incorporated in this Ph.D. thesis entitled "**Desymmetrization of Diazabicyclic Olefins via Transition Metal Catalyzed sp^2 C-H Activation: Access to Functionalized Cyclopentenes**" submitted by **Ms. Aparna P. S.** to Academy of Scientific and Innovative Research (AcSIR), New Delhi, in partial fulfilment of the requirements for the award of the **Degree of Doctor of Philosophy in Chemical Sciences**, embodies original research work carried out under our combined supervision and guidance at the Organic Chemistry Section, Chemical Sciences and Technology Division, CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST), Thiruvananthapuram. We 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.*

R. Luxmi Varma
(Thesis Supervisor)

K. V. Radhakrishnan
(Thesis Supervisor)

Thiruvananthapuram
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Aparna P S

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Abbreviations

ACN	acetonitrile	ESI	electron spray ionisation
AcO^-	acetate ion	Et	ethyl
AcOH	Acetic acid	Et_3N	triethylamine
Ar	aryl	EtOAc	Ethyl acetate
Bn	benzyl	FT-IR	Fourier transform infrared spectroscopy
Calcd	calculated	HAT	Hydrogen Atom Transfer
Cat	catalyst	HMBC	Heteronuclear Multiple Bond Correlation
$CDCl_3$	Chloroform-d	HMQC	Heteronuclear Multiple-Quantum Correlation
cm^{-1}	Centi $metre^{-1}$	HRMS	high resolution mass
COSY	correlated spectroscopy	Hz	Hertz
Cp	cyclopentadienyl	^iPr	isopropyl
Cp*	pentamethylcyclopentadienyl	*J*	Coupling constant
D	doublet	L	litre
DCE	dichloroethane	mL	millilitre
Dd	double doublet	m	multiplet
DEPT	distortionless enhancement by polarisation transfer	*m/z*	Mass to charge ratio

DG	directing group	mg	milligram
DMF	Dimethyl formamide	ROM/CM	ring opening metathesis/ cross metathesis
DMSO	Dimethyl sulfoxide	rt	room temperature
Equiv.	equivalent	S	singlet
mol	mole	T	triplet
MHz	Mega hertz	^{t}Bu	Tertiary butyl
NMP	N-Methyl-2-pyrrolidone	THF	tetrahydrofuran
NMR	nuclear magnetic resonance	TMS	tetramethylsilane
NOE	nuclear overhauser effect	$\propto$	alpha
NOESY	nuclear Overhauser effect spectroscopy	B	Beta
NR	No reaction	δ	delta
Nu^-	nucleophile		
1,10-Phen	Phenanthroline		
ppm	Parts per million		
R_f	retention factor		

Preface

Advances in organometallic chemistry made a great impact on the reactivity and selectivity in C-H bond functionalizations. In the past decades, transition metal-catalyzed synthetic transformations have been considered as one of the most powerful and reliable tools for those bond formations, giving complex molecular structures in an efficient and economical manner. C-H bonds to C-Z bond transformations, where Z is any atom other than hydrogen is the fascinating transformation in organic chemistry. In nature, these transformations are essential for metabolism and there are individual enzymes to carry out them. In industry, these reactions can be utilized in various fields such as energy, fine chemicals and pharmaceutical industry. Due to the presence of number of C-H bonds control over selectivity is complicated. One of the most promising strategies to achieve high selectivity is to utilize a directing group (DG).

The enhanced reactivity of strained molecules has attracted the synthetic chemists. Transition metals can readily activate the bicyclic alkenes due to their unique structure and intrinsic angle strain.The geometry of these substrates allow for reactivity not available in other alkenes. Among various bicyclic alkenes, diazabicyclic olefins are potential synthons for the synthesis of functionalized cyclopentenes. Desymmetrization of these diazabicyclic olefins has been well documented by various research groups including ours. Ring opening reactions of diazabicyclic olefins with a number of monocentered nucleophiles in the presence of transition metal complexes deliver disubstituted cyclopentenes. A few bicentered reactive species has also been employed for the desymmetrization of the olefins. However, the application of C-H activation strategy remains less explored for the desymmetrization and thus is challenging. Our investigations in this line using ruthenium, rhodium, palladium, *etc.* catalysts form the content of this thesis entitled "**Desymmetrization of Diazabicyclic Olefins *via* Transition Metal Catalyzed sp^2 C-H Activation: Access to Functionalized Cyclopentenes**"

The thesis is divided into four chapters. The **Chapter 1** gives an overview on synthetic utility of strained systems with an emphasis to diazabicyclic olefins. These azabicyclic alkenes exhibit diverse reactivity patterns due to the presence of the strained double bond. Ring fragmentations via nitrogen-nitrogen bond reduction, carbon-carbon oxidative cleavage,

ring-opening metathesis or allylic carbon-nitrogen cleavage, and skeletal rearrangements involving carbocationic intermediates, typically observed in the norbornene series, could also be observed with this cycloadducts. The combination of all these transformations should provide a useful synthetic arsenal for a large-scale elaboration of various functionalized amino-, diamino- or hydrazinocyclopentanes, potentially valuable scaffolds for target- or diversity-oriented synthesis of biologically active compounds.

Chapter 2 is divided into two parts. First part describes the first time a ruthenium catalyzed redox-neutral C–H activation of phenylazoles toward the ring-opening of diazabicyclic olefins. Incorporation of biologically relevant cyclopentene ring to these heteroaromatics expands the biological applications. The second part deals with DMSO mediated thermal rearrangement of diazabicyclic olefins and sequential imine formation. The reaction explains the thermal rearrangement of diazabicyclic olefin in the absence of any metal catalysts.

In **Chapter 3**, regioselective C-2/C-3 activation of indoles with diazabicyclic olefins is discussed. It includes, a ruthenium (II) catalyzed stereoselective C-N bond cleavage of diazabicyclic olefins through C-H bond activation of suitably protected indoles and $AgSbF_6$ catalyzed mild C-3 cyclopentenylation of indoles with diazabicyclic olefins.

Chapter 4 explains the simultaneous ring opening and annulation of diazabicyclic olefins with *o*-vinylphenols by Rh(III)/Cu(III) co-catalysis. Palladium catalyzed intramolecular cyclization of the ring opened product is also demonstrated. The methodology provdes significant carbocycles and heterocycles.

Chapter 1

Diazabicyclic Olefins : An Overview

1.1. Introduction

Direct and selective transformation of unfunctionalized feedstocks into complex molecules represents an important goal of synthetic organic chemistry.[1] Synthetic organic chemists were successful in replicating some of the most intriguing molecules of nature in the laboratory. Many of these molecules often find importance in drug discovery. In addition, by introducing sophisticated catalytic reactions and suitably designed synthetic processes, they were triumphant in synthesizing organic molecules for potential applications in many areas of science, technology, and everyday life.

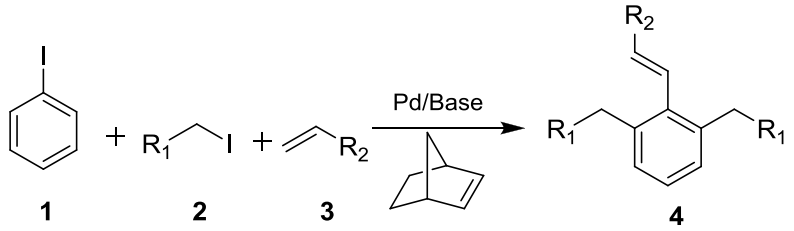
1.2. Strained Systems as Synthons in Organic Chemistry

Strained molecules continue to evoke the curiosity of synthetic organic chemists since their high energy bonds stands as a driving force for complex synthetic transformations. The relationship between strain, stability, and reactivity was always an area of interest.[2] Developments in this field boosted the emergence of strained olefins as dependable intermediates in natural product synthesis. Cyclopropenes, cyclobutadienes, bicyclooctenes *etc*. are important members of this category. The cycloaddition and sigmatropic reactions of these olefins resulting in multifunctionalized products are well documented in the literature.[3]

1.2.1. Norbornenes and its Analogues

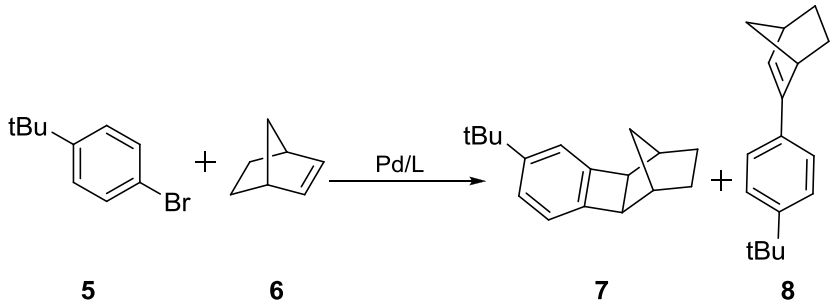
Norbornenes are susceptble towards rapid reactions and can undergo cycloadditions.[4] The utility and potential of the palladium/norbornene catalytic system for the total synthesis of natural products are well recorded in the literature. The extraordinary developments in transition metal catalysis in recent years have enhanced and expanded the synthetic potential of this methodology.

Catellani and coworkers reported palladium/norbornene catalyzed synthesis of polysubstituted arenes from aryl iodides resulting in bi- or tri-functionalization (Scheme 1.1). It is a palladium-catalysed C–H functionalization reaction mediated by norbornene.The reaction is named as Catellani reaction after Marta Catellani and it cleverly uses norbornene as a template for ortho-substitution.[5]



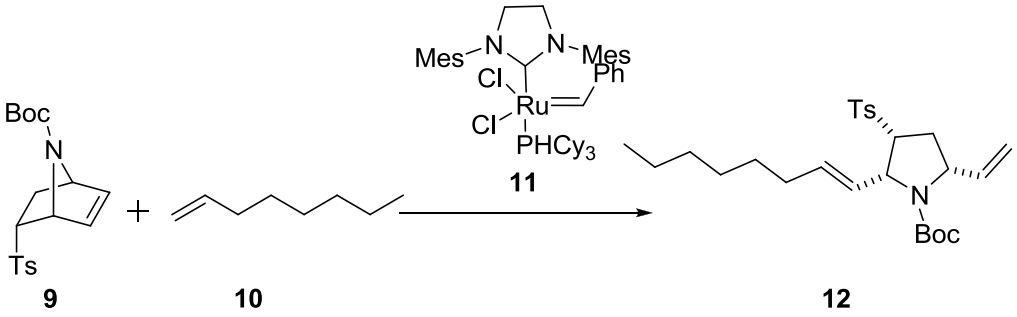
Scheme 1.1

Zhou and coworkers reported a new method that allows selective production of Catellani-Heck isomers for various aryl halides **5**. The bulky ligand tetrabutyl phosphine promoted C-C reductive elimination from the palladacycle and thereby prevented side reactions (Scheme 1.2).[6]



Scheme 1.2

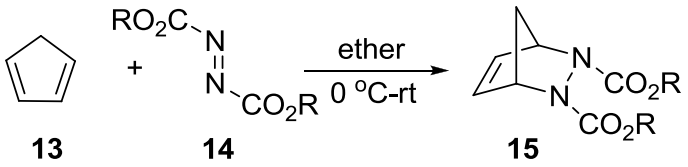
Rainer and coworkers reported the ring opening metathesis/cross metathesis reactions of 2-tosyl-7-azanorbornene **9** and 2-tosyl-7-oxanorbornene resulting in the stereoselective generation of 2,3,5-trisubstituted pyrrolidines **12** and furans, respectively.[7] This shows the scope of azanorbornenes as substrates for ROM/CM. It also depicts the efficient synthesis of a variety of highly substituted pyrrolidine-containing alkaloids from different norbornene derivatives.



Scheme 1.3

1.3. Diazabicyclic Olefins

Diazabicyclic alkenes are a unique class of highly reactive diaza analogues of norbornene, utilized well for the synthesis of biologically active heterocycles and carbocycles. The diazabicyclic alkene **3** is easily accessible by the Diels-Alder reaction of cyclopentadiene **1** with dialkyl azodicarboxylate **2** (Scheme 1.4).[8] Cycloadducts are commonly obtained from cyclopentadiene and acyldiazenes in nearby quantitative yield. Cycloadducts **15** are preferentially obtained as endo isomers. The symmetrical, bi- and polycyclic hydrazines have been known for a long time, but there are only few reports on their desymmetrization as well as ring opening.



Scheme 1.4

These alkenes are susceptible towards face-selective activation by transition metal complexes due to their unique geometry and intrinsic angle strain on the carbon-carbon double bond.[8] The *meso* symmetry of these compounds enables the development of stoichiometric or catalytic desymmetrization reactions. Diazabicyclic 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. The pyramidal character of nitrogens ensures that the *endo*-face of the bicycles is permanently shielded by one carbamate group, preventing any addition from this face. Accordingly, all the intermolecular

reactions of the double bond should be exclusively *exo* diastereoselective. The instability of the diazanorbornene ring systems has been exploited as one-pot stereo- and regio-selective synthetic approaches for the preparation of a variety of functionalized carbocycles and heterocycles, not generally accessible by traditional methods.[9a,b]

Desymmetrization of meso-bicyclic hydrazines offers a facile entry into the class of functionalized cyclopentenes. Various methodologies used along this direction are described in this chapter. Diazanorbornenes have great synthetic potential and possess multiple points of cleavage/ reaction modes. The major reactivity patterns include, nitrogen–nitrogen and carbon–nitrogen bond cleavages giving interesting synthetic transformations (Figure 1.1).[9a] Number of synthetic transformations of these building blocks have been developed, including the electrophilicity of their strained double bond and ring-opening reactions or skeletal rearrangements via β-nitrogen elimination or N-N bond cleavage. Desymmetrization of meso-compounds provides an efficient route to valuable synthons *via* a limited number of steps for target- or diversity-oriented synthesis of biologically active compounds. An overview of the chemistry of diazabicyclic olefins is discussed in this chapter.

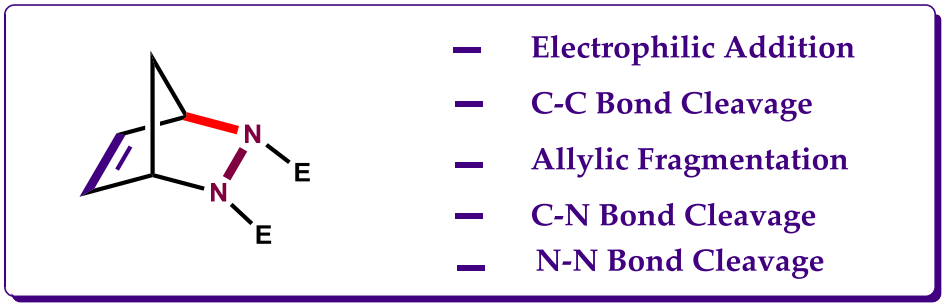
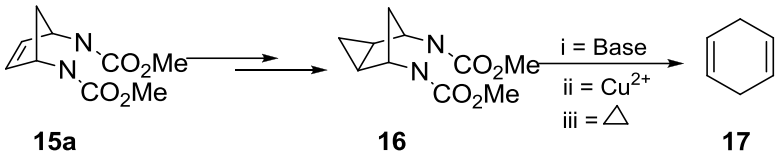


Figure 1.1. Major Reactivity Patterns of Diazabicyclic Olefins

1.4. Ring Fragmentations/Expansions

1.4.1. Synthesis of 1,4-cyclohexadiene

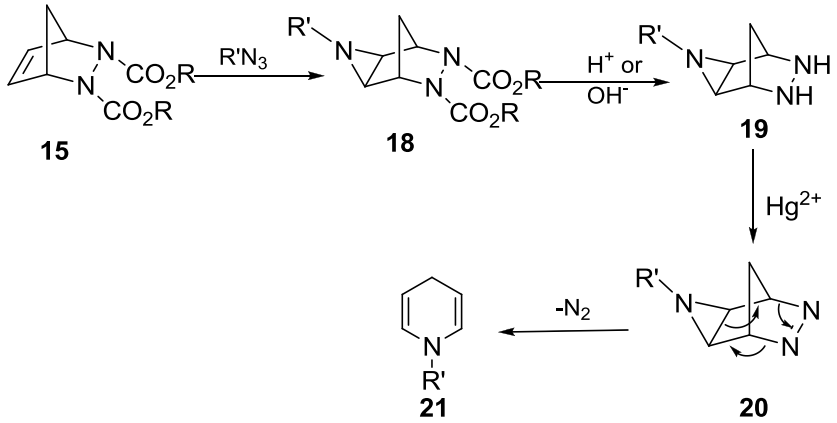
One among the initial studies on the synthetic transformation of bicyclic hydrazine was reported by Allred and coworkers in 1969.[11] In the reaction, 1, 4-cyclohexadiene **17** was easily produced from **15a** by initial transformation to the cyclopropano derivative **16**



Scheme 1.5

1.4.2. Synthesis Of 1,4-Dihydropyridines

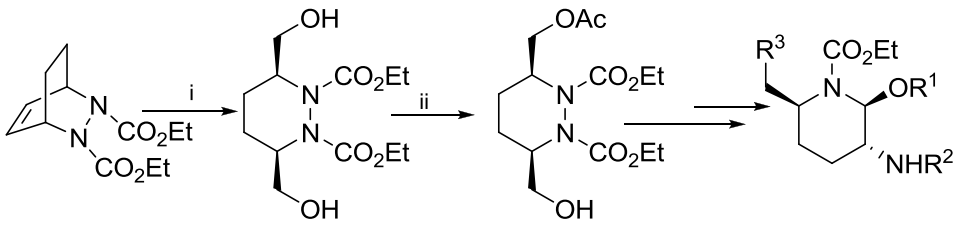
Subsequently, Deyrup and Meyers[12a, b] independently reported the synthesis of 1,4-dihydropyridines **21** from bicyclic hydrazines **15** by a retro-Diels–Alder reaction. Deyrup reported the synthesis of N-phenyl-1,4 dihydropyridine and Meyers described the synthesis of N-benzenesulphonyl derivative. The speciality of this reaction is the symmetry allowed extrusion of nitrogen from **18**, which resulted in biologically important 1,4-dihydropyridines (Scheme1.6)



Scheme1.6

1.4.3 Synthesis Of Glycosyl Donors

Prinzbach and coworkers reported the synthesis of enantiopure glycosyl donors of D-/L-azapurpurosamine C **24** from the cycloadducts **15f** of 1,3-cyclohexadiene with aza dienophile by utilizing biocatalytic asymmetrizations.[13] The reaction sequence is shown in scheme 1.7.[13]



i = a) O_3/EtOH; b) $NaBH_4$, -50 - 40 ^oC, 85%.

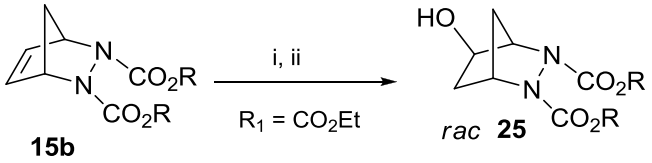
ii = a) Ac_2O/Pyridine/DMAP, 0 ^oC, 12 h; b) Phosphate buffer/n-hexane, lipase, RT.

Scheme 1.7

1.5. Electrophilic Additions to Olefinic Bond

1.5.1. Hydroboration

Desymmetrization of bicyclic hydrazines via a hydroboration reaction was also found to be an easy methodology.[14]The classical hydroboration reaction employed with these substrates afforded the products as racemic mixtures.

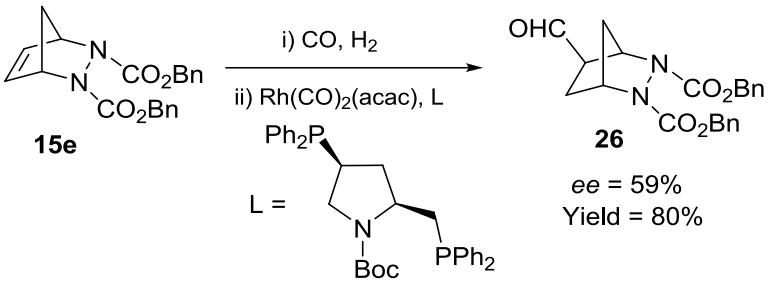


i = BH_3.THF, THF, 0 ^oC, 3 h. ii = aq. NaOH, H_2O_2, RT, 2 h.

Scheme1.8

1.5.2. Hydroformylation and Halocarbomethoxylation

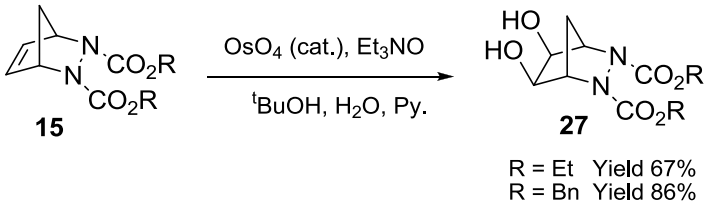
The asymmetric transformation was done with the combination of $Rh(CO)_2(acac)$ and diphosphine ligand which enabled the hydroformylation to proceed with excellent conversion and *ee* up to 60% (Scheme 1.9).[15]



Scheme 1.9

1.5.3. Dihydroxylation and Aminohydroxylation

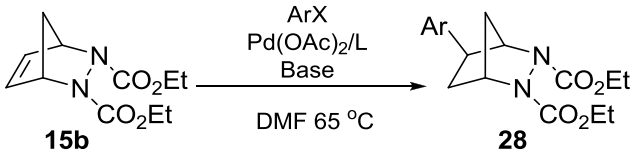
Prinzbach *et al*. reported OsO_4 catalyzed dihydroxylation of diazabicyclic olefin. The excellent reactivity of the double bond of azabicyclic olefins, as for norbornene, enables smooth dihydroxylation using a small amount of osmium tetroxide catalyst (Scheme 1.10).[16]



Scheme 1.10

1.5.4. Hydroarylation

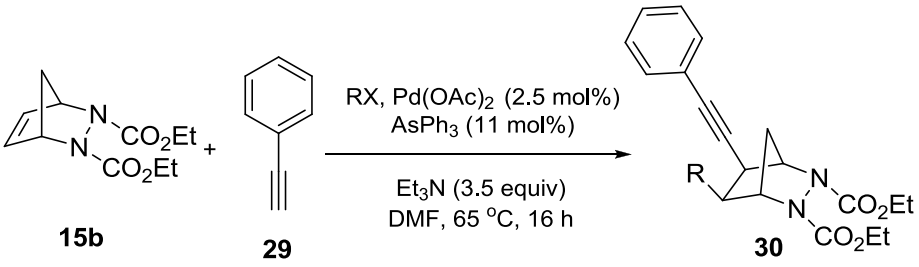
The palladium-catalyzed hydroarylation of hydrazine has been reported by Kaufman and coworkers. It delivers the hydroarylated hydrazine as a side product (Scheme 1.11).[17] The arylation occurs exclusively in an exo manner. Also The N-N bond cleavage of these products afforded stereoselectively cis-1,3-diamino-trans-4-cyclopente derivatives.



Scheme 1.11

1.5.5. Sequential Arylation-Alkynylation

The palladium catalyzed domino coupling of aryl halide and phenylacetylene **29** with the bicyclic alkene **15b** resulted in the formation of a bis-coupled product. The relative stability of the organopalladium intermediate of the arylation reaction enables a tandem coupling process with alkynes.[18]

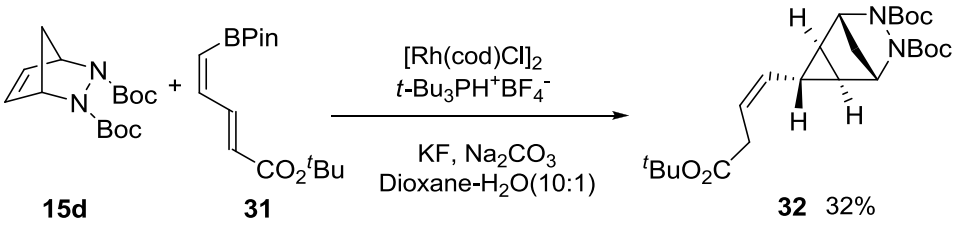


15b **29** **30**

Scheme 1.12

1.5.6. Cyclopropanation

In 2006, a new vinyl cyclopropanation reaction involving a rare 1,6-addition of an alkylrhodium(I) species has been developed by Lautens *et al* (Scheme 1.13). They also suggested that the substituent α to the boron plays a significant role on the relative rates of 1,4- versus 1,6-addition. The exclusive formation of a *Z*-olefin is the result of the protodemetalation of an oxo--allyl rhodium intermediate complex.[19]



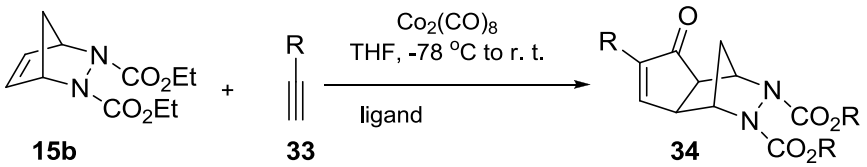
15d **31** **32** 32%

Scheme 1.13

1.5.7. Pauson-Khand Reaction

The use of conjugated bifunctional vinylboron reagents instead of aromatic analogues is an extension of the preceding reaction. In this case, the initial carborhodation is followed by a rare 1,6-conjugate addition, leading to the formation of a cyclopropyl ring (Scheme

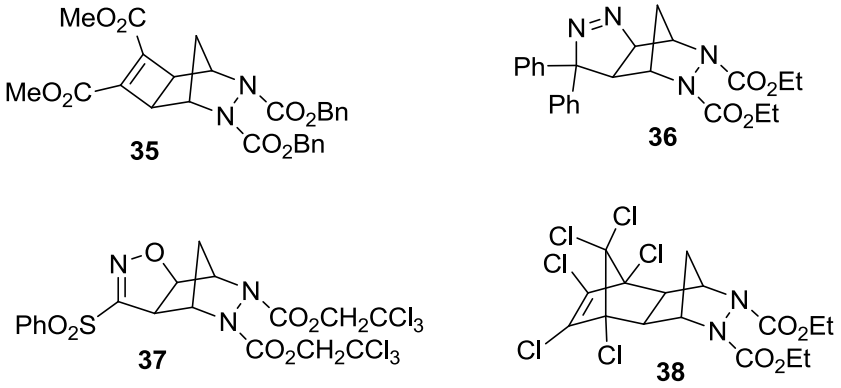
1.14).[20] The exclusive formation of a Z-olefin is the result of the proto-demetalation of an oxo-p-allyl rhodium intermediate complex.



Scheme 1.14

1.5.8. Cycloaddition Reactions

Several [2+2], [3+2], and [4+2] cycloaddition reactions have been reported on bicyclic hydrazines. All occurred diastereoselectively, generally with excellent chemical yields.[21] Scheme 1.15 shows the cycloadducts formed with various diazanorbornenes.



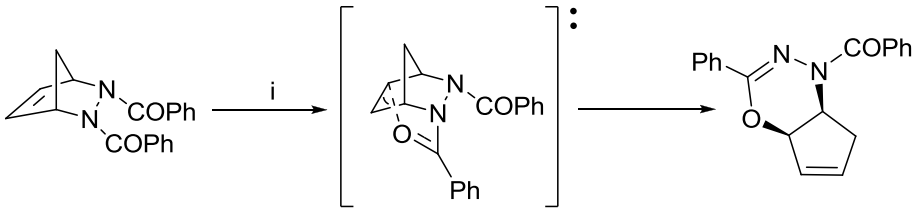
Scheme 1.15

1.6. Stereoselective Synthesis of Disubstituted Cyclopentenes

Desymmetrization of meso-bicyclic hydrazines offers a facile entry into the class of functionalized cyclopentenes. Disubstituted cyclopentanes are versatile intermediates for the construction of numerous biologically important cyclopentene derivatives. They are well utilized for the preparation of glycosidase inhibitors, antiviral and anti-tumor carbonucleosides, and in prostaglandin research.

1.6.1. Rearrangements

The acid catalysed or thermal rearrangement of diazanorbornene **39** enables the formation of compound **41**. It can be explained on the basis of a [3,3]-sigmatropic rearrangement (Scheme 1.16).[22a] The presence of an acid was found to dramatically accelerate this transformation.[22b] Kinetic studies were employed for assessing the preference of a concerted pathway over the two step process.

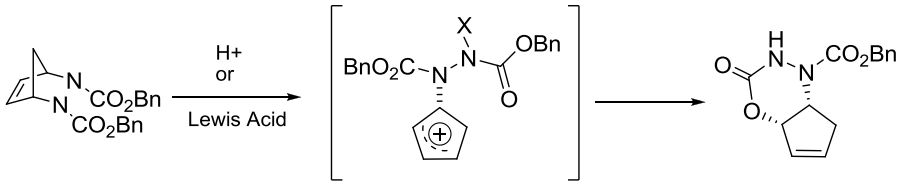


39 **40** **41**

i = Acidic or thermal activation

Scheme 1.16

The Lewis acid catalyzed ring opening of bicyclic olefin by the cleavage of C-N bond has only scarcely been achieved. Micouin *et al*. explored the acid catalyzed ring opening of N,N-benzyloxy-2,3-diazabicyclo[2.2.1]heptanes.[23] Bicyclic olefin **15e** underwent acid catalyzed rearrangement to afford the carbazate **43** (Scheme1.17).

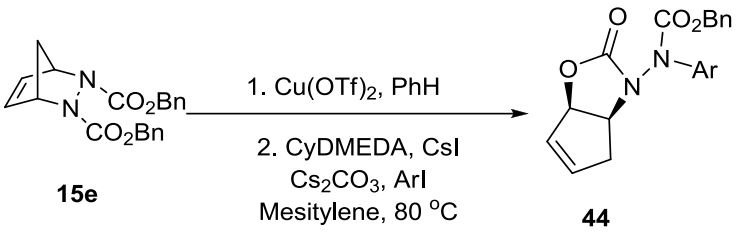


15e **42** **rac 43**

X = H or Lewis Acid

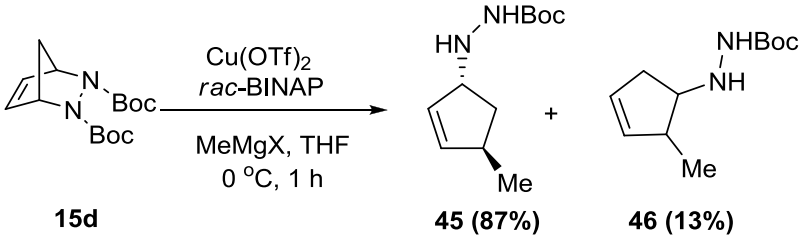
Scheme 1.17

But the correct structure of the rearranged product **43** was then reassigned as **44** with the help of X-ray crystallography by Lautens *et al*. [24] This correct structural assignment ruled out a concerted [3,3]-sigmatropic pathway for this transformation (Scheme 1.18). Lautens and co-workers then introduced a new method for the synthesis of N′-arylaminooxazolidinones **44** through a Lewis acid catalyzed rearrangement of **15e** followed by N-arylation.



Scheme 1.18

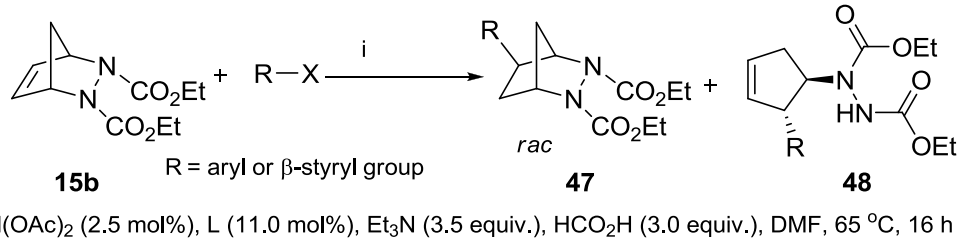
Simultaneously, Pineschi and co-workers also came forward with the correct structure for the rearranged product.[25] In the same report, they demonstrated the synthesis of *trans*-3,5-disubstituted monoprotected hydrazinocyclopentenes **45** by a $Cu(OTf)_2$/BINAP catalyzed reaction.



Scheme 1.19

1.6.2. Palladium Catalyzed Cross Couplings

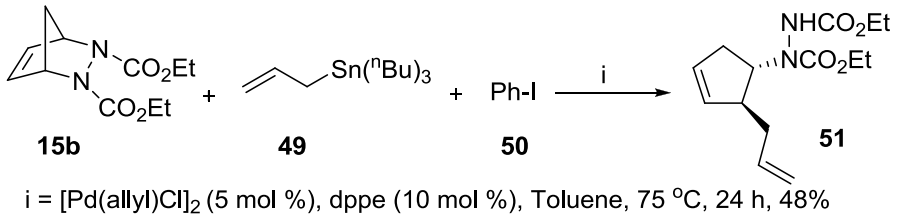
Along with the hydroarylation of diazabicyclic alkenes, a small amount of side product was formed by the N-N bond cleavage of the diazabicyclic olefin was observed in the reaction. (Scheme 1.20).[17]



Scheme 1. 20

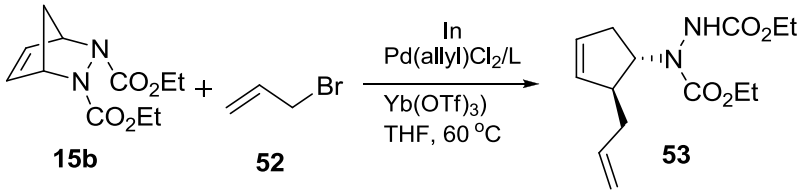
The investigations on the palladium catalyzed ring opening of diazabicyclic olefins with organometallic reagents was pioneered by our group in 2005 (Scheme 1.21).[26] The reaction is

milder and is the first general methodology developed for the stereoselective synthesis of *trans*, vicinal disubstituted cyclopentenes **51**. The results show that organostannanes with easily functionalizable moieties can be efficiently utilized in the ring opening of bicyclic hydrazines leading to the stereoselective formation of 3,4-disubstituted cyclopentenes



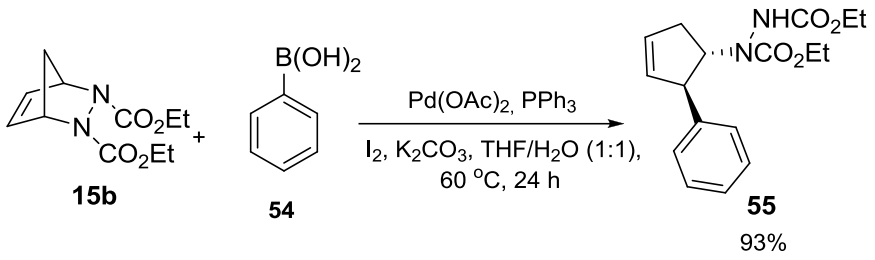
Scheme 1.21

Similarly palladium/Lewis acid catalyzed reaction of allyltributyltin and allyltrimethylsilane was reported by our group. Also we had demonstrated the transformations like dihydroxylation and conversion of the hydrazine to amine could result in the formation of versatile synthons, which can be used for the synthesis of many biologically active molecules like glycosidase inhibitors, carbocyclic nucleosides, antiviral and antitumor agents.[27]



Scheme 1.22

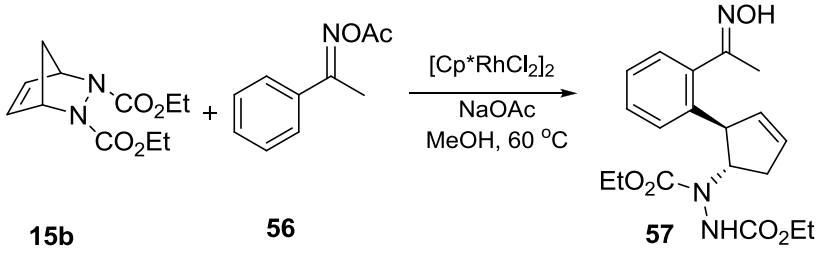
In 2006, we unravelled a novel reactivity of organoboronic acids with bi- and tricyclic hydrazines leading to the stereoselective formation of *trans*-vicinal disubstituted cyclopentenes in good to excellent yields (Scheme 1.23).[28] This palladium-catalyzed fragmentation is assisted by iodine, which proved to be superior to scandium triflate in this case. This was the first report on the use of the modified Suzuki reaction for the synthesis of functionalized cyclopentenes.



Scheme 1.23

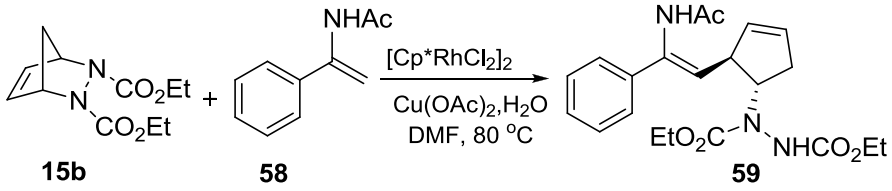
1.6.3. C-H Activation Reaction

We have developed a Rh(III) catalyzed desymmetrization of strained olefins through C–H activation of O-acetyl ketoximes **56** under mild reaction conditions.[29] This strategy utilizes inert C-H bond instead of halides and triflates as in the previous section.



Scheme 1.24

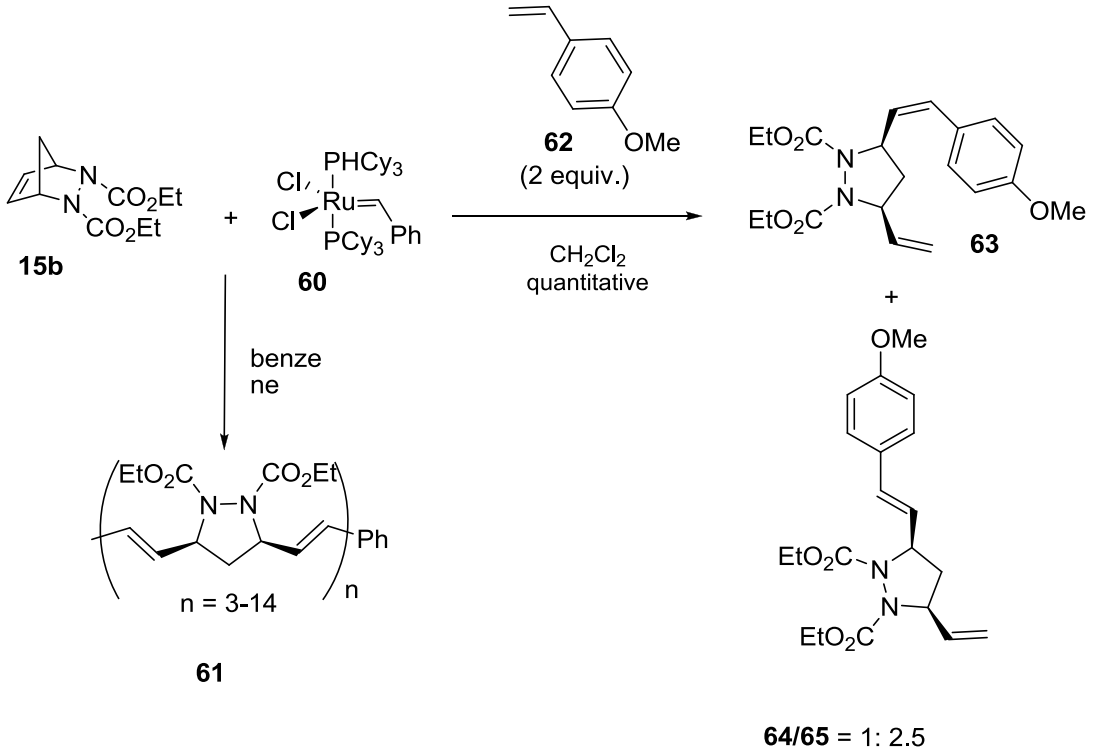
Based on our previous reports on rhodium catalyzed C-H activation reactions, we reported the reaction of bicyclic olefin and aryl enamide under rhodium catalysis. The reaction of aryl enamide **58** with diazabicyclic olefin **15b** in the presence of $[Cp^*RhCl_2]_2$ as catalyst afforded trans-3,4-disubstituted cyclopentene derivatives **59** in good yield.[30]



Scheme 1.25

1.6.4. Metathesis

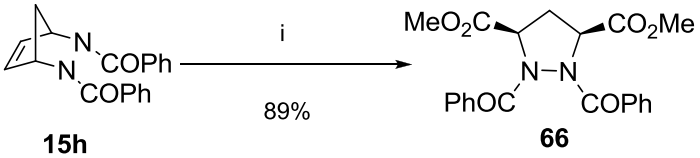
By analogy with norbornene, the ring opening metathesis of diazabicyclic olefins has been investigated. As expected, oligomerization is promoted by Grubbs' catalyst whereas cross-metathesis product is obtained as a *Z*/*E* mixture in the presence of a terminal aromatic alkene.[31]



Scheme 1.26

1.6.5. Oxidative Cleavage

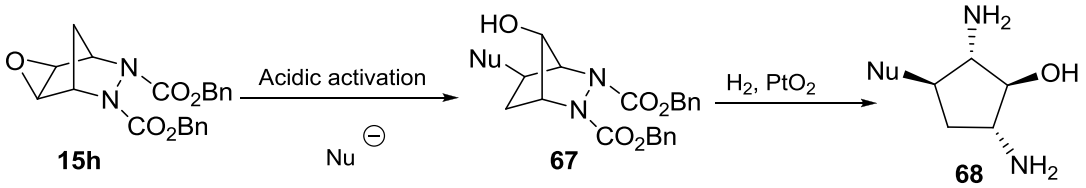
Arakawa *et al*. demonstrated an efficient synthesis of cyclic hydrazoacetic ester by the ruthenium tetroxide mediated oxidative cleavage of the diazabicyclic olefin **15h** (Scheme 1.27).[32]



Scheme 1.27

1.6.6. N-N Bond Cleavage

In 2005, Micouin *et al*. described a skeletal rearrangement of the bicyclic hydrazine-epoxide through acidic activation in the presence of a nucleophile.[33]The hydrogenolysis of disubstituted bicycles enables the preparation of several polyfunctional diaminocyclopentanes. A reactive aziridinium intermediate can indeed be generated from diazabicyclic olefins under various acidic conditions, and trapped regioselectively by several nucleophiles, leading to polyfunctional bicycles in a diastereoselective manner and control of the relative configuration of four contiguous stereogenic centers in a single operation. (Scheme 1.28**)**



Scheme 1.28

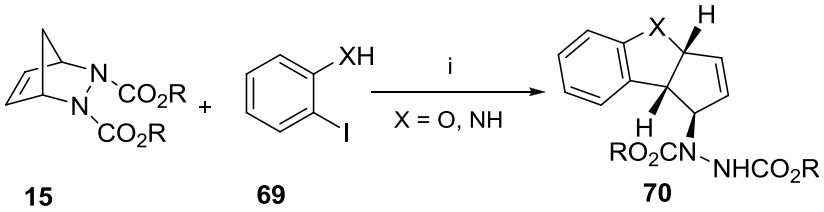
1.7. Carbo/Heterocycle Synthesis from Bicentered Aromatics

Synthesis of carbo/heterocycles has been always the topic of interest in synthetic organic chemistry. The scope of a handful of annulation of diazabicyclic olefin was reported from our laboratory. A brief account on the transition metal catalyzed desymmetrization/annulation of diazabicyclic olefins with different bicentered species' are listed below.

1.7.1. Benzofurans and Indoles

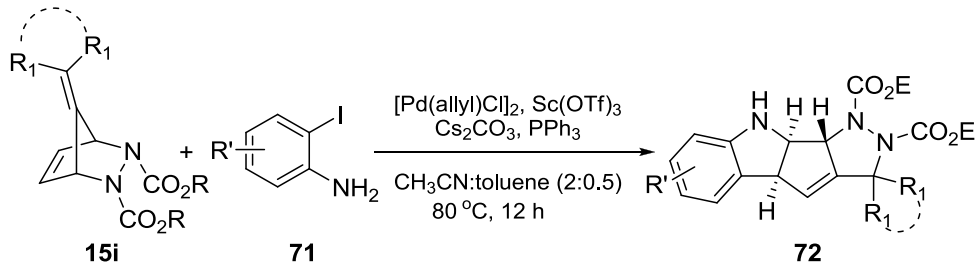
We have reported a palladium-catalyzed annulation of o-iodophenols and o-iodoanilines with azabicyclic olefin (Scheme 1.29).[34] The reaction afforded cyclopentene fused benzofuran and indoles, through a tandem ring opening-ring closing pathway. Using this methodology, we could tune the reaction to the formation of either 3,4 disubstituted

cyclopentenes or cyclopentene fused heterocycles by careful manipulation of the reaction parameters.



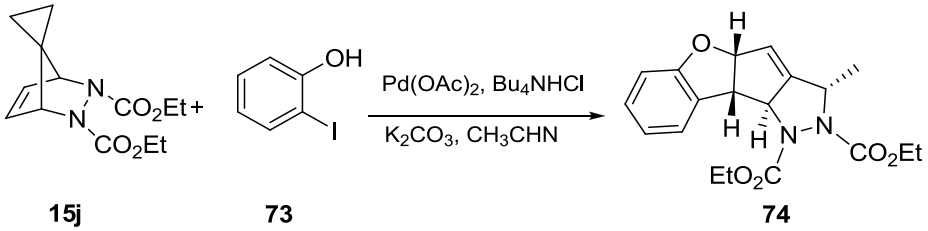
Scheme 1.29

Our investigations revealed the Lewis acid/palladium mediated transformation of pentafulvene derived bicyclic hydrazines leading to the formation of a new spiropentacyclic framework having cyclopentene fused to indoline and pyrazolidine skeletons **72** .[35]



Scheme 1.30

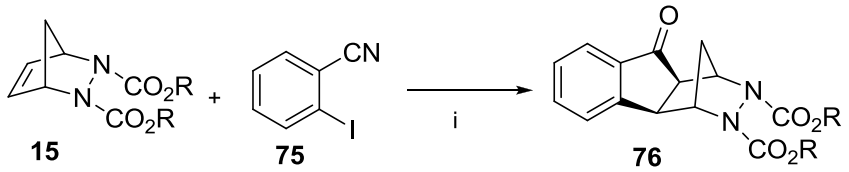
Similarly, a domino reaction of the spirotricyclic olefin bearing a cyclopropane ring with o-iodophenols resulting in a tetracyclic framework with multiple stereocentres **74** was reported by our group (Scheme 1.31**)**. This reaction also involved a ring opening- ring closing pathway.



Scheme 1.31

1.7.2. Indanones

Subsequently the synthesis of fused indanones by the reaction of various *o*-functionalized aryl halides like o-iodobenzonitrile and boronic acids with diazabicyclic olefins under palladium and rhodium catalysis was reported from our laboratory.[37] Precisely, we reported a carboannulation of bicyclic hydrazines with 2-iodobenzonitrile, 2-cyanophenylboronic acid and 2-formylphenylboronic acid leading to the synthesis of highly functionalized indanones **76** and indanols (Scheme 1.32).

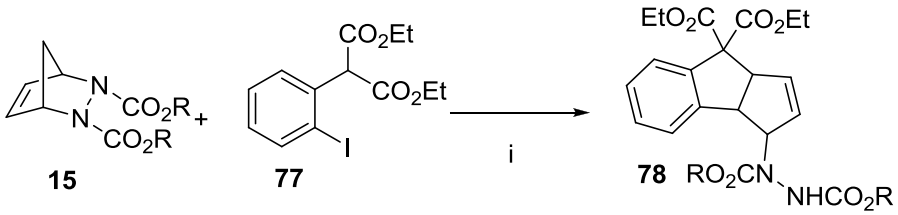


i = Pd_2(dba)$_3$.$CHCl_3$, PPh_3, Et_3N, CH_3CN/H_2O (9:1), 80 ^oC, 24 h

Scheme 1.32

1.7.3. Indanes

An efficient one pot strategy for the synthesis of cyclopentene fused indanes **78** was reported from our laboratory (Scheme 1.33).[38a] The indane ring systems are very significant as they are important structural motifs in many drug candidates such as Gnetuhainin E and Mirabiloside C.

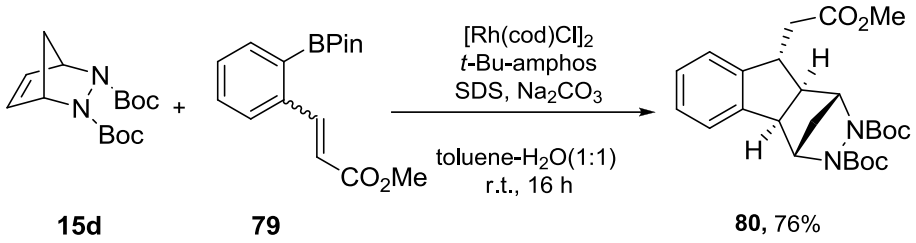


i = [Pd(allyl)Cl]$_2$, KOAc, TBAC, DMF, 100 ^oC, 12 h

Scheme 1.33

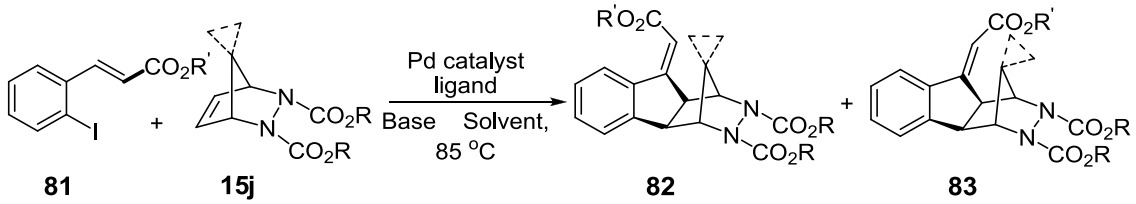
Lautens and Mancuso developed a rhodium-catalyzed tandem carbocyclization of arylboronic esters bearing a pendant Michael-acceptor alkene and azabicyclic olefin to produce highly functionalized indanes **80**.[38b] The catalytic system involves the use of an

electron-rich, sterically bulky ligand to stabilize the organorhodium intermediate and reduce the incidence of protodeboronation in aqueous media (Scheme 1.34). The reaction gives access to highly functionalized polycyclic systems with the generation of three asymmetric centers in a single step, in a fully diastereoselective manner.



Scheme 1.34

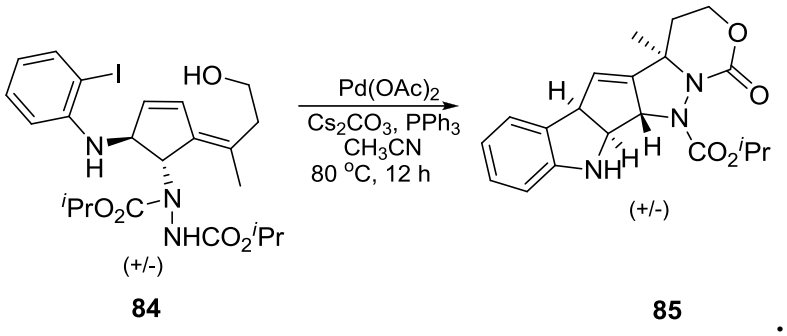
Palladium-catalyzed carboannulation of bicyclic and tricyclic hydrazines with substituted *o*-iodostyrenes resulting in the formation of functionalized indanes **82** & **83** was reported by our group. The reaction proceeded in good to excellent yields. [38c]



Scheme 1.35

1.7.4. Highly Functionalized Indolines

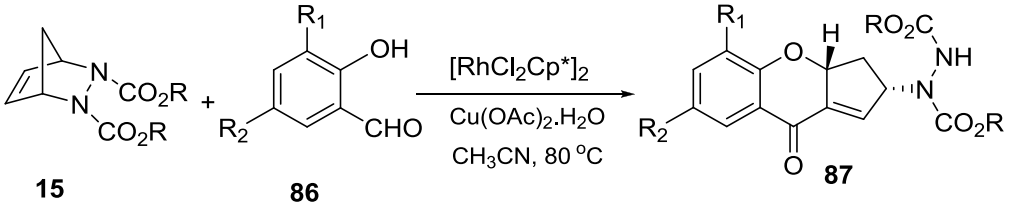
A sequential Lewis acid/palladium mediated transformation of diazanorbornenes containing tethered hydroxy groups to give tetrahydrocyclopenta[b]pyrans or novel pentacyclic frameworks containing cyclopentene moieties fused to indoline, pyrazolidine, or 1,3-oxazinan-2-one skeletons was reported from our group.[39] In this strategy, the strain release of fulvene derived diazanorbornenes with internal/external nucleophiles to give products with multiple stereocenters is efficiently exploited. It is an interesting domino process leading to polycyclic motifs with cyclopentene moieties.



Scheme 1.36

1.7.5. Chromanones

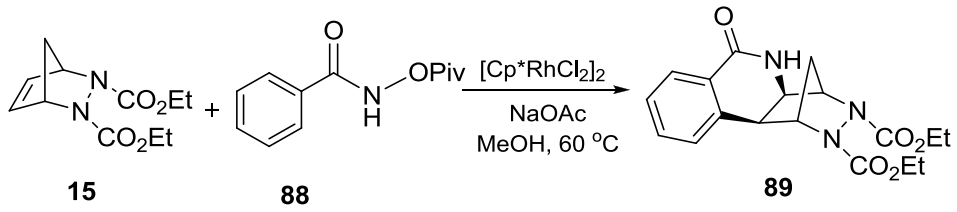
An efficient one pot strategy for the synthesis of cyclopentene fused chromanone derivatives through the direct oxidative coupling of salicylaldehydes with bicyclic olefins in the presence of a rhodium/copper catalyst system was recently reported (Scheme 1.37).[40] This was the first report on the ring opening–ring closing of bicyclic hydrazines via metal catalyzed oxidative coupling reaction.



Scheme 1.37

1.7.6. Isoquinolines

The C–H activation of N-pivaloyloxy benzamides with diazabicyclic olefins derived from cyclopentadiene as well as pentafulvenens were investigated.[41] This is one of the first example of the annulation of diazabicyclic olefin guided by C-H activation reaction.

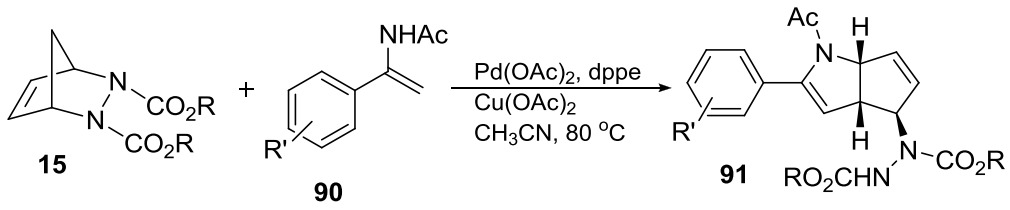


15 88 89

Scheme 1.38

1.7.7. Pyrrolines

Another excellent example in this category was reported from our group recently.[30] The reaction include a palladium catalyzed synthesis of cyclopentene fused 2-pyrrolines in gram scale, through alkenyl C-H activation of aromatic enamide. A rhodium catalyzed stereoselective C-N bond cleavage of the diazabicyclic olefins towards trans-disubstituted cyclopentenes is also explained.



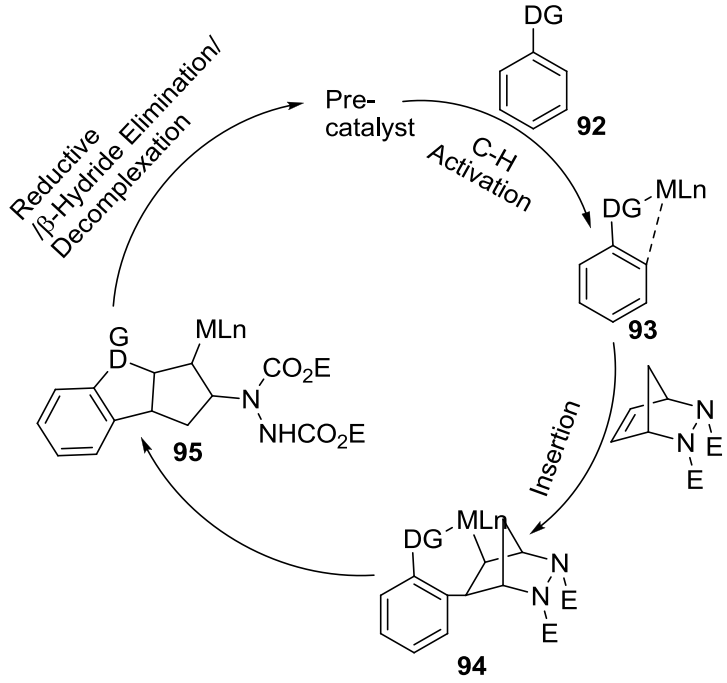
15 90 91

Scheme 1.39

1.8. Conclusions and Present Work

Diazabicyclic olefins represent a unique class of strained systems which are potential synthons for the construction of cyclopentenes. Transition metal catalyzed desymmetrization of diazabicyclic olefins opens a plethora of methods for the synthesis of biologically relevant comounds. Transition metal catalyzed carbon–carbon bond formation via cleavage of inert C–H bonds represents a proficient, atom-economical, and environmentally friendly strategy in organic synthesis. Last two decades have witnessed a tremendous leap in transition metal catalysis, in which C-H bond activation reactions stand a step forward for utilizing the technically inactive C-H bonds (both sp^2 and sp^3). Exploitation of less explored C-H activation strategy for the desymmetrization of these strained olefins leads to biologically relevant motifs.

Thus we envisage the endless hope for different courses of reactions utilizing the functional group directed C-H activation strategies (**Scheme 1.40**). The suitably tethered aromatic substrate clearly will be able to afford the metallacycle **93**, which will be a host for the strained olefin resulting in a high energy intermediate **94**. The fate of the species **94** as well as **95** will lead to value added functionalized cyclopentenes in a step economic manner.



Scheme 1.40

Following this strategy, the applicability of different heterocycles as directing group was tested. The second chapter explains the ruthenium catalyzed C-H activation reaction of phenyl azoles with diazabicyclic olefin to get biologically relevant cyclopentene appended heteroaromatics. The C-H activation driven C-N bond cleavages are less explored.

The third chapter explores the regioselective C-2/C-3 activation of indoles with diazabicyclic olefins. The C-2 selectivity is attained by ruthenium catalyzed C-H activation of suitably protected indole with diazabicyclic olefin. $AgSbF_6$ catalyzed C-3 cyclopentenylation is also discussed.

The Rh (III)/Cu (II) catalyzed ring opening and annulation of *o*- vinylphenols with diazabicyclic olefins is the subject matter of the final chapter. Also, the palladium catalyzed intramolecular reaction of the ring opened product is also discussed.

1.9. References

1. Nicolaou, K. C. *Proc. R. Soc. A* **2014,** *470*, 20130690
2. Wiberg, K. B. *Angew. Chem. Int. Ed.* **1986**, *25*, 312.
3. Wilson, M.R.; Taylor, R. E. *Angew. Chem. Int. Ed*. **2013**, *52*, 4078.
4. Spanget, J.; Gleite, R. *Tetrahedron* **1983**, *39*, 3345.
5. *Catellani et al*. *Angew. Chem. Int. Ed*. **1997,** *36*, 119.
6. *Zhou et al. Chem. Commun.* **2013,** *49, 11035*.
7. *Rainier et al. Org. Lett*. **2004,** *6, 1625.*
8. Diels, O.; Blom, J. H.; Knoll, W. *Justus Liebigs Ann. Chem.* **1925**, *443*, 242.
9. Rayabarapu, D. K.; Cheng, C.-H. *Acc. Chem. Res*., **2007**, *40*, 971
10. (a). Bournaud, C.; Chung, F.; Luna, A. P.; Pasco, M.; Errasti, G.; Lecourt, T.; Micouin L. *Synthesis* **2009,** 869. (b) Radhakrishnan, K. V.; Sajisha, V.; Anas, S.; John, J. *Synlett,* **2009**, 2885.
11. Allred, E. L.; Hinshaw, J. C.; Johnson, A. L. *J. Am. Chem. Soc.*, **1969**, *91*, 3382.
12. (a)Deyrup, J. A.; Horwell, D. C. *J. Chem. Soc., Chem. Commun.,* **1972**, 485. (b)Meyers, A. I.; Stout, D. M.; Takaya, T. *J. Org. Chem. **1975**, 40, 563.*
13. Grabowski, S.; Prinzbach, H. *Tetrahedron Lett*. **1996**, *37*, 7951.
14. Allred, E. L.; Anderson, C. L.; Smith, R. L. *Tetrahedron Lett.* **1966**, 9, 951.
15. Micouin, L.; Bournaud, C.; Lecourt, T.; Méliet, C.; Agbossou-Niedercorn, F. *Eur. J. Org. Chem.,* **2008**, 2298.

16. (a) Mellor, J. M.; Smith, N. M. *J. Chem. Soc., Perkin Trans.* **1984**, *1*, 2927. (b) Grabowski, S.; Armbruster, J.; Prinzbach, H. *Tetrahedron Lett.*, **1997**, *38*, 5485.

17. Kaufmann, D. E.; Storsberg, J.; Nandakumar, M. V.; Sankaranarayanan, S *Adv. Synth. Catal.*, **2001**, *343*, 177.

18. Storsberg, J.; Nandakumar, M. V.; Sankaranarayanan, S.; Kaufmann, D. E. *Adv. Synth. Catal.* **2001**, *343*, 177.

19. Tseng, N.-W.; Mancuso, J.; Lautens, M. *J. Am. Chem. Soc*. **2006**, *128*, 5338.

20. Pauson, P. L.; Khand, I. U. Ann. N. Y. Acad. Sci**. 1977**, *295*, 2.

21. Kuderna, J. G.; Sims, J. W.; Wikstrom, J. F.; Soloway, S. B. *J. Am. Chem. Soc*. **1959**, *81*, 382.

22. (a)Mackay, D.; Campbell, J. A.; Jennison, C. P. R. *Can. J. Chem.,* **1970**,*48* , 81. (b)Chung, C. Y.-J.; Mackay, D.; Sauer, T. D. *Can. J. Chem.*, **1972**, *50*, 1568.

23. Micouin, L.; Luna, A. P.; Cesario, M.; Bonin, M. *Org. Lett.*, **2003**, *5*, 4771.

24. Lautens, M.; Martins, A.; Lemouzy, S. *Org. Lett.*, **2009**, *11*, 181.

25. Pineschi, M.; Crotti, S.; Bertolini, F.; Macchia, F. "*Adv. Synth. Catal.,* **2009**, *351*, 869.

26. Radhakrishnan, K. V.; Sajisha, V. S.; Anas, S.; Krishnan, K. S *Synlett*, **2005**, 2273.

27. Radhakrishnan, K. V.; John, J.; Anas, S.; Sajisha, V. S.; Viji, S. *Tetrahedron Lett.*, **2007**, *48*, 7225.

28. Radhakrishnan, K. V.; John, J.; Sajisha, V. S.; Mohanlal, S. *Chem. Commun.,* **2006**, 3510.

29. E. Jijy, Praveen Prakash, M. Shimi, S. Saranya, P. Preethanuj, Petri M. Pihko, Sunil Varughese and K. V. Radhakrishnan *Tetrahedron Lett.* **2013**, *54***,** 7127.

30. P. V. Santhini, G. Nimisha, Jubi John, E. Suresh, R. Luxmi Varma K. V. Radhakrishnan *Chem. Commun.*, **2017**, *53*, 1848.

31. (a) Ellis, J. M.; King, S. B. *Tetrahedron Lett., 43*, **2002**, 5833 (b) Radhakrishnan, K. V.; Anas, S.; Sarika, C.; Rajan, R. *Ind. J. Chem. B., 47*, **2008**, 1063.

32. Arakawa, Y.; Goto, T.*;* Kawase, K.; Yoshifuji, S. *Chem. Pharm. Bull.*, **1998**, *46*, 674.

33. Micouin, L.; Bournaud, C.; Robic, D.; Bonin, M. "*J. Org. Chem*., **2005**, *70*, 3316.

34. Radhakrishnan, K. V.; John, J.; Indu, U.; Suresh, E. *J. Am. Chem. Soc., 131*, **2009**, 5042.

35. Chand, S. S.; Jijy, E.; Prakash, P.; Szymoniak, J.; Preethanuj, P.; Dhanya, B. P.; Radhakrishnan, K. V., *Org. Lett*., **2013**, *15*, 3338.

36. Radhakrishnan, K. V.; Prakash, P.; Jijy, E.; Preethanuj, P.; Pihko, P. M.; Chand, S. S. *Chem. Eur. J., 19*, **2013**, 10473.

37. Radhakrishnan, K. V.; Joseph, N.; John, J.; Rajan, R.; Thulasi, S.; Mohan, A.; Suresh, E. "*Tetrahedron*, **2011**, *67*, 4905.

38. (a)(b) (c)Radhakrishnan, K. V.; Jijy, E.; Prakash, P.; Saranya, S.; Suresh, E. *Synthesis, 45*, **2013**, 2583.

39. Preethanuj P., Jijitha V., Ajesh Vijayan, Jubi John and K. V. Radhakrishnan, *Synthesis* **2017**, *49*,1816.

40. K. V. Radhakrishnan, E. Jijy, P. Prakash, M. Shimi, P. M. Pihko, Joseph. N, *Chem. Commun.* **2013**, *49*, 7349.

41. Praveen Prakash, E. Jijy, P. S. Aparna, S. Viji, K. V. Radhakrishnan *Tetrahedron Lett*. **2014,** *55*, 916.

Chapter 2

Ruthenium Catalyzed Desymmetrization of Diazabicyclic Olefins through C–H Activation of Phenylazoles

&

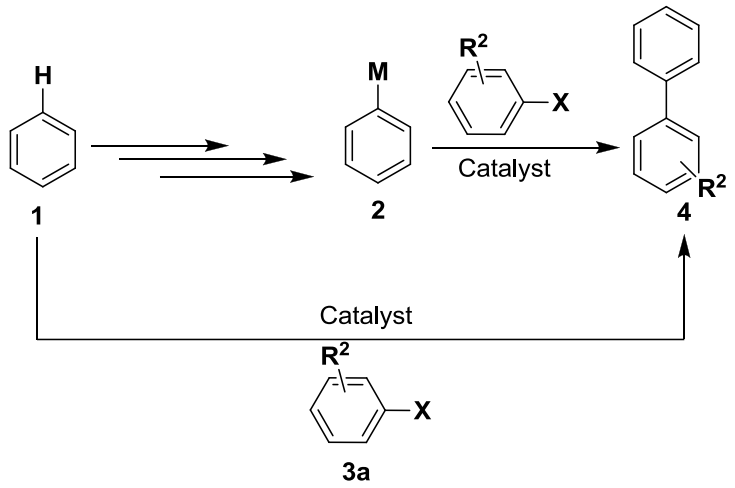
Transition Metal Free Thermal Rearrangement of Diazabicyclic Olefins and Sequential Imine Formation in DMSO

2.1. Introduction

Synthetic organic chemistry has benefited in plenty from organometallic chemistry. Transition metal complexes can significantly alter the reactivity of organic compounds. The synthetic potential of transition metal catalysis is well documented over the years.[1] The tunability of the course of the reaction in terms of reaction parameters such as additives, ligands, temperature, solvents, and bases makes them more desirable. Different catalysts from transition metals such as palladium, nickel, cobalt, rhodium, ruthenium, copper, *etc.* were employed for C-C as well as C-heteroatom bond formations. In this context transition metal catalyzed carbon–carbon bond formation *via* cleavage of inert C–H bonds represents a proficient, atom-economical and environmentally friendly strategy in organic synthesis.[2]

2.2. C-H Activation Reactions

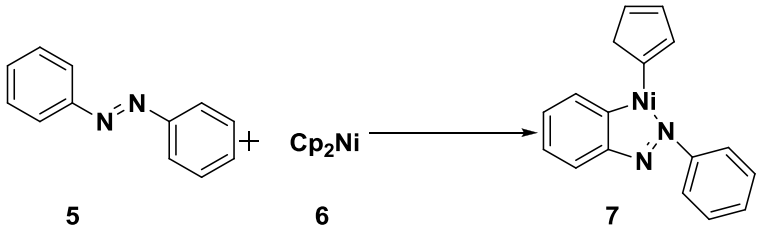
Last two decades have witnessed a tremendous leap in transition metal catalysis, in which C-H bond activation reactions are an important category by utilizing the technically inactive C-H bonds (both sp^2 and sp^3).[3] The important advantage of this category of reaction is that the traditional halide/organometallic coupling partners of transition metal coupling are replaced by properly focused C-H bonds.



Scheme 2.1

2.2.1. Chelation

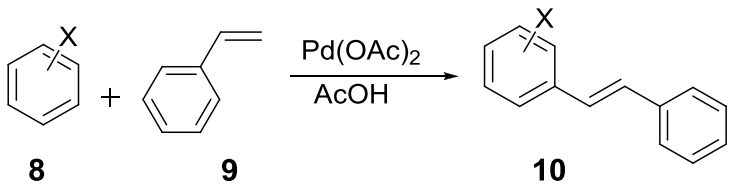
In 1963, Kleiman and Dubeck reported the possibility of C-H bond cleavage in azobenzene by dicyclopentenyl nickel complex.[4] An *ortho* C-H bond of azobenzene **8** is cleaved with a stoichiometric amount of dicyclopentadienylnickel (Cp_2Ni) forming 5-membered nickelacycle **7** (scheme 2.2). It was the first proof of concept for the activation of inert carbon-hydrogen bonds. The reaction mechanism for this reaction has not been elucidated, but the *ortho* C-H bond was apparently cleaved.



Scheme 2.2

2.2.2. Fujiwara Moritani Reaction

Pioneering work on the palladium catalyzed aromatic C-H activation reaction was reported by Fujiwara and Moritani in 1964.[5] The reaction depicted a novel method of synthesizing stilbene derivatives **10** by substitution of aromatic compounds for hydrogen on the double bond of styrene-palladium chloride complex (Scheme 2.3)

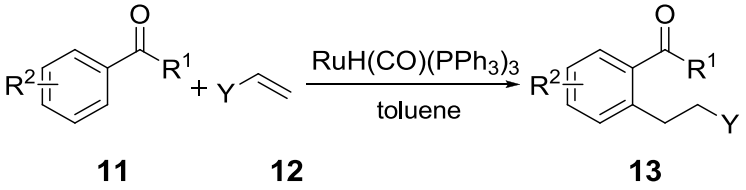


Scheme 2.3

Despite the potential of Fujiwara-Moritani transformation, it has not been often utilized by organic chemists due to the typically harsh reaction conditions, which most functional groups cannot survive. Even though a dormant period followed this report, a plethora of explorations had come in this line later on.

2.2.3. Murai Reaction

The catalytic reactions using the concept of chelation assistance have been rather undeveloped. In 1993, Murai *et al.* reported a breakthrough discovery in this field using ruthenium complex to efficiently catalyze a series of coupling reactions between aromatic ketones and olefins (Scheme 2.4).[6] This reaction uses C-H activation to create a new C-C bond between a terminal or strained internal alkene and an aromatic compound using a ruthenium catalyst. The reaction, named after Shinji Murai, who reported this in 1993.



Scheme 2.4

2.2.4. Directing Groups

Since there are plenty of C-H bonds present in a molecule, the selectivity issue remained unsolved until the idea of coordinating directing groups was experimented. Directing groups are any functional group which can act as an anchoring group to the transition metal towards the proximal hydrogen. Various functional groups have been tested as a directing group (DG) among which nitrogen containing aromatic rings were found to be

efficient and strongly coordinating.[7] Various directing groups, such as heterocycles, carbonyl related functional groups, amines and alcohols, have been employed for catalytic arene C–H bond functionalization (Figure 2.1) and can be categorized into three different classes.[8] First class contains those directing groups which remain as part of the system or undergo further cyclization. Second class constitutes the directing groups which can be removed in additional steps. And the final class comprises of those directing groups which will be removed in one pot and are known as traceless.

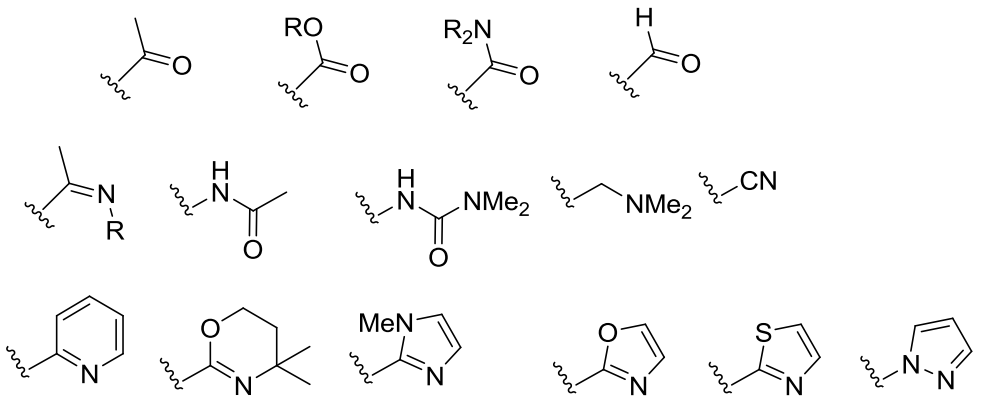
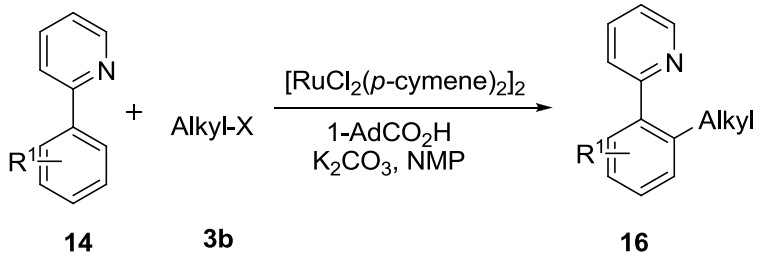


Figure 2.1. Functional Groups Used as Directing Groups

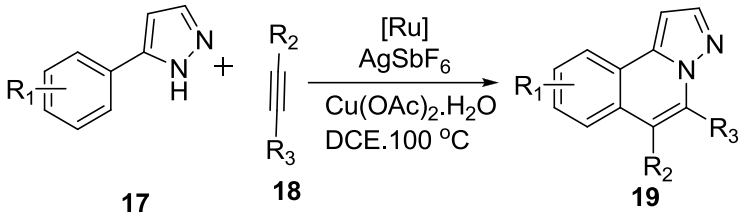
2.3. Heterocycles as Directing Groups

Ackermann and coworkers reported the development of the first ruthenium-catalyzed direct alkylation of arenes with unactivated alkyl halides bearing *β*-hydrogen atoms (Scheme 2.5). A catalytic system derived from carboxylic acid 1-AdCO_2H enabled regioselective intermolecular alkylation of pyridine, pyrazole, or ketimine derivatives with primary as well as secondary alkyl halides.[9]



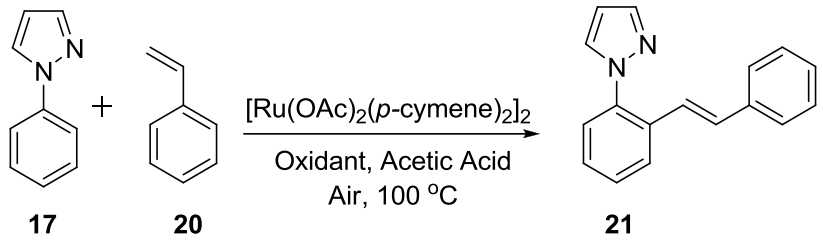
Scheme 2.5

The same group had also reported a ruthenium catalyzed oxidative alkyne annulations by 1H-pyrazoles.[10] Thus, a ruthenium complex allowed for C-H/N-H functionalizations of aryl-, heteroaryl-, and alkenyl-substituted 1H-pyrazoles with ample substrate scope and set the stage for the oxidative annulation of aryl- and alkyl-alkynes with excellent chemo- and regioselectivities (Scheme 2.6).



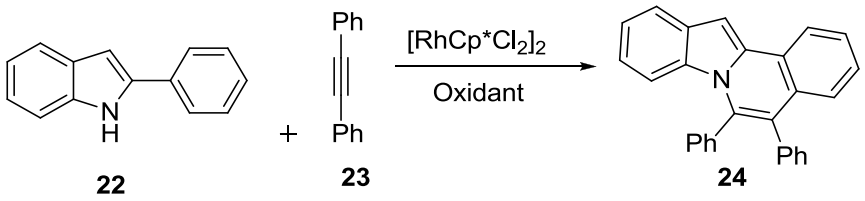
Scheme 2.6

In 2011, Dixneuf *et al.* reported a $[RuCl_2(p\text{-cymene})]_2$ catalyzed *ortho* monoalkenylation of arenes directed by an oxazoline group. Also they have come up with a ruthenium catalyzed directed dehydrogenative alkenylation of N-aryl pyrazoles by styrene and alkyl acrylates in the presence of a catalytic or stoichiometric amount of $Cu(OAc)_2 \cdot H_2O$ in air; the acetic acid solvent played a key role (Scheme 2.7). [11]



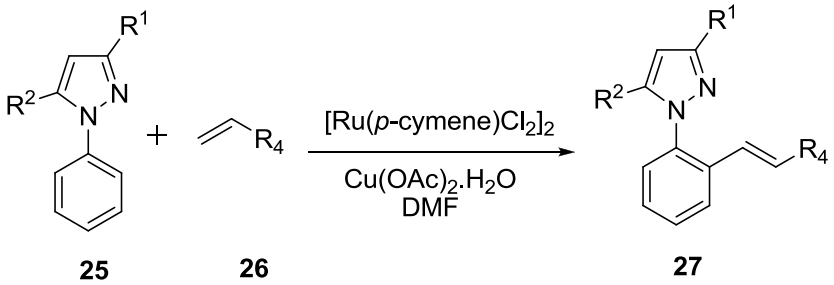
Scheme 2.7

Indoles have been used as a directing group. In 2010, Miura and coworkers attempted rhodium-catalyzed the C-H bond functionalization followed by annulation of 2-phenyl indoles.[12] The methodology enabled straightforward and efficient synthesis of indolo[2,1-a]isoquinoline derivatives (Scheme 2.8).



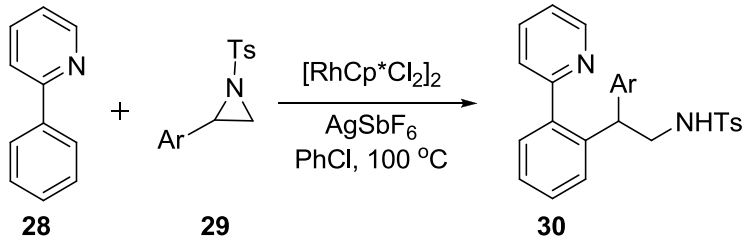
Scheme 2.8

The same group had also demonstrated that phenylpyrazoles and benzanilide could efficiently undergo regioselective alkenylation. The olefination was reported in the presence of a ruthenium catalyst and a copper oxidant with alkenes such as acrylates furnishing regioselective C-H bond cleavage (Scheme 2.9).[13]



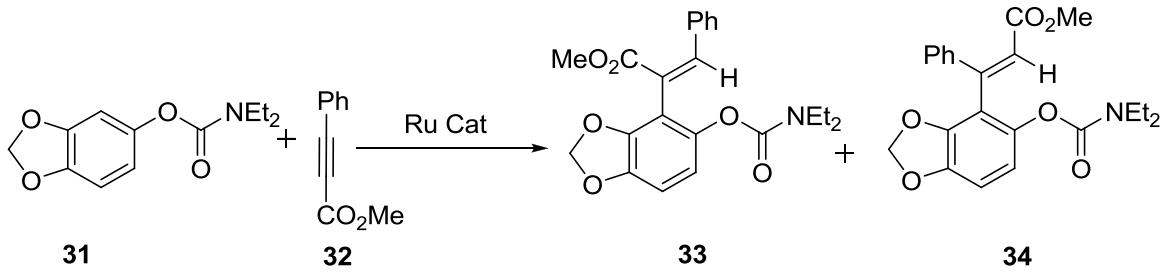
Scheme 2.9

In 2012 Li *et al.* reported a redox-neutral C-C coupling between aziridines and electron-poor arenes under chelation assistance (Scheme 2.10).[14] This process occurs by a C-H activation pathway, and a series of *β*-branched amines have been synthesized. The scope of this coupling reaction was examined and a key intermediate in the catalytic cycle has been isolated.



Scheme 2.10

Jeganmohan *et al.* reported a ruthenium catalyzed alkenylation of ortho C–H bond of aryl carbamates with alkynes to afford substituted alkene derivatives.[15] The reaction is given in Scheme 2.11.



Scheme 2.11

Very recently, Simon and Darses demonstrated a ruthenium catalyzed co-dimerization of bicyclic alkenes and Michael acceptors to provide the *exo*-(E) adducts.[16] In addition to this, carrying out the reaction in protic media led to the reduced product resulting from the tandem co-dimerization/reduction sequence (Scheme 2.12).

Scheme 2.12

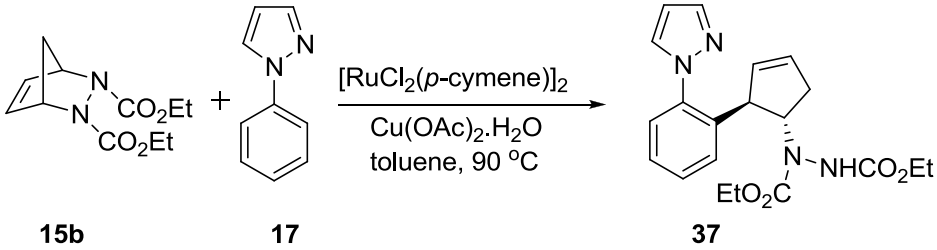
2.4. Statement of the Problem

Azaheteroaromatics such as imidazole, pyrazole, benzimidazole are highly valuable scaffolds of many important natural products and synthetic drugs. Incorporation of biologically relevant cyclopentene ring to these heteroaromaticss attracts synthetic curiosity. Phenyl azoles have been utilized as effective substrates in C-H activation reactions with alkynes and alkenes. Even though, very limited number of reports are available on the rhodium catalyzed C–H activation/ring-opening of strained systems, to the best of our knowledge, there were no attempts for the ring-opening of bicyclic olefins through the Ru(II) catalysed C-H bond activation of biologically significant aza-heteroaromatics.

2.5 Results and Discussion

2.5.1. Ruthenium catalyzed Desymmetrization of Diazabicyclic Olefins *via* C–H Activation of Phenylazoles

Our investigations commenced with the reaction of diazabicyclic olefin **15b** and 1-phenylpyrazole **17** in the presence of $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%) and $Cu(OAc)_2.H_2O$ (1.5 equiv) in toluene at 90 ^oC. As expected, we observed the formation of the desired 3,4-disubstituted cyclopentene **37** in 62% yield (Scheme 2.13). The structure of the product was established by usual spectroscopic techniques.



15b **17** **37**

Scheme 2.13

The structure of monocyclopentenyl functionalized phenylpyrazole was assigned on the basis of spectral data. The ^1H NMR spectrum gives comparatively broader patterns, presumably due to the restricted rotation of the carbamate group.[17] The compound showed characteristic -NH stretching at 3369 cm^{-1} and carbonyl stretching at 1740 cm^{-1} in the IR spectrum. In the ^1H NMR spectrum of **37** (Figure 2.2) the proton on the C-5 carbon of pyrazole ring resonated as a singlet at δ 6.42 ppm. The alkene protons appeared as two singlets at δ 5.77 and 5.41 ppm. The proton on the carbon bearing hydrazine was discernible as a multiplet in the region δ 4.97-4.73 ppm. The signal of the ester CH_2- group along with the proton at the carbon with N-phenylpyrazole as a substituent was observed as a multiplet between δ 4.10-3.85 ppm. The methylene protons of the cyclopentene ring resonated as a multiplet in the region δ 2.60-2.49 ppm. The multiplet in the region δ 1.24-1.10 ppm was assigned to the methyl protons of ester groups.

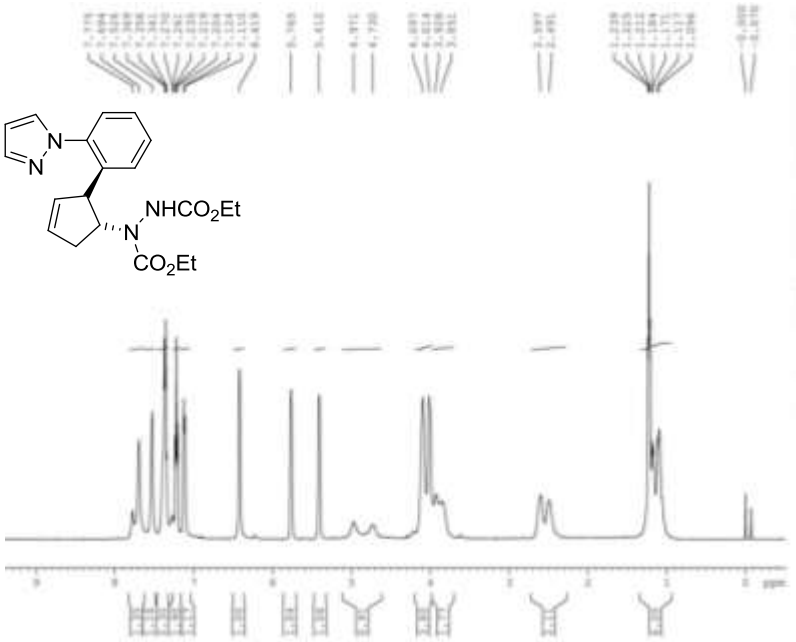


Figure 2.2. ^{1}H NMR spectrum of compound 37

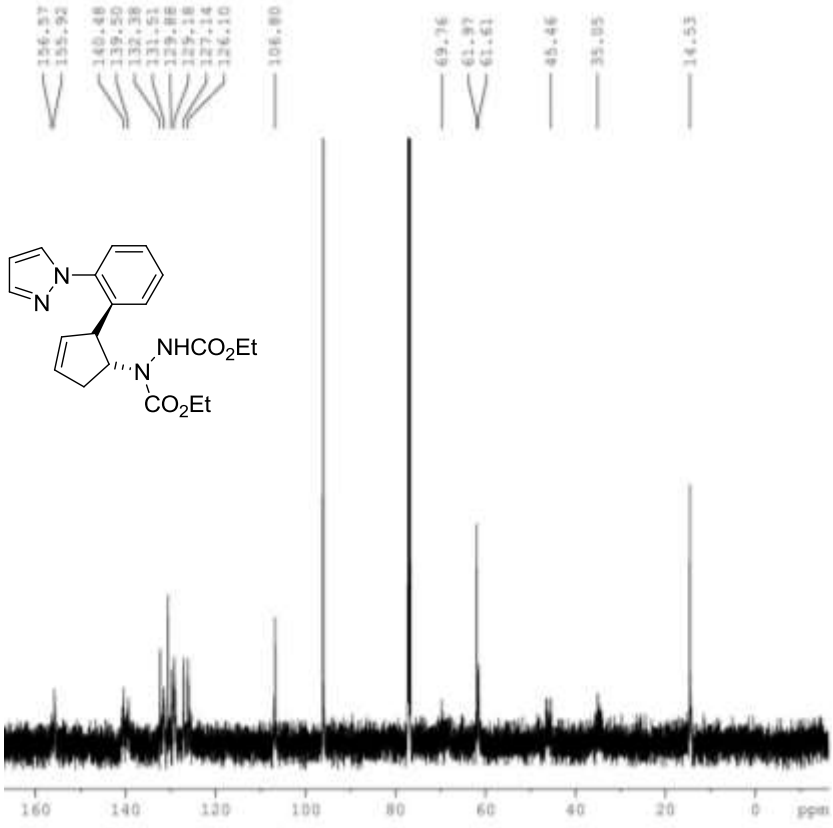


Figure 2.3. ^{13}C NMR spectrum of compound **37**

In the ^{13}C NMR spectrum (Figure 2.3), the carbonyl carbons were seen at δ 156.6 and 155.6 ppm. The carbons attached to the hydrazine moiety and that to N-phenylpyrazole were identified at δ 69.8 and 49.5 ppm respectively. The methylene carbon of the cyclopentene ring resonated at δ 35.1 ppm. The methyl carbons of ester groups showed an intense signal at δ 14.5 ppm. All other signals in the ^{1}H and ^{13}C NMR spectra were in agreement with the proposed structure. The high resolution mass spectral analysis showed a peak at *m/z* 407.16980 $(M+Na)^+$, which also supported the proposed structure.

Detailed optimization studies were performed to obtain the best reaction conditions for the formation of **37**.

Table 2.1. Optimization Studies

Entry	Catalyst	Additive	Solvent	Yield %
1	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	DMF	50
2	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	1,4-dioxane	49
3	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	xylene	46
4	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	1,2-DCE	23
5	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	CH_3CN	No reaction
6	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	toluene	62
7	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	toluene	19
8	$[RuCl_2(p\text{-cymene})]_2$	CsOAc	toluene	14
9	$[RuCl_2(p\text{-cymene})]_2$	AgOAc	toluene	25
10	$[RuCl_2(p\text{-cymene})]_2$	Ag_2CO_3	toluene	No reaction
11[a]	**$[RuCl_2(p\text{-cymene})]_2$**	**$Cu(OAc)_2.H_2O$**	**toluene**	**73**

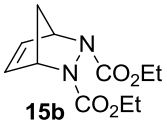
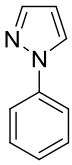
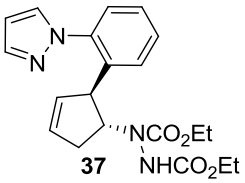
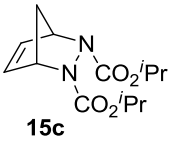
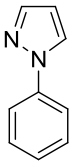
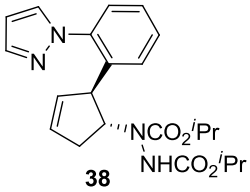
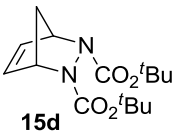
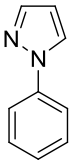
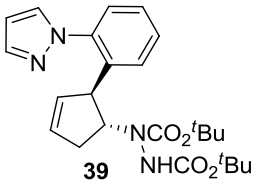
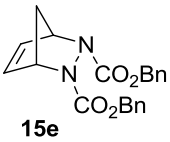
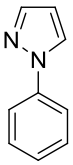
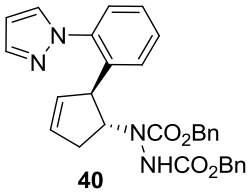
Reaction conditions: alkene (1.0 equiv.), 1-phenylpyrazole (1.0 equiv.), catalyst (5 mol %), additive (1.5 equiv.), solvent (2 mL), 90 °C, 12h. [a]: at 110 °C.

Screening of various solvents such as toluene, xylene, 1,4-dioxane, DMF,and DMSO displayed toluene as the most favorable reaction medium for the transformation. In the next stage, a number of additives such as $Cu(OAc)_2.H_2O$, NaOAc, CsOAc, AgOAc, and Ag_2CO_3 were tested for their efficiency in the present protocol.

Among them the non-acetate source, Ag_2CO_3 inhibited the reactivity and $Cu(OAc)_2.H_2O$ was found to be the most proficient one. When the reaction was conducted in the presence of NaOAc or CsOAc, it resulted in the formation of the product in lower yields along with a minor amount of homocoupled product of N-phenylpyrazole as reported by Dixneuf *et al*. The effect of temperature was finally studied and the results revealed that the reaction proceeded more efficiently at elevated temperature, 110 ^oC yielding 73% of **37**. Eventually, diazabicyclic olefin **15b** (1 equiv) and 1-phenylpyrazole **17** (1 equiv) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) and $Cu(OAc)_2.H_2O$ (1.5 equiv) in toluene at 110 ^oC was accomplished as the optimal reaction conditions for the formation of **37**. The reults are summarized in table 2.1.

The scope of various diazabicyclic olefins in the present protocol was proved by the reaction with N-phenylpyrazole under optimal catalytic conditions. Ring-opening of bicyclic olefins underwent smoothly to afford the corresponding cyclopentene derivatives in good yields (Table 2.2). Similarly the generality of differently substituted imidazoles were also tested with various diazabicyclic olefins. The results are summarized in table 2.3.

Table 2.2. Reaction of various diazabicyclic olefins with N-Phenyl Pyrazole

Entry	Bicyclic Olefin	N-Phenyl Pyrazole(17)	Product	Yield (%)
1.	 **15b**		 **37**	73%
2.	 **15c**		 **38**	72%
3.	 **15d**		 **39**	52%
4.	 **15e**		 **40**	60%

Reaction conditions: alkene (1.0 equiv.), 1-phenylpyrazole (1.0 equiv.), catalyst (5 mol %), additive (1.5 equiv.), solvent (2 mL), 110 ^{o}C, 12h.

The structure of **42** was assigned with the help of various spectroscopic techniques. The IR spectrum of **42** indicated the –NH stretching at 3284 cm^{-1} and the characteristic absorption of carbonyl group at 1716 cm^{-1}. In the ^{1}H NMR spectrum, multiplet in the region δ 7.41-7.03 ppm was assigned to aromatic protons. Two –NH protons resonated as a multiplet in the region δ 10.71-10.17 ppm. The alkene protons appeared as two singlets at δ 5.81 and 5.45 ppm. The multiplets at δ 4.19-4.17 and δ 3.92-3.72 ppm were assigned to methylene protons of carboethoxy groups. Proton on the carbon bearing hydrazine moiety was discernible at δ 5.04-4.86 ppm along with the proton on the carbon to which 2-phenylimidazole is attached. Multiplet in the region δ 2.59-2.56 corresponds to the methylene

protons of the cyclopentene ring The methyl protons of the carboethoxy groups resonated as multiplets in the region δ 1.32- 0.77 ppm. The ^{1}H NMR spectrum of the compound is shown in figure 2.4.

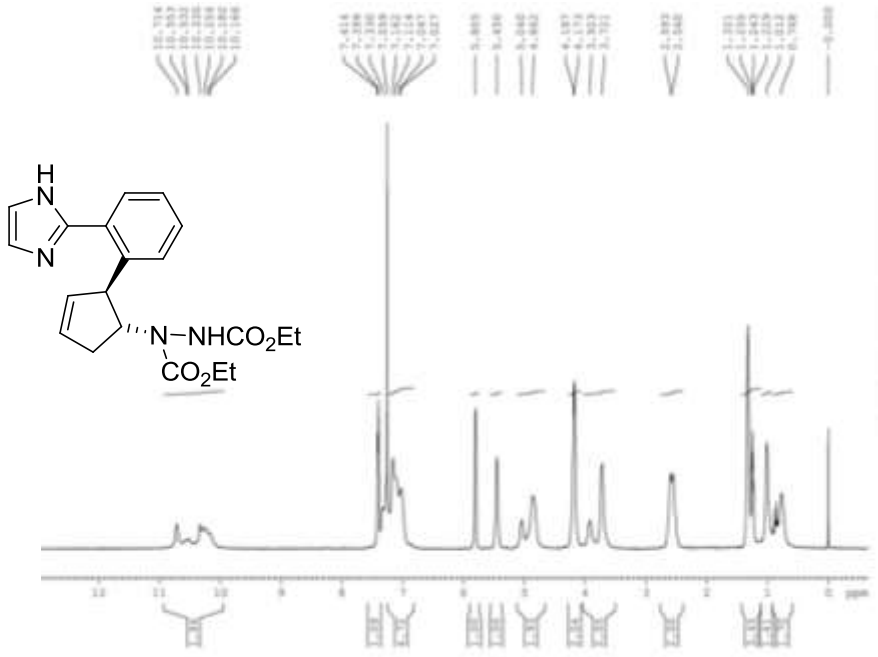


Figure 2.4. ^{1}H NMR Spectrum of Compound **42**

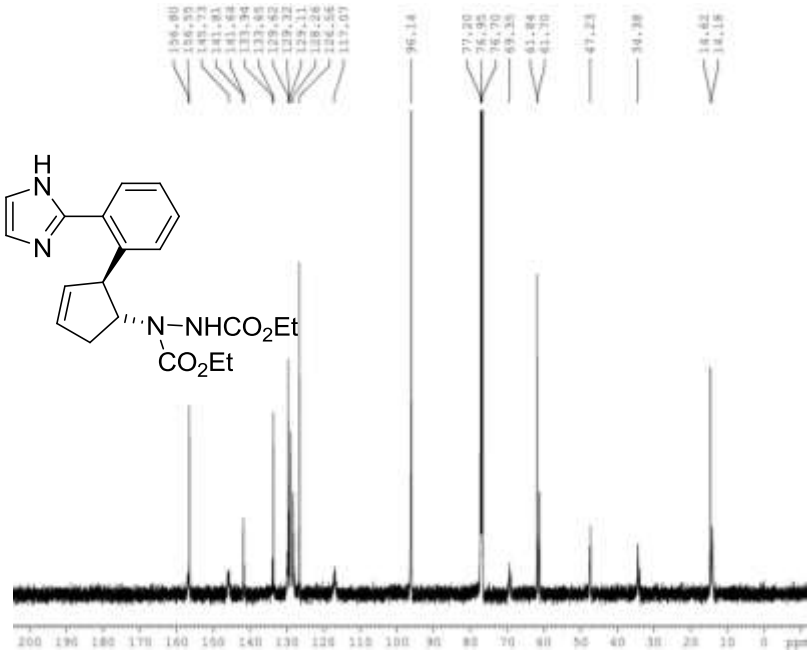
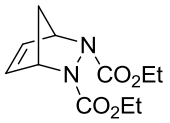
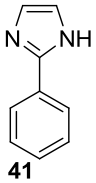
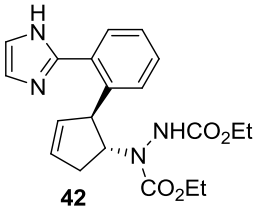
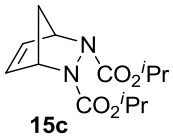
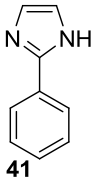
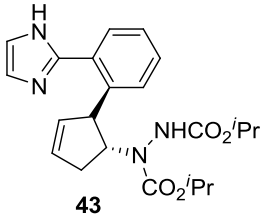
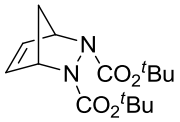
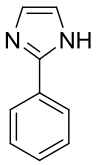
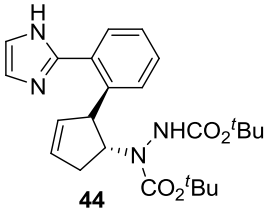


Figure 2.5. ^{13}C NMR Spectrum of Compound **42**

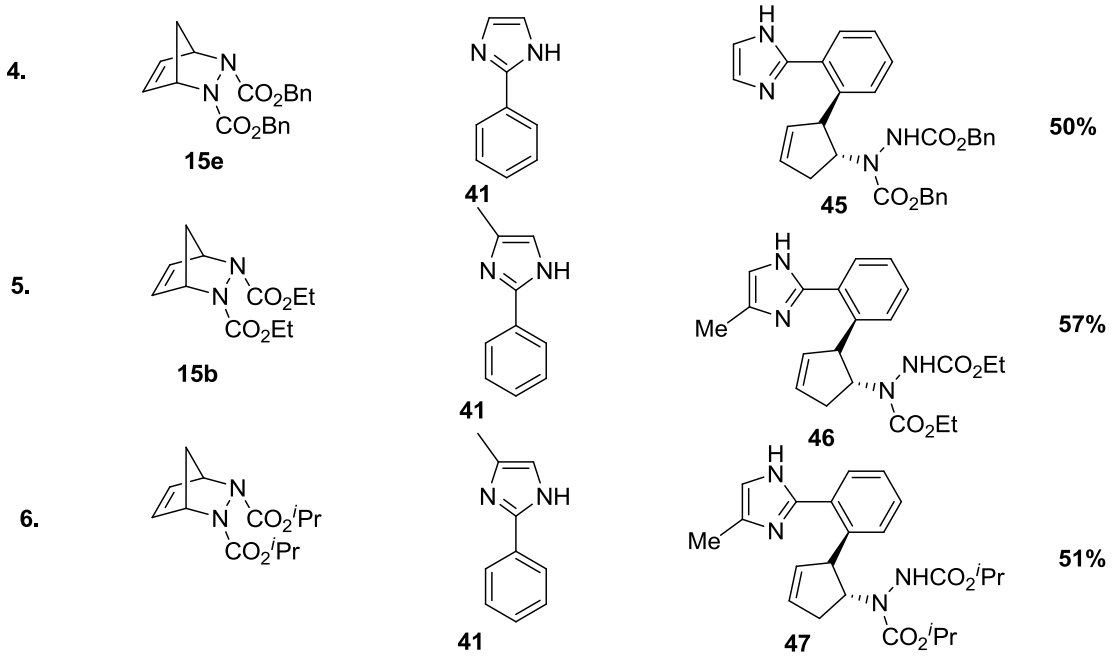
The ^{13}C NMR spectrum showed peaks due to ester carbonyl carbons at δ 156.8 and 156.6 ppm. The signal at δ 69.4 ppm corresponds to the carbon bearing hydrazine moiety. The signal resonated at δ 47.2 ppm was identified as the characteristic peak of the carbon to which 2-phenylimidazole is attached. The methylene carbon of the cyclopentene skeleton was discernible at δ 34.4 ppm. The $–CH_2$ carbons of the ester group resonated at δ 61.8 and 61.7 ppm. The methyl carbons of the carboethoxy groups showed sharp peaks at δ 14.6 and 14.2 ppm. All other signals in ^{13}C NMR spectra were in agreement with the proposed structure (Figure 2.5). The structure assigned was confirmed by high resolution mass spectral analysis which showed a molecular ion peak at *m/z* = 407.17032 (M+Na).

It was indeed clear that all of them furnished the expected product in moderate to good yields. Methyl substitutions at the imidazole ring also didn't alter the yield much.

Table 2.3. Reaction of various diazabicyclic olefins with Imidazoles

Entry	Bicyclic Olefin	N-Phenyl Imidazole	Product	Yield (%)
1.	 **15b**	 **41**	 **42**	**63%**
2.	 **15c**	 **41**	 **43**	**48%**
3.	 **15d**	 **41**	 **44**	**53%**

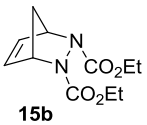
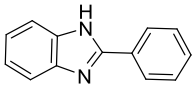
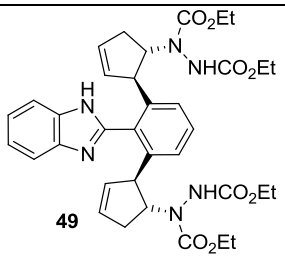
Continued.



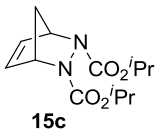
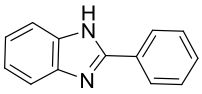
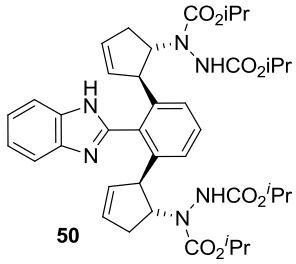
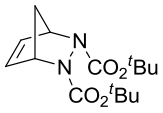
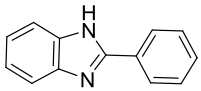
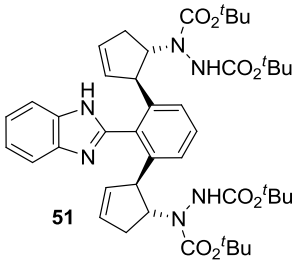
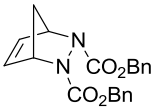
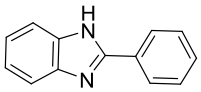
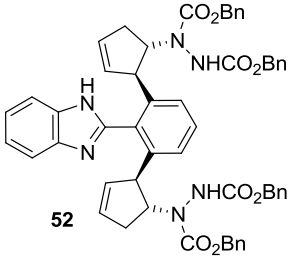
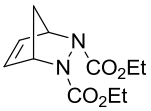
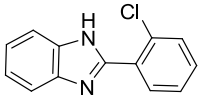
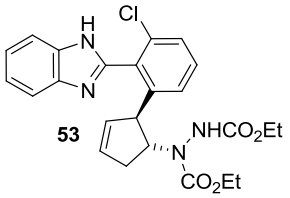
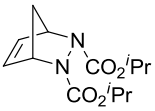
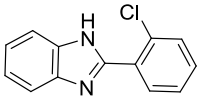
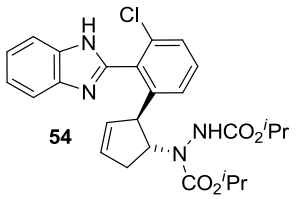
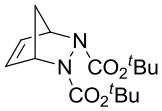
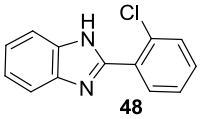
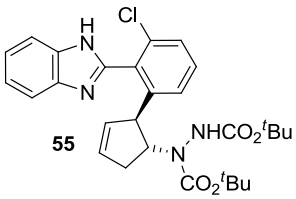
Reaction conditions: alkene (1.0 equiv.), azole (1.0 equiv.), $[RuCl_2(p\text{-}cymene)]_2$ (5 mol %), $Cu(OAc)_2$. H_2O (1.5 equiv.), toluene (2 mL), 110 ^oC, 12h.

In contrast, the reaction of diazanorbornene **15** with 2-phenylbenzimidazole furnished bis-cyclopentenyl functionalized benzimidazole in 67% yield *via* two fold coupling by dual C–H bond activation (Table 2.4). Diazabicyclic olefins **15b–d** smoothly underwent ring opening through dual C–H activation of 2-phenylbenzimidazole and provided the products in good yields.

Table 2.4. Reaction of various diazabicyclic olefins with Benzimidazoles

Entry	Bicyclic Olefin	2-Phenyl Benzimidazole(48)	Product	Yield (%)
1.	 15b		 49	67%

Continued.

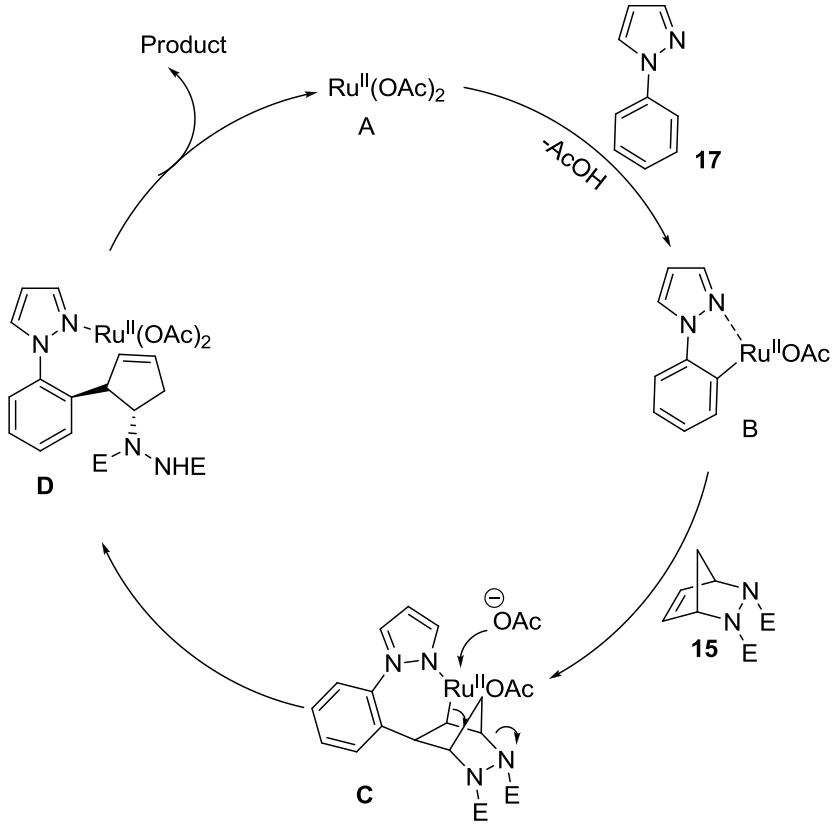
2.	 **15c**		 **50**	41%
3.	 **15d**		 **51**	52%
4.		 **48**	 **52**	47%
5.		 **48**	 **53**	72%
6.		 **48**	 **54**	68%
7.		 **48**	 **55**	40%

Continued

Reaction conditions: alkene (1.0 equiv.), azole (1.0 equiv.), $[RuCl_2(p\text{-}cymene)]_2$ (5 mol %), $Cu(OAc)_2$. H_2O (1.5 equiv.), toluene (2 mL), 110 ^oC, 12h.

2.6. Mechanism

A plausible mechanism for the ring-opening of diazanorbornenes is outlined in Scheme 5 on the basis of the literature reports on the ruthenium catalyzed C–H bond functionalization reactions. Catalytic cycle is initiated by the generation of an active ruthenium acetate species **A** by ligand exchange with an acetate source. In the next step, nitrogen atom of phenylazole **17** is co-ordinated to species A followed by cyclometalation to give a five membered metallacycle **B** with the liberation of a molecule of acetic acid. Insertion of bicyclic olefin into the metallacycle provides an intermediate **C** and subsequent *β*-nitrogen elimination with the assistance of acetate ion furnishes the product **3** with the regeneration of active catalytic species.



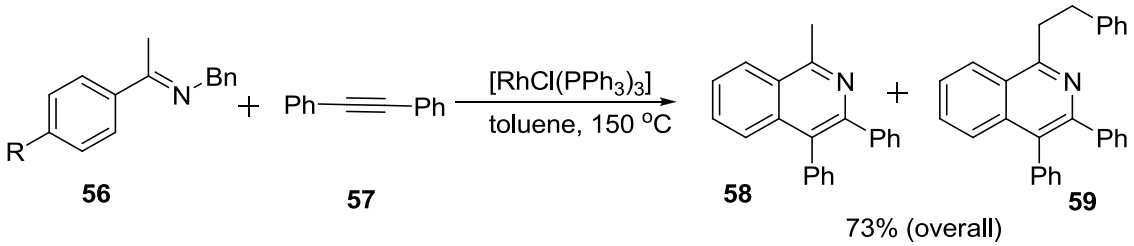
Scheme 2.14

2.7. Transition Metal Free Thermal Rearrangement of Diazabicyclic Olefins and Sequential Imine Formation in DMSO

Nitrogen-containing chelating groups have been identified as a suitable directing group for C-H bond activation processes. The expected reactivity of various azoles were giving clear directions to the possibility of coordinating nitrogens of different aromatic systems. This prompted us to attempt the C-H functionalization of aromatic imines, such as aldimine and ketimines for creating new C-C bond in the *ortho* position catalyzed by transition metals. Imine directing groups are equally suitable for a similar cascade reaction yielding isoquinoline derivatives. The use of aldimines and ketimines was independenly reported by Jun, Fagnou, Satoh and Miura to produce highly substituted isoquinolines from rhodium-catalyzed oxidative coupling with internal alkynes

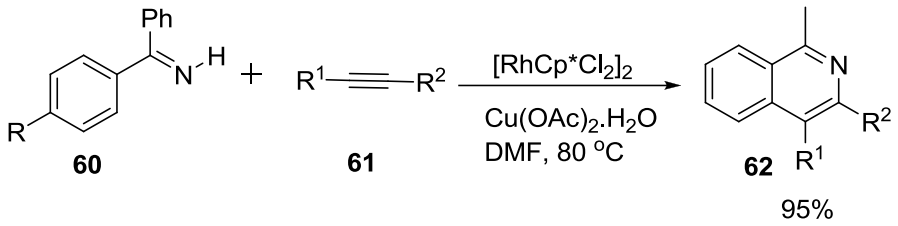
2.7.1. Imines as Directing Groups

A highly efficient single-step synthesis of isoquinoline derivatives was reported by Jun *et al.* by Rh(I)-catalyzed direct ortho-alkenylation of common aromatic ketimines with alkynes (Scheme 21.5).[17] In this case mixture of products was formed.



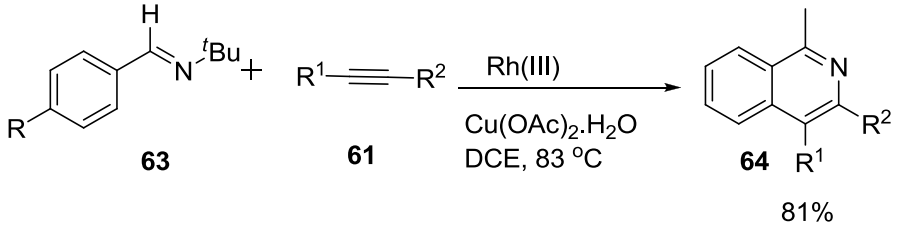
Scheme 2.15

With a range of different aldimines and alkynes under Rh(III) catalysis was utilized for the preparation of other isoquinoline molecules by Miura and Satoh (Scheme 2.16). [17b] The desired isoquinoline was obtained in excellent yield.



Scheme 2.16

Fagnou had come up with another report on the rhodium-catalyzed oxidative coupling of aromatic imines with alkynes which effectively proceeds *via* regioselective C–H bond cleavage to produce isoquinoline derivatives (Scheme 2.17).[19]



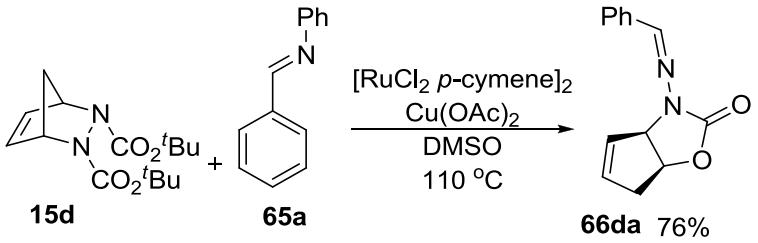
Scheme 2.17

2.8. Statement of the Problem

The literature reports ensure the possibility of formation of isoquinoline moiety by the C-H activation/ annulation of aromatic imines with suitable coupling partners. The annulation of diazabicyclic olefin could result in cyclopentene fused isoquinolines. They are privileged moieties in pharmaceutical chemistry. Herein we describe a facile one-pot metal free reaction of Boc protected diazabicyclic olefins with benzaldehydes/acetophenones in DMSO.

2.9. Results and Discussion

The experiment was initiated by heating diazabicyclic olefin **15d** (1 equiv.), N-benzylideneaniline (1 equiv.) in presence of catalytic amount of $[RuCl_2$ *p*-cymene$]_2$ and $Cu(OAc)_2$ in DMSO at 110 ^oC for 10 hours. The expected product was not formed. Instead, a rearranged product **66da,** with an imine linkage was formed in 76% yield.



Scheme 2.18

The structure of the product **66da** was confirmed using various spectroscopic techniques; such as ^{1}H NMR, ^{13}C NMR as well as mass spectral analyses.

In the ^{1}H NMR spectrum, the imine proton resonated as a singlet at δ 8.21 ppm. The aromatic protons were found to be resonate as a two proton triplet at δ 7.73 ppm and a three proton multiplet from δ 7.30 to 7.38 ppm. The cyclopentene olefins appeared as two multiplets from δ 6.14 to 6.12 ppm and δ 5.98 to 5.96 ppm. The methylene protons resonated as a multiplet from δ 2.88 to 2.74 ppm (figure 2.6).

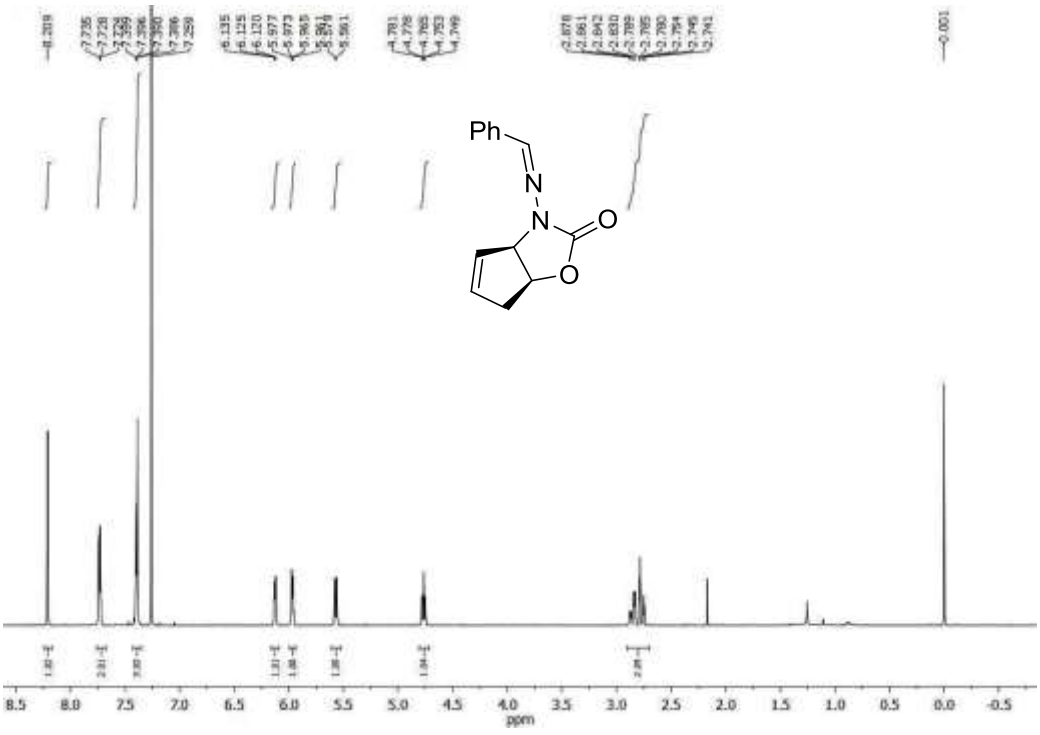


Figure 2.6. ^{1}H NMR Spectrum of Compound **66da**

In the ^{13}C NMR spectrum, the amide carbonyl resonated at δ 152.9 ppm. The imine carbon appeared at δ 145.9 ppm. The sp^3 carbon attached to oxygen resonated at δ 82.3 ppm. Similarly, the sp^3 carbon attached to nitrogen was found to be resonating at δ 56.3 ppm. The methylene carbon resonated at δ 37.6 ppm (figure 2.7).

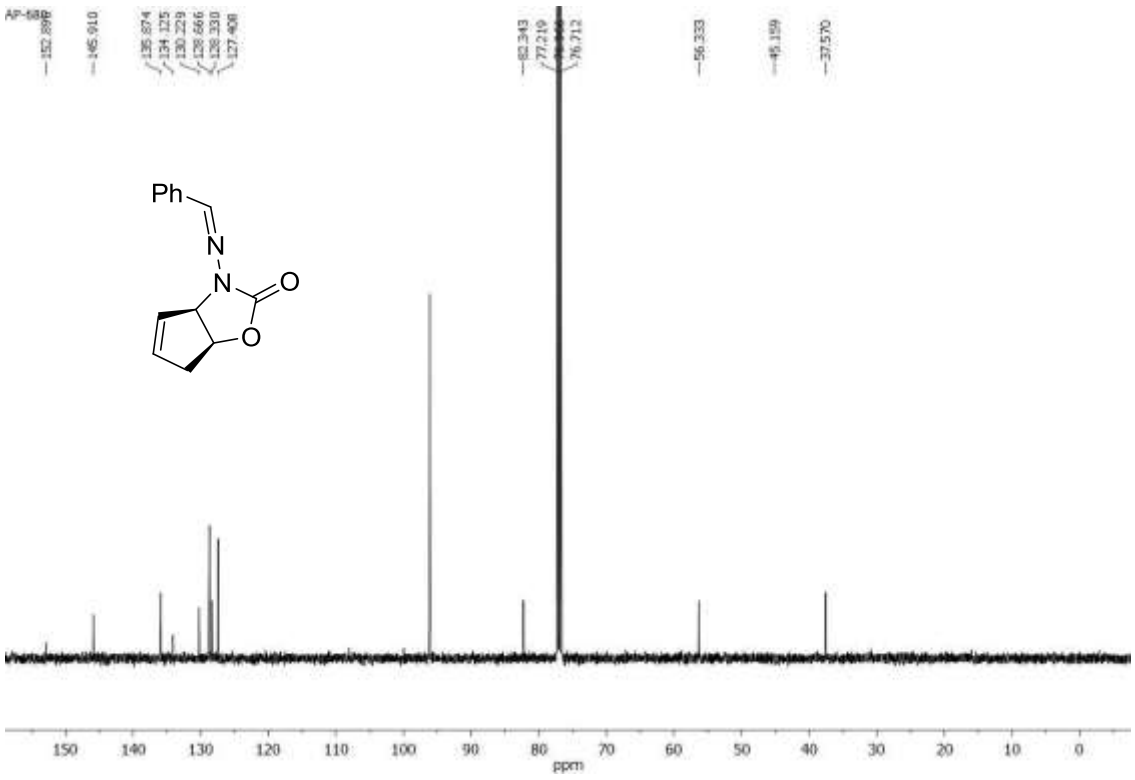
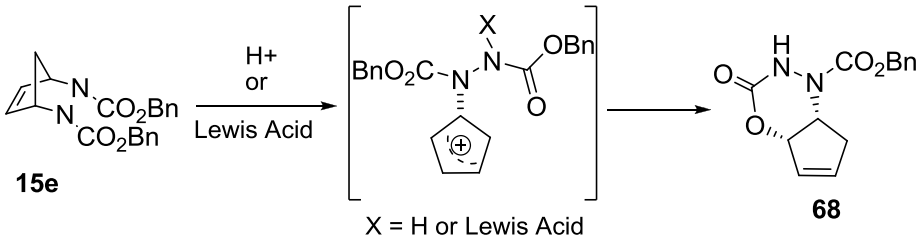


Figure 2.7. ^{13}C NMR Spectrum of Compound **66da**

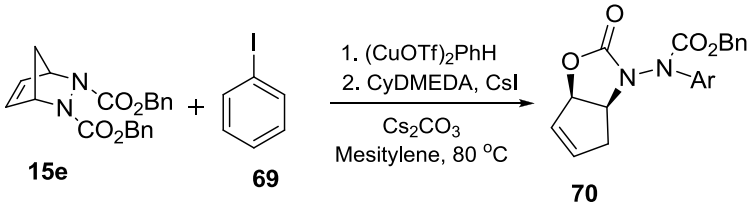
2.9.1 Previous Reports

There are a few reports on the rearrangements of diazabicyclic olefins in thermal as well as Lewis acid conditions. Micouin and coworkers had reported an acid catalyzed stereoselective rearrangement of diazabicyclic olefins leading to the bicyclic cyclopentene **68**.[18]



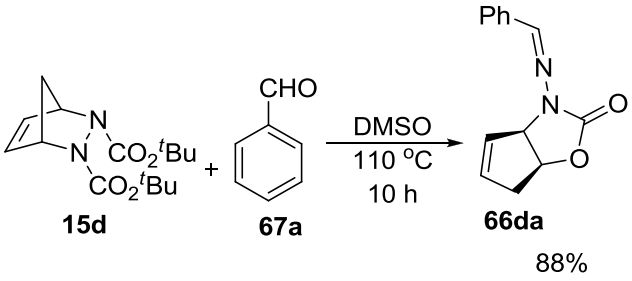
Scheme 2.19

The correct structure of the rearranged product was correctly assigned by Lautens *et al.* (Scheme 2.21). They demonstrated a one-pot synthesis of N′-arylaminooxazolidinones through a Lewis acid catalyzed rearrangement followed by an N-arylation reaction.[19]



Scheme 2.20

The literature reports assure that the rearrangement which took place as in scheme 2.18, may not require the Ru(II)/Cu(II) catalytic system; which is quite essential for cyclometallation deprotonation(CMD) pathways. So we investigated the reaction, initially in the absence of the ruthenium catalyst and later in the absence of both the catalyst as well as additive. In both the cases the reaction afforded the product **66da** without fail. In addition to that, when the imine **65a** was replaced with the corresponding aldehyde **67a** the reaction occurred in the same manner with an elevated yield of 88%.



Scheme 2.21

2.9.2. Role of DMSO

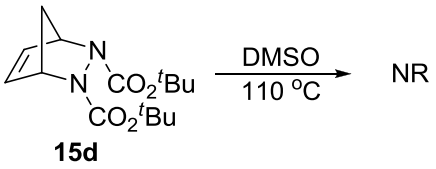
The actual role of DMSO in the reaction mixture is unclear. But during the optimization studies it was clear that the presence of DMSO is essential for the reaction to happen. When other different solvents such as DMF, acetonitrile, DCE, and toluene were used, the reaction was found to be futile. Also significantly, when the temperature of the reaction was decreased from 110 ^{o}C to 80 ^{o}C, the reaction didn't furnish any product. From these observations it is evident that the reaction will occur in DMSO at elevated temperatures. The details of the optimization studies are listed in table 2.5. The entry 1 was selected as the favorable condition for the rection.

Table 2.5. Optimization Studies

Sl No	Solvent	Temperature (^{o}C)	Yield (%)
1.	DMSO	110	88
2.	toluene	110	NR
3.	DMF	110	NR
4.	ACN	110	NR
5.	DCE	110	NR
6.	DMSO	80	NR

Reaction conditions :diazabicyclic olefin (1 equiv.), N-benzylideneaniline (1 equiv.),DMSO at 110 ^{o}C.

Using the optimized reaction condition, we have checked the generality of the reaction with respect to different diazabicyclic olefins. None of the diazabicyclic olefins except **15d**, which is having a Boc protecting group could furnish the product. The other diazabicyclic olefins **15b, 15c,** and **15e** which are having ethyl, isopropyl, and benzyl groups couldn't render the reaction. Also it could be noted that when the reaction was carried out in the absence of the aldehyde, the expected product was not formed (scheme 2.22).

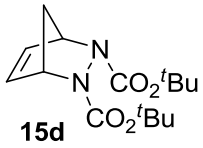
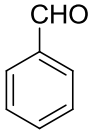
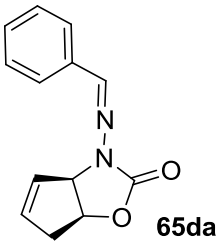
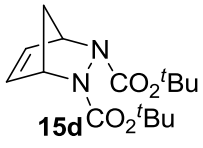
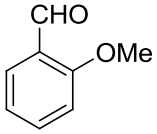
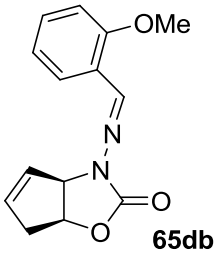
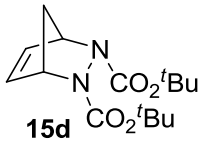
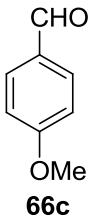
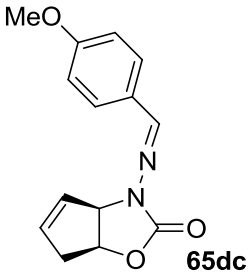


15d

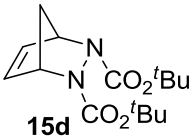
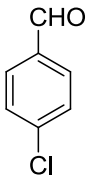
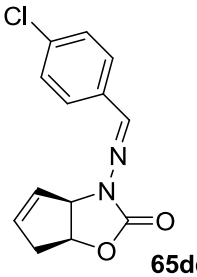
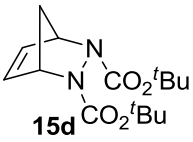
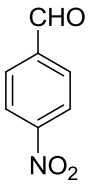
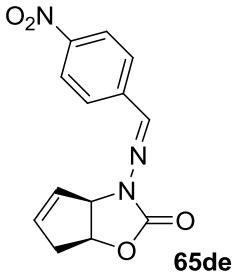
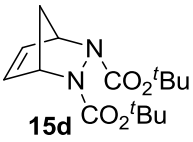
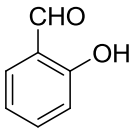
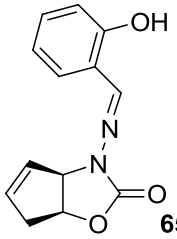
Scheme 2.22

Different benzaldehydes and acetophenones were investigated for the DMSO mediated rearrangement and sequential imine formation. And all of them (Tabl 2.6 &2.7) underwent the reaction in good to excellent yield. The electronic nature of the substituents on the aldehyde did not alter the outcome of the reaction much.

Table 2.6. Reaction of diazabicyclic olefin **15d** with Benzaldehydes

Entry	Bicyclic Olefin	Benzaldehyde	Product	Yield (%)
1.	 **15d**	 **66a**	 **65da**	**88%**
2.	 **15d**	 **66b**	 **65db**	**85%**
3.	 **15d**	 **66c**	 **65dc**	**90%**

Continued.

4.	 **15d**	 **66d**	 **65dd**	**93%**
5.	 **15d**	 **66e**	 **65de**	**80%**
6.	 **15d**	 **66f**	 **65df**	**85%**

Reaction conditions :diazabicyclic olefin (1 equiv.),N-benzylideneaniline (1 equiv.),DMSO at 110 ^{o}C, 10h

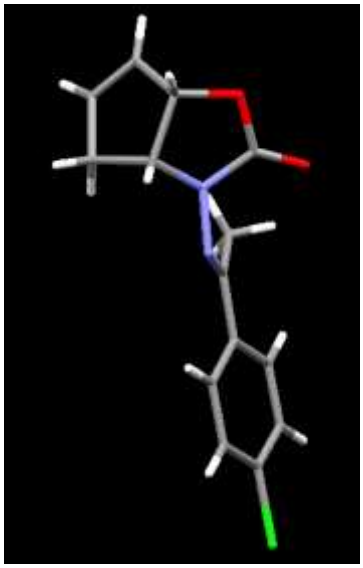
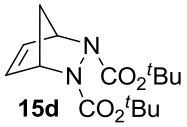
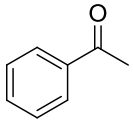
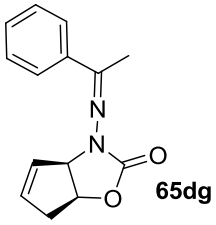
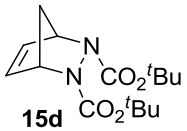
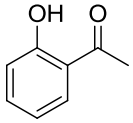
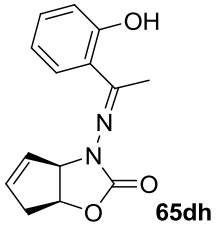
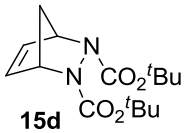
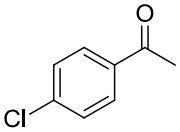
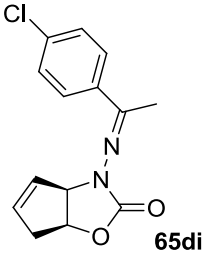
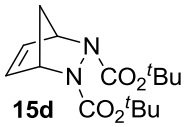
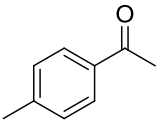
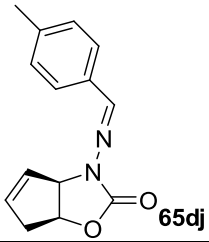


Figure 2.8. Single Crystal X- Ray of **65dj**

The yield of the reaction was found to be decreasing in the case of aldehyde/ketones with electron withdrawing functional groups as well as *ortho* substituents. Also the electron donating substituents slightly enhance the outcome of the reaction. Finally the stereochemistry of the product was confirmed unambiguously by the single crystal X-ray crystal of one of the derivative synthesized; compound **65dj** (Figure 2.8).

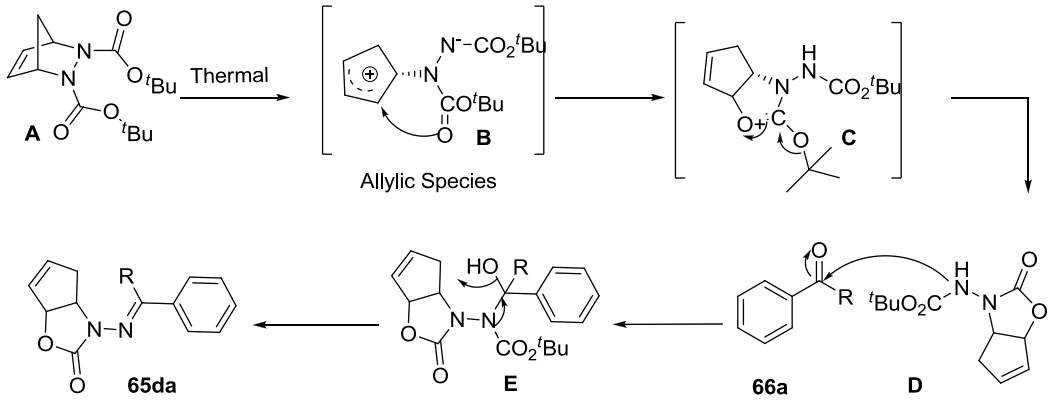
Table 2.7. Reaction of diazabicyclic olefin **15d** with Acetophenones

Entry	Bicyclic Olefin	Benzaldehyde	Product	Yield (%)
1.	 **15d**	 **66g**	 **65dg**	84%
2.	 **15d**	 **66h**	 **65dh**	74%
3.	 **15d**	 **66i**	 **65di**	79%
4.	 **15d**	 **66j**	 **65dj**	81%

Reaction conditions :diazabicyclic olefin (1 equiv.),N-benzylideneaniline (1 equiv.),DMSO at 110 ^{o}C, 10h.

2.10. Mechanistic Pathway

It is a thermal isomerization of the Diels-Alder adducts **15d** and sequrntial imination in DMSO (Scheme 2.23). The mechanism may be initiated with the C-N bond cleavage which is thermally driven, ends up in the allylic species **B**. The allylic carbocation could be conveniently attacked by the carbonyl oxygen to give the intermediate **C**. Which upon elimination of one tertiary butoxy group and subsequent imination with the aldehyde **66a** ends up in the product **65da**.



Scheme 2.23

2.11. Conclusion

In summary, we have developed for the first time a ruthenium catalyzed redox-neutral C–H activation of phenylazoles toward the ring-opening of diazabicyclic olefins. The reaction provides an efficient access to heteroaryl substituted cyclopentenes by employing less-expensive ruthenium catalyst. In addition, we have observed a novel ring opening of Boc protected diazabicyclic olefins in presence of aromatic aldehyde/ketone exclusively in DMSO.

2.12. Experimental Section

2.12.1. General methods: All reactions were conducted in oven-dried glasswares. Solvents used for the experiments were distilled and degassed with Argon. All other reagents were purchased from local suppliers. All reactions were monitored by TLC (Silica gel 60 F_{254}, 0.25 mm, Merck), visualization was effected with UV and/or by staining with Enholm yellow

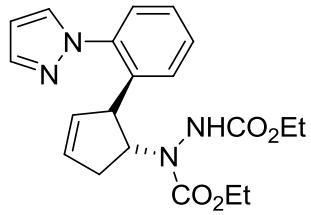
solution. Gravity column chromatography was performed using 100-200 mesh silica gel and mixtures of hexane- ethyl acetate were used for elution. Melting points were determined on a Buchi melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker Avance DPX 300 and Bruker AMX 500 spectrophotometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.25, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); dd (double doublet); m (multiplet). Coupling constants are reported as *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). Mass spectra were recorded under EI/HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer. IR spectra were recorded on Bruker FT-IR spectrometer.

2.12.2. General Experimental Procedure for Ruthenium catalyzed Desymmetrization of Diazabicyclic Olefins through C–H Activation of Phenylazoles

The diazabicyclic olefin (1.0 equiv.), azole **50** (1.0 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) and $Cu(OAc)_2.H_2O$ (1.5 equiv) were added to a Schlenk tube and were degassed for five minutes. To this, 2 mL toluene was added and was purged with argon. The resulting mixture was refluxed at 110 °C under argon atmosphere for 12 h. The solvent of crude reaction mixture was removed *in vacuo*. On performing column chromatographic purification, the product was obtained.

Diethyl 1-(2-(2-(1H-pyrazol-1-yl)phenyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 37

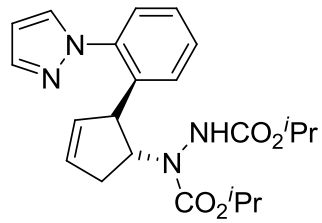
Following the general experimental procedure, the diazabicyclic olefin **15b** (50 mg, 0.21 mmol), *N*-phenylpyrazole **17** (30 mg, 0.21 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3 mg, 0.005 mmol) and $Cu(OAc)_2.H_2O$ (62 mg, 0.31 mmol) in 2 mL toluene at 110 °C under argon atmosphere for 12 h gave the product **37** as a colourless viscous liquid (58 mg, 73%).



R_f : 0.53 (7:3 hexane/EtOAc). **IR (neat) λ_{max}:** 3369, 2922, 2851, 2730, 1740, 1649, 1541, 1513, 1458, 1398, 1211, 1164, 1128, 1046, 939, 689, 597, 558 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.78-7.69 (m, 1H), 7.53 (s, 1H), 7.37-7.34 (m, 2H), 7.27-7.20 (m, 1H), 7.12 (d, *J* = 7 Hz, 1H), 6.42 (s, 1H), 5.77 (s, 1H), 5.41 (s, 1H), 4.97-4.73 (m, 1H), 4.10-3.85 (m, 6H), 2.60-2.49 (m, 2H), 1.24-1.10 (m, 6H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.6, 155.6, 140.5, 139.5, 132.4, 131.5, 129.9, 129.2, 127.1, 126.1, 106.8, 69.8, 62.0, 61.6, 45.5, 35.1, 14.5 ppm. **HRMS (ESI):** Calcd for $C_{20}H_{24}N_4O_4$, $(M+Na)^+$: 407.16952; Found: 407.16980.

Diisopropyl 1-(2-(2-(1H-pyrazol-1-yl)phenyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 38

Following the general experimental procedure, the diazabicyclic olefin **15c** (50 mg, 0.19 mmol), *N*-phenyl pyrazole **17** (27 mg, 0.19 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3 mg, 0.005 mmol) and $Cu(OAc)_2.H_2O$ (56 mg, 0.28 mmol) in 2 mL toluene at 110 °C under argon atmosphere for 12 h gave the product **38** as a colourless viscous liquid (52 mg, 72 %).

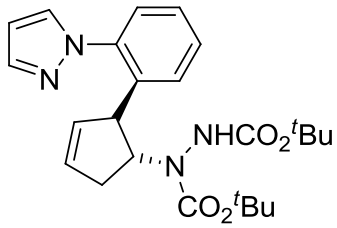


R_f : 0.73 (7:3 hexane/EtOAc). **IR (neat) λ_{max}:** 3345, 3118, 3057, 2977, 2931, 1744, 1708, 1606, 1482, 1456, 1394, 1334, 1250, 1158, 1048, 1022, 950, 892, 854, 759, 696, 665, 617, 557 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.84-7.76 (m, 1H), 7.59 (s, 1H), 7.44-7.42 (m, 2H), 7.31-7.28 (m, 1H), 7.20-7.12 (m, 2H), 6.49 (s, 1H), 5.84 (s, 1H), 5.49 (m, 1H), 5.03-4.76 (m, 3H), 4.06 (s, 1H), 2.67-2.55 (m, 2H), 1.27-1.07 (m, 12H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 155.7, 154.1, 141.1, 132.3, 130.6, 129.2, 127.0, 126.1, 107.0, 69.5, 69.0, 51.7, 34.4, 22.1, 22.0 ppm. **HRMS (ESI):** Calcd for $C_{22}H_{28}N_4O_4$, $(M+Na)^+$: 435.20083.; Found: 435.20111.

Di-tert-butyl 1-(2-(2-(1H-pyrazol-1-yl)phenyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 39

Following the general experimental procedure, the diazabicyclic olefin **15d** (50 mg, 0.17 mmol), *N*-phenylpyrazole **17** (24 mg, 0.17 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3 mg, 0.004 mmol)

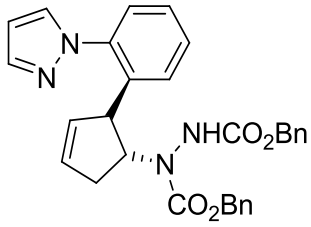
and $Cu(OAc)_2.H_2O$ (51 mg, 0.25 mmol) in 2 mL toluene at 110 °C under argon atmosphere for 12 h gave the product **39** as a colourless viscous liquid (43 mg, 52 %).



R_f : 0.81 (7:3 hexane/EtOAc). **IR (neat) λ_{max}:** 3347, 3056, 2956, 2921, 2854, 1734, 1718, 1654, 1609, 1491, 1459, 1395, 1372, 1331, 1266, 1160, 1050, 744, 696, 668, 556 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.82-7.73 (m, 1H), 7.58 (s, 1H), 7.44-7.41 (m, 2H), 7.29-7.19 (m, 2H), 6.83 (m, 1H), 6.48 (s, 1H), 5.84 (m, 1H), 5.49 (s, 1H), 4.97-4.74(m, 1H), 4.03(s, 1H), 2.63-2.46 (m, 2H), 1.47-1.11 (m, 18H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 155.8, 154.7, 140.7, 140.3, 132.4, 131.3, 130.7, 129.3, 129.0, 126.9, 126.1, 106.6, 80.6, 80.4, 67.2, 46.2, 34.7, 28.3, 28.2 ppm. **HRMS (ESI):** Calcd for $C_{24}H_{32}N_4O_4$, (M+Na)+: 463.23213; Found: 463.23306.

Dibenzyl-1-(2-(2-(1H-pyrazol-1-yl)phenyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 40

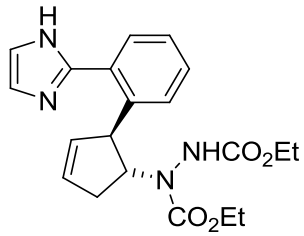
Following the general experimental procedure, the diazabicyclic olefin **15e** (50 mg, 0.14 mmol), *N*-phenylpyrazole **17** (20 mg, 0.14 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2 mg, 0.003 mmol) and $Cu(OAc)_2.H_2O$ (41 mg, 0.21) in 2 mL toluene at 110 °C under argon atmosphere for 12 h gave the product **40** as a yellow viscous liquid (46 mg, 60%).



R_f : 0.68 (7:3 hexane/EtOAc).**IR (neat) λ_{max}:** 3337, 3033, 2956, 2920, 1738, 1459, 1380, 1269, 1208, 1165, 1107, 1048, 835, 756, 696, 666, 612, 558 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.51-7.14 (m, 16H), 6.50-6.37 (m, 2H), 5.83-5.76 (m, 1H), 5.48-5.47 (m, 1H), 5.08-4.89 (m, 5H), 4.12 (s, 1H), 2.70-2.41 (m, 2H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.2, 155.7, 141.9, 140.6, 139.4, 136.1, 135.9, 132.4, 131.6, 130.6, 129.3, 129.1, 128.5, 128.3, 128.1, 127.9, 127.5, 127.1, 126.2, 106.9, 68.0, 67.3, 65.4, 48.1, 35.0 ppm. **HRMS (ESI):** Calcd for $C_{30}H_{28}N_4O_4$, $(M+Na)^+$: 531.20083; Found: 531.20105.

Diethyl 1-((1R,2S)-2-(2-(1H-imidazol-2-yl)phenyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 42

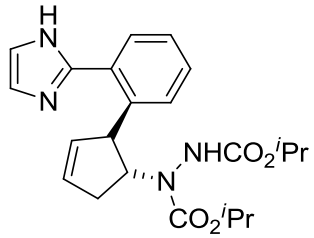
Following the general experimental procedure, the diazabicyclic olefin **15b** (50 mg, 0.21 mmol), *N*-phenylimidazole **41** (30 mg, 0.21 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3 mg, 0.005 mmol) and $Cu(OAc)_2.H_2O$ (62 mg, 0.31 mmol) in 2 mL toluene at 110 °C under argon atmosphere for 12 h gave the product **42** as a colourless viscous liquid (63%).



R_f : 0.65 (5:5 hexane/EtOAc). **IR (neat) λ_{max}:** 3284, 3059, 2981, 2929, 2863, 1716, 1634, 1593, 1472, 1416, 1380, 1273, 1245, 1217, 1165. 1130, 1098, 1059, 950, 863, 809, 763, 664, 661, 557 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 10.71-10.17 (m, 2H), 7.41-7.33 (m, 1H), 7.16-7.03 (m, 5H), 5.81 (s, 1H), 5.45 (s, 1H), 5.04-4.86 (m, 2H), 4.19-4.17 (m, 2H), 3.92-3.72 (m, 2H), 2.59-2.56 (m, 2H), 1.32-1.23 (m, 3H), 1.01- 0.77 (m, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.8, 156.6, 145.7, 141.8, 141.6, 133.9, 133.7, 129.6, 129.3, 129.1, 128.3, 126.6, 117.1, 69.4, 61.8, 61.7, 47.2, 34.4, 14.6, 14.2 ppm. **HRMS (ESI):** Calcd for $C_{20}H_{24}N_4O_4$, $(M+Na)^+$: Exact Mass: 407.16952; Found: 407.17032.

Diethyl 1-((1R,2S)-2-(2-(1H-imidazol-2-yl)phenyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 43

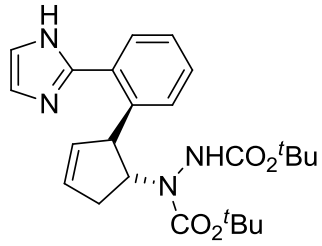
Following the general experimental procedure, the diazabicyclic olefin **15b** (50 mg, 0.21 mmol), *N*-phenylimidazole **43** (30 mg, 0.21 mmol), $[RuCl2(p\text{-cymene})]_2$ (3 mg, 0.005 mmol) and $Cu(OAc)_2.H_2O$ (62 mg, 0.31 mmol) in 2 mL toluene at 110 °C under argon atmosphere for 12 h gave the product **43** as a colourless viscous liquid (73%).



R_f : 0.68 (5:5 hexane/EtOAc). **IR (neat) λ_{max}:** 3284, 3058, 2978, 2925, 2858, 1714, 1636, 1464, 1410, 1379, 1305, 1271, 1247, 1219, 1178, 1108, 1040, 962, 763, 664, 611, 558 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.41-7.37 (m, 2H), 7.19-7.11 (m, 4H), 5.75 (s, 1H), 5.47 (s, 1H), 4.88-4.78 (m, 3H), 3.86-3.77 (brs, 1H), 2.65-2.50 (m, 2H), 1.33-1.11 (m, 12H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.4, 156.2, 144.9, 133.6, 132.8, 130.0, 129.7, 125.7, 117.1, 69.6, 69.2, 50.4, 36.0, 22.6, 22.0, 21.9 ppm. **HRMS (ESI):** Calcd for $C_{22}H_{28}N_4O_4$, $(M+1)^+$: 413.21106; Found: 413.20142.

Di-tert-butyl-1-(-5-(2-(1H-imidazol-2-yl)phenyl)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 44

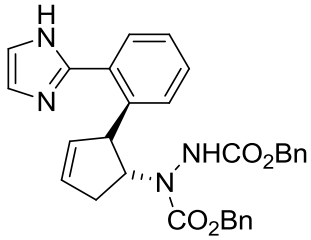
Following the general experimental procedure, the diazabicyclic olefin **15d** (50 mg, 0.17 mmol), 2-phenylimidazole **41** (14 mg, 0.10 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2 mg, 0.002 mmol) and $Cu(OAc)_2.H_2O$ (29 mg, 0.14 mmol) in 2 mL toluene at 110 °C under argon atmosphere for 12 h gave the products **44** as a yellow viscous liquid (18 mg, 53%).



R_f : 0.88 (5:5 hexane/EtOAc). **IR (neat) *λmax*** 3272, 3058, 2956, 2919, 2851, 1714, 1601, 1552, 1464, 1416, 1370, 1269, 1219, 1158, 1056, 892, 851, 753, 661, 608 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.44-7.39 (m, 2H), 7.22-7.05 (m 4H), 5.77 (m, 1H), 5.50-5.44 (m, 1H), 4.90-4.52 (brm, 1H) 4.14- 3.66 (m, 3H), 2.67-2.47 (m, 2H), 1.45-1.21 (m, 18H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.1, 155.3, 144.4, 133.6, 129.9, 128.3, 125.8, 116.6, 80.7, 68.3, 49.6, 34.9, 29.7, 29.6, 29.5 ppm. **HRMS (ESI):** Calcd for $C_{24}H_{32}N_4O_4$, $(M+1)^+$: 441.24236; Found: 441.24863.

Dibenzyl 1-(-5-(2-(1H-imidazol-2-yl)phenyl)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 45

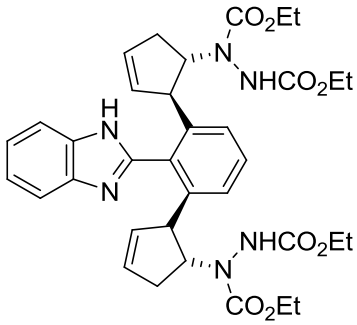
Following the general experimental procedure, the diazabicyclic olefin **15e** (50 mg, 0.14 mmol), 2-phenylimidazole **41** (11 mg, 0.08 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2 mg, 0.002 mmol) and $Cu(OAc)_2.H_2O$ (24 mg, 0.12) in 2 mL toluene at 110 °C under argon atmosphere for 12 h gave the products **45** as a yellow viscous liquid (16 mg, 50 %).



R_f : 0.48 (5:5 hexane/EtOAc). **IR (neat) *λmax*:** 3277, 3061, 2925, 2857, 1718, 1496, 1452, 1413, 1270, 1214, 1132, 1052, 980, 913, 741, 698, 669, 556 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 10.26 (brs, 1H), 7.30-7.23 (m, 16H), 5.75-5.71 (m, 1H), 5.43 (s, 1H), 5.14-4.86 (m, 6H), 3.78-3.63 (m, 1H), 2.64-2.45 (m, 2H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 155.8, 145.2, 136.0, 132.6, 130.3, 128.4, 128.3, 128.1, 127.8, 125.7, 116.5, 67.9, 67.3, 49.8, 34.9 ppm. **HRMS (ESI):** Calcd for $C_{30}H_{28}N_4O_4$, $(M+1)^+$: 509.21106; Found: 509.21921.

Tetraethyl 1,1'-2,2'-(2-(1H-benzo[d]imidazol-2-yl)-1,3-phenylene)bis(cyclopent-3-ene-2,1-diyl)bis(hydrazine-1,2-dicarboxylate) 49

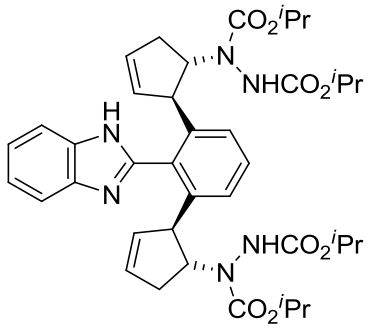
Following the general experimental procedure, the diazabicyclic olefin **15b** (50 mg, 0.21 mmol), 2-phenylbenzimidazole **48** (22 mg, 0.12 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2 mg, 0.003 mmol) and $Cu(OAc)_2.H_2O$ (35 mg, 0.17 mmol) in 2 mL toluene at 110 °C under argon atmosphere for 12 h gave the product **49** as a yellow viscous liquid (59 mg, 67%).



R_f : 0.83 (5:5 hexane/EtOAc). **IR (neat) *λmax*** 3314, 2956, 2920, 2851, 1734, 1586, 1463, 1416, 1375, 1310, 1266, 1178, 1106, 1046, 969, 914, 892, 850, 740, 609, 558 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.85 (m, 2H), 7.48-7.19 (m, 5H), 5.73 (s, 2H), 5.45 (s, 2H), 4.99-4.51 (brm, 2H), 4.20-3.83 (m, 12H), 2.62-2.42 (m, 4H), 1.28-1.21 (m, 12H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 158.8, 157.0, 156.0, 148.2, 140.1, 134.0, 126.7, 125.6, 124.4, 122.8, 121.5, 119.8, 110.7, 65.2, 62.4, 49.7, 29.7, 14.5 ppm. **HRMS (ESI):** Calcd for $C_{35}H_{42}N_6O_8$, (M^+): 675.30641; Found: 675.31409.

Tetraisopropyl 1,1'-2,2'-(2-(1H-benzo[d]imidazol-2-yl)-1,3-phenylene)bis(cyclopent-3-ene-2,1-diyl)bis(hydrazine-1,2-dicarboxylate) 50

Following the general experimental procedure, the diazabicyclic olefin **15c** (50 mg, 0.19 mmol), 2-phenyl benzimidazole **48** (21 mg, 0.12 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2 mg, 0.003 mmol) and $Cu(OAc)_2.H_2O$ (29 mg, 0.16 mmol) in 2 mL toluene at 110 °C under argon atmosphere for 12 h gave the product **50** as a yellow viscous liquid (41 mg, 41%).

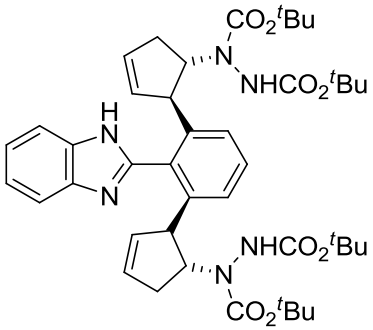


R_f : 0.88 (5:5 hexane/EtOAc). **IR (neat) *λmax*** 3266, 3058, 2978, 2925, 2857, 1713, 1460, 1378, 1309, 1270, 1177, 1140, 1107, 1041, 963, 748, 652, 554 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.47-7.40 (m, 3H), 7.35-7.24 (m, 5H), 5.70 (s, 2H), 5.45-5.41 (m, 2H), 5.04-4.74 (m, 7H), 4.04-3.80 (m, 3H), 2.60-2.38 (m, 4H), 1.37-1.12 (m, 24H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 157.3, 156.7, 155.4, 144.7, 143.9, 143.4, 134.0, 132.8, 130.9, 128.2, 125.8, 123.6,

123.3, 70.9, 70.1, 68.8, 50.5, 36.6, 29.6, 22.6, 21.9 ppm. **HRMS (ESI)**: Calcd for $C_{39}H_{50}N_6O_8$, $(M+1)^+$: 731.36901; Found: 731.37354.

1,2-Di-tert-butyl 1,1'-2,2'-(2-(1H-benzo[d]imidazol-2-yl)-1,3-phenylene)bis(cyclopent-3-ene-2,1-diyl)bis(hydrazine-1,2-dicarboxylate) 51

Following the general experimental procedure, the diazabicyclic olefin **15d** (50 mg, 0.17 mmol), 2-phenylbenzimidazole **48** (19 mg, 0.10 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2 mg, 0.002 mmol) and $Cu(OAc)_2.H_2O$ (29 mg, 0.15 mmol) in 2 mL toluene at 110 °C under argon atmosphere for 12 h gave the product **51** as a yellow solid (40 mg, 52%).

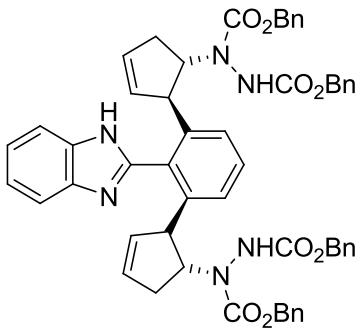


Mp: 158-160 °C. **R_f :** 0.41 (5:5 hexane/EtOAc). **IR (neat) *λmax*** 3280, 3061, 2981, 2927, 2856, 1713, 1605, 1554, 1494, 1465, 1411, 1379, 1268, 1179, 1141, 1108, 1047, 955, 849, 766, 712, 665, 611, 557 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.92-7.82 (m, 1H), 7.40-7.03 (m, 7H), 5.66 (m, 2H), 5.35 (m, 2H), 4.91-4.14 (m, 2H), 3.75-3.67 (m, 2H), 2.76-2.31 (m, 4H), 1.42-0.98 (m, 36H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 155.6, 154.6, 153.7, 143.0,

142.2, 141.0, 132.9, 129.3, 128.8, 128.2, 125.0, 121.7, 120.7, 119.2, 118.8, 110.5, 80.2, 79.4, 69.9, 68.5, 51.2, 47.9, 33.2, 32.9, 27.2, 26.8 ppm. **HRMS (ESI):** Calcd for $C_{43}H_{58}N_6O_8$, $(M+1)^+$: 787.43161; Found: 787.44092.

1,2-Di-benzyl 1,1'-2,2'-(2-(1H-benzo[d]imidazol-2-yl)-1,3-phenylene)bis(cyclopent-3-ene-2,1-) diyl)bis(hydrazine-1,2-dicarboxylate 52

Following the general experimental procedure, the diazabicyclic olefin **15e** (50 mg, 0.14 mmol), 2-phenylbenzimidazole **48** (15 mg, 0.08 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2 mg, 0.002 mmol) and $Cu(OAc)_2.H_2O$ (24 mg, 0.12) in 2 mL toluene at 110 °C under argon atmosphere for 12 h gave the product **52** as a yellow viscous liquid (42 mg, 47%).

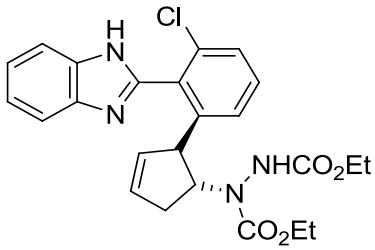


R_f : 0.53 (5:5 hexane/EtOAc). **IR (neat) *λmax*:** 3284, 3060, 3034, 2929, 2857, 1717, 1619, 1587, 1497, 1454, 1408, 1307, 1270, 1213, 1131, 1051, 845, 804, 744, 698, 663, 610, 557 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.32-6.85 (m, 27H), 5.66 (m. 2H), 5.43-5.42 (m, 2H), 5.29-4.80 (m, 11H), 3.95-3.79 (m, 2H), 2.64 (m, 4H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** 156.7, 156.3, 155.8, 142.9, 142.8, 142.5, 136.2, 135.7, 135.5, 133.9, 133.5, 128.5, 128.3, 128.2, 128.1, 128.0, 126.8, 125.7, 123.3, 122.8, 119.7, 110.7, 68.7, 67.8, 67.4, 49.4, 34.7, 29.7 ppm.

HRMS (ESI): Calcd for $C_{55}H_{50}N_6O_8$, $(M+1)^+$: 922.36901; Found: 923.37872.

Diethyl 1-(5-(2-(7-chloro-1H-benzo[d]imidazol-2-yl)phenyl)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 53

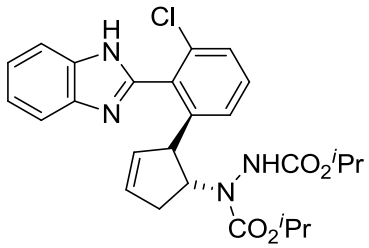
Following the general experimental procedure, the diazabicyclic olefin **15b** (50 mg, 0.21 mmol), 2-(2-chlorophenyl)-1H-benzo[*d*]imidazole **48** (47 mg, 0.21 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3 mg, 0.005 mmol) and $Cu(OAc)_2.H_2O$ (62 mg, 0.31 mmol) in 2 mL acetonitrile at 80 °C under argon atmosphere for 12 h gave the product **53** as a yellow viscous liquid (62 mg, 72%).



R_f : 0.61 (5:5 hexane/EtOAc). **IR (neat) *λmax*:** 3266, 3059, 2957, 2919, 2852, 1713, 1595, 1565, 1452, 1415, 1377, 1306, 1273, 1216, 1172, 1137, 1060, 957, 794, 742, 665, 611, 557 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 10.92-10.47 (m, 1H), 9.48 (s, 1H), 8.02-7.82 (m, 1H), 7.47-7.21 (m, 6H), 5.75 (m, 1H), 5.37-5.36 (m, 1H), 5.02-4.56 (m, 1H), 4.19-3.80 (m, 5H), 2.59-2.42 (m, 2H), 1.30-0.81 (m, 6H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.7, 156.2, 148.2, 146.4, 142.5, 134.0, 132.5, 131.8, 131.2, 130.3, 128.0, 126.9, 123.4, 122.4, 119.8, 111.2, 70.2, 62.2, 61.6, 49.1, 34.2, 14.5, 14.1 ppm. **HRMS (ESI):** Calcd for $C_{24}H_{25}ClN_4O_4$, $(M+1)^+$: 469.15643; Found: 469.16211.

Diisopropyl 1-(5-(2-(1H-benzo[d]imidazol-2-yl)-3-chlorophenyl)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 54

Following the general experimental procedure, the diazabicyclic olefin **15c** (50 mg, 0.19 mmol), 2-(2-chlorophenyl)-1H-benzo[*d*]imidazole **48** (43 mg, 0.19 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3 mg, 0.005 mmol) and $Cu(OAc)_2.H_2O$ (56 mg, 0.28 mmol) in 2 mL acetonitrile at 80 °C under argon atmosphere for 12 h gave the product **54** as a white powder (50 mg, 68%).

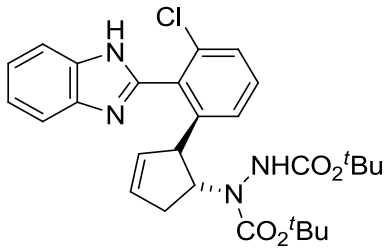


Mp: 176-178 °C **R_f :** 0.61 (5:5 hexane/EtOAc). **IR (neat) λ_{max}:** 3255, 3059, 2981, 2935, 1714, 1621, 1595, 1565, 1452, 1409, 1379, 1272, 1245, 1217, 1179, 1141, 1108, 1070, 1039, 963, 927, 861, 834,792, 743, 709, 669, 610, 557 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 10.32-10.11 (m, 1H), 9.25-9.21 (m, 1H), 8.06-7.84 (m, 1H), 7.42-7.26 (m, 6H), 5.77 (s, 1H), 5.38 (s, 1H), 4.92 (m, 2H), 4.72-4.53 (m, 1H), 4.03 (s, 1H), 2.59-2.44 (m, 2H), 1.35-0.78 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.6, 155.7, 148.2, 146.4, 142.7, 133.7, 132.5, 131.1, 130.4, 127.9, 127.0, 123.4, 122.3, 119.8, 111.2, 69.9, 69.1, 48.7, 35.2, 22.2, 22.0, 21.8, 21.0 ppm. **HRMS (ESI):** Calcd for $C_{26}H_{29}ClN_4O_4$, $(M+1)^+$: 497.18773; Found: 497.19522.

Di-tert-butyl 1-(5-(2-(1H-benzo[d]imidazol-2-yl)-3-chlorophenyl)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 55

Following the general experimental procedure, the diazabicyclic olefin **15d** (50 mg, 0.17 mmol), 2-(2-chlorophenyl)-1H-benzo[*d*]imidazole **48** (39 mg, 0.17 mmol), $[RuCl_2(p\text{-cymene})]_2$ (3 mg, 0.004 mmol) and $Cu(OAc)_2.H_2O$ (51 mg, 0.25 mmol) in 2 mL acetonitrile at 80 °C under argon atmosphere for 12 h gave the product **55** as a crystalline solid (55 mg, 40%).



Mp: 222-224 °C **R_f :** 0.61 (5:5 hexane/EtOAc). **IR (neat) λ_{max}:** 3355, 3062, 2957, 2918, 2850, 1714, 1620, 1591, 1570, 1457, 1398, 1368, 1340, 1275, 1249, 1221, 1156, 1047, 1027, 960, 852, 789, 742, 666, 611, 557 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 9.62-9.48 (m, 1H),8.74-8.72 (m, 1H), 7.94 (s, 1H), 7.49-7.28

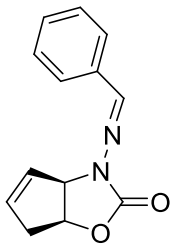
(m, 6H), 5.81 (s, 1H), 5.42 (s, 1H), 4.98 (s, 1H), 4.05 (s, 1H), 2.62-2.42 (m, 2H), 1.56-1.47 (m, 10H), 1.34-1.04 (m, 8H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 155.9, 155.2, 146.9, 143.8, 132.2, 131.6, 130.9, 130.8, 130.6, 127.5, 123.2, 82.4, 68.8, 45.5, 29.7, 29.6, 29.5 ppm. **HRMS (ESI):** Calcd for $C_{28}H_{33}ClN_4O_4$, $(M+1)^+$: 525.21903; Found: 525.22461.

2.12.3. General Experimental Procedure for DMSO Mediated Thermal Rearrangement of Diazabicyclic Olefins and Sequential Imine Formation

The diazabicyclic olefin (1.0 equiv.) and benzaldehyde (1.0 equi) were taken in a Schlenk tube. To this, 2 mL DMSO was added and the resulting mixture was refluxed at 110 °C for 12 h. Then the reaction was quenched with water and was extracted with ethylacetate. The solvent was removed *in vacuo*. On performing column chromatographic purification, the product was obtained.

3-(Benzylideneamino)-3,3a,6,6a-tetrahydro-2H-cyclopenta[d]oxazol-2-one 65da

Following the general experimental procedure, the diazabicyclic olefin **15d** (50 mg, 0.17 mmol) and benzaldehyde **66a** (18 mg, 0.17 mmol) were taken in a Schlenk tube. To this, 2 mL DMSO was added and the resulting mixture was refluxed at 110 °C for 12 h. Then the reaction was quenched with water and was extracted with ethylacetate. The solvent was removed *in vacuo*. On performing column chromatographic purification, the product was obtained as a white solid (34 mg) in 88 % yield.



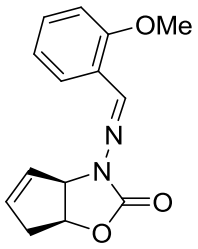
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.21 (s, 1H), 7.73 (dd, J_1= 10 Hz, J_2= 5Hz,1H), 7.4 (dd, J_1=5 Hz, J_2= 2Hz,1H), 6.13-6.12 (m, 1H), 5.98-5.96 (m, 1H), 5.57 (d, J= 10 Hz, 1H), 4.78-4.75 (m, 1H), 2.84-2,74(m,2H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 152.9., 145.9,

135.8, 134.1, 130.2, 128.7, 128.3, 127.4, 127.4, 82.3, 56.3, 37.5 ppm. **HRMS (ESI):** calcd for $C_{13}H1_2N_2NaO_2$ $(M+Na)^+$: 251.07965; found :251.07995.

3-(2-Methoxybenzylideneamino)-3,3a,6,6a-tetrahydro-2H-cyclopenta[d]oxazol-2-one 65db

Following the general experimental procedure, the diazabicyclic olefin **15d** (50 mg, 0.17 mmol) and benzaldehyde **66c** (23 mg, 0.17 mmol) were taken in a Schlenk tube. To this, 2

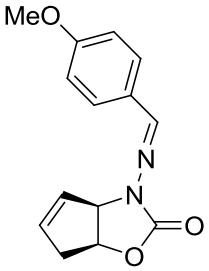
mL DMSO was added and the resulting mixture was refluxed at 110 °C for 12 h. Then the reaction was quenched with water and was extracted with ethylacetate. The solvent was removed *in vacuo*. On performing column chromatographic purification, the product was obtained as a white solid in 85 % (37 mg) yield.



^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.30 (s, 1H), 8.32 (d, *J*=7.5 Hz, 1H), 7.38-7.34 (m,1H), 7.03-6.97 (m, 1H), 6.90 (d, J= 8.5 Hz, 1H), 6.13-6.03 (M, 1h), 5.98-5.96 (M,1H), 5.58 (D, *J*=8Hz, 1H), 4.78 (t, *J*=7Hz, 1H), 3.87 (s, 3H), 2.91-2.70 (m, 2H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 157.9, 152.7, 140.2, 136.1, 131.2, 128.4, 126.4, 120.6, 114.6, 111.1, 82.2, 55.3, 37.4, 28.4 ppm. **HRMS (ESI):** calcd for $C_{14}H_{14}N_2NaO_3$ $(M+Na)^+$: 281.09021; found : 281.09037.

3-(4-Methoxybenzylideneamino)-3,3a,6,6a-tetrahydro-2H-cyclopenta[d]oxazol-2-one 65dc

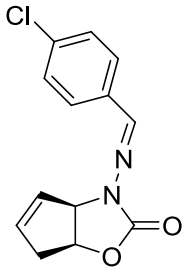
Following the general experimental procedure, the diazabicyclic olefin **15d** (50 mg, 0.17 mmol) and benzaldehyde **66c** (23 mg, 0.17 mmol) were taken in a Schlenk tube. To this, 2 mL DMSO was added and the resulting mixture was refluxed at 110 °C for 12 h. Then the reaction was quenched with water and was extracted with ethylacetate. The solvent was removed *in vacuo*. On performing column chromatographic purification, the product was obtained as a white solid in 90 % (39 mg) yield.



^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.06 (s,1H), 7.69 (d, *J*= 6Hz, 1H), 6.92 (d, J= 8.5 Hz, 1H), 6.12-6.10 (m, 1H), 5.97-5.96 (m, 1H), 5.57 (d, *J*= 8Hz, 1H), 4.75 (t, *J*= 6.5Hz, 1H), 3.84 (s, 3H), 2.86-2.68 (m, 2H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 161.4, 153.2, 145.4, 135.9, 130.6, 128.9, 128.3, 126.8, 114.1, 82.3, 56.0, 55.4, 37.5 ppm. **HRMS (ESI):** calcd for $C_{14}H_{14}N_2NaO_3$ $(M+Na)^+$: 281.09021; found : 281.09085.

3-(4-Chlorobenzylideneamino)-3,3a,6,6a-tetrahydro-2H-cyclopenta[d]oxazol-2-one 65dd

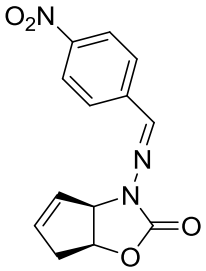
Following the general experimental procedure, the diazabicyclic olefin **15d** (50 mg, 0.17 mmol) and benzaldehyde **66e** (4 mg, 0.17 mmol) were taken in a Schlenk tube. To this, 2 mL DMSO was added and the resulting mixture was refluxed at 110 °C for 12 h. Then the reaction was quenched with water and was extracted with ethylacetate. The solvent was removed *in vacuo*. On performing column chromatographic purification, the product was obtained as a white solid in 93 % (41 mg) yield.



^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.13 (s, 1H), 7.68(d, *J*= 6 Hz, 1H), 7.38 (d, *J*= 8.5 Hz, 1H), 6.14-6.13 (m, 1H), 5.98-5.96 (m, 1H), 5.59 (d, J= 8 Hz, 1H), 4.76 (t, *J*= 6.5 Hz, 1H), 2.88-2.72 (m, 2H) ppm.**^{13}C NMR (125 MHz, $CDCl_3$):** δ 153.0, 144.1, 136.0, 134.2, 132.6, 129.0, 128.5, 128.2, 82.5, 56.1, 37.4 ppm. **HRMS (ESI):** calcd for $C_{13}H_{11}ClN_2NaO_2$ $(M+Na)^+$: 285.04067; found : 285.0400:

3-(4-Nitrobenzylideneamino)-3,3a,6,6a-tetrahydro-2H-cyclopenta[d]oxazol-2-one 65de

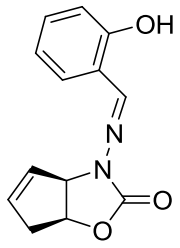
Following the general experimental procedure, the diazabicyclic olefin **15d** (50 mg, 0.17 mmol) and benzaldehyde **66f** (24 mg, 0.17 mmol) were taken in a Schlenk tube. To this, 2 mL DMSO was added and the resulting mixture was refluxed at 110 °C for 12 h. Then the reaction was quenched with water and was extracted with ethylacetate. The solvent was removed *in vacuo*. On performing column chromatographic purification, the product was obtained as a white solid in 80 % (37 mg) yield.



^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.34 (s, 1H), 8.26 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* =8.5 Hz, 2H), 6.16 (d, *J* = 6 Hz, 1H), 5.99 (d, *J* = 3.5 Hz, 1H), 5.63 (d, *J* = 7.5 Hz, 1H), 4.79 (t, *J* = 7Hz, 1H), 2.93-2.76 (m, 2H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 153.2, 145.1, 136.1, 134.0, 133.6, 130.2, 128.7, 128.4, 128.2, 127.5, 82.6, 55.75, 37.4 ppm. **HRMS (ESI):** calcd for $C_{13}H_{11}N_3NaO_4$ $(M+Na)^+$: 296.06473; found.: 296.06456

3-(2-Hydroxybenzylideneamino)-3,3a,6,6a-tetrahydro-2H-cyclopenta[d]oxazol-2-one 65df

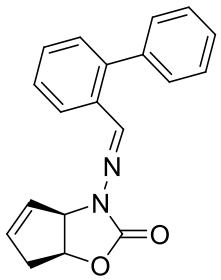
Following the general experimental procedure, the diazabicyclic olefin **15d** (50 mg, 0.17 mmol) and benzaldehyde **66g** (21 mg, 0.17 mmol) were taken in a Schlenk tube. To this, 2 mL DMSO was added and the resulting mixture was refluxed at 110 °C for 12 h. Then the reaction was quenched with water and was extracted with ethylacetate. The solvent was removed *in vacuo*. On performing column chromatographic purification, the product was obtained as a white solid in 81 % (33 mg) yield.



^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 10.34 (s, 1H), 8.33 (s, 1H), 7.33-7.29 (m, 1H), 7.24 (dd, J_1=7.5 Hz, J_2= 1.5 Hz, 1H), 6.16-6.14 (m, 1H), 5.99-5.97 (m, 1H), 5.63-5.61 (m, 1H), 2.89-2.73 (m, 2H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** 153.2, 145.1, 136.1, 134.0, 133.6, 130.2, 128.7, 128.4, 128.2, 127.5, 82.6, 55.75, 37.4 ppm. **HRMS (ESI):** calcd for $C_{13}H_{12}N_2NaO_3$ $(M+Na)^+$: 267.07456; found: 267.07409.

3-(Biphenyl-2-ylmethyleneamino)-3,3a,6,6a-tetrahydro-2H-cyclopenta[d]oxazol-2-one

Following the general experimental procedure, the diazabicyclic olefin **15d** (50 mg, 0.17 mmol) and benzaldehyde 66h (20 mg, 0.17 mmol) were taken in a Schlenk tube. To this, 2 mL DMSO was added and the resulting mixture was refluxed at 110 °C for 12 h. Then the reaction was quenched with water and was extracted with ethylacetate. The solvent was removed *in vacuo*. On performing column chromatographic purification, the product was obtained as a white solid in 84 % (34 mg) yield.

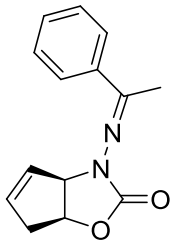


^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.12 (d, *J*= 7.5 Hz, 1H), 8.04 (S, 1H), 7.74 (dd, J_1=7.5 Hz, J_2=3.5 Hz, 2H), 7.61 (t, *J*= 7.5Hz, 1H)7.47 (t, *J*= 8Hz, 1H), 7.39-7.38 (3H), 6.12-6.11 (m, 1H), 5.96-5.94 (m, 1H), 5.57 (d, *J*= 8Hz, 1H), 4.76 (t, *J*=8 Hz, 1H), 2.89-2.69 (m, 2H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 153.3, 145.2, 136.1, 134.0, 133.7, 130.3, 130.2, 128.7, 128.5, 128.2, 127. 5, 82.6, 55.8, 37.4 ppm. **HRMS (ESI):** calcd for $C_{19}H_{16}N_2NaO_2$ $(M+Na)^+$: 327.11095; found: 327.11083.

3-(1-Phenylethylideneamino)-3,3a,6,6a-tetrahydro-2H-cyclopenta[d]oxazol-2-one 65dg

Following the general experimental procedure, the diazabicyclic olefin **15d** (50 mg, 0.17 mmol) and benzaldehyde **66h** (23 mg, 0.17 mmol) were taken in a Schlenk tube. To this, 2

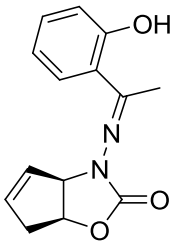
mL DMSO was added and the resulting mixture was refluxed at 110 °C for 12 h. Then the reaction was quenched with water and was extracted with ethylacetate. The solvent was removed *in vacuo*. On performing column chromatographic purification, the product was obtained as a white solid in 74 % (32 mg) yield.



^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.73 (d, *J*= 8 Hz, 1H), 7.20 (d, *J*= 7.5 Hz, 1H), 6.11-6.09 (m, 1H), 5.96-5.94 (m, 1H), 5.54 (d, *J*= 7.5 Hz, 1H), 4.79 (t, *J*= 7 Hz, 1H), 2.67-2.53 (m, 2H, 2.38 (s, 3H), 2.32 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 171.1, 152.6, 140.9, 135.4, 134.4, 129.1, 128.8, 127.1, 82.6, 61.17, 37.8, 21.4, 17.7 ppm. **HRMS (ESI):** calcd for $C_{15}H_{16}N_2NaO_2$ $(M+Na)^+$: 279.11095; found : 279.11108.

3-(1-(2-Hydroxyphenyl)ethylideneamino)-3,3a,6,6a-tetrahydro-2H-cyclopenta[d]oxazol-2-one 65dh

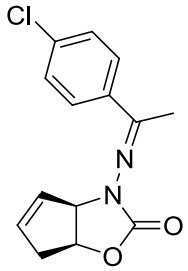
Following the general experimental procedure, the diazabicyclic olefin 15d (50 mg, 0.17 mmol) and **66i** (20 mg, 0.17 mmol) were taken in a Schlenk tube. To this, 2 mL DMSO was added and the resulting mixture was refluxed at 110 °C for 12 h. Then the reaction was quenched with water and was extracted with ethylacetate. The solvent was removed *in vacuo*. On performing column chromatographic purification, the product was obtained as a white solid in 84 % (34 mg) yield.



^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 12.38 (s, 1H), 7.58 (dd, J_1= 8 Hz, J_2= 1.5 Hz, 1H), 7.35 (t, *J*= 8.5 Hz, 1H), 6.99 (d, *J*= 6.5 Hz, 1H), 6.92 (t, *J*= 8.5 Hz, 1H), 6.15-6.13 (m, 1H), 5.99-5.98 (m, 1 H), 5.59 (d, *J*= 7.5 Hz, 1H), 4.77 (t, *J*= 6.5 Hz, 1H), 2.72 (m, 2H), 2.42 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 176.0, 175.3, 160.1, 153.0, 135.5, 133.2, 133.0, 129.7, 129.4, 129.1, 128.6, 123.0, 118.9, 118.9, 118.6, 118.1, 117.9, 82.9, 61.2, 37.5, 21.6, 17.0 ppm. **HRMS (ESI):** calcd for $C_{14}H_{14}N_2NaO_3$ $(M+Na)^+$: 281.09021; found: 281.08940.

3-(1-(4-Chlorophenyl)ethylideneamino)-3,3a,6,6a-tetrahydro-2H-cyclopenta[d]oxazol-2-one 65di

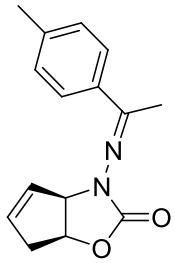
Following the general experimental procedure, the diazabicyclic olefin 15d (50 mg, 0.17 mmol) and benzaldehyde **66j** (26 mg, 0.17 mmol) were taken in a Schlenk tube. To this, 2 mL DMSO was added and the resulting mixture was refluxed at 110 °C for 12 h. Then the reaction was quenched with water and was extracted with ethylacetate. The solvent was removed *in vacuo*. On performing column chromatographic purification, the product was obtained as a white solid in 79 % (37 mg) yield.



^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.79 (d, *J*= 8.5 Hz, 1H), 7.37 (d, *J*=9 Hz, 1H), 6.12-6.11 (m, 1H), 5.97-5.95 (m, 1H), 5.55 (d, *J*= 7.5 Hz, 1H), 4.79 (t, *J*= 6.5 Hz, 1H), 2.69-2.53 (m, 2H), 2.32 (s, 1H) ppm.**^{13}C NMR (125 MHz, $CDCl_3$):** δ 169.9, 152.4, 136.8, 135.6, 128.7, 128.61, 128.5, 82.5, 60.7, 37.6, 17.3 ppm. **HRMS (ESI):** calcd for $C_{15}H_{16}N_2NaO_2$ $(M+Na)^+$: 279.11095; found : 279.11108.

3-(1-*p*-Tolylethylideneamino)-3,3a,6,6a-tetrahydro-2H-cyclopenta[d]oxazol-2-one 65dj

Following the general experimental procedure, the diazabicyclic olefin 15d (50 mg, 0.17 mmol) and benzaldehyde **66k** (23, 0.17 mmol) were taken in a Schlenk tube. To this, 2 mL DMSO was added and the resulting mixture was refluxed at 110 °C for 12 h. Then the reaction was quenched with water and was extracted with ethylacetate. The solvent was removed *in vacuo*. On performing column chromatographic purification, the product was obtained as a white solid in 81 % (35 mg) yield.



^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.73 (d, *J*= 8 Hz, 1H), 7.20 (d, *J*= 7.5 Hz, 1H), 6.11-6.09 (m, 1H), 5.96-5.94 (m, 1H), 5.54 (d, *J*= 7.5 Hz, 1H), 4.79 (t, *J*= 7 Hz, 1H), 2.67-2.53 (m, 2H, 2.38 (s, 3H), 2.32 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.1, 152.6, 140.9, 135.4, 134.4, 129.1, 128.8, 127.1, 82.6, 61.17, 37.8, 21.4, 17.7 ppm. **HRMS (ESI):** calcd for $C_{15}H_{16}N_2NaO_2$ $(M+Na)^+$: 279.11095; found : 279.11108.

2.13. References

1. (a) Fairlamb, I. S. *J. Annu. Reports Sect. "B" Organic Chem.* **2007**, *103*, 68. (b) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (c)

Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (d) Song, G.;Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, **41**, 3651; (e) Satoh, T.; Miura, M. *Chem. Eur. J.* **2010**, **16**,11212.

2. (a) Gutekunst, W. R., Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976. (b). Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 575. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.
3. Liu, F.; Glorius, F.; Wencel-delord, J. *Chem. Soc. Rev.* **2011**, 4740.
4. Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879.
5. Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119.
6. Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc*. **1963**, *85*, 1544.
7. Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani,N. *Nature* **1993**, *366*, 529.
8. Zhang, F.; Spring, D. R. *Chem. Soc. Rev.* **2014**, *43*, 6906.
9. Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350.
10. Ackermann, L.; Novak, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045.
11. (a)Li, B.; Devaraj, K.; Darcel, C.; Dixneuf, P. H. *Green Chem.* **2012**, *14*, 2706.
12. Hashimoto, Y.; Ueyama, T.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, .*Chem. Lett*. **2011**, *40*, 1165.
13. Arockiam, P. B.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *Green Chem.* **2011**, *13*, 3075.
14. Li, X.; Yu, S.; Wang, F.; Wan, B.; Yu, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 2577.
15. Reddy, M. C.; Jeganmohan, M. *Chem. Commun*. **2013**, *49*, 481.
16. Simon, M.-O.; Darses, S. *J. Org. Chem*. **2013**, *78*, 9981.
17. (a) Hu, D. X.; Grice, P.; Ley, S. V. *J. Org. Chem.* **2012**, *3*, 2. (b) Wang, J.-T.; Lin, T.-C.; Chen, Y.-H.; Lin, C.-H.; Fang, J.-M. *Med. chemcomm* **2013**, *4*, 783.
18. (a) Bournaud, C.; Chung, F.; Luna, A.; Pasco, M.; Errasti, G.; Lecourt, T.; Micouin, L. *Synthesis* **2009**, *2009* , 869. (b) Luna, A. P.; Cesario, M.; Bonin, M.; Micouin, L. *Org. Lett.* **2003**, *5*, 4771
19. Martins, A.; Lemouzy, S.; Lautens, M. *Org. Lett.* **2009**, *11* , 181.

Ruthenium/Silver Catalyzed Regioselective C-2/C-3 Activation of Indoles with Diazabicyclic Olefins: An Easy Access to Cyclopentenylated Indoles

3.1. Introduction

The prime goal of synthetic organic chemists is to develop easy and reliable methodologies for the construction of value added products. Heterocyclic cores are known for their biological relevance. They possess various levels of biological activities ranging from antifungal to anti-HIV (Figure 3.1). Among various heterocycles, nitrogen heterocycles are prestigious, among which indole family comes first.[1] It is present in a number of natural and unnatural biologically significant molecules.[2] This makes the synthesis and functionalization of this fused ring highly significant.

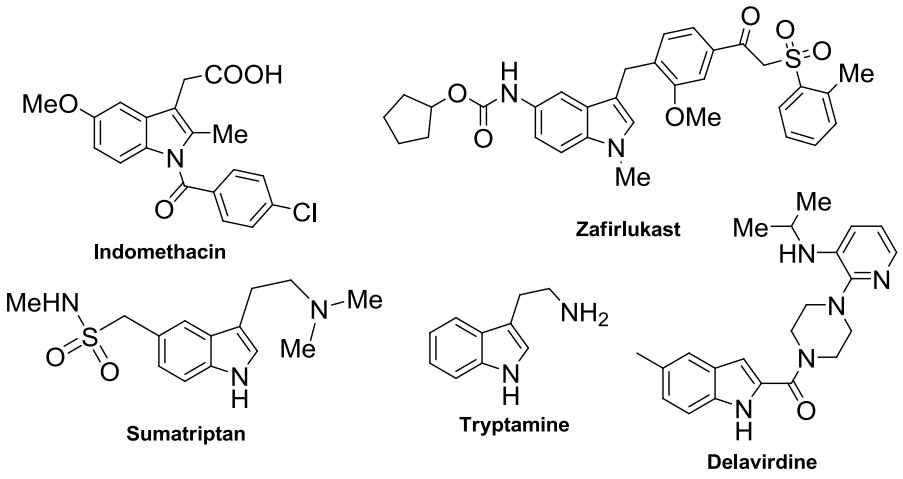


Figure 3.1. Important Indole Cores

Indole is the trivial name of benzo[b]pyrrole, which has revived the areas such as pharmaceuticals, fragrances, agrochemicals, pigments, and material science. Indole chemistry received particular interest in the mid-1950s, when the alkaloid reserpine was introduced as one of the first drugs for the treatment of diseases of the central nervous system (CNS) such as anxiety and mental disorders.[3] In the 1960s, highly efficient indolyl-based antitumor

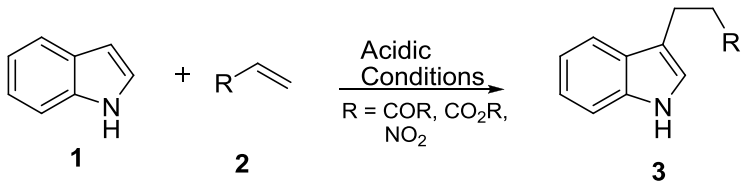
vincristine was discovered, and later the diverse physiological significance of indolyl alkaloids was expanded to anti-inflammatory, tranquilizing, and antihypertensive activities.[4]

3.2. Selective Functionalization of Indoles

Indole functionalization is an important area in synthetic organic chemistry since its discovery. As the functionalization of indole core concerns, regioselectivity is the first issue to be confronted. The indole ring tends to undergo metalation and subsequent C-C bond formation at the C-3 position, the activation of comparatively inert C-2 position is still a challenge. Like its influence in many other areas of synthetic organic chemistry, C-H bond activation strategy has revolutionized indole functionalizations by opening efficient methodologies for a variety of site-selective C-C bond formations. These C-H activation reactions were successful in functionalizing C-2, C-3, and C-7 positions of the indole nucleus with the aid of various transition metals such as palladium, rhodium, ruthenium, copper and iridium etc.[5] Directing group assisted, as well as non-directed methodologies were reported in this category wherein different catalysts decide the reactivity pattern.[6] Significant reactions describing the selective functionalization of indole are listed below.

3.2.1. C-3 Functionalization of Indoles

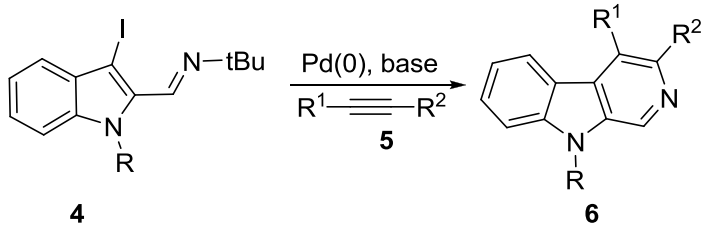
Being an electron rich aromatic ring, it shows attractive reactivity in electrophilic substitution reactions compared to benzene. The most reactive position of indole towards electrophilic substitution reaction is its C-3 carbon (Scheme 3.1). A plethora of indole derivatives for various medicinal purposes were synthesized by the conjugate addition of indoles to the electron deficient carbon-carbon double bonds.[7] The use of catalytic amount of either Brønsted or Lewis acids generally assists the Friedel–Crafts alkylation through activation of the Michael acceptor.[8] Among the numerous Michael acceptors, enals and enones have been overwhelmingly adopted for the functionalization of indoles.[9] However, nitro olefins have recently risen to prominence as a result of the synthetic versatility of the resulting nitroindolyl compounds in the synthesis of indole alkaloids.



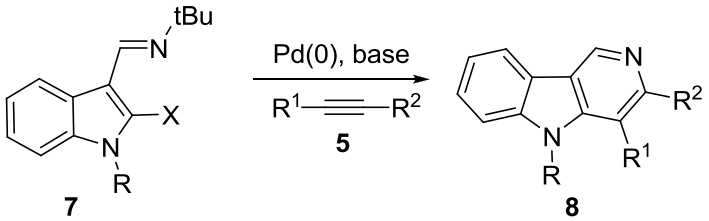
Scheme 3.1. Common Scheme for Michael Addition

3.2.2. Heck Type and Related Functionalizations

Larock *et al.* reported the annulation of variety of N-substituted 2-halo-1H-indole-3-carboxaldehydes/3-halo-1H-indole-2-carboxaldehydes by incorporating an alkyne-containing tether (Scheme 3.2A & 3.2B). The aldehyde was converted to the corresponding tert-butylimines, which have been subjected to palladium-catalyzed intramolecular iminoannulation, affording various-carboline derivatives with an additional ring fused across the 4- and 5-positions in good to excellent yields.[10]

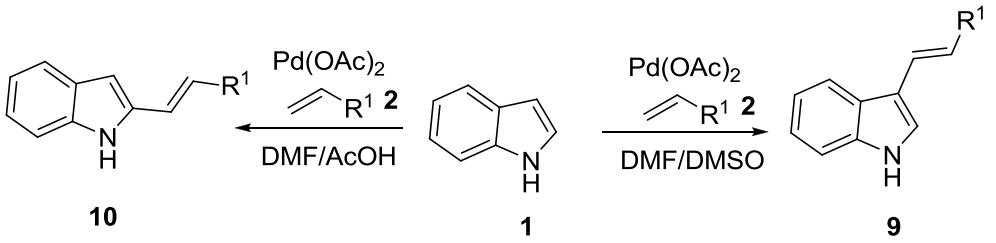


Scheme 3.2A



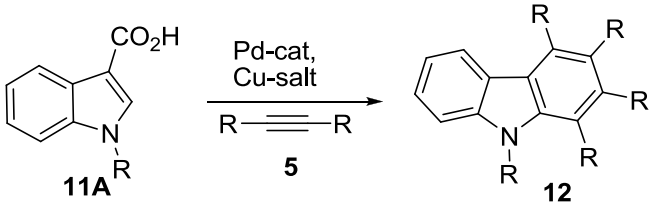
Scheme 3.2B

Gaunt and co-workers reported unexpected palladium catalyzed site selectivity between C-2 and C-3 position of indole (Scheme 3.3).[11] The nature of the solvent determined the regioselectivity of the reaction, so that the alkenylation can be directed to either the 2- or the 3- position of free (NH) indoles.

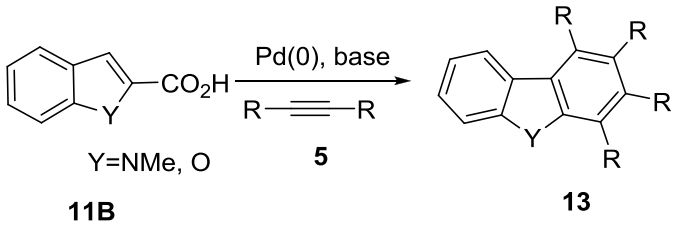


Scheme 3.3

Miura and Satoh reported, the palladium-catalyzed oxidative coupling of indole-3-carboxylic acids with alkynes leading to the corresponding 1,2,3,4-tetrasubstituted carbazoles (Scheme 3.4A and 3.4B).[12] Pyrrole, benzofuran, and furan carboxylic acids also underwent the decarboxylative coupling to afford highly substituted indole, dibenzofuran, and benzofuran derivatives, respectively.



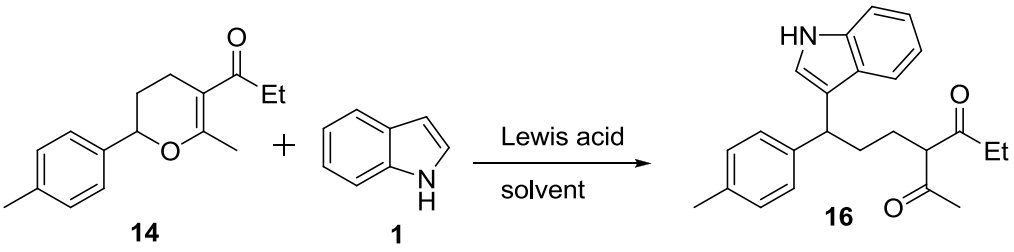
Scheme 3.4A



Scheme 3.4B

3.2.3. C-3 Functionalization *via* Ring Opening

Gu and coworkers reported ring-opening reactions of 2-aryl-3, 4-dihydropyrans with indoles.[12s] Indoles, 2-naphthol and 4-hydroxy-6-methyl-2-pyrone could be used to react with an appropriate dihydropyran to form the corresponding ring opened products (Scheme 3.5).

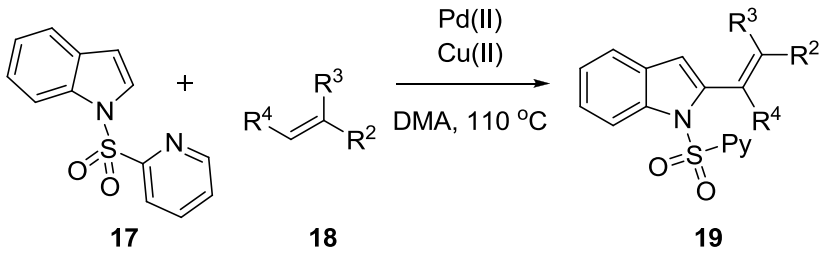


Scheme 3.5

3.2.4. C-2 Functionalization

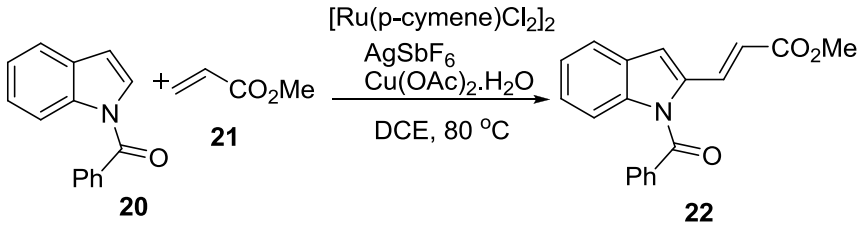
C-2 position is rather inactive compared to C-3. C-2 selectivity, can be achieved by introduction of a suitable coordinating group on the indole nitrogen facilitating the formation of metallacycle intermediate by the cleavage of the C-2 hydrogen bond. Various groups have developed different promising synthetic protocols for the C-2 selective functionalization of indoles.

One among the first report came in 2004, when Ricci *et al.* reported palladium catalyzed C-2 alkenylation of indoles with nitrogen containing 2-pyridylmethyl substituent (Scheme 3.6).[14] Followed by this revelation Arrayas, Carretero and others reported similar palladium catalyzed C-2 alkenylations by the use of indole nitrogen substituted with (2-pyridyl)sulfonyl group as a readily removable protecting group. C-2 alkenylations of pyrroles were also achieved.[15]



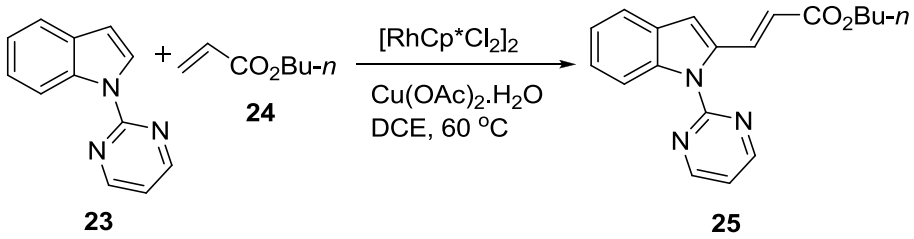
Scheme 3.6

In 2013, Prabhu and co-workers utilized benzoyl group as the directing group for ruthenium catalyzed C-2 olefination of indoles.[16] The benzoyl group had to be removed from the olefinated product in a subsequent step (Scheme 3.7).



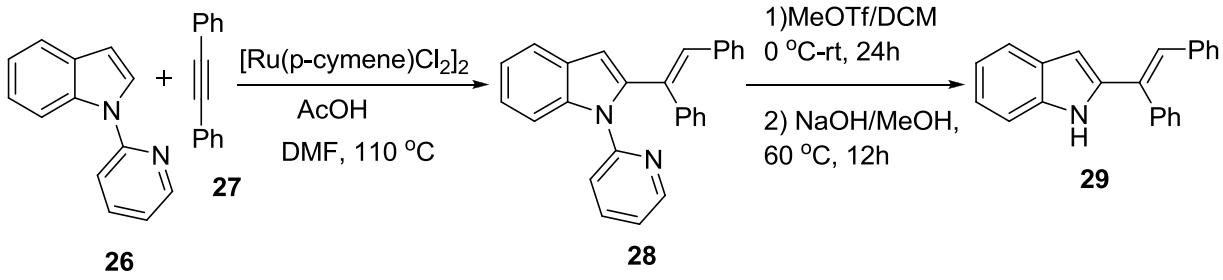
Scheme 3.7

Later on, different cleavable or traceless directing groups such as pyridyl, pyrimidyl, carboxamides etc. were employed for the successful C-2 functionalization. In line with this, Binwei Gong and others reported regioselective direct C-2 alkenylation of indoles assisted by the removable N-(2-pyrimidyl) group (Scheme 3.8).[17] They were successful in expanding the substrate scope to pyrroles also. Eventhough these strategies afforded good product yields, wide tolerance of various functional groups, and excellent regio-/site-specificities, an additional step is still required for the removal of the directing group.



Scheme 3.8

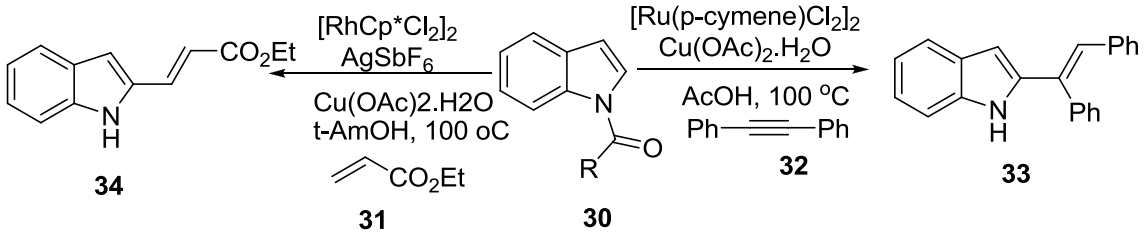
Later in 2014, Zeng *et al.* demonstrated ruthenium catalyzed C-2 alkenylation reactions of N-pyridyl indoles with alkynes (Scheme 3.9).



Scheme 3.9

They extended the strategy by deprotecting the pyridyl group of the alkenylation product under CH_3OTf/NaOH condition.[18]

Followed by this in 2014, Kim and Zeng independently reported rhodium and ruthenium catalyzed C-2 alkenylation reactions of indoles with traceless directing group (Scheme 3.10). [19] As discussed in chapter 2, traceless directing groups eventually get cleaved in the catalytic cycle. Rapid access to free (N−H) C-2 alkenylated indole derivatives makes this strategy more acceptable.



Scheme 3.10

3.3. Statement of the Problem

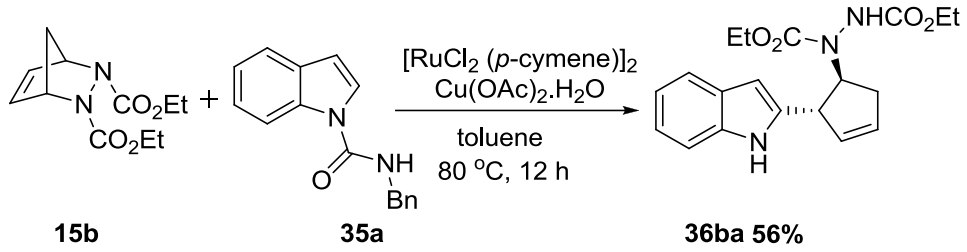
Our continued interest in the utilization of the strained olefins as synthons toward the construction of biologically relevant motifs prompted us to investigate their reactivity with heterocycles like indole. Based on the aforementioned C-H activation reports, the installation of suitable protecting groups on the -NH group of indole will lead to the formation the ruthenacycle incorporating the C-2 position of indole. We envisaged that the reaction of this ruthenacycle with azabicyclic olefins would facilitate ring opening *via* the strain release furnishing cyclopentenylated indoles. The results of these studies are presented in the following section.

3.4. Results and Discussion

3.4.1. Ruthenium Catalyzed C-2 Activation of Indoles with Bicyclic Olefins

We initiated our investigations with the reaction of bicyclic olefin **15b** and N-carboxamide indole **35a** in the presence of $[RuCl_2(p\text{-cymene})]_2$ (3 mol%) and $Cu(OAc)_2.H_2O$ (20 mol%) in toluene at 80 ^oC for 12 h (Scheme 3.11). To our delight, the reaction afforded

C-2 cyclopentenyl N-unprotected indole **36ba** in 56% yield. The carboxamide directing group preferably cleaved off at the end of the catalytic cycle.



15b **35a** **36ba 56%**

Scheme 3.11

The structure of the product was confirmed by various spectroscopic techniques like ^{1}H NMR, ^{13}C NMR and HRMS analyses.

In the ^{1}H NMR spectrum (Figure 3.2), the –NH of indole ring appeared as a broad singlet at δ 9.99 ppm. Similarly the –NH of hydrazine was found to resonate at δ 6.57 ppm as a broad singlet. The hydrogen attached to the C-3 carbon showed up as at δ 6.19 ppm as a sharp singlet. The two olefins of the cyclopentene ring appeared as two singlets at δ 5.94 and 5.88 ppm. The sp^3 C-H of the cyclopentene ring attached to the hydrazine group was found to be resonated as a broad singlet at δ 4.76 ppm. The other sp^3 C-H resonated as a multiplet between δ 4.33 and 3.99 along with the $–CH_2$ protons of the carboethoxy group. The methylene protons appeared as a broad singlet at δ 2.57 ppm.

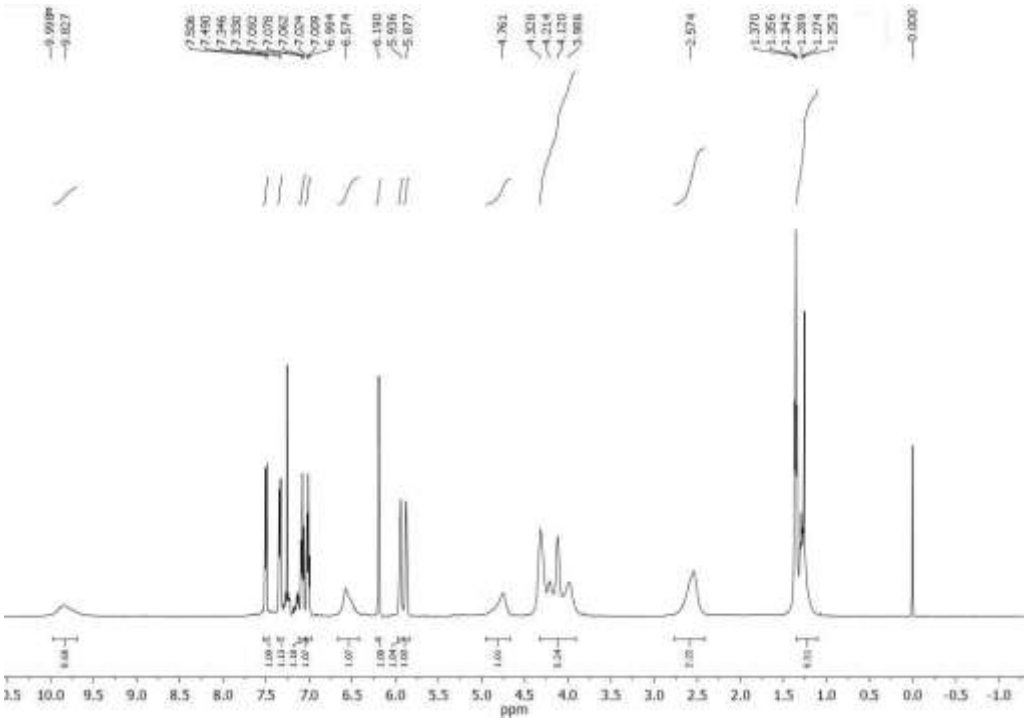


Figure 3.2. [1] H NMR spectrum of compound **36ba**

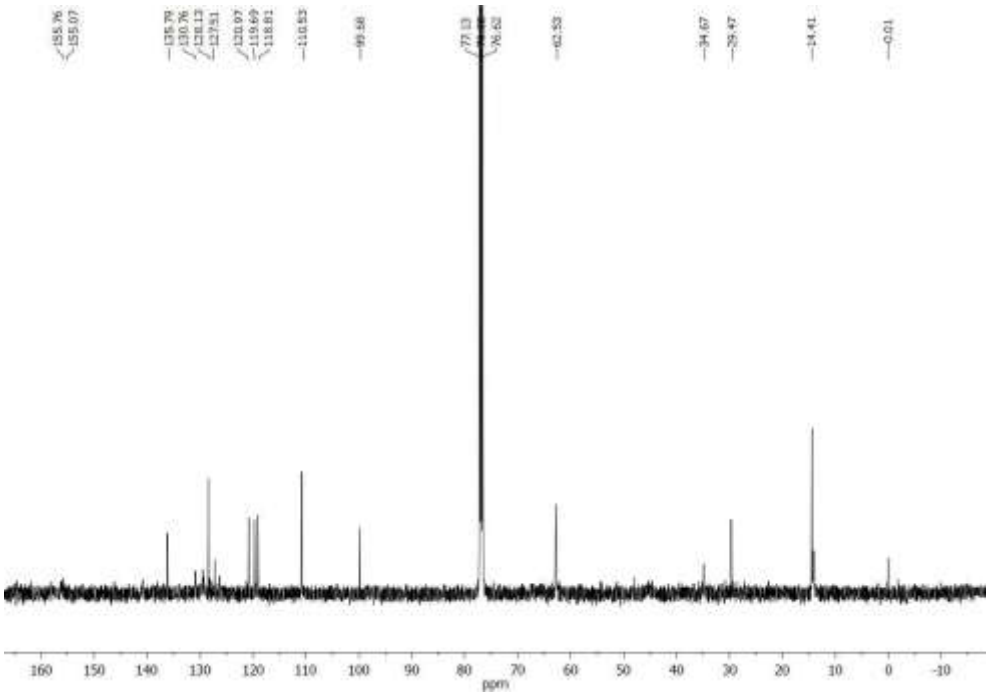


Figure 3.3. [13]C NMR spectrum of compound **36ba**

The two methyl groups of the ester moiety were seen as a multiplet from δ 1.37 to 1.25 ppm. In the ^{13}C NMR spectrum, the amide carbonyls were seen at δ 155.76 and 155.07 ppm. Aromatic carbons resonated between δ 135.8 to 110.6 ppm. The C-3 carbon was discernible at δ 99.7 ppm. The methylene carbons of the ester group were appeared at δ 62. 5 ppm. Also the methyl group was discernible at δ 14.41 ppm (Figure 3.3).

Further various protecting groups such as Boc, tosyl were tested for the directing ability, but none could furnish the expected product. Next, various reaction parameters were screened to explore the best condition for this reaction (Table 3.1). After the detailed optimization studies, a maximum yield of 80% was obtained using 3 mol% of $[RuCl_2(p\text{-cymene})]_2$ as the catalyst, 20 mol% of $Cu(OAc)_2.H_2O$ as the acetate source in toluene at 110 ^oC for 12 h.

Table 3.1. Optimization of Reaction Conditions

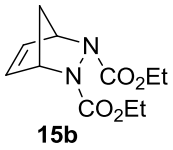
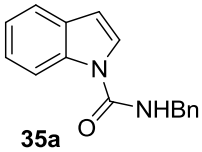
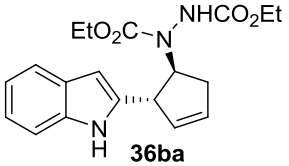
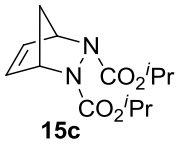
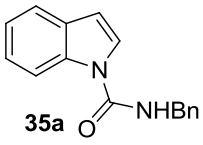
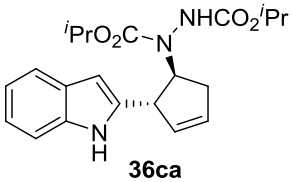
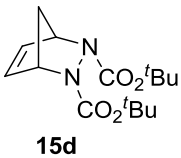
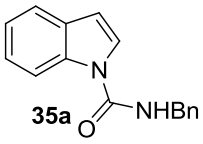
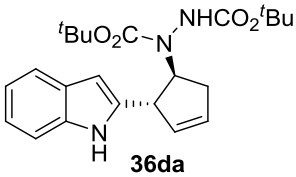
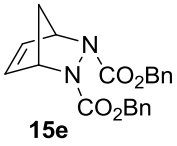
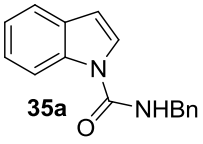
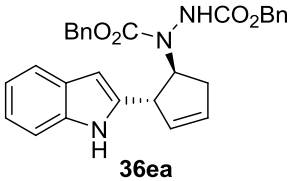
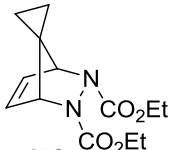
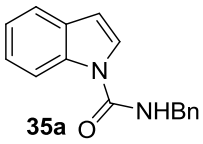
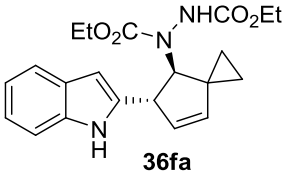
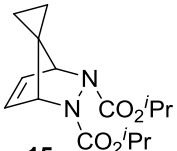
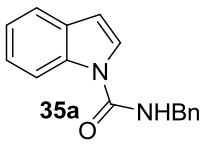
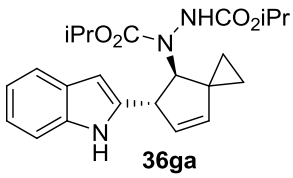
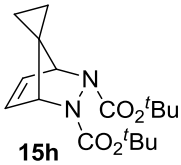
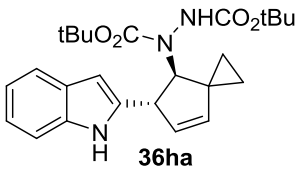
entry	catalyst	acetate source	solvent	temp (°C)	yield (%)
1	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	toluene	80	56
2	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	toluene	110	80
3	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	xylene	110	NR
4	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	dioxane	110	NR
5	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	DMF	110	NR
6	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2.H_2O$	t-amyl alcohol	110	NR
7	$[RuCl_2(p\text{-cymene})]_2$	AgOAc	toluene	110	20
8	$[RuCl_2(p\text{-cymene})]_2$	CsOAc	toluene	110	22
9	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	toluene	110	48
10	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	toluene	110	51

Reaction Conditions : 1a (1.5 equiv.), 2a (1 equiv.), catalyst (3 mol%), acetate source (20 mol%), solvent (2 mL), 110 oC, 12 h.

The yield of the reaction was found to be increasing dramatically when the reaction temperature was changed to 110 ^oC. Changing the catalyst system to $[RhCp^*Cl_2]_2$ furnished the product in 51% yield only. Toluene was chosen as the optimal solvent for the transformation, and the reaction was futile with other solvents like xylene, dioxane, DMF and

t-amyl alcohol. Among the different acetate sources tested, NaOAc provided a moderate yield of 48% (Table 3.1, entry 9).

Table 3.2. Reaction of diazabicyclic olefins with Indole

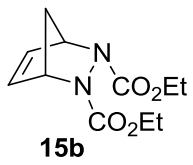
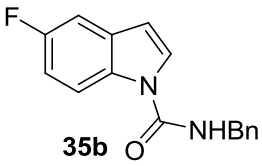
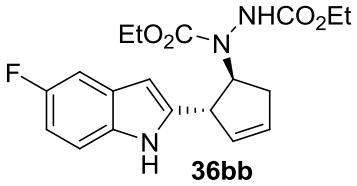
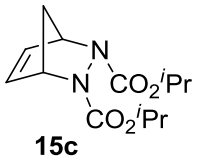
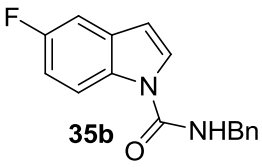
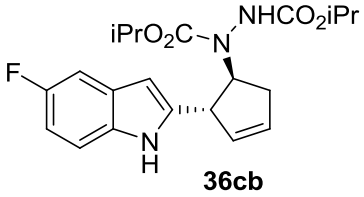
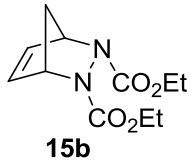
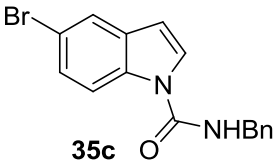
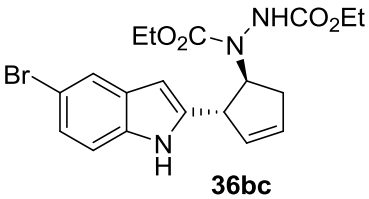
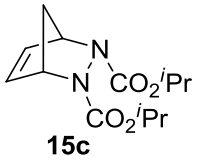
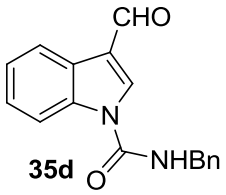
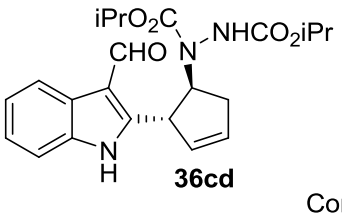
Entry	Diazabicyclic Olefin	Indole	Product	Yield
1.	 **15b**	 **35a**	 **36ba**	80%
2.	 **15c**	 **35a**	 **36ca**	65 %
3.	 **15d**	 **35a**	 **36da**	58 %
4.	 **15e**	 **35a**	 **36ea**	22%
5.	 **15f**	 **35a**	 **36fa**	34%
6.	 **15g**	 **35a**	 **36ga**	40 %
7.	 **15h**	 **35a**	 **36ha**	24 %

Reaction conditions: diazabicyclic olefin (1.5 equiv.), N-carboxamide indole (1 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (3 mol%), $Cu(OAc)_2.H_2O$ (20 mol%), toluene (2 mL), 110 °C, 12 h.

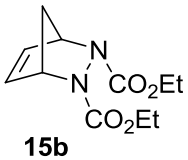
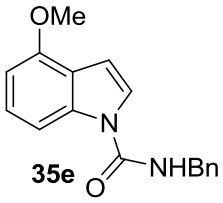
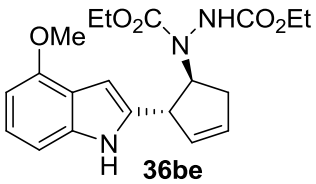
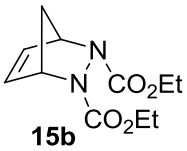
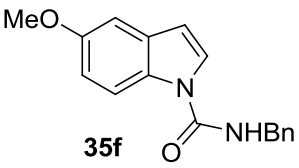
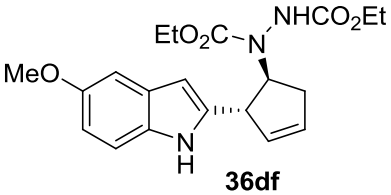
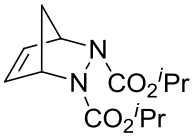
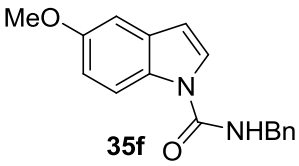
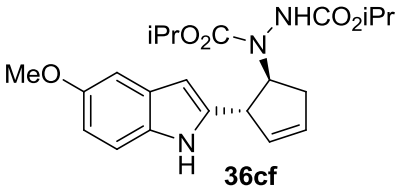
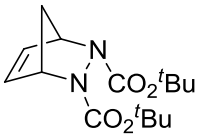
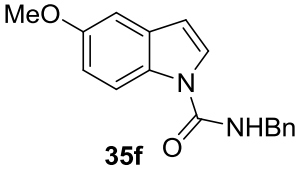
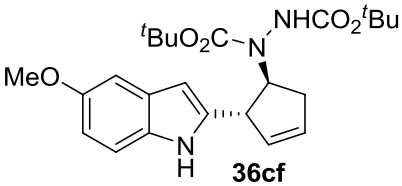
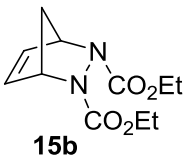
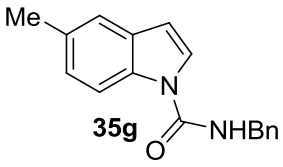
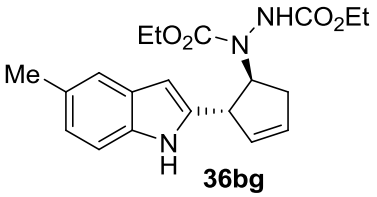
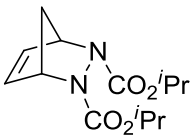
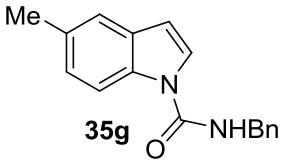
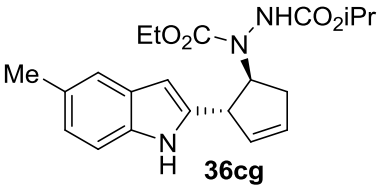
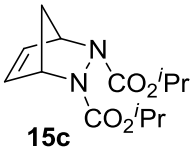
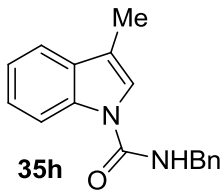
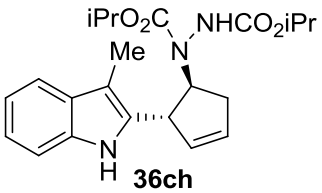
The scope of the reaction was tested with various diazabicyclic olefins 15b-e under the optimized reaction conditions. All of them underwent C-2 cyclopentenylation with the N-carboxamide protected indole in moderate to good yields. However, the reaction of various spirotricyclic olefins gave the C-2 cyclopentenylated indole in poor yields. The results are summarized in table 3.2.

We further decided to investigate the generality of the reaction with different substituted indoles. The studies showed that the electronic effect of various functional groups present on the indole ring had no remarkable effect on the outcome of the reaction. The results are summarized in the table 3.3. Similarly, the position of the respective functional groups on the indole nucleus also could not contribute much to the yield of the reaction. We were successful in analysing the generality with C-3, C-4, and C-5 substituted indoles.

Table 3.3. Reaction of diazabicyclic olefins with Substituted Indoles

Entry	Diazabicyclic Olefin	Indole	Product	Yield
1.	 **15b**	 **35b**	 **36bb**	74 %
2.	 **15c**	 **35b**	 **36cb**	70%
3.	 **15b**	 **35c**	 **36bc**	75 %
4.	 **15c**	 **35d**	 **36cd**	73%

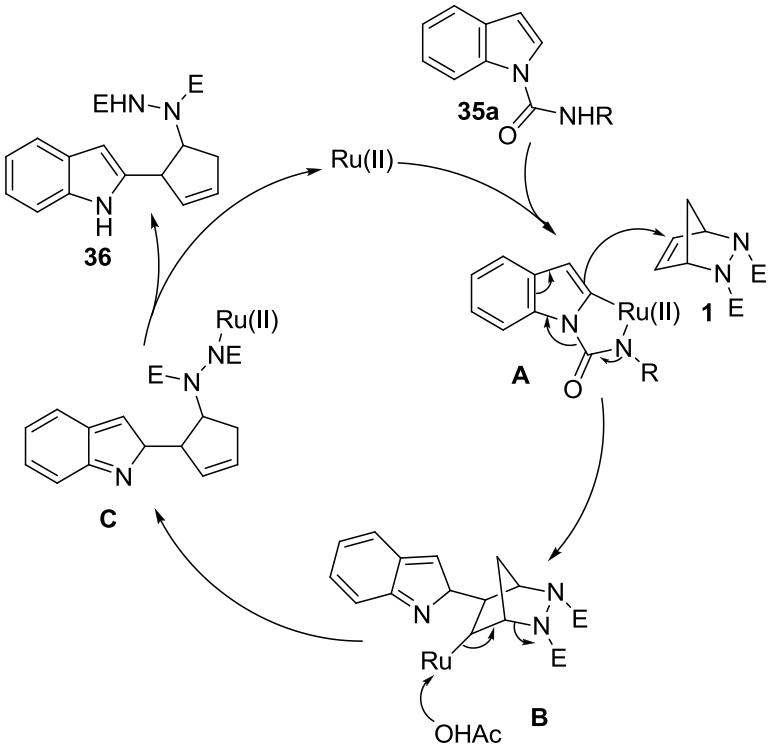
Continued

5.	 **15b**	 **35e**	 **36be**	66 %
6.	 **15b**	 **35f**	 **36df**	63 %
7.	 **15c**	 **35f**	 **36cf**	61%
8.	 **15d**	 **35f**	 **36cf**	60 %
9.	 **15b**	 **35g**	 **36bg**	71 %
10.	 **15c**	 **35g**	 **36cg**	73%
11.	 **15c**	 **35h**	 **36ch**	60%

Reaction conditions: diazabicyclic olefin (1.5 equiv.), N-carboxamide indole (1 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (3 mol%), $Cu(OAc)_2.H_2O$ (20 mol%), toluene (2 mL), 110 °C, 12 h.

3.5. Mechanism of Ru(II) Catalyzed C-2 Cyclopentenylation

Based on these results and previous C-H activation reports, we propose a plausible mechanism for the reaction as illustrated in Scheme 3. 12. The first step is the formation of a five-membered ruthenacycle **A** *via* the C-H bond cleavage and coordination of the active ruthenium species to the nitrogen atom of **35a**. C-N bond cleavage of the protecting group triggered the nucleophilic attack on the strained alkene **1**5 forming the intermediate **B**. In the next step, subsequent C-N bond cleavage of the bicyclic olefin along the endo-face *via* the addition of acetate ion to the ruthenium species results in the formation of **C**. Demetallation of intermediate **C** furnished the product **36**, and the active ruthenium species is regenerated for the next catalytic cycle.



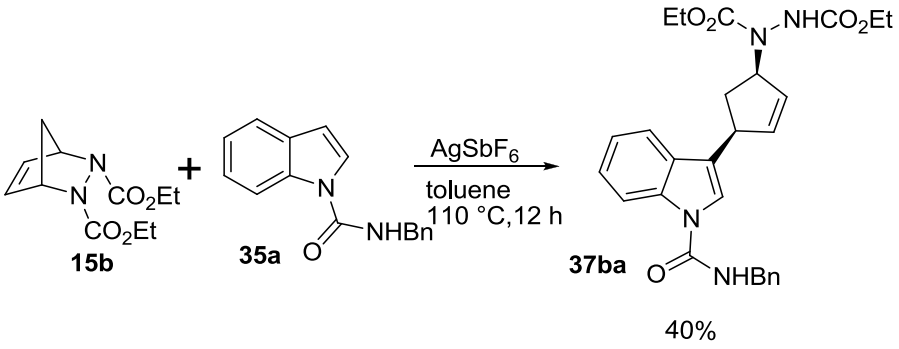
Scheme 3.12

3.6. Lewis Acid catalyzed C-3 Cyclopentenylation of Indoles with Diazabicyclic Olefins

The course of the reaction was found to be altered when $AgSbF_6$ was used as an additive one new product was formed instead of the C-2 functionalized product. And from the NMR

data, it was assigned as the C-3 cyclopentenylated product with the retainment of the protecting group.

We repeated the reaction only in the presence of 10 mol% of $AgSbF_6$ as a catalyst in toluene at 110 ^oC, the reaction gratifyingly resulted in the C-3 cyclopentenylated product in 40% yield (Scheme 3.13). The structure of the product formed was confirmed with various NMR techniques and the stereochemistry of the cyclopentene was assigned by comparing with literature reports.[20]



Scheme 3.13

In the ^1H NMR, the –NH proton of indole was found to be resonated as a doublet at δ 8.10 ppm. The aromatic protons appeared between δ 7.41 to 7.12 ppm. The two olefin protons of the cyclopentene ring appeared as two broad singlets at δ 6.31 and 6.14 ppm respectively. The sp^3 C-H attached to the hydrazine moiety appeared as a broad singlet at δ 5.49 ppm. The methylene group of the benzyl group appeared as a doublet at 4.64 ppm. The sp^3 C-H of the cyclopentene, attached to the indolyl ring resonated as a multiplet between δ 4.22 and 4.21 ppm along with the methylene group of the ester. The methylene group of the cyclopentene appeared as a multiplet between δ 2.46 to 2.12 ppm. The methyl groups of the carboethoxy group appeared as multiplet at δ 1.32 to 1.25 ppm (Figure 3.4).

In the ^{13}C NMR, the amide carbonyl resonated at δ 152.0 ppm. The methylene carbons of carboethoxy groups were found to appear along with the sp^3 carbon at δ 6.61 and 61.1 ppm. The methyl carbons of the ester group were found to resonate at δ 14.5 ppm.

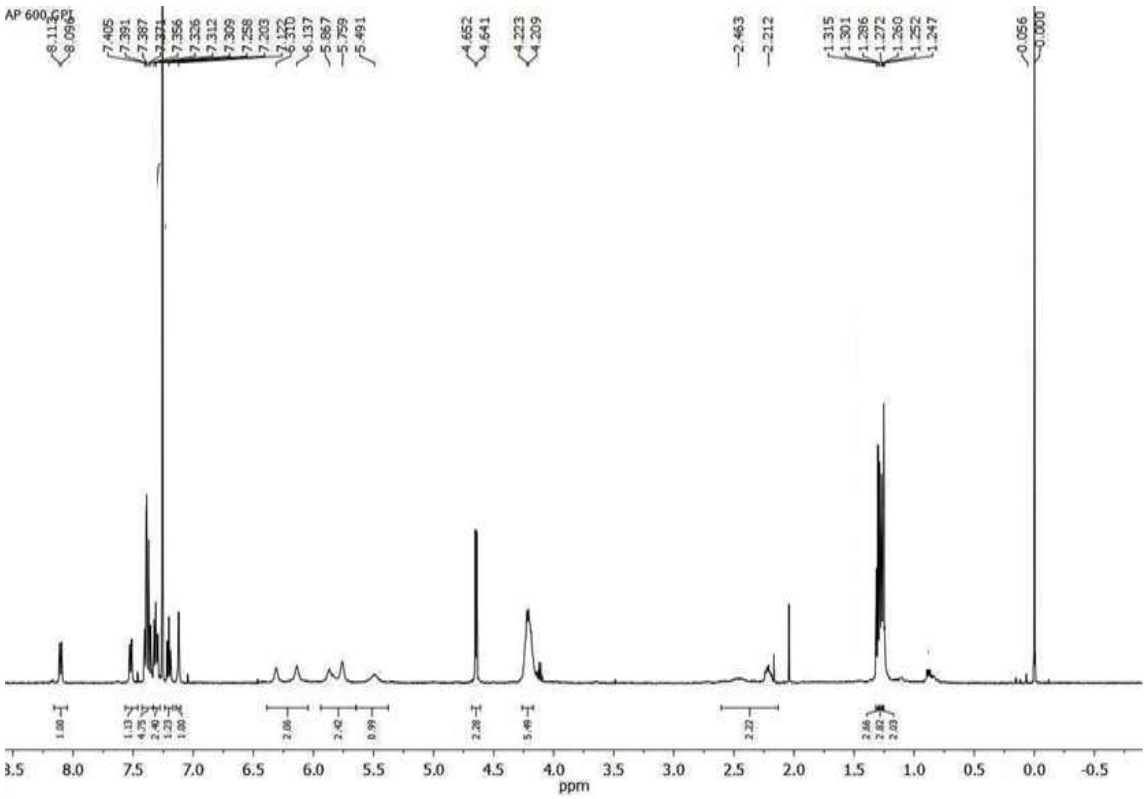


Figure 3.4. ^{1}H NMR spectrum of compound **37ba**

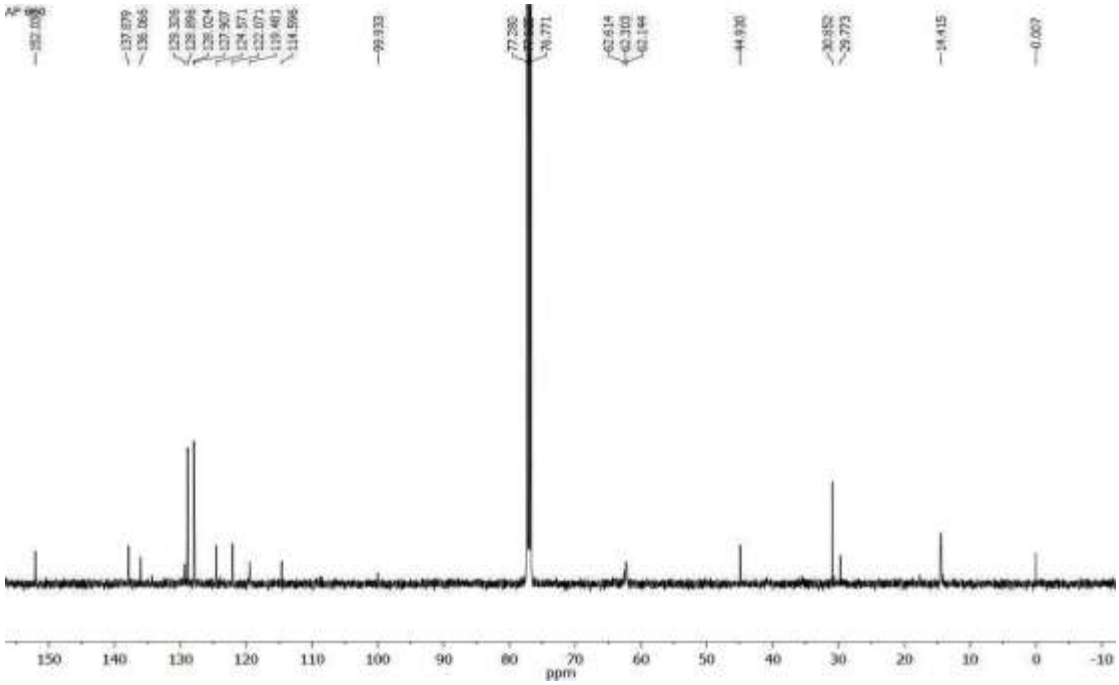
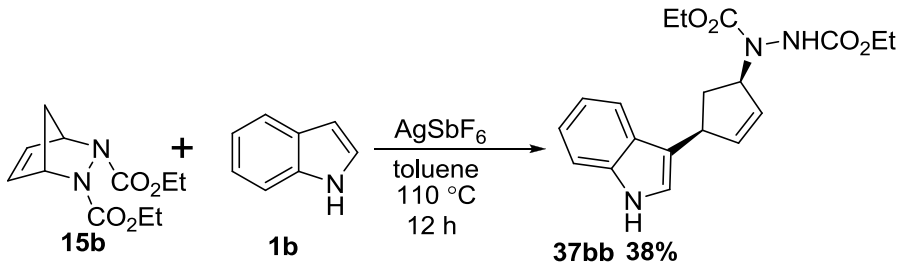


Figure 3.5. ^{13}C NMR spectrum of compound **37ba**

We next attempted the $AgSbF_6$ catalyzed cyclopentenylation of N- free indoles with diazabicyclic olefins in toluene at 110 ^oC. The reaction proceeded to give the expected product **37bb** in 38% yield as expected.



Scheme 3.14

The structure of the product was confirmed as similar to the previous case.

In the ^1H NMR spectrum (Figure 3.6), the –NH proton of indole was found to resonate as doublet at δ 8.02 ppm. The aromatic protons appeared between δ 7.59 to 7.09 ppm. The two olefin protons of the cyclopentene ring appeared as two broad singlets at δ 6.48 and 6.39 ppm respectively. The sp^3 C-H attached to the hydrazine moiety appeared as a broad singlet at δ 5.53 ppm. The methylene group of the benzyl group appeared as doublet at 4.64 ppm. The other sp^3 C-H of the cyclopentene ring resonated as multiplet between δ 4.30 and 3.94 ppm along with the methylene group of the ester. The methylene group of the cyclopentene appeared as multiplet between δ 2.85 to 2.27 ppm. The methyl groups of the carboethoxy group was appeared as a multiplet from δ 1.31 to 1.25 ppm.

In the ^{13}C NMR spectrum, the carbonyls of the hydrazine were found to resonate at δ 158.62 and 156.94 ppm. The C-3 carbon of indole appeared at δ 111.27 ppm. The sp^3 carbon of cyclopentenyl ring which is attached to the hydrazine moiety appeared at δ 62.44 ppm. Also the methylene groups of the carboethoxy group were found to resonate at δ 60.25 ppm. The other sp^3 carbon of cyclopentenyl ring resonated at δ 43.03 ppm. The methyl groups of the hydrazine moiety was found at δ 14.53 and 14.49 ppm(Figure 3.7).

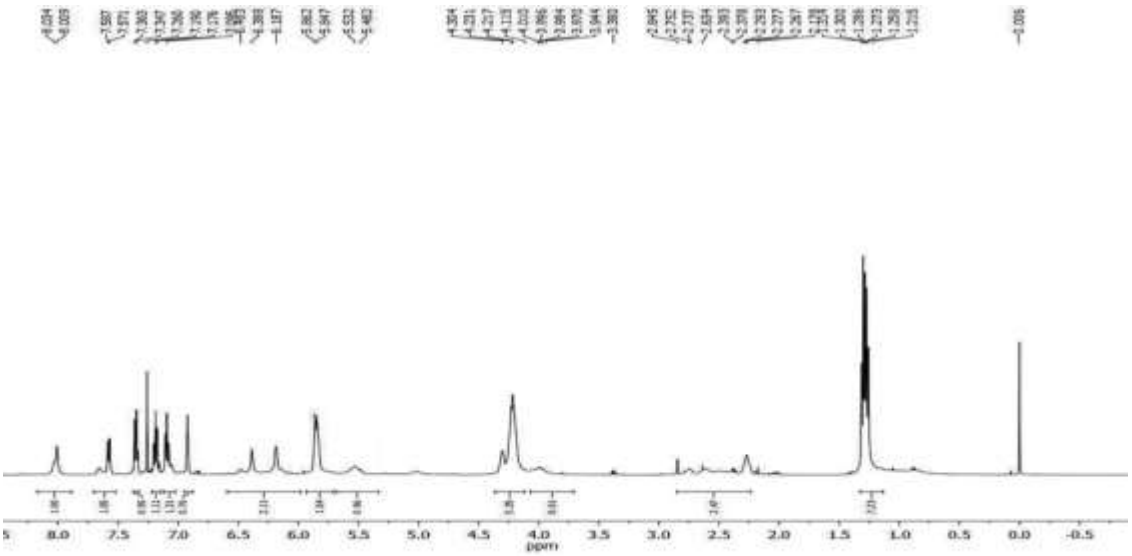


Figure 3.6 ^{1}H NMR spectrum of compound 37bb

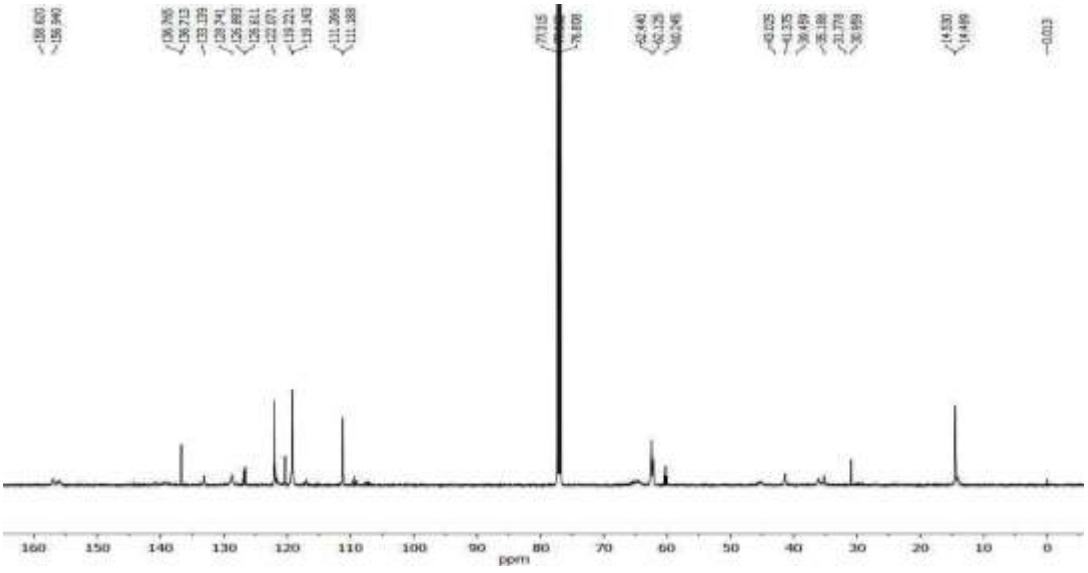
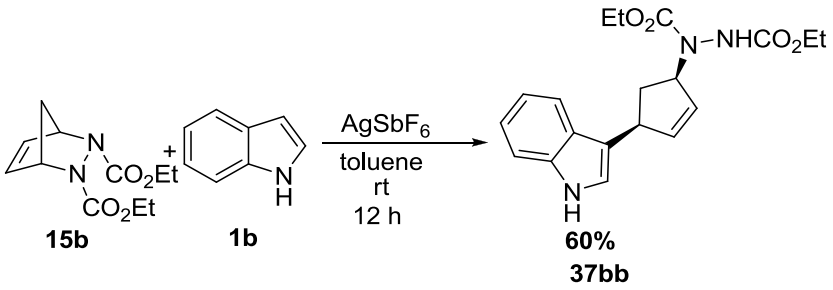


Figure 3.7 ^{13}C NMR spectrum of compound 37bb

The reaction conditions were screened to get the best catalytic condition for the reaction. When the temperature was reduced to room temperature, gratifyingly the yield of the product **37bb** was increased to 60%.



Scheme 3.15

We went on to explore different Lewis acids such as AgOTf, $Sc(OTf)_3$, $Cu(OTf)_2$. None of them provided better yield as $AgSbF_6$. $AlCl_3$ was also found to be futile for the reaction.

Table 3.4. Optimization Studies

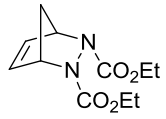
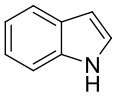
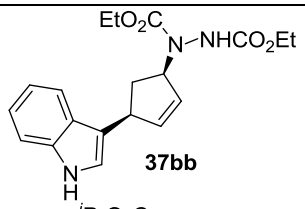
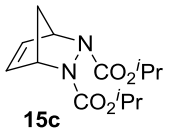
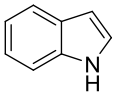
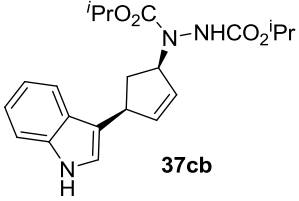
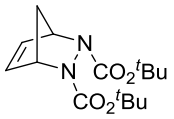
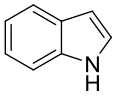
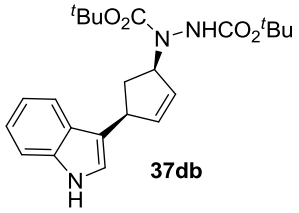
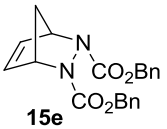
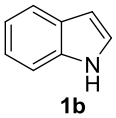
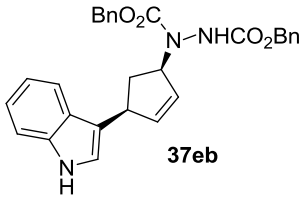
entry	catalyst	solvent	temp (°C)	yield (%)
1	$AgSbF_6$	toluene	rt	**62**
2	AgOTf	toluene	rt	20
3	$Sc(OTf)_3$	toluene	rt	30
4	$Cu(OTf)_2$	toluene	rt	40
5	$AlCl_3$	toluene	rt	34
6	$AgSbF_6$	DCE	rt	trace
7	$AgSbF_6$	ACN	rt	28
8	$AgSbF_6$	DMF	rt	trace
9	$AgSbF_6$	toluene	60	50

Reaction Conditions : 1a (1.5 equiv.), 2a (1 equiv.), $AgSbF_6$ (5 mol%) solvent (2 mL), 12 h.

Afterwards, we attempted the reaction in different solvents such as, acetonitrile, dimethyl formamide, dichloroethane etc. But none of them were superior to toluene. Thus, $AgSbF_6$ in toluene at room temperature was found to be best condition for this reaction (entry 1, table 3.4), was taken as the best reaction condition.

The scope of the reaction was examined with respect to different diazabicyclic olefins as well as substituted indoles. Table 3.5 summarizes the generality of different diazabicyclic olefins **15b to 15e** with simple indole. It follows the trend of decrease in yield with increase in the bulkiness of the alkoxy group. All four of them provided moderate to good yield.

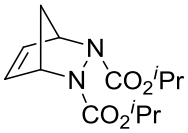
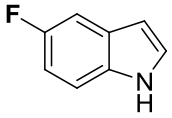
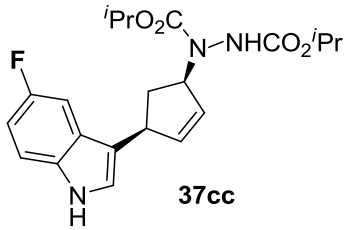
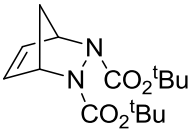
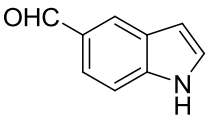
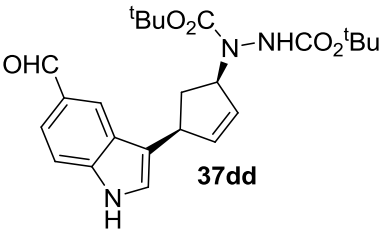
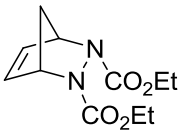
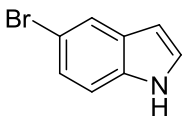
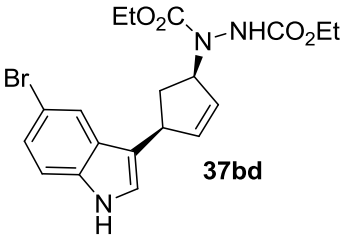
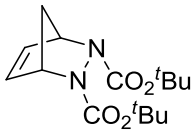
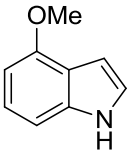
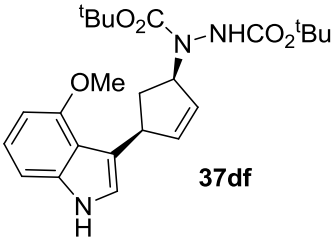
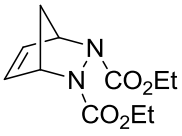
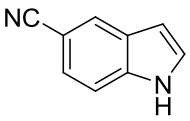
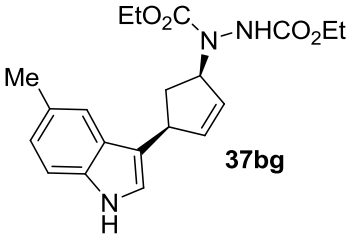
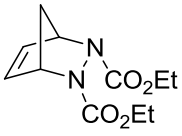
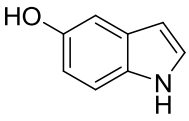
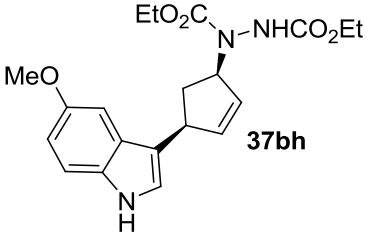
Table 3.5. $AgSbF_6$ catalyzed reaction of diazabicyclic olefins with indoles

Entry	Diazabicyclic Olefin	Indole	Product	Yield
1.	 **15b**	 **1b**	 **37bb**	62%
2.	 **15c**	 **1b**	 **37cb**	60 %
3.	 **15d**	 **1b**	 **37db**	55 %
4.	 **15e**	 **1b**	 **37eb**	47%

Reaction Conditions : 1a (1.5 equiv.), 2a (1 equiv.), $AgSbF_6$ (5 mol%) toluene (2 mL), 12 h.

The scope of different indoles was tested. Comparing C-4 and C-5 substituted indoles, C-4 substitution reduced the yield compared to the C-5 substitution. Electron donating groups on the indole ring gave slightly higher yield. Likewise, indole with electron withdrawing group as –CHO, gave the least yield in the series. Whereas, the indole substituents such as –CN, -OH gave no reaction. The results are summarized in table 3.6.

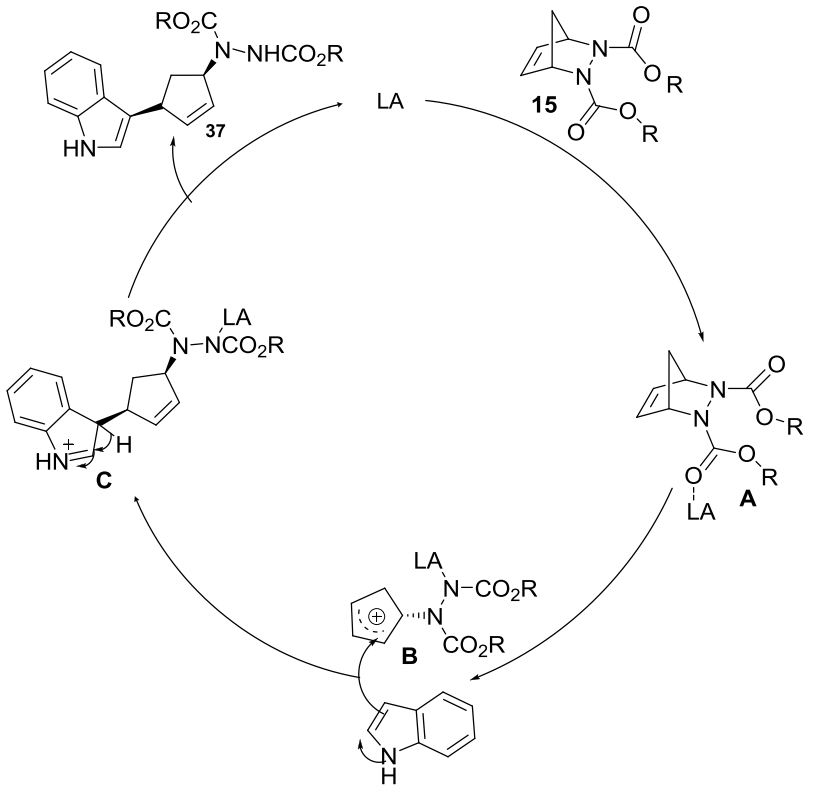
Table 3.6. $Agsbf_6$ Catalyzed Reaction of Diazabicyclic Olefins with Indoles

Entry	Diazabicyclic Olefin	Indole	Product	Yield
1.	 **15c**	 **1c**	 **37cc**	57 %
2.	 **15d**	 **1d**	 **37dd**	43 %
3.	 **15b**	 **1d**	 **37bd**	53 %
4.	 **15d**	 **1f**	 **37df**	44 %
5.	 **15b**	 **1g**	 **37bg**	0 %
6.	 **15b**	 **1h**	 **37bh**	0 %

Reaction Conditions : 1a (1.5 equiv.), 2a (1 equiv.), $AgSbF_6$ (5 mol%) toluene (2 mL), 12 h.

3.7. Mechanism of $AgSbF_6$ Catalyzed C-2 Cyclopentenylation

The mechanism of the reaction is postulated on the basis of previous reports. Thus it is evident that the reaction is not following the concerted metallation deprotonation pathway (CMD). The catalytic cycle is initiated by coordination of the Lewis acid with the carbonyl oxygen of the ester group of diazabicyclic olefin **15.** Subsequently, C–N bond is cleaved leading to the generation of a allylic cation species **B**. The intrinsic nucleophilic nature of C-3 position of indole will trigger the attack on the allylic cation resulting in species **C**. It will regain aromaticity to get the final product **37**.



Scheme 3.16

3.8. Conclusion

We have developed a ruthenium (II) catalyzed stereoselective C-N bond cleavage of diazabicyclic olefins through C-H bond activation of suitably protected indoles. Regioselective C-2 functionalization of indoles has been achieved. The protecting group acts as a traceless directing group, which cleaves away from the substrate at the end of the

catalytic cycle. Also, the presence of $AgSbF_6$ in the medium rendered a C-3 functionalized product *via* C-N bond cleavage of diazabicyclic olefin.

3.9. Experimental Section

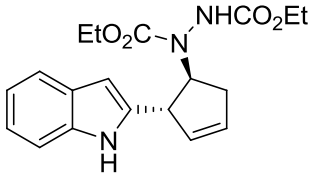
3.9.1. General information about the experiments is given in section Chapter 2.

3.9.2. General Experimental Procedure for the Ruthenium catalyzed regiospecific C-2 cyclopentenylation of suitably protected indoles with bicyclic hydrazines:-

A mixture of diazabicyclic olefin (1.5 equiv.), indole (1.0 equiv.), $[RuCl_2p$- cymene$]_2$ (3 mol%) and $Cu(OAc)_2.H_2O$ (20 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 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded cyclopentene substituted indoles.

Diethyl-1-(2-(1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36ba

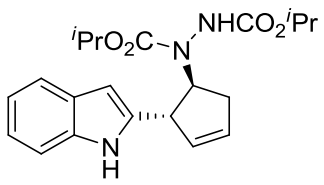
Following the general procedure, diazabicyclic olefin (50 mg, 0.21 mmol), indole (35 mg, 0.14 mmol), $[RuCl_2p$- cymene$]_2$ (3 mg, 0.0049 mmol) and $Cu(OAc)_2.H_2O$ (6 mg, 0.0300 mmol) were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 80% (40 mg) yield.



Yield: 80% as colourless viscous liquid. **R_f :** 0.85 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3289, 2919, 1716, 1606, 1532, 1419, 1262, 1172, 1096, 1061, 758 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 9.99 (brs, 1 H), 7.49 (d, *J* = 8 Hz, 1 H), 7.34 (d, *J* = 8 Hz, 1 H), 7.08 (t, *J* = 7 Hz, 1 H), 7.01 (t, *J* = 7.5 Hz, 1 H), 6.57 (brs, 1 H), 6.19 (s, 1 H), 5.94 (s, 1 H), 5.88 (s, 1 H), 4.76 (brs, 1 H), 4.33-3.99 (m, 5 H), 2.57 (brs, 2 H), 1.37-1.25 (m, 4 H), 0.89-0.85 (m, 2 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 155.7, 138.8, 130.8, 128.1, 127.5, 120.9, 119.7, 118.8, 110.5, 99.7, 62.5, 34.7, 29.5, 14.4. **HRMS (ESI):** *m/z* calcd for $C_{19}H_{23}N_3O_4Na$: 380.15863; Found: 380.15851.

Diisopropyl-1-(2-(1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36ca

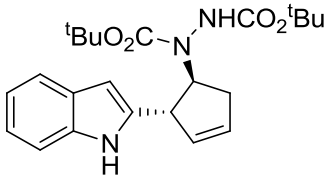
Following the general procedure, diazabicyclic olefin (50 mg, 0.1865 mmol), indole (31 mg, 0.1243 mmol), $[RuCl_2p$- cymene$]_2$ (2 mg, 0.0032 mmol.) and $Cu(OAc)_2.H_2O$ (5 mg, 0.0250 mmol.) were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 65% (31 mg) yield.



Yield: 65% as yellow viscous liquid. $\mathbf{R_f}$ **:** 0.67 (7:3 hexane/ethyl acetate). **IR (neat)** $\mathbf{\nu_{max}}$**:** 3308, 2982, 2935, 1696, 1518, 1459, 1381, 1255, 1106, 953, 746 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 10.29 (brs, 1 H), 8.63-8.34 (m, 1 H), 7.46 (d, *J* = 12 Hz, 1 H) 7.31 (d, *J* = 12 Hz, 1 H), 7.02 (t, *J* = 7.5 Hz, 1 H), 6.95 (t, *J* = 7.5 Hz, 1 H), 6.21 (brs, 1 H), 5.90 (brs, 2 H), 5.03-4.79 (m, 3 H), 4.16 (brs, 1 H), 2. 60 (brs, 2 H), 1.29-1.22 (m, 12 H). **^{13}C NMR (125 MHz, Acetone-d_6):** δ 158.7, 156.3, 129.1, 121.32, 119.9, 119.4, 111.3, 101.1, 96.9, 70.2, 69.9, 58.7, 48.0, 35.7, 21.7. **HRMS (ESI):** *m/z* calcd for $C_{21}H_{27}N_3O_4Na$: 408.18993; Found: 408.18767.

Di-tert-butyl-1-(2-(1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36da

Following the general procedure, diazabicyclic olefin (50 mg, 0.1689 mmol), indole (28 mg, 0.1126 mmol), $[RuCl_2p$- cymene$]_2$ (2 mg, 0.0032 mmol.) and $Cu(OAc)_2.H_2O$ (5 mg, 0.0250 mmol.) 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 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 58% (27) mg yield.

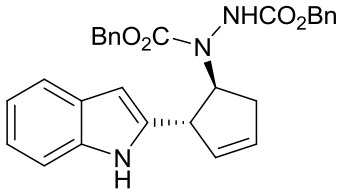


Yield: 58% as colourless liquid. $\mathbf{R_f}$ **:** 0.78 (7:3 hexane/ethyl acetate). **IR (neat)** $\mathbf{\nu_{max}}$**:** 3386, 2984, 1701. 1586, 1212, 1113, 1109, 1016 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 10.26-9.88 (m, 1

H), 8.36-8.12 (m, 1 H), 7.32 (d, *J* = 8 Hz, 1 H), 7.16 (brs, 1 H), 6.89 (t, *J* = 7 Hz, 1 H), 6.81 (t, *J* = 7 Hz, 1 H), 6.06 (brs, 1 H), 5.81-5.77 (m, 2 H), 4.76-4.63 (m, 1 H), 4.11-3.97 (m, 1 H), 2.49-2.42 (m, 2 H), 1.39-1.16 (m, 18 H). **^{13}C NMR (125 MHz, Acetone-d_6):** δ 158.1, 155.2, 143.2, 137.2, 131.6, 129.8, 128.9, 120.2, 119.4, 114.4, 100.9, 97.3, 81.4, 65.2, 46.1, 35.4, 28.3. **HRMS (ESI):** *m/z* calcd for $C_{23}H_{31}N_3O_4Na$: 436.22123; Found: 436.21901.

Dibenzyl-1-(2-(1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36ea

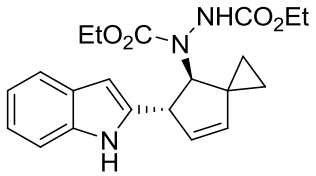
Following the general procedure, diazabicyclic olefin (50 mg, 0.1533 mmol), indole (26 mg, 0.1022 mmol.), [$RuCl_2$*p*- cymene]$_2$ (2 mg, 0.0032 mmol.) and $Cu(OAc)_2.H_2O$ (5 mg, 0.0250 mmol) were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 22% (11 mg) yield.



Yield: 22% as yellow viscous liquid. **R_f :** 0.50 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3298, 3034, 2950, 1709, 1499, 1454, 1386, 1217, 1171, 1108, 1022, 916, 740, 698 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 10.22-9.99 (m, 1 H), 8.98-8.81 (m, 1 H), 7.47-7.31 (m, 12 H), 7.05-6.98 (m, 2 H), 6.24 (s, 1 H), 5.89 (s, 2 H), 5.30-4.97 (m, 5 H), 4.24 (s, 1 H), 2.66 (brs, 2 H). **^{13}C NMR (125 MHz, Acetone-d_6):** δ 156.1, 136.9, 129.3, 128.5, 121.3, 120.2, 119.4, 115.5, 100.9, 97.6, 68.2, 68.1, 48.9, 35.4. **HRMS (ESI):** *m/z* calcd for $C_{29}H_{27}N_3O_4Na$: 504.18993; Found: 504.18736.

Diisopropyl-1-(5-isopropyl-9-oxo-2,3,3a,9-tetrahydrocyclopenta[b]chromen-2-yl)hydrazine-1,2-dicarboxylate 36fa

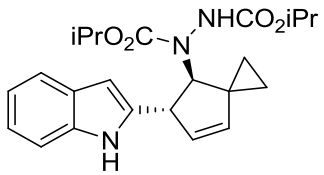
Following the general procedure, diazabicyclic olefin (50 mg, 0.1875 mmol.), indole (31 mg, 0.1249 mmol.), [$RuCl_2$*p*- cymene]$_2$ (2 mg, 0.0032 mmol) and $Cu(OAc)_2.H_2O$ (5 mg, 0.0250 mmol) were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 34% (16 mg) yield.



Yield: 34% as colourless viscous liquid. **R_f :** 0.55 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3317, 2981, 2923, 1700, 1612, 1414, 1297, 1244, 1061, 967 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 10.04-9.96 (m, 1 H), 8.43-8.29 (m,1 H), 7.33 (d, *J* = 7 Hz, 1 H), 7.21 (d, *J* = 8 Hz, 1 H), 6.89 (t, *J* = 7 Hz, 1 H), 6.83-6.81 (m, 1 H), 6.10 (brs, 1 H), 5.71 (d, *J* = 5 Hz, 1 H), 5.37 (d, *J* = 8 Hz, 1 H), 4.74 (brs, 1 H), 4.32 (brs, 1 H), 4.09-3.94 (m,4 H), 1.15-.94 (m, 6 H), .74-.55 (m,4 H). **^{13}C NMR (125 MHz, Acetone–d_6):** δ 158.1, 156.0, 138.7, 137.7, 129.9, 121.5, 120.7, 119.9, 100.9, 62.4, 60.6, 44.9, 14.9, 10.5. **HRMS (ESI):** *m/z* calcd for $C_{21}H_{25}N_3O_4Na$: 406.17428; Found: 406.17515

Diethyl-1-(2-(1-(benzylcarbamoyl)-1H-indol-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36ga

Following the general procedure, diazabicyclic olefin (50 mg, .1699 mmol), indole (28 mg, 0.1133 mmol), $[RuCl_2p$- cymene$]_2$ (2 mg, 0.0032 mmol) and $Cu(OAc)_2.H_2O$ (5 mg, 0.0250 mmol) 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 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 40% (18 mg) yield.

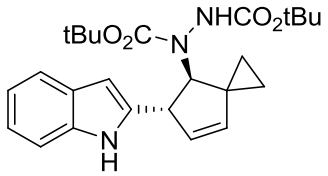


Yield: 40% as colourless viscous liquid. **R_f :** 0.75 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3302, 3056, 2958, 2919, 1699, 1615, 1494, 1381, 1296, 1251, 1106 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ10.06-10.01 (m, 1 H), 8.32-8.19 (m, 1 H), 7.33(d, *J* = 8 Hz, 1 H), 7.19 (d, *J* = 8 Hz, 1 H), 6.89 (t, *J* = 7 Hz, 1 H), 6.82 (t, *J* = 7.5 Hz, 1 H), 6.09 (s,1 H), 5.72 (d, *J* = 6 Hz, 1 H), 5.37-5.35 (m, 2 H), 4.86-4.65 (m, 2 H), 1.15-.88 (m, 12 H), 0.74-0.53 (m, 4 H). **^{13}C NMR (125 MHz, Acetone-d_6):** δ 156.5, 155.9, 138.4, 138.3, 137.2, 135.2, 129.7, 121.5, 120.5, 119.8, 111.5, 100.9, 98.3, 70.4, 47.6, 31.9, 21.9, 12.8, 10.7. **HRMS (ESI):** *m/z* calcd for $C_{23}H_{29}N_3O_4Na$: 434.20558; Found: 434.20396.

Following the general procedure, diazabicyclic olefin (50 mg, 0.1552 mmol), indole (26 mg, 0.1035 mmol), $[RuCl_2p$- cymene$]_2$ (2 mg, 0.0032 mmol) and $Cu(OAc)_2.H_2O$ (5 mg, 0.0250

mmol) 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 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 24% (11 mg) yield.

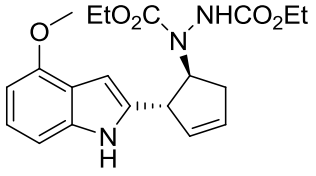
Diisopropyl-1-(2-(1-(benzylcarbamoyl)-1H-indol-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36ga



Yield: 24% as colourless viscous liquid. **R_f :** 0.85 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3315, 3057, 2997, 1698, 1523, 1393, 1250, 1155, 1059 cm^{-1}. **^{1}H NMR (500 MHz, CD_3CN):** 9.90 (brs, 1 H), 7.64-7.61 (m, 1 H), 7.50 (d, *J* = 8 Hz, 1 H), 7.44 (d, *J* = 7 Hz, 1 H), 7.09 (t, *J* = 7 Hz, 1 H),7.02 (t, *J* = 7.5 Hz, 1 H), 6.23 (s, 1 H), 5.86 (s, 1 H), 5.49(s, 1 H), 4.76-4.59 (m, 1 H), 4.58-4.32 (m, 1 H), 1.53-1.29 (m,18 H), .91-.64 (m, 4 H). **^{13}C NMR (125 MHz, CD_3CN):** δ 157.9, 156.2, 129.8, 128.4, 124.9, 123.11, 121.6, 120.5, 120.2, 116.2, 111.8, 110.8, 106.4, 81.6, 45.1, 44.9, 28.6, 12.7, 10.6. **HRMS (ESI):** *m/z* calcd for $C_{25}H_{33}N_3O_4Na$: 462.23688; Found: 462.23740.

Diethyl-1-(2-(4-methoxy-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36ha

Following the general procedure, diazabicyclic olefin (50 mg, 0.2083 mmol), indole (39 mg, 0.1388 mmol), $[RuCl_2p$- cymene$]_2$ (2 mg, 0.0049 mmol) and $Cu(OAc)_2.H_2O$ (6 mg, 0.03 mmol) 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 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 66% (35 mg) yield.

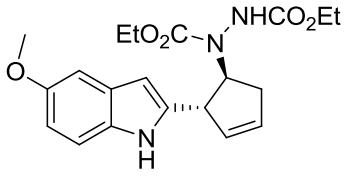


Yield: 66% as yellow viscous liquid. **R_f :** 0.65 (7:3 hexane/ethyl acetate).**IR (neat) ν_{max}:** 3301, 2981, 2935, 1707, 1615, 1511, 1465, 1414, 1375, 1249, 1174, 1102, 1058, 866, 766 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 10.29-9.99 (m, 1 H), 8.78-8.40 (m, 1 H), 6.97-6.93(m, 2 H), 6.47 (d, *J* = 8Hz, 1 H), 6.28 (s, 1 H), 5.89 (s, 2 H), 4.93 (brs, 1 H), 4.23-3.94 (m, 5 H), 3.88 (s, 3 H), 2.62 (brs, 2 H), 1.28-1.04 (m, 6 H). **^{13}C NMR (125 MHz, Acetone-d_6):** δ

156.3, 153.9, 138.7, 131.3, 130.6, 128.7, 127.2, 122.4, 119.8, 104.8, 99.5, 62.6, 54.8, 48.5, 35.6, 14.8. **HRMS (ESI):** *m/z* calcd for $C_{20}H_{25}N_3O_5Na$: 410.16919; Found: 410.16692.

Diethyl-1-(2-(5-methoxy-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36bf

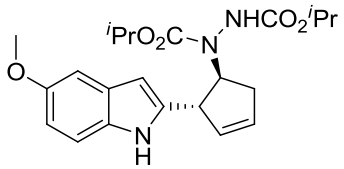
Following the general procedure, diazabicyclic olefin (50 mg, 0.2083 mmol), indole (39 mg, 0.1388 mmol), [RuCl2p- cymene]2 (2 mg, 0.0049 mmol) and Cu(OAc)2.H2O (6 mg, 0.03 mmol) were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 63% (33 mg) yield.



Yield: 63% as yellow viscous liquid. **R_f :** 0.20 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3302, 2983, 2937, 1712, 1625, 1588, 1486, 1450, 1413, 1376, 1254, 1217, 1171, 1124, 1058, 1030, 950, 842, 767 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 9.95 (brs, 1 H), 8.52-8.26 (m, 1 H), 7.07 (d, *J* = 9 Hz, 1 H), 6.84 (d, *J* = 2 Hz, 1 H), 6.55 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1 H), 6.01 (s, 1 H), 5.75 (s, 2 H), 4.11-3.98 (m, 6 H), 3.63 (s, 3 H), 2.48 (brs, 2 H), 1.14-1,08 (m, 6 H). **^{13}C NMR (125 MHz, Acetone-d_6):** δ 157.1, 155.1, 131.7, 129.9, 121.2, 112.2, 111..6, 102.6, 62.6, 55.9, 48.7, 35.7, 14.8. **HRMS (ESI):** *m/z* calcd for $C_{20}H_{25}N_3O_5Na$: 410.16919; Found: 410.16692.

Diisopropyl-1-(2-(5-methoxy-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36cf

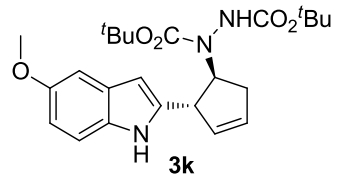
Following the general procedure, diazabicyclic olefin (50 mg, 0.1865 mmol), indole (35 mg, 0.1243 mmol), $[RuCl_2p$- cymene$]_2$ (3 mg, 0.0049 mmol) and $Cu(OAc)_2.H_2O$ (6 mg, 0.03 mmol) were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 61% (32 mg) yield.



Yield: 61% as colourless viscous liquid. **R_f :** 0.25 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3325, 2918, 1716, 1589, 1466, 1157, 1061, 966 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 10.14 (brs, 1 H), 8.58-8.42 (m, 1 H), 7.19 (d, *J* = 8.5 Hz, 1 H), 6.98 (d, *J* = 5 Hz, 1 H), 6.68 (dd, J_1= 9 Hz, J_2=2.5 Hz,1 H), 6.14 (s, 1 H), 5.89 (s, 2 H), 5.17-4.94 (m, 1 H), 4.93-4.87 (m, 2 H), 4.13 (brs, 3 H), 3.77 (s, 3 H) 2.61 (brs, 2 H), 1.35-1,09 (m, 12 H). **^{13}C NMR (125 MHz, Acetone-d_6):** δ 155.1, 131.7, 130.5, 129.7, 128.5, 126.7, 112.3, 110.8, 100.9, 70.8, 55.7, 48.4, 22.4. **HRMS (ESI):** *m/z* calcd for $C_{22}H_{29}N_3O_5Na$: 438.20049; Found: 438.19815.

Di-tert-butyl-1-(2-(5-methoxy-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36df

Following the general procedure, diazabicyclic olefin (50, .1688 mmol), indole (36 mg, 0.1125 mmol), $[RuCl_2p$- cymene$]_2$ (3 mg, 0.0049 mmol) and $Cu(OAc)_2.H_2O$ (6 mg, 0.0300)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 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 60% (30 mg) yield.



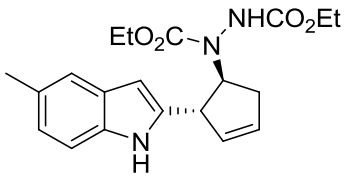
3k

Yield: 60% as yellow viscous liquid. **R_f :** 0.70 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3381, 2977, 2933, 1712, 1588, 1454, 1252, 1112, 965 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 9.91 (brs, 1 H), 7.25-7.22 (m, 1 H), 7.01 (s, 1 H), 6.76 (d, *J* = 9 Hz, 1 H), 6.38 (s, 1 H), 6.13 (s, 1 H), 5.92-5.85 (m, 2 H), 4.62 (s, 1 H), 4.05 (s, 1 H), 3.83 (s, 3 H), 2.53 (brs, 2 H), 1.54-1.43 (m, 18 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 155.6, 153.7, 128.9, 124.3, 114.8, 113.5, 107.1, 103.0, 81.7, 55.8, 47.6, 31.0. **HRMS (ESI):** *m/z* calcd for $C_{24}H_{33}N_3O_5Na$: 466.23179; Found: 466.23260.

Diethyl-1-(2-(5-methyl-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36bg

Following the general procedure, diazabicyclic olefin (50 mg, 0.2083 mmol), indole (37 mg, 0.1388 mmol), $[RuCl_2p$- cymene$]_2$ (3 mg, 0.0049 mmol) and $Cu(OAc)_2.H_2O$ (6 mg, 0.0300

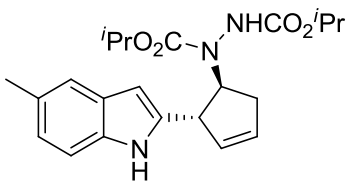
mmol) were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 110 ^{o}C for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 71% (37 mg) yield.



Yield: 71% as yellow viscous liquid. **R_f :** 0.53 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3299, 2983, 2934, 2864, 1699, 1589, 1489, 1452, 1416, 1325, 1270, 1127, 1066, 952 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 10.15-9.84 (m, 1 H), 8.76-8.40 (m, 1 H), 7.21 (d, *J* = 8 Hz, 1 H), 6.87 (d, *J* = 8.5 Hz, 1 H), 6.14 (s, 1 H), 5.89 (s, 2 H), 4.93 (brs, 1 H), 4.24-3.96 (m, 5 H), 2.63 (brs, 2 H), 2.37 (s, 3 H), 1.29-.82 (m, 6 H). **^{13}C NMR (125 MHz, Acetone-d_6):** δ 156.5, 131.6, 130.7, 128.1, 122.9, 120.0, 111.1, 62.8, 46.7, 35.6, 21.4, 14.7. **HRMS (ESI):** *m/z* calcd for $C_{20}H_{25}N_3O_5Na$: 394.17428; Found: 394.17203.

Diisopropyl-1-(2-(5-methyl-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36cg

Following the general procedure, diazabicyclic olefin (50 mg, 0.1865 mmol), indole (33 mg, 0.1243 mmol), [$RuCl_2$*p*- cymene]$_2$ (2 mg, 0.oo32 mmol) and $Cu(OAc)_2.H_2O$ (5 mg, 0.0250 mmol) 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 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 73% (36 mg) yield.

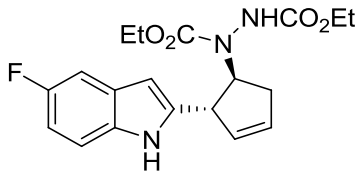


Yield: 73% as yellow viscous liquid. **R_f :** 0.53 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3301, 2982, 1713, 1592, 1496, 1409, 1179, 1143, 1108, 1042 cm^{-1}. **^{1}H NMR (500 MHz, CD_3CN):** δ 9.97-9.95 (m, 1 H), 7.52 (brs, 1 H), 7.29 (s, 1 H), 7.26-7.7.15 (m, 1 H), 6.89

(d, *J* = 8 Hz, 1 H), 6.11 (s, 1 H), 5.88 (s, 1 H), 5.24-4.76 (m, 5 H), 4.06 (brs, 1 H), 2.63-2.53 (m, 2 H), 2.37 (s, 3 H), 1.28-1.21 (m, 6 H). **^{13}C NMR (125 MHz, CD_3CN):** δ 156.3, 154.7, 130.0, 128.6, 127.9, 126.7, 128.8, 121.8, 117.0, 109.9, 99.5, 69.6, 43.5, 34.3, 20.9. **HRMS (ESI):** *m/z* calcd for $C_{22}H_{29}N_3O_4Na$: 422.20558; Found: 422.20508

Diethyl-1-(2-(5-fluoro-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36bb

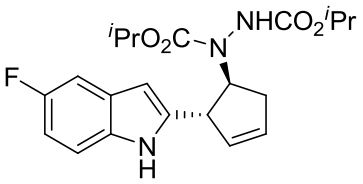
Following the general procedure, diazabicyclic olefin (50 mg, 0.2083 mmol), indole (37 mg, 0.1388 mmol), $[RuCl_2p$- cymene$]_2$ (3 mmol, .0049) and $Cu(OAc)_2.H_2O$ (6 mg, 0.00300 mmol) were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 74% (52 mg) yield.



Yield: 74% as yellow viscous liquid. **R_f :** 0.48 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3289, 2983, 1714, 1533, 1254, 1062, 1016, 966 cm^{-1}. **^{1}H NMR (500 MHz, CD_3CN):** δ 10.35 (brs, 1 H), 8.77 (brs, 1 H), 7.34-7.29 (m, 1 H), 7.18-7.15 (m, 1 H),6.83 (dt, J_1 = 9.5 Hz, J_2 = 2.5 Hz, 1 H), 6.24 (s, 1 H), 5.91 (s, 2 H), 4.93 (brs, 1 H), 4.24-4.04 (m, 5 H), 2.63 (brs, 2 H), 1.29-1,19 (m, 6 H). **^{13}C NMR (125 MHz, CD_3CN):** δ 159.2, 157.5, 133.7, 131.1, 129.9, 128.8, 125.9, 112.3, 109.1, 105.0, 62.7, 46.7, 35.7, 14.8. **HRMS (ESI):** *m/z* calcd for $C_{19}H_{22}FN_3O_4Na$: 398.14920; Found: 398.14697.

Diisopropyl-1-(2-(5-fluoro-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36cb

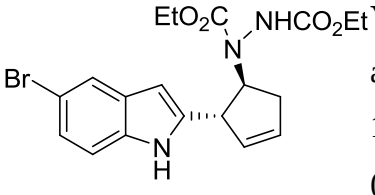
Following the general procedure, diazabicyclic olefin (50 mg, 0.1865 mmol), indole (50, .1243 mmol), $[RuCl_2p$- cymene$]_2$ (2 mg, 0.oo32 mmol) and $Cu(OAc)_2.H_2O$ (5 mg, 0.0200 mmol)were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 70% (53 mg) yield.



Yield: 60% as yellow viscous liquid. **R_f :** 0.70 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3314, 2981, 2922, 2851, 1716, 1485, 1381, 1287, 1230, 1164, 1132, 1059, 1032, 870, 761 cm^{-1}. **^{1}H NMR (500 MHz, CD_3CN):** δ 10.16 (brs, 1 H), 7.51 (brs, 1 H), 7.38-7.26 (m, 2 H), 6.86-6.79 (m, 1 H), 6.20 (brs, 1 H), 5.89 (brs, 2 H), 5.23-4.83 (m, 5 H), 4.08 (brs, 1 H), 2.53 (brs, 2 H), 1.29-1.17 (m, 6 H). **^{13}C NMR (125 MHz, CD_3CN):** δ 156.2, 131.2, 130.1, 129.7, 129.2, 128.4, 118.3, 112.3, 109.2, 105.1, 70.9, 46.4, 35.3, 21.9. **HRMS (ESI):** *m/z* calcd for $C_{21}H_{26}FN_3O_4$: 426.18050; Found: 426.18013.

Diethyl-1-(2-(5-bromo-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36bc

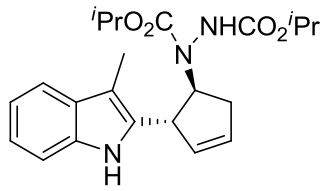
Following the general procedure, diazabicyclic olefin (50 mg, 0.2083 mmol), indole (46 mg, 0.1388 mmol), $[RuCl_2p$- cymene$]_2$ (3 mg, 0.0049) and $Cu(OAc)_2.H_2O$ (6 mg, 0.0300 mmol) were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 75% (45 mg) yield.



Yield: 60% as yellow viscous liquid. **R_f :** 0.73 (7:3 hexane/ethyl acetate). **IR (neat) ν_{max}:** 3229, 2983, 1711, 1576, 1469, 1404, 1376, 1115, 1057, 1018 cm^{-1}. **^{1}H NMR (500 MHz, CD_3CN):** δ 10.18 (brs, 1 H), 7.64 (s, 1 H), 7.27 (d, *J* = 8.5 Hz, 1 H),7.16 (d, *J* = 10.8 Hz, 1 H), 6.51 (brs, 1 H), 6.21 (s, 1 H), 5.90-5.87 (m, 2 H), 4.85-4.77 (m,1 H), 4.21-4.08 (m, 5 H), 2.55 (brs, 2 H), 1.28-1,21 (m, 6 H). **^{13}C NMR (125 MHz, CD_3CN):** δ 160.2, 156.5, 135.5, 131.5, 130.9, 124.6, 122.8, 122.4, 118.3, 113.5, 101.0, 63.1, 48.8, 48.5, 35.6, 14.8. **HRMS (ESI):** *m/z* calcd for $C_{19}H_{22}BrN_3O_5Na$: 458.06914; Found: 458.06876.

Diisopropyl-1-(2-(3-methyl-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36ch

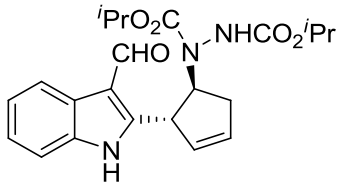
Following the general procedure, diazabicyclic olefin (50 mg, 0.1865 mmol), indole (33 mg, 0.1243 mmol), $[RuCl_2p$- cymene$]_2$ (2 mg, 0.0032 mmol) and $Cu(OAc)_2.H_2O$ (5 mg, 0.00250 mmol)were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 60% (30 mg) yield.



Yield: 60% as yellow viscous liquid. $\mathbf{R_f}$ **:** 0.55 (7:3 hexane/ethyl acetate). **IR (neat)** $\mathbf{\nu_{max}}$**:** 3296, 2977, 2929, 1706, 1584, 1521, 1455, 1392, 1368, 1253, 1156, 1052, 854, 755 cm^{-1}. **^{1}H NMR (500 MHz, Acetone-d_6):** δ 9.80 (brs, 1 H), 8.17 (brs, 1 H), 7.44 (d, *J* = 7.5 Hz, 1 H), 7.23-7.22 (m, 1 H), 6.57 (s, 1 H), 5.88-5.79 (m, 2 H), 5.10-4.86 (m, 2 H), 4.29 (s, 1 H), 2.6 (brs, 2 H), 2.28 (s, 3 H), 1.49-1.29 (m, 12 H). **^{13}C NMR (125 MHz, Acetone-d_6):** δ 155.2, 129.7, 129.1, 126.2, 121.3, 118.9, 118.0, 111.1, 100.4, 70.5, 65.6, 48.2, 35.7, 21.9, 9.0. **HRMS (ESI):** *m/z* calcd for $C_{22}H_{29}N_3O_4Na$: 422.20558; Found: 422.20205.

Diisopropyl-1-(2-(3-formyl-1H-indol-2-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 36cd

Following the general procedure, diazabicyclic olefin (50 mg, 0.1865 mmol), indole (35 mg, 0.1.1243 mmol), $[RuCl_2p$- cymene$]_2$ (2 mg, 0.0032 mmol) and $Cu(OAc)_2.H_2O$ (5 mg, 0.0200 mmol)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 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the product in 67% (34 %) yield.



Yield: 67% as yellow viscous liquid. $\mathbf{R_f}$ **:** 0.30 (7:3 hexane/ethyl acetate). **IR (neat)** $\mathbf{\nu_{max}}$**:** 3299, 2983, 2934, 2864, 1699, 1589, 1489, 1452, 1416, 1325, 1270, 1127, 1066, 952 cm^{-1}. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 11.06, 10.04 (s, 1 H), 9.29 (s, 1 H), 8.31-8.29 (m, 1 H), 7.44-7.42 (m, 1 H), 7.31-7.29 (m, 2 H), 6.69 (s, 1 H), 6.09 (t,

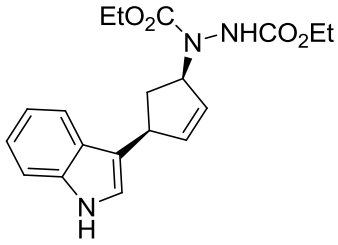
J = 3 Hz, 1 H), 5.87-5.86 (m, 1 H), 5.49 (d, *J* =7.5 Hz, 1 H), 5.00-4.45 (m, 2 H), 4.55 (brs, 1 H), 2.69-2.56 (m, 2 H), 1.29-1.25 (m, 12 H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 184.9, 155.2, 135.2, 127.9, 124.5, 124.1, 122.7, 121.7, 119.5, 111.5, 99.8, 57.9, 30.6, 29.8, 21.9. **HRMS (ESI):** *m/z* calcd for $C_{22}H_{27}N_3O_5$: 436.18484; Found: 436.18499.

3.9.3. General Procedure for the $AgSbF_6$ catalyzed regiospecificC-3 cyclopentenylation of N-H free indoles with bicyclic hydrazines:-

A mixture of diazabicyclic olefin (1.5 equiv.), indole (1.0 equiv.), $AgSbF_6$ (10 mol%) and $Cu(OAc)_2.H_2O$ (20 mol%) were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and allowed to stir at room temperature for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded cyclopentene substituted indoles.

Diethyl 1-(4-(1H-indol-3-yl)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 37bb

Following the general procedure, diazabicyclic olefin (50 mg, 0.21 mmol), indole (16 mg, 0.14 mmol), and $AgSbF_6$ (2 mg, 0.0069 mmol) and were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and allowed to stir at room temperature for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography the product in 62%30 mg) yield.

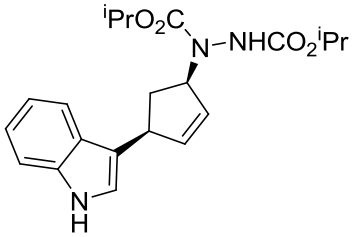


Yield: 62% as yellow viscous liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10-8.08 (m, 1 H), 7.65-7.57 (m, 1 H), 7.35-7.33 (m, H), 7.11-7.08 (m, 1H), 6.91 (s, 1H), 6.56-6.46 (m,1H), 6.18 (brs, 1H), 5.86-5.83 (m, 1H), 5.53-5.08 (m, 1H), 4.29-4.09 (m,4H), 3.99-3.92 (m, 1H), 2.73-2.26 (m, 2 H), 1.29-1.27 (m, 12 H) ppm. **^{13}C NMR (126 MHz, $CDCl_3$)** δ 156.9, 136.8, 136.7, 133.1, 128.7, 126.9, 126.6, 122.1, 121.9, 120.3, 119.2, 119.1, 111.3, 111.3, 109.3, 77.32, 77.1, 76.8, 62.1, 60.5, 60.3, 60.02, 41.4, 35.2, 30.9, 14.5, 14.5 ppm. **HRMS (ESI):** *m/z* calcd for $C_{19}H_{23}N_3NaO_4$: 380.15863; Found: 380.15791.

Diisopropyl-1-4-(1H-indol-3-yl)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 37cb

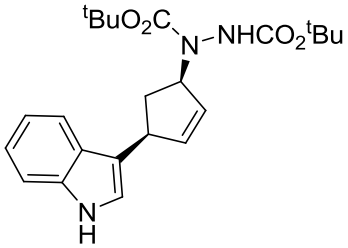
Following the general procedure, diazabicyclic olefin (50 mg, 0.2083 mmol), indole (15 mg, 0.1244 mmol), and $AgSbF_6$ (2 mg, 0.0059 mmol) and were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and allowed to stir at room temperature for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography the product in 60% (28 mg) yield.



Yield: 60% as yellow viscous liquid. **^{1}H NMR (500 MHz, Acetone):** δ 7.67 (m, 1H), 7.39-7.38 (m,1H), 7.16-7.12 (m,2H), 7.06-7.01 (m, 2H), 6.32-6.19 (m, 2H), 5.90-5.81 (m,1H), 5.01-4.89 (m, 2H), 4.38-4.33 (m,1H), 2.73-2.19 (m,2H), 1,38-1.32 (m, 12H) ppm.**^{13}C NMR (126 MHz, Acetone)** δ 13C NMR (126 MHz, Acetone) δ 155.9, 154.9, 141.6, 137.3, 130.3, 121.3, 120.9, 120.7, 119.0, 118.7, 118.6, 118.46, 114.3, 111.4, 109.4, 68.2, 67.3, 55.6, 40.2, 21.4 ppm. **HRMS (ESI):** *m/z* calcd for $C_{21}H_{27}N_{3Na}O_5$: **408.18993**; Found: 408.18499.

Di-tert-butyl-1-4-(1H-indol-3-yl)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 37db

Following the general procedure, diazabicyclic olefin (50 mg,.17 mmol), indole (13 mg, 0.11 mmol), and $AgSbF_6$ (2 mg, 0.0059 mol) and were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and allowed to stir at room temperature for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography the product in 55%(26 mg)yield.

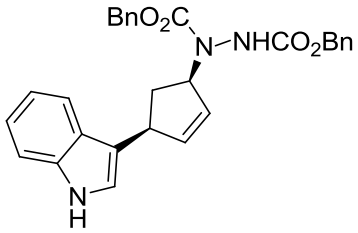


Yield: 55 % as brown viscous liquid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 9.88 (m, 1H), 7.25-7.23 (m,1H), 7.10-7.09 (m,1H), 7.04-7.03 (m, 2H), 6.95-6.92 (m,1H), 6.86-6.83 (m,1H), 6.04-5.61 (m, 2H), 5.36-4.93 (m,1H), 4.18-4.10 (m,1H), 2.60-2.28 (m,2H), 1.34-1.24 (m,18H) ppm. **^{13}C NMR (126 MHz, Acetone) δ** 155.9, 154.6, 137.6, 137.3, 128.9, 128.2, 127.2,

127.1, 126.9, 125.9, 125.2, 121.3, 120.6, 118.7, 118.4, 118.3, 112.1, 111.4, 111.2, 79.6, 63.6, 41.2, 35.39, 27.6, 21.9. **HRMS (ESI):** *m/z* calcd for $C_{23}H_{31}N_{3Na}O4$: 436.22123; Found: 436.22134.

Dibenzyl -1-(-4-(1H-indol-3-yl)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 37eb

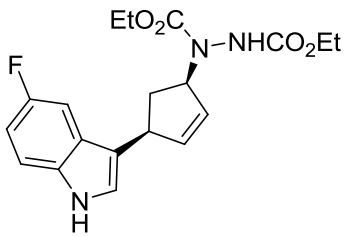
Following the general procedure, diazabicyclic olefin (50, .1373 mmol), indole (12 mg, 0.0916 mmol), and $AgSbF_6$ (2 mg, 0.0059 mol) and were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and allowed to stir at room temperature for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography the product in 47% (21 mg) yield.



Yield: 47% as yellow viscous liquid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 9.88 (s, 1H), 7.24-7.02 (m, 13H), 6.99-6.92 (m,1H), 6.87-6.83 (m,1H), 6.17-5.94 (m, 1H), 5.71 (brs, 1H), 5.48-5.44 (m, 1H), 5.05-4.88 (m, 5H), 4.21-4.12 (m, 1H), 2.75-2.03 (m, 2H) ppm. **^{13}C NMR (126 MHz, Acetone)** δ 170.1, 158.8, 137.2, 136.8, 128.4, 128.2, 127.9, 127.9, 127.8, 127.7, 121.3, 120.8, 118.5, 111.4, 67.1, 66.4, 59.7, 41.8, 32.8 ppm. **HRMS (ESI):** *m/z* calcd for C29H27N3aNaO$_4$: 504.18993; Found: 504.18768.

Diisopropyl 1-(-4-(5-fluoro-1H-indol-3-yl)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate (37cc)

Following the general procedure, diazabicyclic olefin (50, .21), indole (18 mg, 0.14 mmol), and $AgSbF_6$ (2 mg, 0.0059 mol) and were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and allowed to stir at room temperature for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography the product in 57% (30 mg) yield.

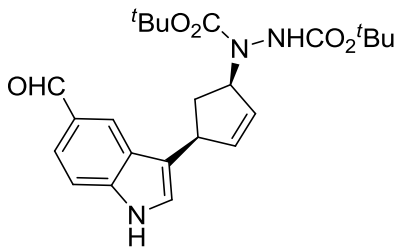


^{1}H NMR (500 MHz, Acetone): δ 9.98 (s, 1H), 8.09 (m, 1H), 7.25-7.23 (m, 1H), 7.08 (s, 1H), 7.03 (s, 1H), 6.78-6.74 (m, 1H), 6.00 (brs, 1H), 5.72-5.69 (m, 1H), 5.39 (brs, 1H), 4.14-3.94 (m, 5H), 2.66-2.26 (m, 2H), 1.12-1.09 (m, 6H) ppm.**^{13}C NMR (126 MHz, Acetone)** δ 158.2, 156.3,

145.5, 133.8, 130.5, 122.9, 120.8, 112.3, 112.2, 109.4, 109.2, 103.4, 103.2, 60.8, 13.9 ppm. **HRMS (ESI):** *m/z* calcd for $C_{19}H_{22}N_3NaO_4$: 398.14920; Found: 398.14110.

Di-tert-butyl 1-(-4-(5-formyl-1H-indol-3-yl)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 37dd

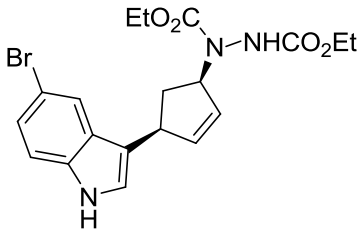
Following the general procedure, diazabicyclic olefin (50 mg, 0.17 mmol), indole (16 mg, 0.11), and $AgSbF_6$ (2 mg, 0.0059 mol) and were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and allowed to stir at room temperature for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography the product in 43% (21 mg) yield.



Yield: 43% as coloueless viscous liquid. **^{1}H NMR (500 MHz, Acetone):** δ 10.41 (s, 1H), 9.89 (s, 1H), 8.19-8.02 (m, 1H), 7.98-7.57 (m, 1H), 7.56- 7.54 (m, 1H), 7.39-7.19 (m, 1H), 6.00-5.80 (m, 1H), 5.42 (s, 1H), 4.92-4.73 (m, 1H), 4.35-4.17 (m, 1H), 2.55-1.91 (m, 2H), 1,19-.77 (m, 18H) ppm.**^{13}C NMR (126 MHz, Acetone)** δ 191.7, **191**.6, 156.5, 155.1, 140.6, 129.2, 126.9, 122.9, 112.1, 111.9, 80.7, 68.9, 68.6, 68.4, 54.6, 41.1, 32.4 31.1, 30.8, 21.4 ppm. **HRMS (ESI):** *m/z* calcd for $C_{24}H_{31}N_3NaO_5$: 464.21614; Found: 464.21226.

Diethyl 1-(-4-(5-bromo-1H-indol-3-yl)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 37bd

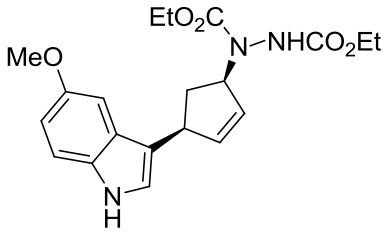
Following the general procedure, diazabicyclic olefin (50 mg, 0.21 mmol), indole (27 mg, 0.1389 mmol), and $AgSbF_6$ (2 mg, 0.0059 mol) and were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and allowed to stir at room temperature for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography the product in 53% yield (32 mg).



Yield: 53% as brown viscous liquid. **^{1}H NMR (500 MHz, Acetone):** δ 10.12 (s, 1H), 7.56 (brs, 1H), 7.24-7.22 (m, 1H), 7.08-7.01 (m, 2H), 6.00 (brs, 1H), 5.73-5.69 (m, 2H), 5.40-4.86 (m, 1H), 4.19-3.71 (m, 5H). 2.54-1.86 (m, 2H), 1.15-.72 (m, 6H) ppm. **^{13}C NMR (126 MHz, Acetone)** δ 155.5, 135.9, 135.9, 128.9, 128.7, 123.9, 123.8, 122.4, 121.1, 113.3, 113.1, 111.4, 63.7, 61.5, 61.2, 60.9, 60.8, 41.2, 37.0, 14.0 ppm. **HRMS (ESI):** *m/z* calcd for $C_{19}H_{22}BrN_3NaO_4$: 458.06914; Found: 458.06499.

Diethyl 1-(-4-(5-methoxy-1H-indol-3-yl)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 37bh

Following the general procedure, diazabicyclic olefin (50 mg, 0.2083 mmol), indole (20 mg, 0.1389 mmol), and $AgSbF_6$ (2 mg, 0.0059 mol) and were weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added and allowed to stir at room temperature for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography the product in 63% (34 mg) yield.



Yield: 63% as yellow viscous liquid. **^{1}H NMR (500 MHz, $CDCl_3$):** δ 9.73 (s, 1H), 8.00 (s, 1H), 7.15-7.10 (m, 2H), 6.94-6.89 (m, 1H), 6.64-6.60 (m, 1H), 6.00 (s, 1H), 5.71 (s, 2H), 5.35-4.88 (s, 1H), 4.19-3.94 (m, 5H), 3.68-3.65 (m, 3H), 2.60-2.46 (m, 2H), 1.16-1.06 (m, 6H) ppm. **^{13}C NMR (125 MHz, Acetone**) δ 153.6, 132.4, 127.2, 122.3, 121.4, 111.9, 111.4, 61.4, 61.0, 60.8, 54.9, 13.9 ppm. **HRMS (ESI):** *m/z* calcd for $C_{20}H_{25}N_3NaO_5$: 410.16919; Found: 410.16499.

3.10. References

1. Van Order, R. B.; Lindwall, H. G. *Chem. Rev*. **1942**, *30*, 69

2. (a) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev*. **2010**, *11*0, 4489. (b) Biswal, S.; Sahoo, U.; Sethy, S.; Kumar, H. K. S.; Banerjee, M.; Asian *J. Pharm. Clin. Res.* **2012**, *5*, 1. (c) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620.

3. Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev*. **2010**, *110*, 4489.

4. Qweider, M.; Gilsbach, J. M.; Rohde, V. *J. Neurosurg.* **2007**,*6*, 280.

5. Selected references: (a) García-Rubia, A.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 6511. (b) Johansen, M. B.; Kerr, M. A. *Org. Lett.* **2010**, *12*, 4956. (c) Zhang, D-H.; Tang, X-Y.; Wei, Y.; Shi, M. *Chem. Eur. J.* **2013**, *19*, 13668. (d) Shi, J.; Zhao, G.; Wang, X.; Xu, H. E.; Yi, W. *Org. Biomol. Chem.* **2014**, *12*, 6831.

6. (a) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (b) Zhou, J.; Hu, P.; Zhang, M.; Huang, S.; Wang, M.; Su, W. *Chem. Eur. J.* **2010**, *16*, 5876. (c) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 3125.

7. (a) T. B. Poulsen, K. A. Jøgensen, *Chem. Rev.* **2008**, *108*, 2903 (b) B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701 (v) Bandini, A. Melloni, S. Tommasi, A. Umani-Ronchi, *Synlett* **2005**, 1199 (d)Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem. Int. Ed.* **2004**, *43*, 550.

8. K.A. Jøgensen, *Synthesis* **2003**, *7*, 1117.

9. L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190.

10. Haiming Zhang and Richard C. Larock *J. Org. Chem*. **2002**, *67*, 9318.

11. Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 3125.

12. Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 2337.

13. Li, M.; Tang, C.; Yang, J.; Gu, Y. *Chem. Commun.* **2011**, *47* , 4529.

14. Capito, E.; Brown, J. M.; Ricci, A. *Chem. Commun. (Camb).* **2005**, *14*, 1854.

15. García-Rubia, A.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 6511.

16. Lanke, V.; Prabhu, K. R. *Org. Lett*. **2013**, *15*, 2818.

17. Liang, L.; Fu, S.; Lin, D.; Zhang, X-Q.; Deng, Y.; Jiang, H.; Zeng, W. *J. Org. Chem.* **2014**, *79*, 9472

18. Sharma, S.; Han, S.; Kim, M.; Mishra, N. K.; Park, J.; Shin, Y.; Ha, J.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Org. Biomol. Chem.* **2014**, *12*, 1703.

19. Zhang, W.; Wei, J.; Fu, S.; Lin, D.; Jiang, H.; Zeng, W. *Org. Lett.* **2015**, *17*, 1349.

20. Luna, A. P.; Cesario, M.; Bonin, M.; Micouin, L. *Org. Lett.* **2003**, *5*, 4771.

Chapter 4

Rh(III)/Cu(II) Catalyzed Ring Opening and Annulation of Diazabicyclic Olefins with *o*-Vinylphenols

4.1. Introduction

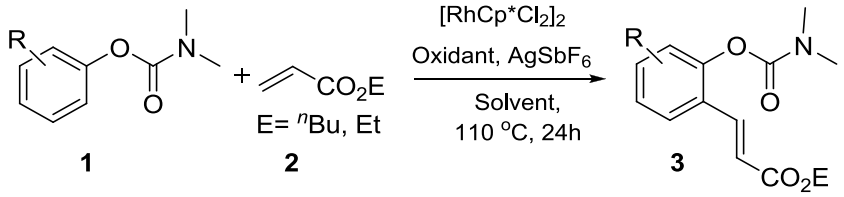
Heterocycles are an important class of compounds which are found in various natural products, biologically active structures, and medicinally relevant compounds.[1] Therefore, there is continuing interest in the development of novel synthetic methods for the construction of different heterocycles. Oxygen containing heterocycles are an important member of the heterocycle family.[2] Phenolic compounds are the cheapest feed stocks for the synthesis of various oxacycles since it is produced on a large scale. Several commercially available compounds as well as natural products are synthesized from a precursors containing phenol.

4.2. Transition Metal Catalyzed C-H Activation Reactions of Phenol

C-H activation reactions emerge as a new arena of synthetic organic chemistry.[2] Different olefinations, alkylations, arylation *etc.* were achieved *via* aromatic C-H activation strategy with directing groups such as amides, heterocycles *etc*.[3] Further attempts were made to test inclusively/cyclatively adding directing groups; which predictably end in constructing value added heterocycles.[3] Many of the aniline-based derivatives, such as N-acetyl, N-pivalyl and N-tosyl substrates, have been widely employed in C–H bond activation. The initiation of C-H activation is hindered in phenolic substrates to an extent. This may be attributed to the more flexible conformation of the transition-metal complex of phenol derivatives compared with that of aniline derivatives. Hydroxyl is a very important functional group in organic chemistry and it exhibits weak coordination to transition metals.[4] This characteristic enables it to play an important role in several transition-metal-catalyzed transformations. There are a few reports proving that phenols are also a suitable candidate in this category owing to give pharmacologically relevant oxacycles.

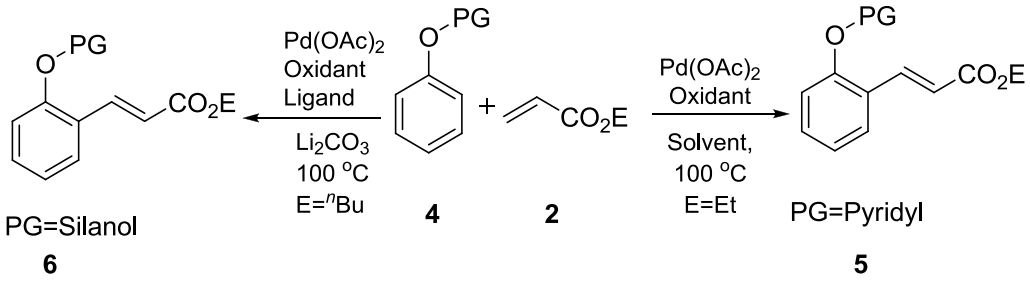
4.2.1. Protected Phenols

In 2011, Liu *et al.*[5a] and Loh *et. al.*[5b] independently reported Rh(III)-catalyzed oxidative Heck reaction of phenol carbamates resulting in *ortho*- C-H activation/olefination. The directing carboxamate group has to be further deprotected to get free hydroxyl group (Scheme 4.1).



Scheme 4.1

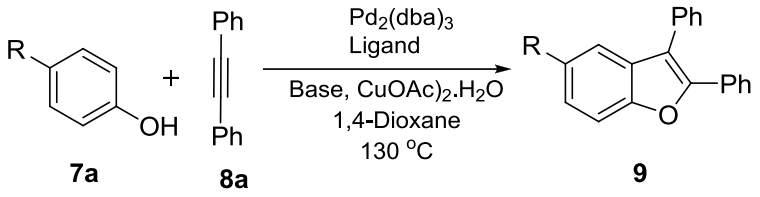
Gevorgyan *et al.* reported a silanol-directed, Pd(II)-catalyzed C-H alkenylation of phenols. The silanol directing group was shown to be convenient as it can easily be removed under mild conditions.[6] In a similar way, Shi *et al.* reported Pd (II)-catalyzed oxidative olefination of phenols bearing removable pyridyl tether.[7] But in this case also the pyridyl group has to be subsequently removed (Scheme 4.2).



Scheme 4.2

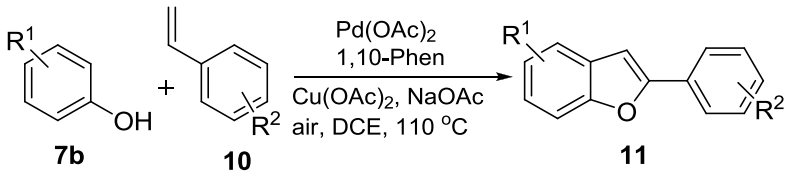
4.2.2. Simple Phenols

In 2013, Sahoo and coworkers reported palladium-catalyzed oxidative annulation of phenols and unactivated internal alkynes giving ubiquitous benzofuran moiety (Scheme 4.3).[8]



Scheme 4.3

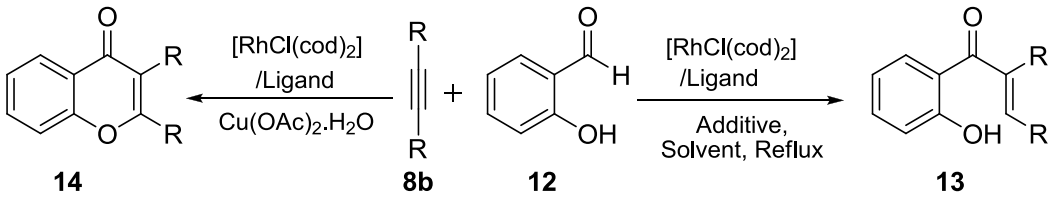
In the same year Maiti *et al.* reported palladium-catalyzed intermolecular annulation of phenols with styrenes and acrylates giving benzofurans and coumarins respectively (Scheme 4.4).[9]



Scheme 4.4

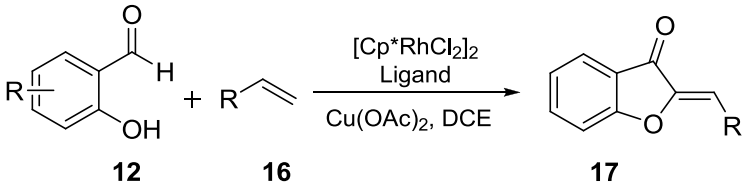
4.2.3. Salicylaldehydes

Salicylaldehydes were also found to be suitably substituted phenols for various catalytic coupling reactions. Miura and coworkers reported two different rhodium catalyzed catalytic coupling reactions of salicylaldehydes and alkynes resulting two distinct products such as hydroacylated as well as chromanone derivatives.[10] It was notable that, in the hydroacylation reaction bases were used as the additive. When it was replaced by oxidants such as $Cu(OAc)_2.H_2O$, reductive elimination of the Rh(I) species leading to the formation of chromanone formation(Scheme 4.5).



Scheme 4.5

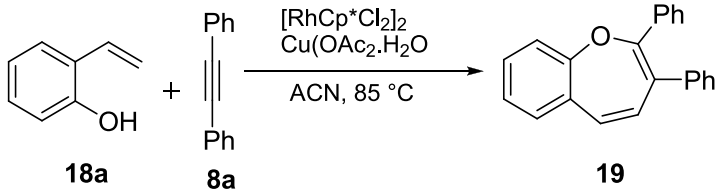
In 2012, Glorius *et al.* had reported a catalytic Dehydrogenative Heck Reaction (DHR) with salicylaldehydes (Scheme 4.6).[11] This methodology is attractive because they have applied this methodology to the synthesis of biologically relevant molecule, thus showing the practicality and value of this method.



Scheme 4.6

4.2.4. *o*-Vinylphenols

In 2013, Gulias *et al.* reported a synthetic route for benzoxepines by Rh(III) catalyzed C-H functionalization of *o*-vinyl phenols with alkynes in a [5+2] cycloaddition manner (Scheme 4.7).[12] Also very recently they have reported dearomatizing [3+2] cycloaddition of the above mentioned coupling partners.



Scheme 4.7

4.3. Statement of the Problem

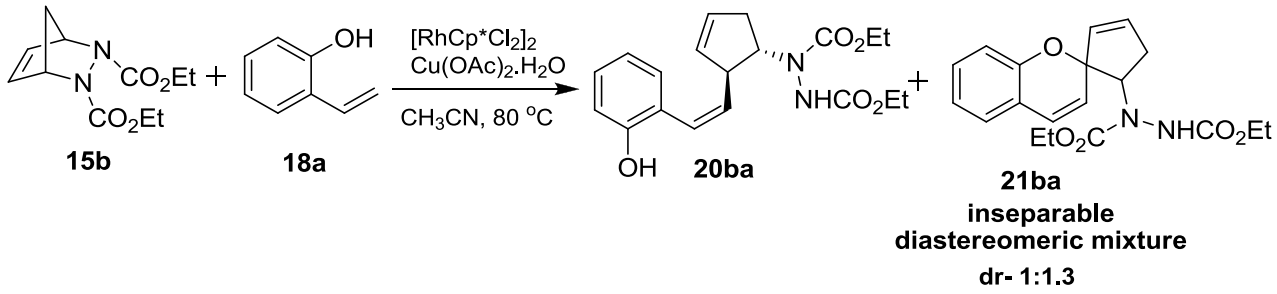
Our group has extensively studied the reactivity of different bicentered substrates with diazabicyclic olefins. Various cyclopentenylated carbocycles, as well as heterocycles, were obtained by respective palladium or rhodium catalyzed annulation strategies. We have excellently demonstrated the palladium/rhodium catalyzed cyclopentanulation of different ortho functionalized aryl halides and phenols. In another attempt, the rhodium catalyzed oxidative coupling of salicylaldehydes with diazabicyclic olefins resulted in privileged chromanone skeletons. It is expected that the choice of *o*-vinylphenols as the bicentered

substrate for C-H activation reactions may lead to novel and versatile heterocyclic scaffolds. A detailed description of the rhodium catalyzed C-H activation reaction of o-vinyl phenols with diazabicyclic olefins is presented in the following sections.

4.4. Results and Discussion

4.4.1. Rhodium/Copper Catalyzed C-H Activation Annulation of *o*-Vinylphenols with Diazabicyclic Olefins

We started our experiments with the reaction of diazabicyclic olefin **15b** with equimolar *o*-vinyl phenol **18a** in presence of the catalyst $[RhCp^*Cl_2]_2$ and the additive $Cu(OAc)_2.H_2O$ in acetonitrile at 80 ^oC for 8 hours. The reaction afforded two products, the ring opened **20ba** and annulated **21ba** in 37 and 21 % yields respectively (Scheme 4.8). The structures of the products **20ba** and **21ba** were characterized by different spectroscopic methods.



Scheme 4.8

From ^1H NMR spectrum of compound **20ba**, the olefinic protons at **e** and **f** were seen at δ 6.47 and 5.71 ppm. The styryl double bond was showing a *cis* stereochemistry. It is evident from the coupling constant of olefin at δ 6.47 ppm, which is J =10.5 Hz. These *cis* styryl bonds are comparatively rare in the literature. This is further supported by a comparative analysis with similar compound synthesized in our laboratory with a *trans* stereochemistry. In the latter case the coupling constant value was foung to be 16 Hz.[13]

The olefins of the cyclopentene ring, **c** and **d** resonated at δ 5.79 and 5.49 ppm respectively. The proton corresponding to **b** was found to be resonated resonated at δ 4.74 ppm as a broad singlet.

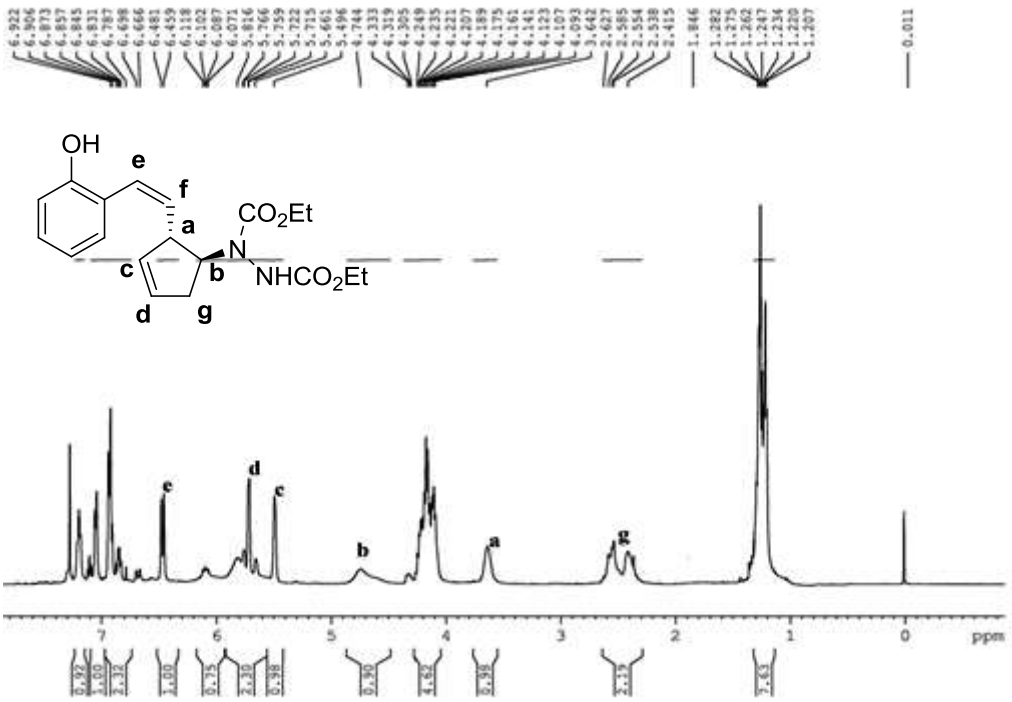


Figure 4.1. ^{1}H NMR Spectrum of Compound **20ba**

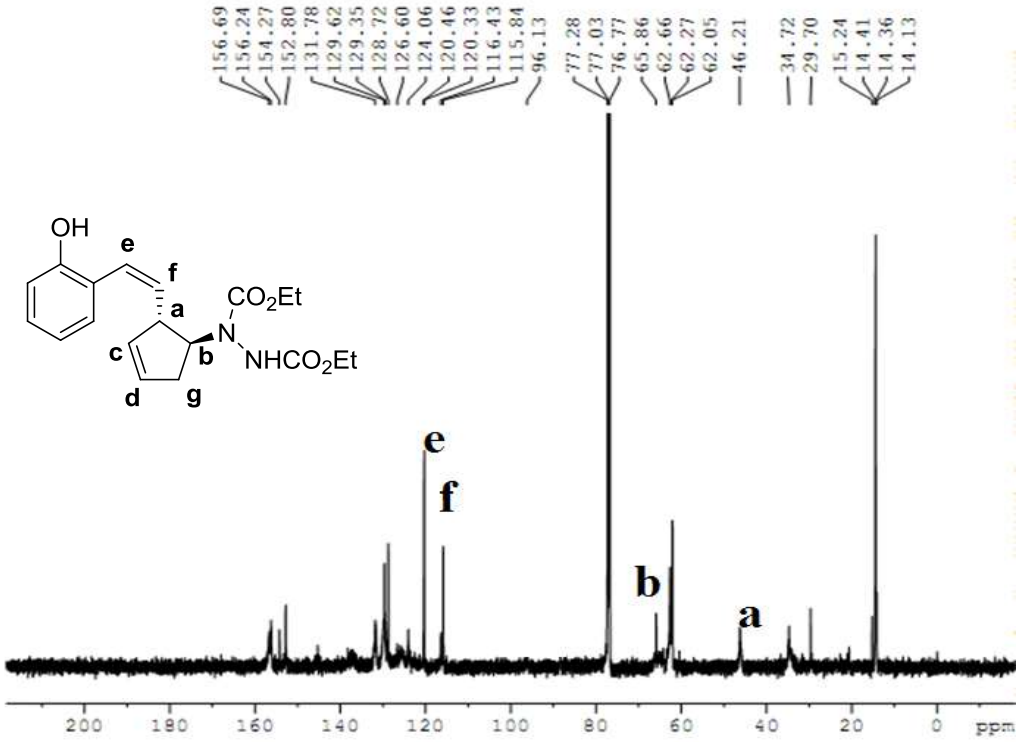


Figure 4.2. ^{13}C NMR Spectrum of Compound **20ba**

The *sp3* proton of the cyclopentene ring, **a** was observed at δ 3.65 ppm. The –OH proton resonated along with the olefin protons **c**, **d**, and **f** as a multiplet. It is further confirmed by the HMQC spectrum of the same compound. Methylene protons of cyclopentene ring were observable as a broad multiplet at δ 2.58-2.35 ppm.

In ^{13}C NMR spectrum, the ester carbonyls resonated at δ 156.7 and 156.2 ppm respectively. The methylene catbons of the carboethoxy group resonated at δ 62.7 and 62.3 ppm. A well-defined molecular ion peak at m/z 383.15881$(M+Na)^+$ provided another convincing evidence for this structure

Similarly the structure of the annulated product **21ba** was characterized by different spectroscopic methods. The spirocycle **21ba** was found to be an inseparable mixture of diastereomers in 1:1.3 ratio from the ^1H NMR spectrum. In ^1H NMR spectrum, the NH protons were observed at δ 6.75 ppm as a broad singlet. The olefin protons **a** resonated as a multiplet at δ 6.41. Olefinic protons **c** and **d** resonated as broad doublets at δ 5.95 and 5.77 ppm. The protons at **e** and **e'** resonated at δ 4.98 and 4.79 ppm as broad singlets. The methylene proton at **f** was observed between δ 2.71 and 2.67 ppm as a multiplet.

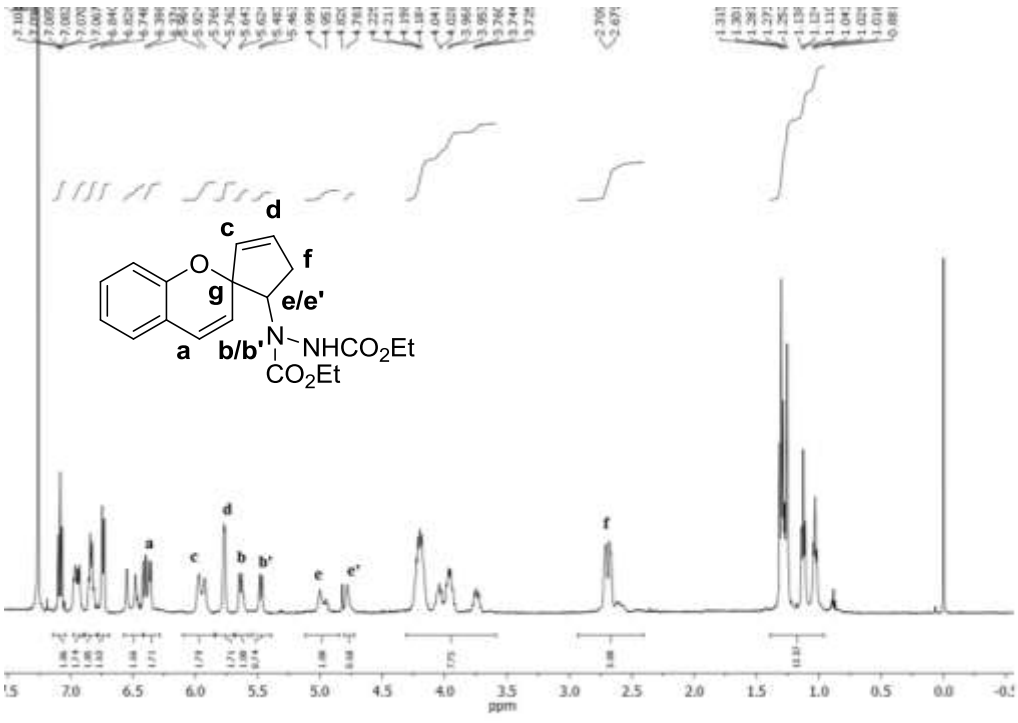


Figure 4.3 ^1H NMR Spectrum of Compound **21ba**

In the ^{13}C NMR spectrum, the ester carbonyls resonated at δ 156.8 and 156.3. ppm. The spiro carbon **g** resonated at δ 89.3 ppm. The carbon attached to the hydrazine was observed at δ 65.3 ppm along with the methylene carbons of the carboethoxy group. The $–CH_2$ group of the cyclopentene resonated at δ 32.6 ppm. Further evidence for the structure was obtained from mass spectral analysis which showed molecular ion peak at *m/z* 381.14082 $(M+Na)^+$.

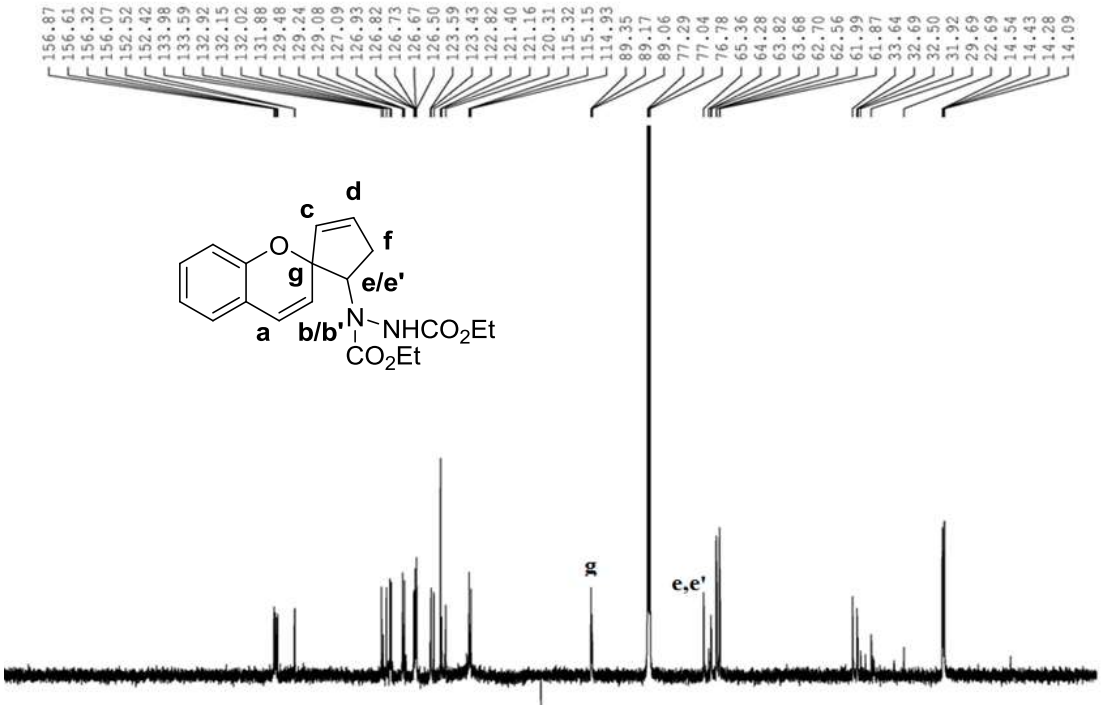


Figure 4.4. ^{13}C NMR Spectrum of Compound **21ba**

In the DEPT 135 spectrum, the quarternary sp^3 carbon was found to be missing as expected. Also, it was clear that the sp^3 carbon of the cyclopentene ring resonated as positive signals at δ 65.86 and 65.69 ppm. The methylene carbons of the carboethoxy group were found as negative signals. Also, the methyl carbon of the carboethoxy group also resonated as positive signals. We were able to clearly identify the –NH protons, sp^3 methine as well as spirocarbon from the HMQC spectral analysis (Figure 4.6). The ^1H-^1H COSY spectrum of the compound **21ba** clearly indicated all the valid correlations. It includes the correlation between the methylene and methyl hydrogens of carboethoxy group. Also the correlation between the sp^3 C-H (**e/e'**) with the methylene CH_2 (f) is clearly seen. The olefins of the

cyclopentene (**c, d**) and the styryl protons (a,b) were showing respective correlations. The methylene hydrogen (f) and sp^3 C-H (e/e') showed strong correlations(Figure 4.7).

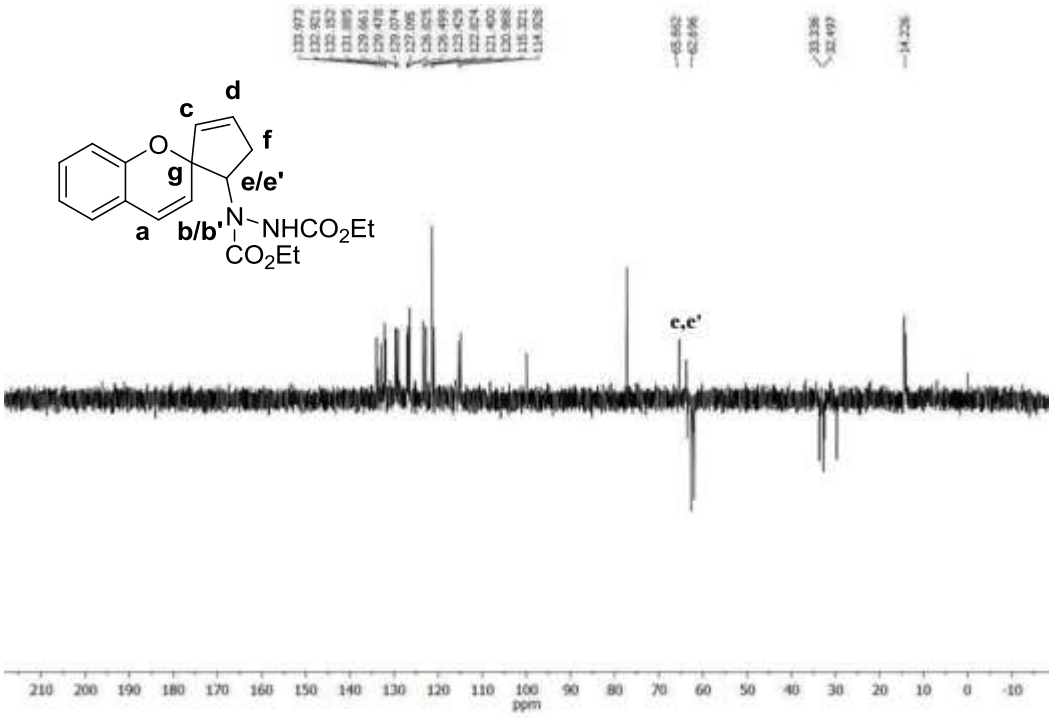
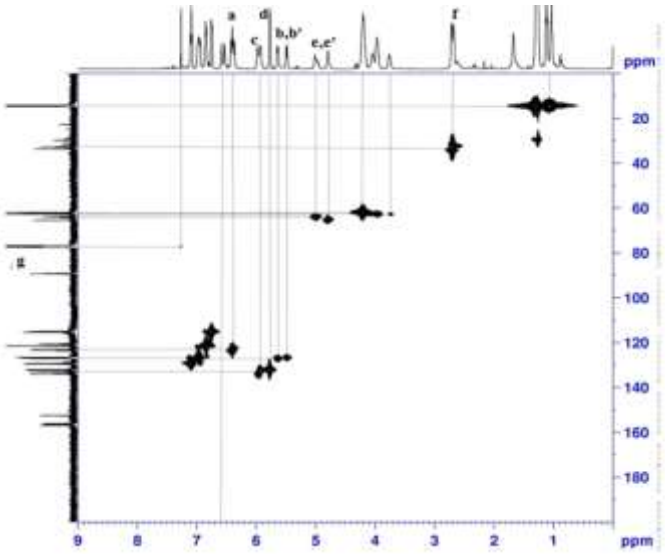


Figure 4.5. DEPT 135 Spectrum of Compound **21ba**



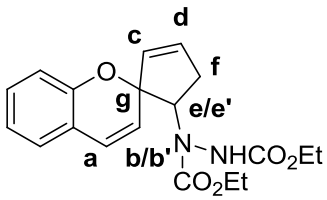
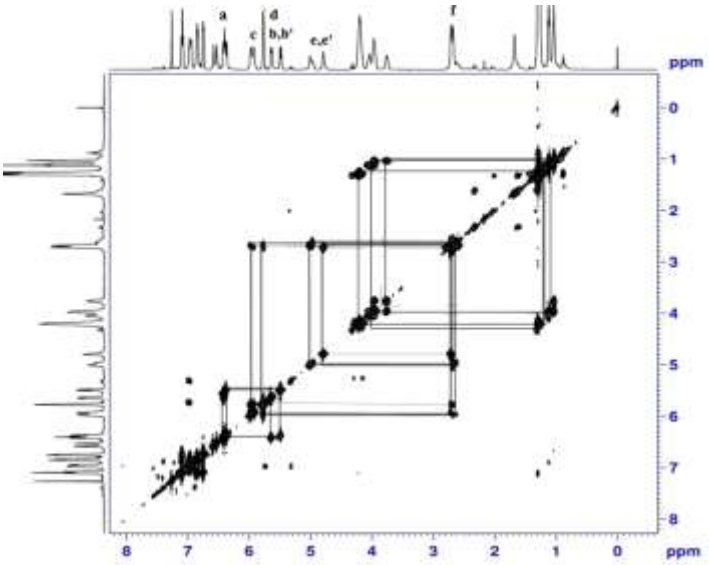


Figure 4.6. HMQC Spectrum of Compound **21ba**



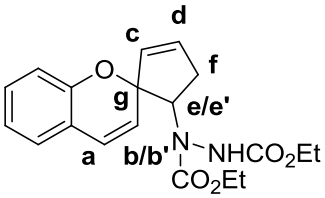
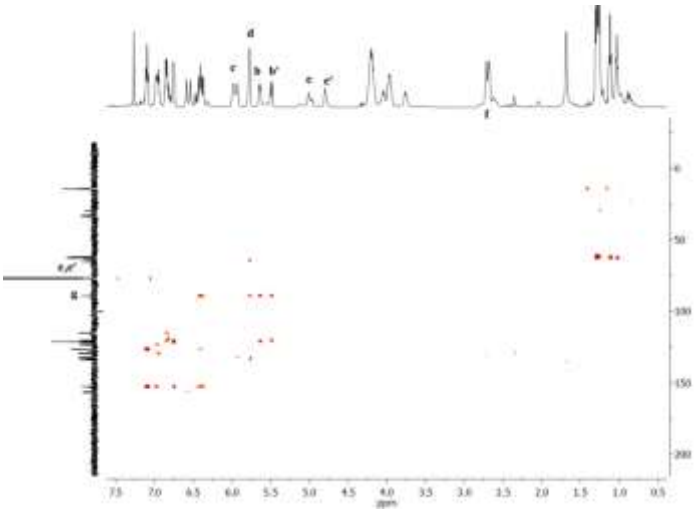


Figure 4.7. ^{1}H-^{1}H COSY Spectrum of Compound **21ba**

In the HMBC analysis, long distant correlations of the spirocarbon **g** with the olefins protons such as **a**, **d** and **c** were observed.



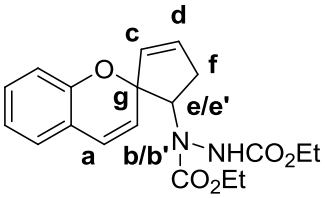


Figure 4.8A. HMBC Spectrum of Compound **21ba**

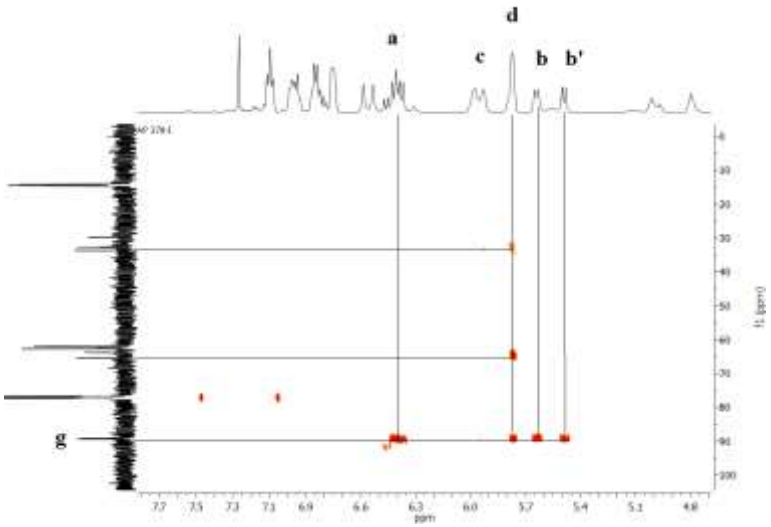
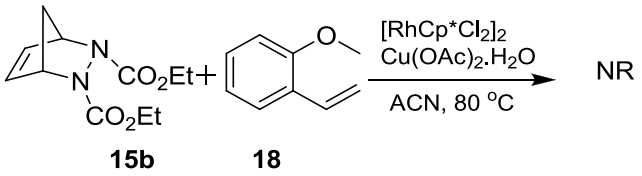


Figure 4.8B. HMBC Spectrum of Compound **21ba**

Detailed optimization studies were carried out to find out the suitable reaction condition which is summarized in Table 4.1. From the optimization data, it is found that certain conditions can selectively form either one of the product. Initially, with 1:1 ratio of the starting materials **15a** and **18a**, 3 mol% of the Rh(III) catalyst and 1.5 equivalents of oxidant in acetonitrile yielded both the ring opened and the annulated products (**20ba** and **21ba**) in 21 and 37% respectively. The effect of various solvents on the reaction outcome was screened and it was found that acetonitrile is the best solvent for the reaction. Then different additives such as AgOAc, NaOAc. Ag_2CO_3, AgOTf, CsOAc were screened. Interestingly, it was found that any other additive than $Cu(OAc)_2.H_2O$ and AgOAC will selectively provide the the ring opened product **20ba** only. Among these additives screened, NaOAc selectively gave the ring opened product **20ba** in 88% yield (table 4.1, entry 5). Similarly elevated equivalents of the starting material **18a** favored the formation of the ring opened product alone. It was evident from the observations that, the role of $Cu(OAc)_2.H_2O$/ AgOAc is necessary for the ring closure. In order to tune the reaction towards the annulated product, the equivalent $Cu(OAc)_2.H_2O$ was increased to 3. Gratifyingly, only the annulated product was formed in 48% yield (table 4.1, entry 10^b).

Also the need of the hydroxyl group for the reaction to furnish either of the products was tested by carrying out the reaction of diazabicyclic olefin **15b** with methyl protected *o*-

vinylphenol in the standard reaction conditions (table 4.1, entry 5 & 10[b]). And the reaction didn't furnish either of the two products (Scheme 4.9).



15b **18**

Scheme 4.9

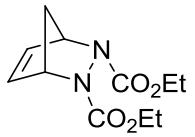
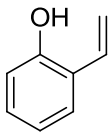
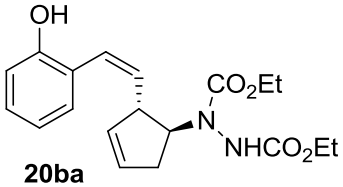
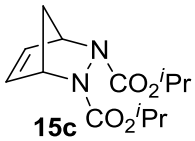
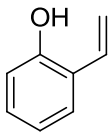
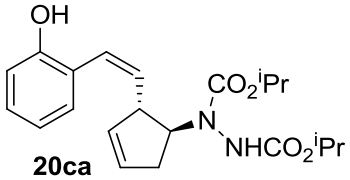
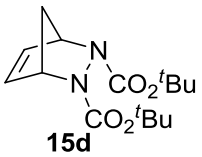
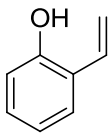
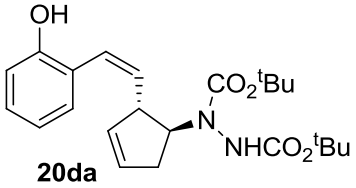
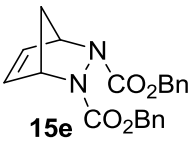
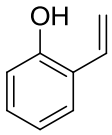
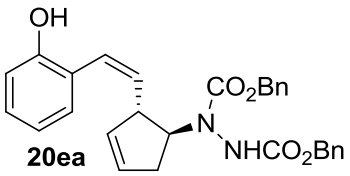
Table 4.1. Optimization Studies

Entry	catalyst	additive	solvent	yield (%) **3a**	**4a**
1	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	ACN	37	21
2	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	toluene	30	13
3	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	DMF	26	13
4	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	DCE	36	20
5	**$[RhCp^*Cl_2]_2$**	**NaOAc**	**ACN**	**88**	**NR**
6	$[RhCp^*Cl_2]_2$	CsOAc	ACN	23	NR
7	$[RhCp^*Cl_2]_2$	AgOAc	ACN	53	trace
8	$[RhCp^*Cl_2]_2$	AgOTf	ACN	NR	NR
9[a]	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2.H_2O$	ACN	32	34
10[b]	**$[RhCp^*Cl_2]_2$**	**$Cu(OAc)_2.H_2O$**	**ACN**	**trace**	**48**
11	Ru(II)	$Cu(OAc)_2.H_2O$	ACN	NR	NR

Reaction Conditions : alkene (1 equiv.), *o*-vinylphenol (1 equiv.), catalyst (3 mol%), additive (1.5 equiv.), solvent (2 mL), 80 °C, 12 h, [a]: *o*-vinylphenol (1.3 equiv.), [b]:$Cu(OAc)_2.H_2O$: 3 equiv.

The generality of the reaction was tested with various diazabicyclic olefins as well as *o*-vinylphenols according to conditions **5** and **10[b]** (Table 4.1). The reactions were found to be general with various substrates in good yields. The results are summarized in table 4.2 and table 4.3**.**

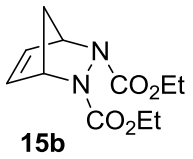
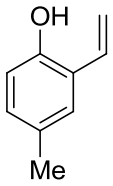
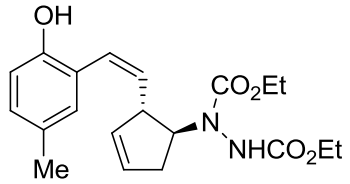
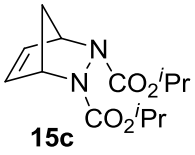
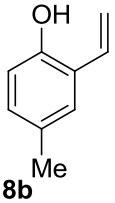
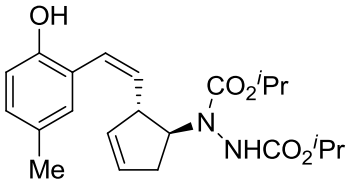
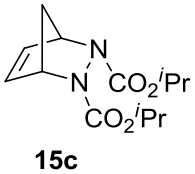
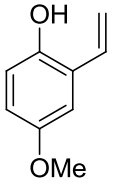
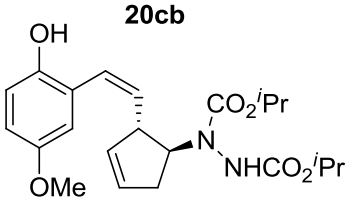
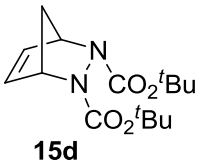
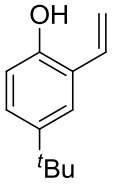
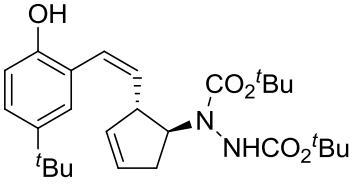
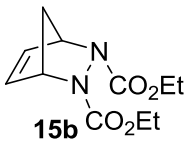
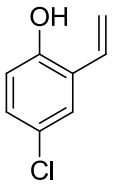
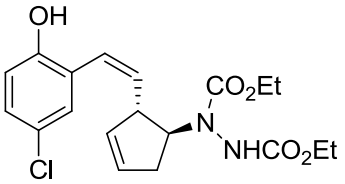
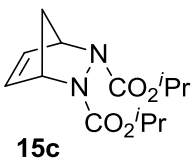
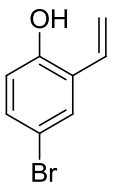
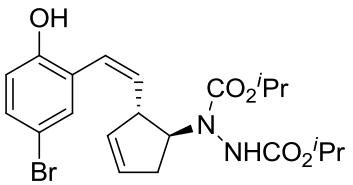
Table 4.2. Rh(III) Catalyzed Reaction of Diazabicyclic Olefins wth *o*- Vinylphenols

entry	diazabicyclic Olefin	*o*-vinlphenol	product	yield
1.	 **15b**	 **18a**	 **20ba**	**88%**
2.	 **15c**	 **18a**	 **20ca**	**83%**
3.	 **15d**	 **18a**	 **20da**	**85%**
4.	 **15e**	 **18a**	 **20ea**	**66%**

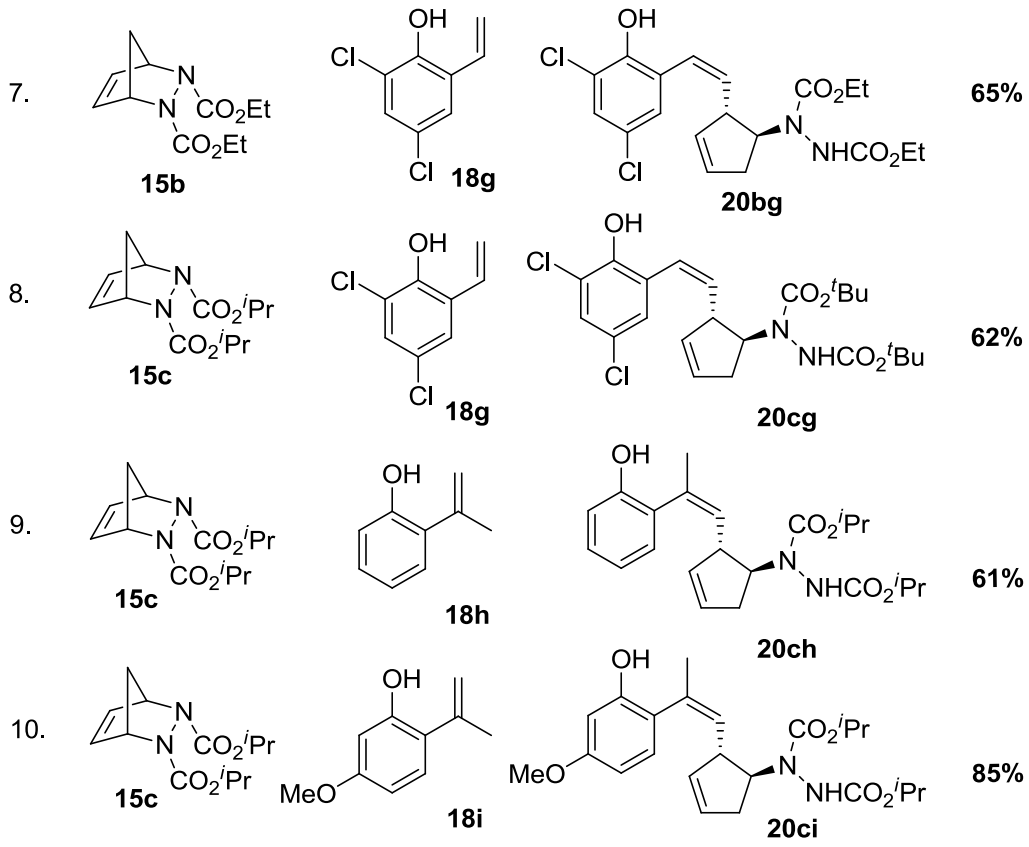
Reaction Conditions : alkene (1 equiv), o-vinylphenol (1.3 equiv.), [$RhCp^*Cl_2$] (3 mol%), NaOAc (1.5equiv.), acetonitrile (2 mL), 80 ^oC, 12 h,

Generality of ring opened products was investigated according to the condition 5 (Table 4.1). The diazabicyclic olefins **15b** to **15e** reacted with o-vinylphenol **18a** to give the product in good to excellent yield (Table 4.2). The reactivity of differently substituted phenols was also explored subsequently. It was found that the ring opening reaction of the diazabicyclic olefin with most of substituted phenols provided the product in moderate to good yield. Electron donating groups on the phenol ring was enhancing the yield of the reaction (entry 3, Table 4.3).

Table 4.3. Rh(III) Catalyzed Reaction of Diazabicyclic Olefins with Substituted *o*-Vinylphenols

entry	diazabicyclic Olefin	*o*-vinlphenol	product	yield
1.	 **15b**	 **18b**	 **20bb**	**77%**
2.	 **15c**	 **18b**	 **20cb**	**75%**
3.	 **15c**	 **18c**	 **20cc**	**85%**
4.	 **15d**	 **18d**	 **20dd**	**66%**
5.	 **15b**	 **18e**	 **20be**	**73%**
6.	 **15c**	 **18f**	 **20cf**	**74%**

Continued.



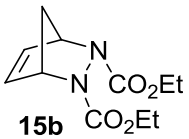
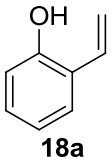
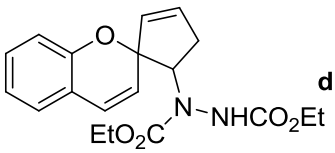
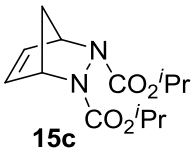
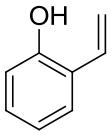
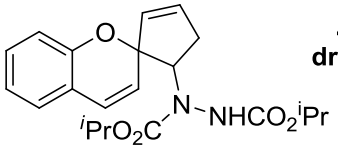
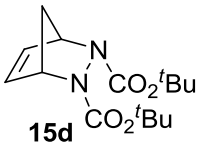
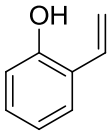
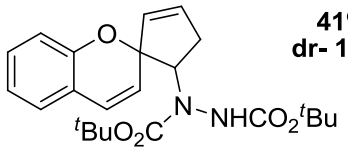
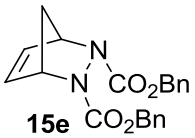
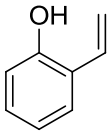
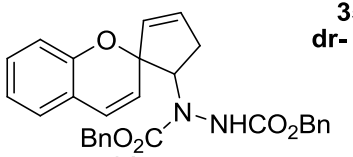
Reaction Conditions : alkene (1 equiv), o-vinylphenol (1.3 equiv.), catalyst (3 mol%), NaOAc (1.5equiv.), acetonitrile (2 mL), 80 ^{o}C, 12 h,

Whereas halogen substitutions on the phenol were negatively affecting the course of the reaction (entries 5 & 6 table 4.3). This was clear as the number of halogens increased the yields further decreased (entries 7 & 8, table 4.3). Similarly bulkier groups on the phenol ring decreased the yield (entry 4, table 4.**3**).

The reaction of phenols with substitutions on the styryl double bond was examined (entry 9, 10, table 4.3). In both cases, the reaction successfully furnished the products in moderate to good yields.

The scope of annulation of different *o*-vinylphenols with diazabicyclic olefins was examined using the optimized reaction condition. (entry 10[b], table 4.1). The results are summarized in table 4.4 and 4.5.

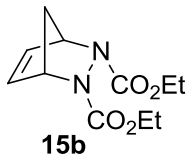
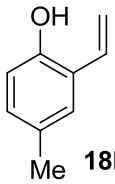
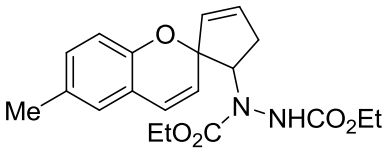
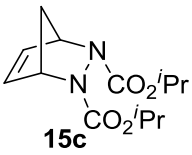
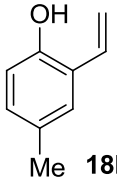
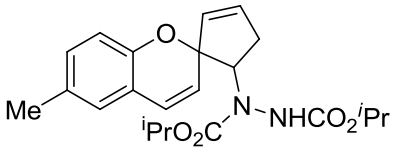
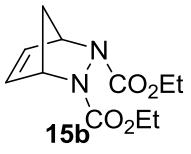
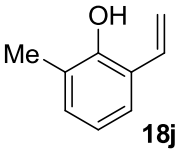
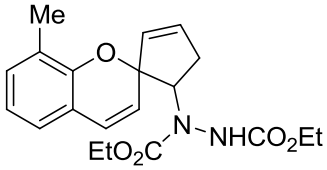
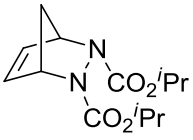
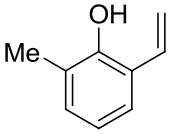
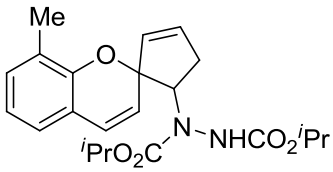
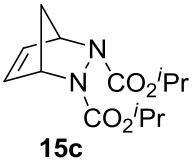
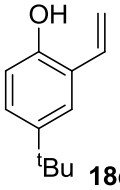
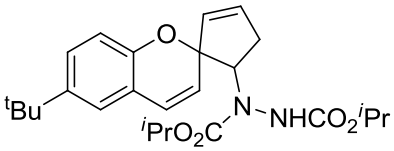
Table 4.4. Rh(III)/Cu(II) Catalyzed Reaction of Diazabicyclic Olefins with o- Vinylphenols

entry	diazabicyclic Olefin	*o*-vinlphenol	product	yield
1.	 **15b**	 **18a**	 **21ba**	**48 %** **dr- 1:1.3**
2.	 **15c**	 **18a**	 **21ca**	**44%** **dr- 1:1.3**
3.	 **15d**	 **18a**	 **21da**	**41%** **dr- 1:1.3**
4.	 **15e**	 **18a**	 **21ea**	**35%** **dr- 1:1.3**

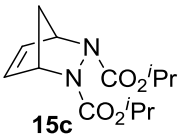
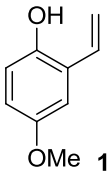
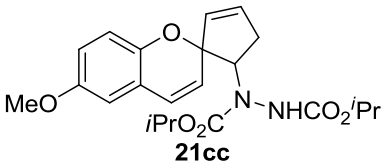
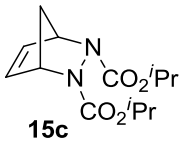
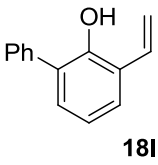
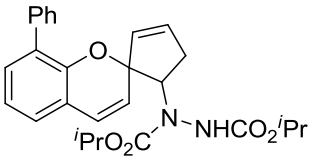
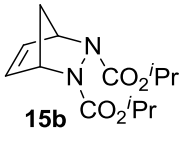
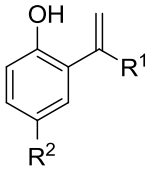
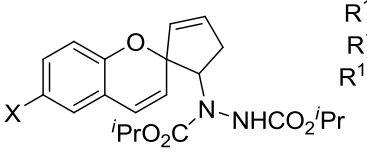
Reaction Conditions : alkene (1 equiv), o-vinylphenol (1.3 equiv.), catalyst (3 mol%), $Cu(OAc)_2.H_2O$ (3 equiv.), acetonitrile (2 mL), 80 ^oC, 12 h,

All of the diazabicyclic olefins **15b** to **15e** reacted with *o*-vinylphenols **18a** furnishing the spiroannulated product as an inseparable mixture of diastereomers in moderate yields. The diastereomeric ratio was found to be 1:1.3 in these four cases (entries 1 to 4, table 4.4). When *o*-vinylphenols with different functional groups were investigated, it was seen that the diastereomeric ratio was slightly increasing with the increase in the bulkiness substitution. Most of the reactions proceeded in moderate yield. Also *o*-vinylphenols with electron deficient functionalities were found to be futile; only electron rich phenols furnished the annulated product (Table 4.5).

Table 4.5. Rh(III)/Cu(II) Catalyzed Reaction of Diazabicyclic Olefins with Substituted *o*-Vinylphenols

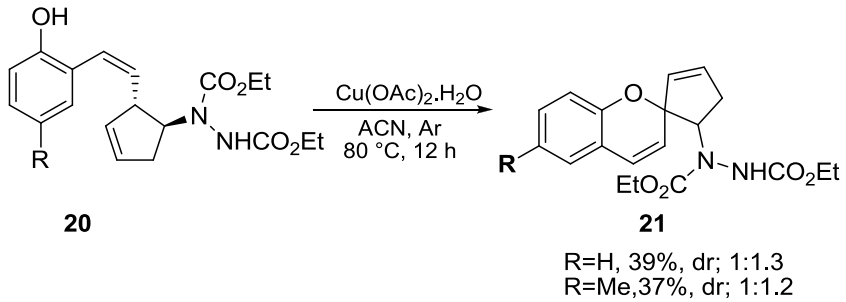
entry	diazabicyclic Olefin	*o*-vinlphenol	product	yield
1.	 **15b**	 **18b**	 **21bb**	**60%** **dr- 1:1.2**
2.	 **15c**	 **18b**	 **21cb**	**56%** **dr- 1:1.1**
3.	 **15b**	 **18j**	 **21bj**	**60%** **dr- 1:1.2**
4.	 **15c**	 **18j**	 **21cj**	**56%** **dr- 1:1.1**
5.	 **15c**	 **18d**	 **21cd**	**58%** **dr- 1:1.6**

Continued.

entry	diazabicyclic Olefin	*o*-vinlphenol	product	yield
6.	 **15c**	 **18c**	 **21cc**	**56%** **dr- 1:1.3**
7.	 **15c**	 **18l**	 **21cl**	**43%** **dr- 1:1.6**
8.	 **15b**			R^1= H, R^2=Cl **0%** R^1=H, R^2=Br **0%** R^1= Me, R^2=H **0%**

Reaction Conditions : alkene (1 equiv), o-vinylphenol (1.3 equiv.), catalyst (3 mol%),$Cu(OAc)_2.H_2O$ (3.0 equiv.), solvent (2 mL), 80 ^oC, 12 h,

From the optimization experiments, it became obvious that as amount $Cu(OAc)_2 .H_2O$ increases, the reaction selectively provides the annulated product. Thus we envisaged that $Cu(OAc)_2 .H_2O$ plays a crucial role in the annulation of the ring opened product 2**0** was treated the with one equivalent $Cu(OAc)_2.H_2O$ in acetonitrile, we were pleased to obtain the annulated product **21** was yielded in 39% yield as a mixture of two diastereomers. The generality of this reaction was also tested with another substrate as well (Scheme 4.10).

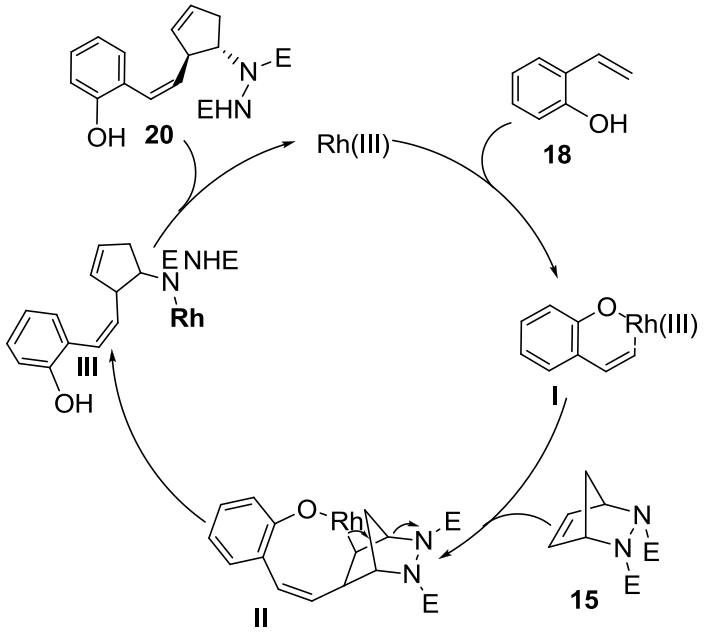


Scheme 4.10

4.4.2. Mechanism

Step 1: Rhodium Catalyzed C-H Activation

Mechanistic route of the reaction is not completely explained so far. Still, on the basis of previous reports herein we propose a plausible mechanism. In the first step, the active form of the catalyst is formed by the replacement of two chloride ions by acetate ions.

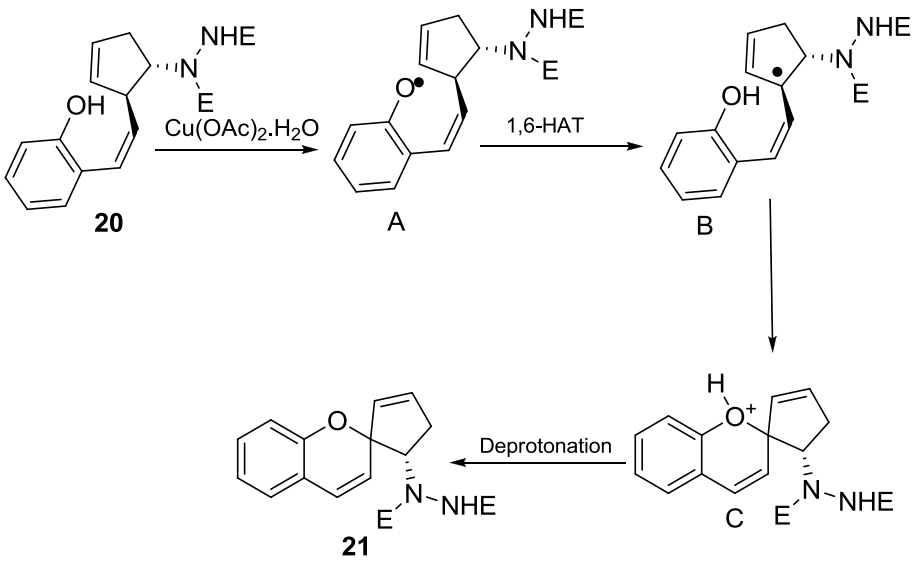


Scheme 4.11

Then the phenolic substrate replaces one acetate ion to furnish intermediate **I**. It results in intermediate **II** by the heterobicyclic olefin insertion to this intermediate. On *β*-heteroatom elimination of the rhodium species provides the ring opened product **20** (Scheme 4.11).

Step 2: Cu(II) Mediated Annulation

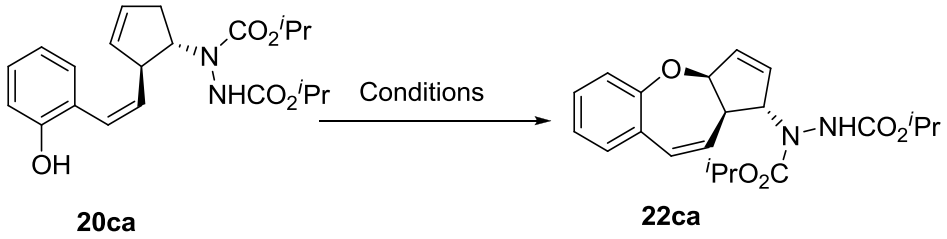
The second step of the mechanism may follow a copper mediated radical pathway; which is well described in the literature.[14] Cu(II) species would provide hydroxyl radical **A**, which may undergo a 1,6-H radical shift to afford **B**.[15] The hydroxyl group would attack on the radical **B** in an intramolecular way to result in the species **C**. The intermediate upon deprotonation results in the spiroannulated product **21**.



Scheme 4.12

4.4.3. Palladium Catalyzed Intramolecular Cyclization of the Ring Opened Product

The structure of the ring opened product widens the scope of further annulations. We utilized different annulation methods taking **20ca** as the starting material (table 4.6, entries 1-4), but initial attempts were not succeeded. Afterwards, when we adapted the catalytic system $Pd(OAc)_2$, 1,10-phenanthroline in presence of $Cu(OAc)_2$ as the oxidant in acetonitrile at 80 ^oC,[8] the annulated product **22ca** was furnished in 24 % yield (Scheme 4.13). The yield increased gratifyingly when the reaction was tried in DCE. Further, when the temperature of the reaction was increases to 110 ^oC, the yield of the reaction was increased to 60% (table 4.7, entry 7).



Scheme 4.13

Table 4.6. Optimization of Reaction Conditions

Sl No	Catalytic System	Additive	Solvent	Temperature	Yield
1.	I_2	K_2CO_3	THF	rt	NR
2.	$PhI(OAc)_2$	-	ACN	rt	NR
3.	DDQ	-	Benzene	80 ^oC	NR
4.	$Pd(OAc)_2$	$Cu(OAc)_2$	ACN	80 ^oC	NR
5.	$Pd(OAc)_2$/1,10-Phen	$Cu(OAc)_2$	ACN	80 ^oC	24%
6.	$Pd(OAc)_2$/1,10-Phen	$Cu(OAc)_2$	DCE	80 ^oC	33%
7.	$Pd(OAc)_2$/1,10-Phen	$Cu(OAc)_2$	DCE	110 ^oC	60%

The structure of the compound **22ca** was elucidated based on ^1H and ^{13}C NMR techniques. And the stereochemistry of the compound was confirmed on the basis of different 2D NMR analyses such as COSY, NOESY, NOE difference analysis *etc.*

In the proton NMR spectrum, the olefinic proton **a** was found as a doublet δ 6.41 ppm. The aromatic protons were discernible between δ 7.08 and 7.02 ppm. The two olefins of the cyclopentene (**c** & **d**) as well the styryl olefin **b** were found as a broad singlet at δ 6.21 ppm. Among the three sp^3 hydrogens of the cyclopentene ring, the one which is on the carbon attached to the nitrogen was found as multiplet between δ 5.33 to 5.39 ppm. The second one **f** on the carbon attached to the oxygen atom was found as a singlet at δ 4.85 ppm. Third one among them **g** resonated at δ 2.95 ppm as a singlet. The two isopropyl C-H groups resonated as multiplet between δ 5.01 and 4.96 ppm. Also the six methy groups of each isopropyl groups resonated as multiplet between δ 1.29 to 1.26 ppm. The ^{13}C NMR gave the carbonyl carbon at δ 152.9 ppm. The aromatic carbon attached to the oxygen resonated at δ 157. 59 ppm. Apart from the olefins and other aromatic protons in the region 137.36 and 121.81 ppm, the sp^3 carbon **f** resonated at δ 86.51 ppm. Similarly the carbon **e** and **g** were discernible at δ 68.71 and 48.50 ppm respectively. The isopropyl methine carbon appeared at δ 70.59 ppm. Also the methyl carbons of the isopropyl group resonated at δ 20.01 ppm. The mass

spectrum which showed a peak at *m/z* = 409.17469 corresponding to the $[M+Na]^+$ peak; provided additional evidence for the structure assigned.

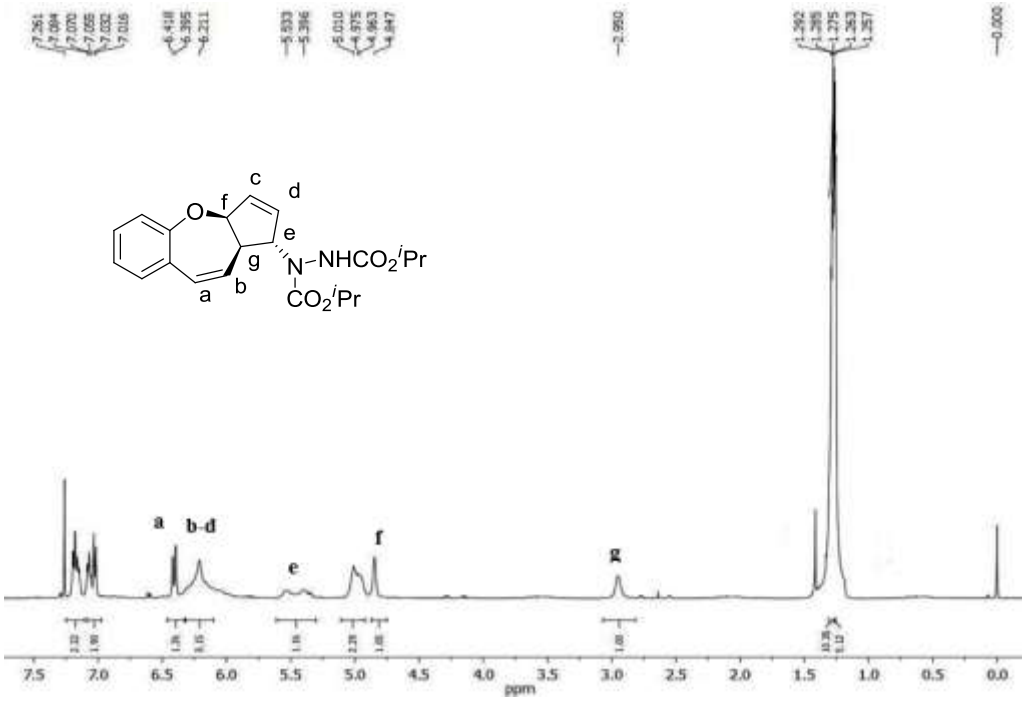


Figure 4.9. ^{1}H NMR Spectrum of Compound **22ca**

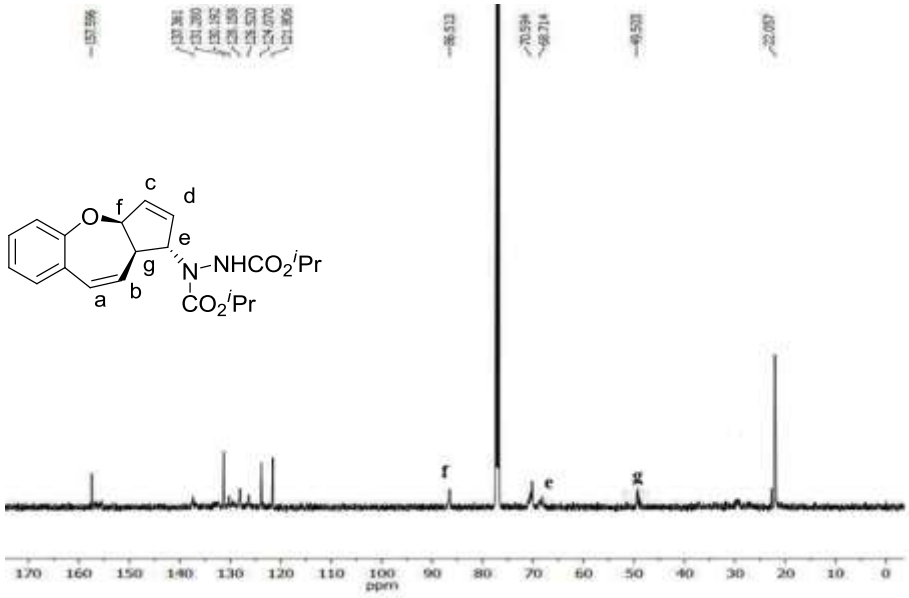
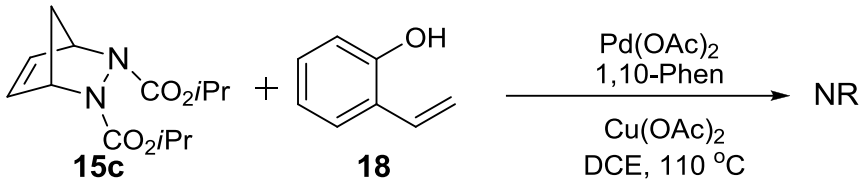


Figure 4.10. ^{13}C NMR Spectrum of Compound **22ca**

Also out of curiosity, we considered the one pot synthesis of the cyclopentene fused oxepines by reacting diazabicyclic olefin **15c** and *o*-vinylphenol **18** in the optimized reaction condition. But our efforts were unsuccesful (Scheme 4.14**)**.



Scheme 4.14

It is evident from the literature that the compounds synthezised, benzoxepines are privileged motifs in the world of natural products.[16,17] Figure 4.11 shows some of the important benzoxepines found in natural sources.

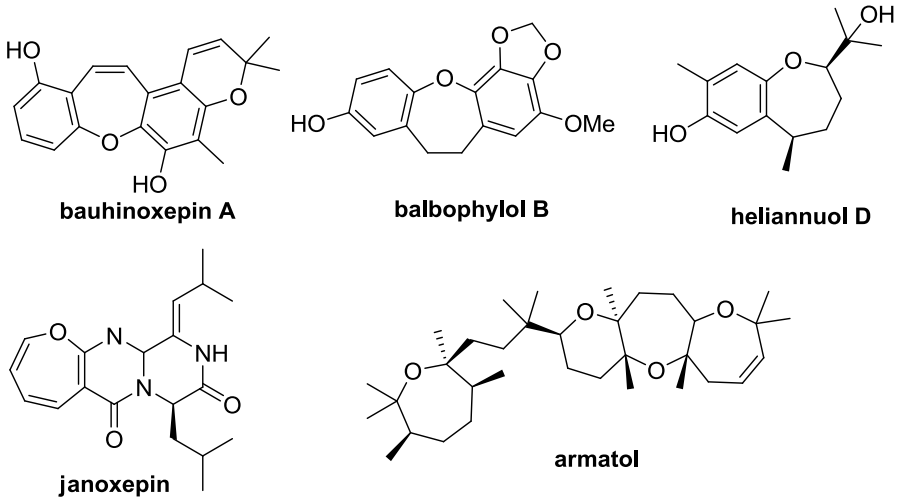
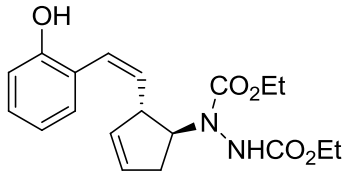
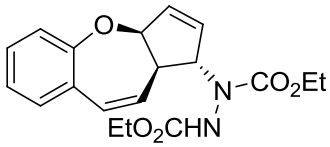
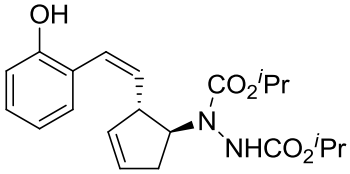
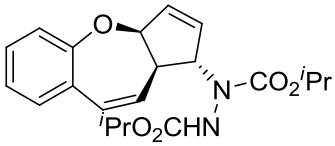
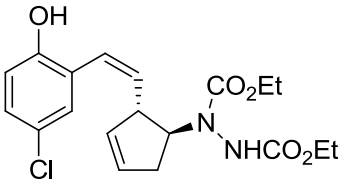
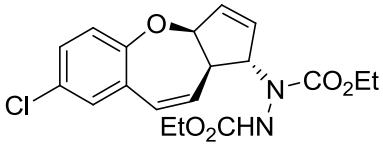
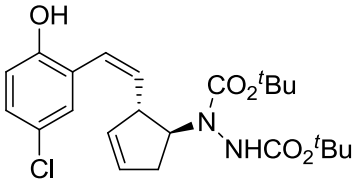
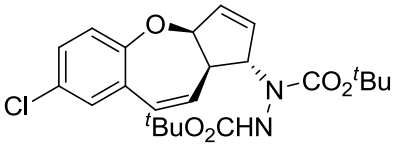


Figure 4.11

By considering the biological significance of the synthesized core, we went on to explore the scope of the reaction in terms of different substrates. The reaction was found to be feasible with respect to different substrates including electron deficient functional group. All of them provided moderate yield (Table 4.8).

Table 4.7. Palladium Catalyzed Intramolecular Reaction Ring Opened Product

entry	starting material	product	yield
1.	 **20bb**	 **22bb**	**66%**
2.	 **20ca**	 **22ca**	**60%**
3.	 **20be**	 **22be**	**63%**
4.	 **20de**	 **22de**	**50%**

Reaction Conditions: ring opened product **25** (1 equiv.), $Pd(OAc)_2$(5 mol%), $Cu(OAc)_2$ (1.0 equiv.),1,10-phenanthroline (10 mol%) in DCE (2 mL) for 12h

4.4.4. Assigning Stereochemistry

To assign the structure and stereochemistry of the cyclopentene fused benzoxepine derivatives, we have carried out various 2D NMR experiments of one of the synthesized compounds **22be**.

In the ^{1}H NMR spectrum (Figure 4.12), the aromatic protons were discernible between δ-7.16 to 6.94 ppm. The olefinic protons of both cyclopentene and the oxepine ring resonated as multiplets between δ 6.33 to 6.19 ppm. The sp^3 C-H, attached to the oxygen atom appeared as mutltiplet between δ 5.53 to 5.51 ppm. Also the sp^3 C-H, attached to the nitrogen was discernible as a singlet at δ 4.81 ppm. Similarly the other sp^3 C-H of the cyclopentene ring resonated at δ 2.96 ppm as a singlet. The methylene protons of the carboethoxy group resonated as multiplet between δ 4.23 to 4.22 ppm. Finally, the methyl groups of the carboethoxy group was appeared as a multiplet between δ 1.29 to 1.28 ppm.

In the ^{13} C NMR spectrum, the ester carbonyl resonated at δ 155.9 ppm. The sp^3 carbon of the cyclopentene ring attached to the nitrogen atom resonated at δ 86.7 ppm. Also the sp^3 carbon of the cyclopentene ring attached to the oxygen atom appeared at δ 68.5 ppm. . Similarly the other sp^3 carbon of the cyclopentene ring resonated at 49.2 ppm. The methylene carbon of the carboethoxy group was discernible at δ 62.2 ppm. Whereas the methyl carbons of the carboethoxy groups resonated at δ 14.5 ppm (Figure 4.13).

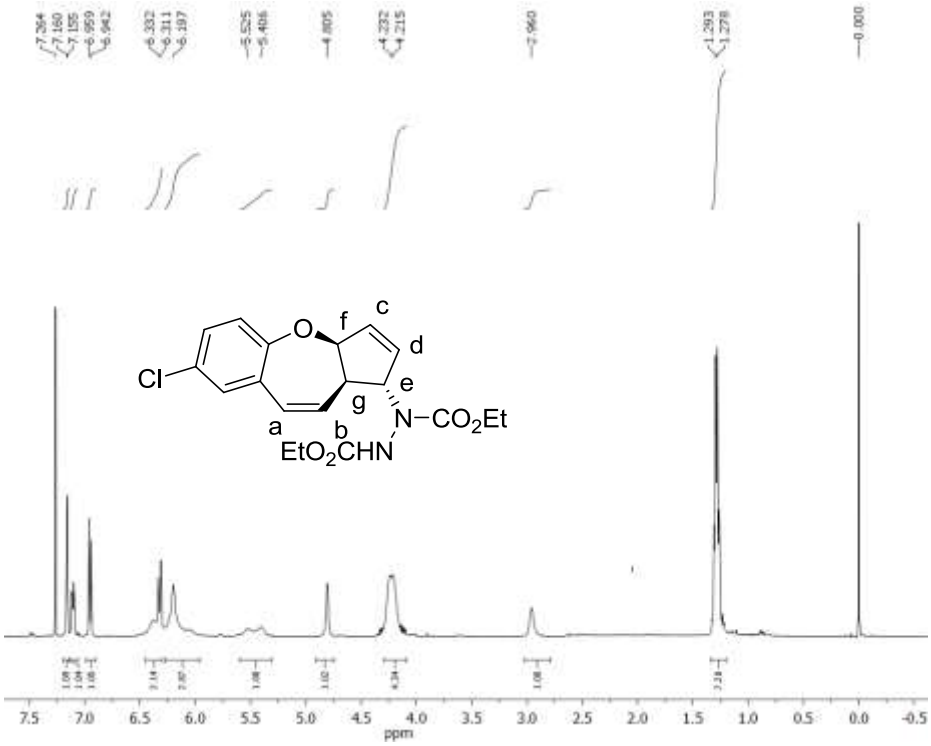


Figure 4.12. ^{1}H NMR Spectrum of **22be**

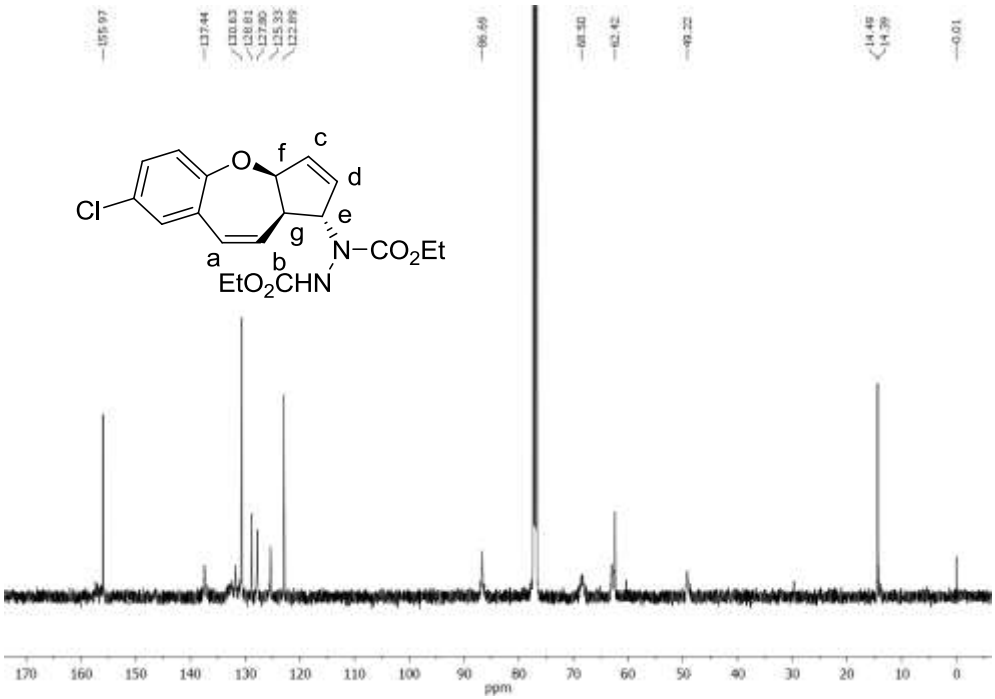


Figure 4.13. ^{13}C NMR Spectrum of **22be**

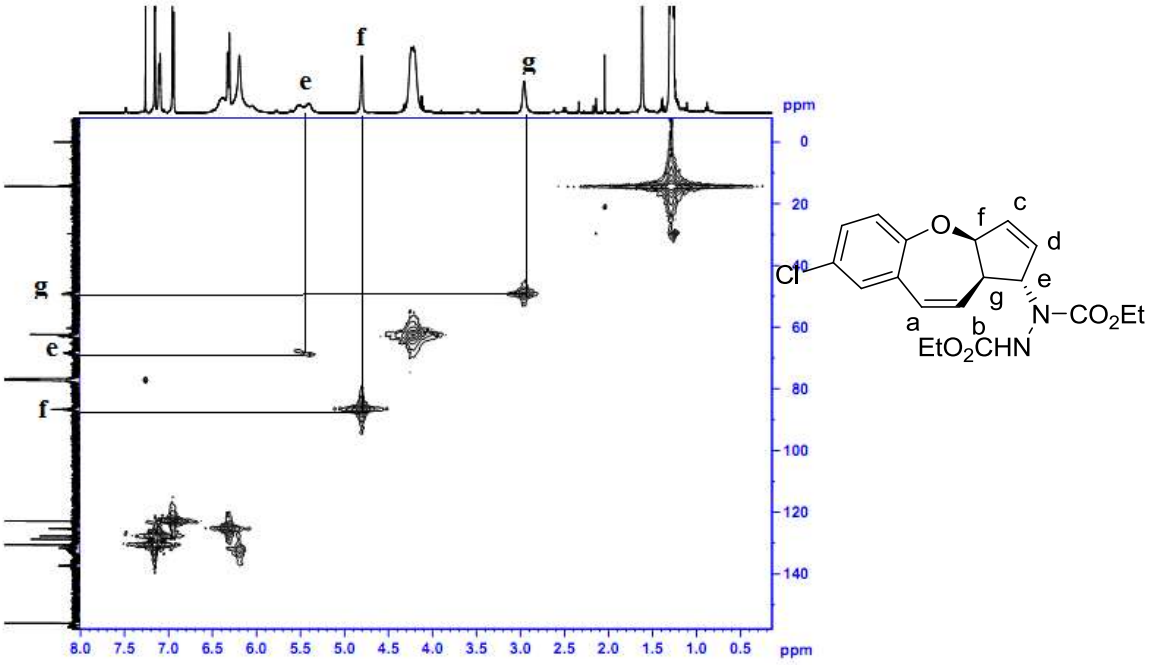
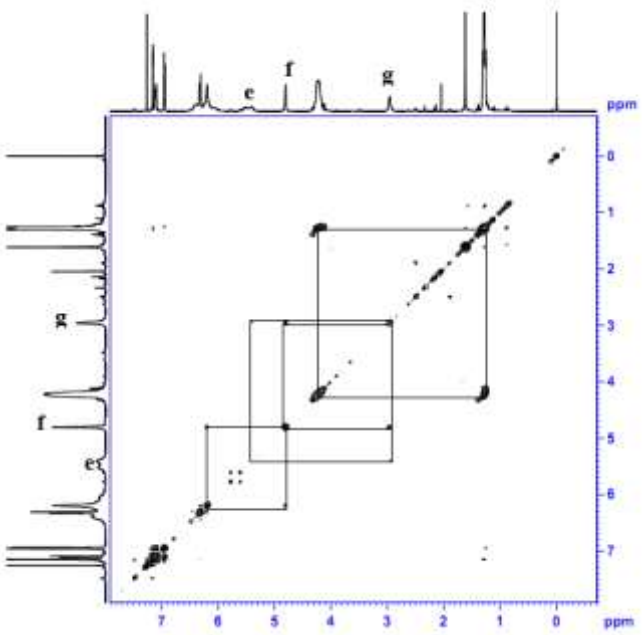


Figure 4.14. HMQC Spectrum of **22be**



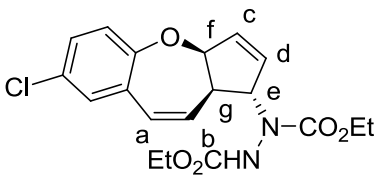
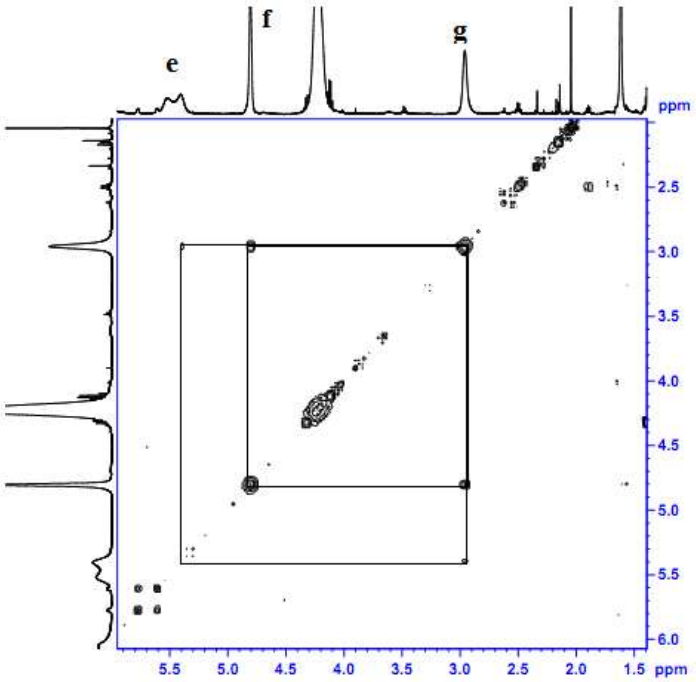


Figure 4.15A. ^{1}H-^{1}H COSY Spectrum of **22be**



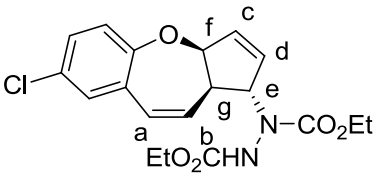


Figure 4.15B. ^{1}H-^{1}H COSY Spectrum of **22be**

In the HMQC the carbons corresponding to each protons were able to assign correctly to their respective carbons (Figure 4.14).

In the ^{1}H-^{1}H COSY spectra, the sp^3 proton **e** showed correlations with the neighbouring sp^3 protons **e** and **f**. Also it is clearly seen that the olefinic protons have correlation with the neighboring sp^3 protons. Proton attached to the oxygen **f** atom and proton on the carbon bearing hydrazine moiety **e** didn't exhibited correlations (Figure 4.15A and B.).

The correlations between nearby protons became more visible in NOESY spectrum Figure 4.16). In the NOESY spectrum of **22be,** the sp^3 proton **f** showed interactions with the multiplet of the olefin proton as well as **g**. Also it was evident that the olefin proton clearly gives a correlation with the sp^3 proton **g**. The interaction between the sp^3 protons **f** and **e** were absent as expected.

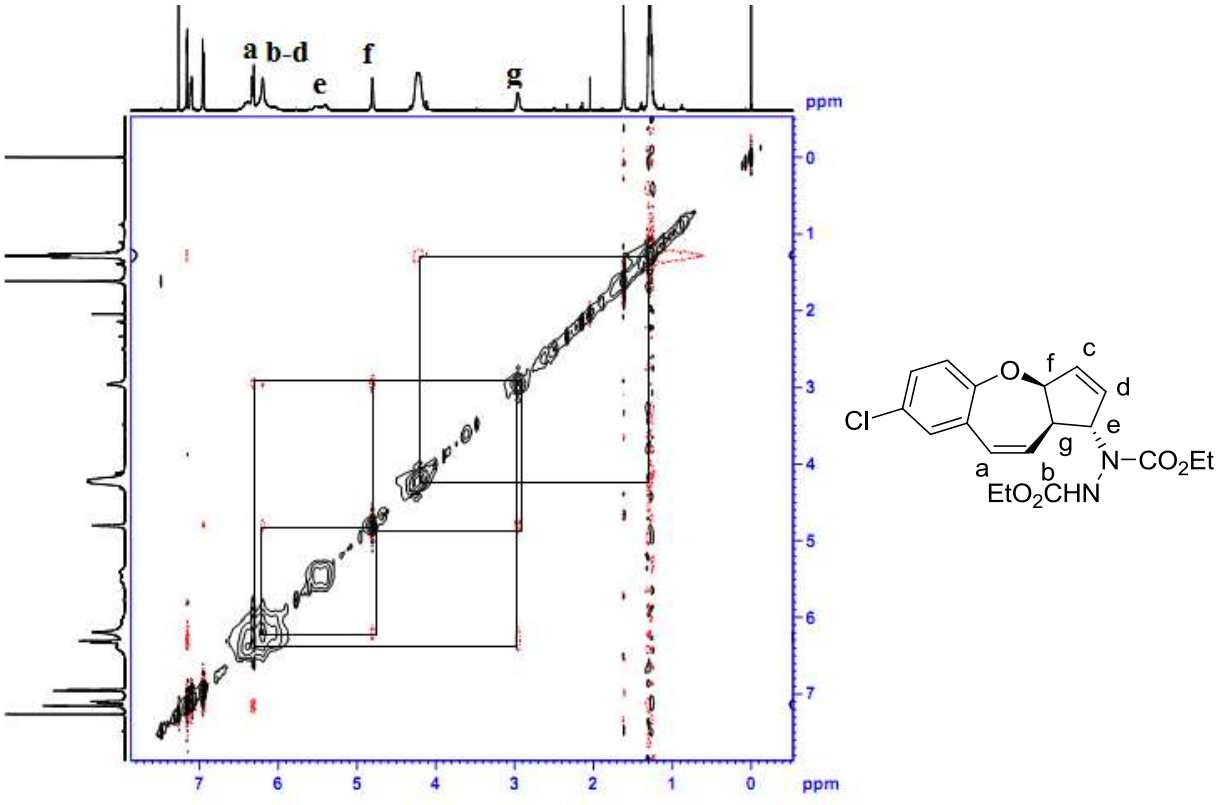


Figure 4.16 NOESY spectrum of **22be**

We have also carried out 1D NOE experiments of **22be** (Figure 4.17). Irradiation of one of the sp^3 proton **f**; attached to the carbon bearing oxygen, the other sp^3 proton of the cyclopentene ring **g** showed enhancement. Whereas the sp^3 proton **e** was unaffected. Similarly, when **g** was irradiated, only the signal corresponding to **f** was enhanced. Also there were no enhancements in any of the signals on irradiation of **e**. This gives a clear indication that both the ring junction protons have a *cis* stereochemistry to each other whereas the sp^3 proton on the carbon bearing nitrogen **e** has the opposite stereochemistry compared to the ring junction methine protons.

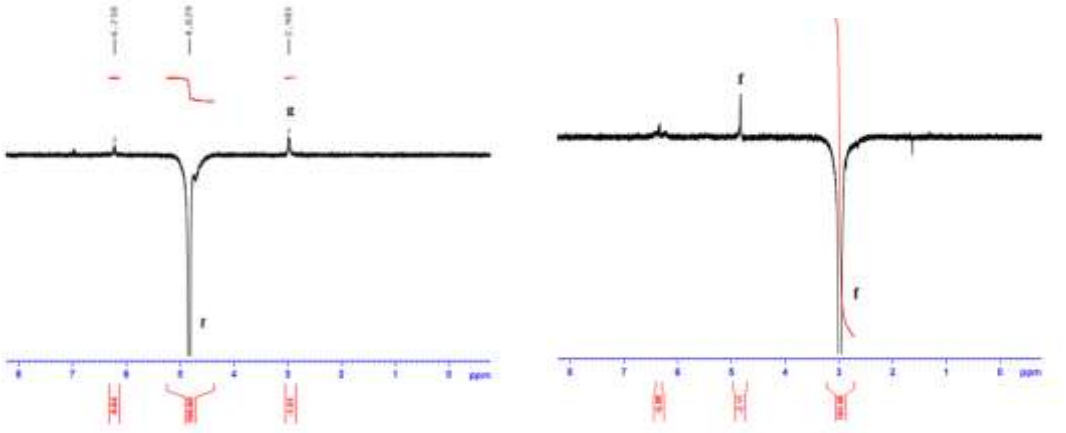
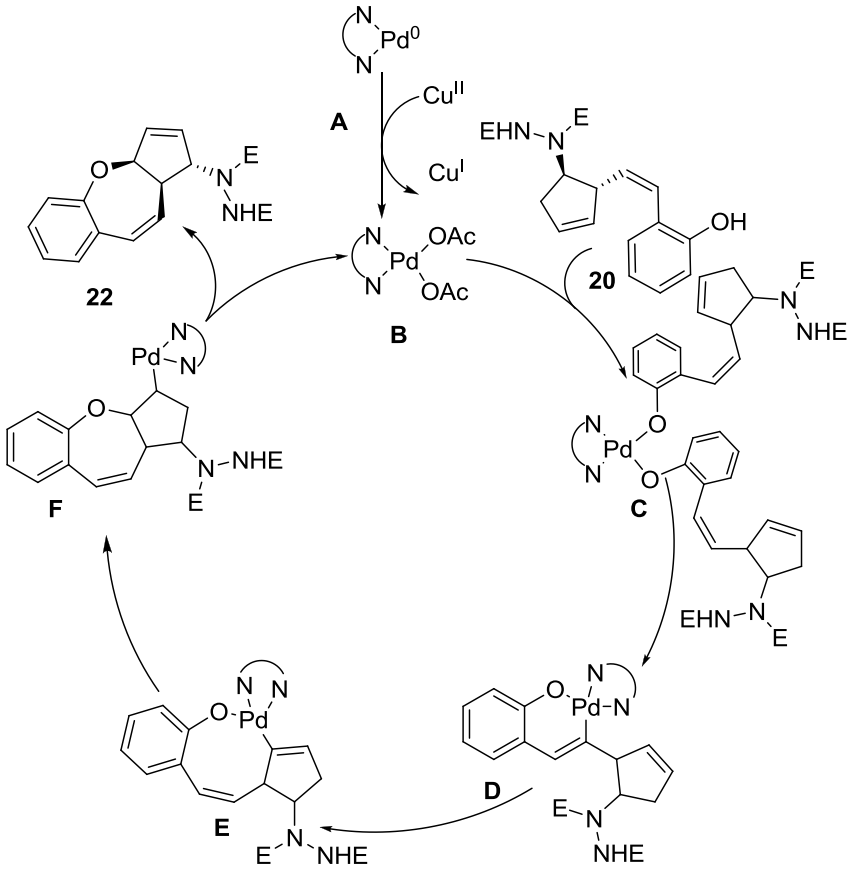


Figure 4.17. NOE Difference spectrum of **22be**

4.4.5. Mechanism

A plausible mechanism for the palladium catalyzed intramolecular cyclization of the ring opened product is detailed in the following scheme (Scheme 4.16). The catalytic cycle is initiated by the oxidation of the Pd(0) species to Pd(II) by the oxidant. Followed by this, the phenol derivative **25** attacks on the electrophilic palladium species to get **C**. Intramoleclar C-H insertion by the palladium complex leads to the species **D**. Successively, the metallacycle expands from **D** to **E** by 1, 3- palladium migration. Later, **E** delivers the key intermediated **F**.[18] The catalytic cycle is completed by the liberation of the product **27** along with the subsequent β-hydride elimination of the palladium complex.



Scheme 4.16

4.5. Conclusions

The ability to tune the reaction conditions by varying the ligand, base, solvent, temperature and additives to optimize the desired process makes transition metal catalyzed reactions so versatile. Herein we disclosed a Rh(III) catalyzed additive driven, one pot strategy for the access of a cyclopentene fused spirocycle from easily accessible vinyl phenols and diazabicyclic olefins along with the access of sp^2 C-H activated ring opened product. This methodology helps in the synthesis of heterocycles which are otherwise difficult to synthesis. Also we have successfully demonstrated the palladium catalyzed intramolecular annulation of the ring opened product.

4.6. Experimental Section

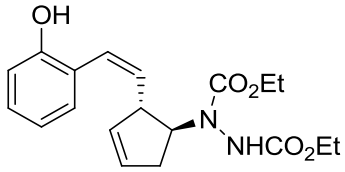
4.6.1. General methods are briefly described in Chapter 2.

4.6.2. General Experimental Procedure for Rhodium Catalyzed C-N Bond Cleavage of Diazabicyclic Olefins *via* C-H Activation of *o*-Vinylphenols

A mixture of diazabicyclic olefin (1 equiv.), o-vinylphenol (1.3 equiv.), $[RhCl_2Cp^*]_2$ (3 mol%) and NaOAc (1.5 equiv.) were weighed in a Schlenk tube and degassed for 10 minutes. Dry acetonitrile (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 80 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the ring opened product *via* C-H activation.

Diethyl 1--2-(2-hydroxystyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 20ba

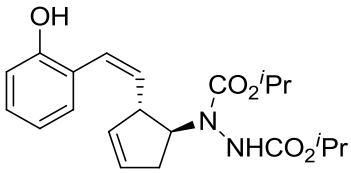
Following the general procedure, diazabicyclic olefin (50 mg, 0.2083 mmol), o-vinylphenol (33 mg, 0.2708 mmol), $[RhCl_2Cp^*]_2$ (4 mg, 0.0062 mmol)and NaOAc (26 mg, 0.3125 mmol) in 2 mL CH_3CN at 80 ^oC under argon atmosphere for 16 h gave the product as a coloueless viscous liquid in 88% (66 mg) yield.



R_f : 0.48 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.18 (brs, 1H), 7.04 (d, J=10 Hz, 1H), 6.92-6.84 (m, 2H), 6.46 (d, J=11 Hz, 1H), 5.78 (brs, 1H), 5.70 (s, 1H), 5.49 (s, 1H), 4.73 (brs, 1H), 4.17- 4.10 (m, 4H), 3.65 (s, 1H), 2.57-2.34 (m, 2H),1.38-1.13 (m, 6H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.7, 156.2, 154.3, 131.8, 129.6, 129.4, 128.7, 126.6, 124.1, 120.5, 120.3, 116.4, 115.8, 65.7, 62.3, 46.2, 34.7, 14.4, 14.1 ppm. **HRMS (ESI):** calcd for $C_{19}H_{24}N_2NaO_5$ $(M+Na)^+$: 383.15829; found 383.15881.

Diisopropyl 1-(2-(2-hydroxystyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 20ca

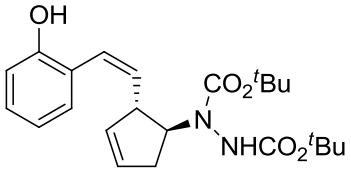
Following the general procedure, diazabicyclic olefin (50 mg, 0.1866 mmol), o-vinylphenol (33 mg, 0.2749 mmol), $[RhCl_2Cp^*]_2$ (4 mg, 0.0062 mmol)and NaOAc (26 mg, 0.3125 mmol) in 2 mL CH_3CN at 80 ^oC under argon atmosphere for 16 h gave the product as a coloueless viscous liquid in 83 % (66 mg) yield.



R_f : 0.51 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.18-7.17(m, 1H), 7.01 (d, J =7.5 Hz, 1H), 6.93-6.83 (m, 2H), 6.44 (d, J =11 Hz, 1H), 5.87 (brs, 1H), 5.70(s, 1H), 5.45(s, 1H), 4.92-4.48 (m, 3H), 3.57 (s, 1H), 2.57-2.39 (m, 2H), 1.27-1.20 (m, 12H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 153.3, 153.1, 145.9, 134.8, 129.9, 128.3, 119.9, 116.5, 70.3, 60.4, 47.9, 32.2, 21.9, 21.8 ppm. **HRMS (ESI):** calcd for $C_{21}H_{28}N_2NaO_5$ $(M+Na)^+$: 411.18959; found 411.18833.

Di-tert-butyl 1-(2-(2-hydroxystyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 20da

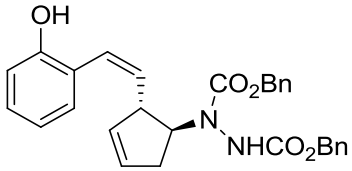
Following the general procedure, diazabicyclic olefin (50 mg, 0.1677 mmol), o-vinylphenol (26 mg, 0.2181 mmol), $[RhCl_2Cp^*]_2$ (3 mg, 0.0050 mmol) and NaOAc (21 mg, 0.2516 mmol) in 2 mL CH_3CN at 80 ^oC under argon atmosphere for 16 h gave the product as a yellow viscous liquid 79% (55 mg) yield.



R_f : 0.53 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.16-7.13 (m,1H), 7.03-7.02 (m, 1H), 6.89-6.84 (m, 2H), 6.44 (d, J = 10.5 Hz, 1H), 5.97-5.82 (m, 1H), 5.69 (s, 1H), 5.47-5.45 (brs, 1H), 4.70 (brs, 1H), 3.54 (brs, 1H), 2.53- 2.39 (m, 2H), 1.47-1.40 (m, 18H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** 155.9, 155.1, 152.8, 131.7, 129.6, 128.9, 128.7, 128.5, 128.2, 126.9, 124.8, 120.6, 120.8, 116.0, 81.6, 64.2, 63.2, 46.6, 34.7, 28.2, 28.2, 28.2 ppm. **HRMS (ESI):** calcd for $C_{23}H_{32}N_2NaO_5$ $(M+Na)^+$: 439.22089; found. 439.22089.

dibenzyl 1-(2-(2-hydroxystyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 20ea

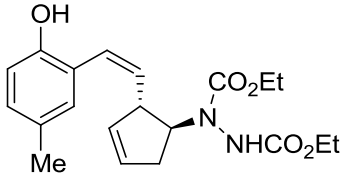
Following the general procedure, diazabicyclic olefin (50 mg, 0.1373 mmol), o-vinylphenol (21 mg, 0.1785 mmol), $[RhCl_2Cp^*]_2$ (4 mg, 0.0062 mmol) and NaOAc (17 mg, 0.2059 mmol) in 2 mL CH_3CN at 80 ^oC under argon atmosphere for 16 h gave the product as a yellow viscous liquid 66 % (44 mg) yield.



R_f : 0.48 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.29-7.23 (m, 2H), 7.09 (t, 1H), 6.94 (s, 1H), 6.83-6.82 (m, 2H), 6.41 (d, J=10.5 Hz, 1H), 6.02-5.69 (m,2 H), 5.46 (s, 1H), 5.12-5.04 (m, 4H), 4.77 (brs, 1H), 3.62 (s,1H), 2.54-2.28 (m, 2H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 154.9, 152.0, 135.7, 135.5, 128.6, 128.5, 128.2, 127.9, 122.8, 120.6, 67.4, 60.3, 44.8, 34.2 ppm. **HRMS (ESI):** calcd for $C_{29}H_{28}N_2NaO_5$ $(M+Na)^+$: 507.18959; found 507.19073.

Diethyl 1-(-2-(2-hydroxy-5-methylstyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 20bb

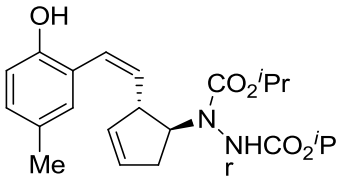
Following the general procedure, diazabicyclic olefin (50 mg, 0.2083mmol), o-vinylphenol (36 mg, 0.2708mmol), $[RhCl_2Cp^*]_2$ (4 mg, 0.0062 mmol) and NaOAc (26 mg, 0.3125 mmol) in 2 mL CH_3CN at 80 ^oC under argon atmosphere for 16 h gave the product as a yellow viscous liquid 77% (60 mg) yield.



R_f : 0.67 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 6.98-6.93 (m, 1H), 6.81-6.79 (m, 2H), 6.41 (d, J = 11 Hz, 1H), 5.78-5.69 (m, 3H), 5.47 (s, 1H), 4.74 (brs, 1H), 4.19-4.07 (m, 4H), 3.59 (s, 1H), 2.56-2.38 (m, 2H), 2.28 (s, 1H), 1.26-1.22 (m, 6H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 157.2, 151.1, 129.8, 129.7, 129.4, 128.1, 127.7, 125. 6, 124.4, 123.7, 115.7, 72.6, 62.6, 44.9, 30.9, 20.4 ppm. **HRMS (ESI):** calcd for $C_{20}H_{26}N_2NaO_5$ $(M+Na)^+$: 397.17394; found 397.17360.

Diisopropyl 1-(2-(2-hydroxy-5-methylstyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 20cb

Following the general procedure, diazabicyclic olefin (50 mg, 0.1866 mmol o-vinylphenol (33 mg, 0.2426 mmolv.), $[RhCl_2Cp^*]_2$ (4 mg, 0.0062 mmol) and NaOAc (23 mg, 0.2799 mmol) in 2 mL CH_3CN at 80 ^oC under argon atmosphere for 16 h gave the product as a coloueless viscous liquid in 75 % (56 mg) yield.

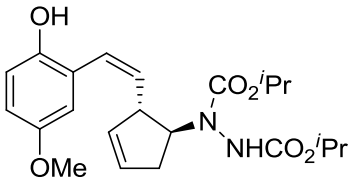


R_f : 0.71 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 6.99-6.97 (m, 1H), 6.82-6.79 (m, 2H), 6.40 (d, J = 10.5 Hz, 1H), 5.85-5.69 (m, 3H), 5.46 (brs, 1H), 4.93-4.76 (m, 3H), 3.54 (brs, 1H), 2.53-2.51(m, 2H), 2.28 (s, 1H), 1.25-1.20 (m,12H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 154.2, 152.0, 133.9, 132.9, 129.9, 129.4, 129.26, 128.9, 127.2, 126.8, 126.4, 121.6, 117.2, 72.6, 69.9, 67.8, 65.8, 62.6, 47.9, 34.5, 21.9, 21.3, 20.9, 20.5 ppm.

HRMS (ESI): calcd for $C_{22}H_{30}N_2NaO_5$ $(M+Na)^+$: 425.20524; found 425.20547.

Diisopropyl 1-(2-(2-hydroxy-5-methoxystyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 20cc

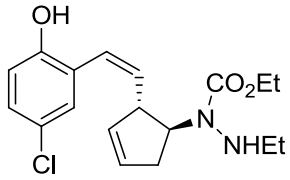
Following the general procedure, diazabicyclic olefin (50 mg, 0.1866 mmol), o-vinylphenol (36 mg, 0.2425 mmol), $[RhCl_2Cp^*]_2$ (4 mg, 0.00662 mmol) and NaOAc (23 mg, 0.2799 mmol) in 2 mL CH_3CN at 80 ^oC under argon atmosphere for 16 h gave the product as a coloueless viscous liquid in 81 % yield (63 mg) yield.



R_f : 0.65 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$,):** δ 6.83(d, J= 9Hz, 6.72 (s, 1H), 6.56 (s, 1H), 6.41 (d, J= 11 Hz, 1H), 5.83 (brs, 1H), 5.79-5.69 (m, 1H), 5.45 (brs, 1H), 4.92-4.83 (m, 2H), 4.54 (brs, 1H), 3.75 (s, 3H), 3.58 (brs, 1H), 2.57-2.39 (m, 2H), 1.25-1.21 (m, 12H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** **δ** 156.3, 155.7, 153.3, 146.5, 131.7, 129.8, 124.8, 116.7, 114.8, 113.9, 110.0, 70.2, 69.6, 55.6, 46.7, 34.8, 29.7, 22.0 ppm. **HRMS (ESI):** calcd for $C_{22}H_{30}N_2NaO_6$ $(M+Na)^+$: 441.20016; found 441.20119.

ethyl 1-(2-(5-chloro-2-hydroxystyryl)cyclopent-3-enyl)-2-ethylhydrazine-1,2-di carboxylate 20be

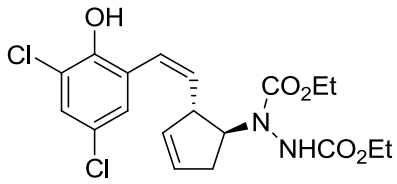
Following the general procedure, diazabicyclic olefin (50 mg, 0.2083 mmol), o-vinylphenol (42 mg, 0.2708 mmol), $[RhCl_2Cp^*]_2$ (4 mg, 0.0062 mmol) and NaOAc (26 mg, 0.3125 mmol) in 2 mL CH_3CN at 80 ^oC under argon atmosphere for 16 h gave the product as a yelloe viscous liquid in 73% (60 mg) yield.



R_f : 0.78 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.11 (d, J=8.5 Hz), 7.03-7.02 (m, 1H), 6.84 (d, J= 8.4 Hz, 1H), 6.38 (d, J=11 Hz, 1H), 6.10-6.05 (m, 1H), 5.77-5.71 (m, 4H), 5.45 (d, J= 4.5 Hz), 2.64-2.44 (m, 2H), 1.35-1.12 (m, 6H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ 156.8, 151.6, 131.7, 129.9, 129.2, 128.8, 128.3, 127.3, 125.2, 117.3, 62.8, 6232, 46.7, 35.0, 34.6, 31.7, 14.4 ppm. **HRMS (ESI):** calcd for $C_{18}H_{23}ClN_2NaO_3$ (M+Na)+: 373.12949; found.373.13007

Diethyl 1-(2-(3,5-dichloro-2-hydroxystyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 20bg

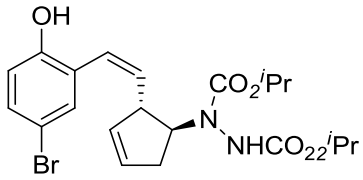
Following the general procedure, diazabicyclic olefin (50 mg, 0.2083 mmol), o-vinylphenol (51 mg, 0.2708 mmol), $[RhCl_2Cp^*]_2$ (4 mg, 0.0062 mmol) and NaOAc (26 mg, 0.3125 mmol) in 2 mL CH_3CN at 80 ^oC under argon atmosphere for 16 h gave the product as a coloueless viscous liquid in 65% (58 mg) yield.



R_f : 0.81 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.19-7.18 (m, 1H), 6.60-6.50 (m, 1H), 6.42 (d, J = 11.5 Hz, 1H), 6.26-6.17 (m, 2H), 6.08 (s, 1H), 5.48 (s, 1H), 4.72-4.68 (m,1H), 4.24-4.13 (m, 4H), 3.65 (s, 1H), 2.64-2.49 (m,2H), 1.30-1.21 (m, 6H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.6, 155.9, 147.7, 147.3, 1137.6, 130.1, 128.4, 126.9, 125.2, 120.9, 62.7, 62.2, 53.4, 47.1, 34.9, 14.4, 14.3 ppm. **HRMS (ESI):** calcd for $C_{19}H_{22}Cl_2N_2NaO_5$ (M+Na)+: 451.08035; found 451.08065.

Diisopropyl 1-(2-(5-bromo-2-hydroxystyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 20cf

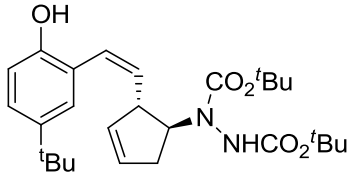
Following the general procedure, diazabicyclic olefin (50 mg, 0.1866 mmol), o-vinylphenol (48 mg, 0.2425 mmol), $[RhCl_2Cp^*]2$ (4 mg, 0.0062 mmol) and NaOAc (23 mg, 0.2799 mmol) in 2 mL CH_3CN at 80 ^oC under argon atmosphere for 16 h gave the product as a colorless viscous liquid in 74% (64 mg) yield.



R_f : 0.75(7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.26-7.15 (m, 2H), 6.80 (d, J = 8.5 Hz, 1H), 6.38(d, J = 8..5 Hz, 1H), 6.02 (brs, 1H), 5.73-5.71 (m, 1H), 5.52 (s, 1H), 4.98-4.78 (m, 3H), 3.65-3.59 (m, 1H), 2.61-2.36 (m, 2H), 1.28-1.22 (m, 12H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.5, 152.3, 132.1, 131.4, 130.8, 128.2, 117.8, 113.7, 112.1, 70.2, 70.0, 65.6, 46.5, 34.7, 22.0, 21.9 ppm. **HRMS (ESI):** calcd for $C_{21}H_{27}BrN_2NaO_5$ $(M+Na)^+$: : 489.10010; found 489.10211

Di-tert-butyl 1-((2-(5-tert-butyl-2-hydroxystyryl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 20dd

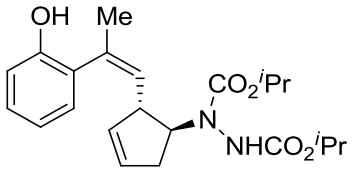
Following the general procedure, diazabicyclic olefin (50 mg, 0.1677 mmol), o-vinylphenol (38 mg, 0.2180 mmol), $[RhCl_2Cp^*]_2$ (3 mg, 0.0050 mmol) and NaOAc (21 mg, 0.2516 mmol) in 2 mL CH_3CN at 80 ^oC under argon atmosphere for 16 h gave the product as a yellow viscous liquid in 69% (54 mg) yield.



R_f : 0.68 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.21 (d, J= 10 Hz. 1H), 7.04 (brs, 1H), 6.87 (d, J=10 Hz, 1H), 6.50-6.43 (m, 1H), 5.86-5.76 (m, 1H), 5.72-5.71 (m, 1H), 5.50-5.49 (m, 1H), 5.35 (brs, 1H), 4.70 (brs, 1H), 3.56 (brs, 1H), 2.54-2.33 (m, 2H), 1.48-1.39 (m, 18H), 1.31(s, 9H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ 154.9, 154.3, 150.2, 143.4, 142.9, 131.2, 126.1, 115.7, 110.8, 83.6, 81.2 64.1, 45.8, 34.5, 31.3, 28.1 ppm. **HRMS (ESI):** calcd for $C_{27}H_{40}N_2NaO_5$ $(M+Na)^+$: 495.28349; found 495.28492.

Diisopropyl 1-((2-((Z)-2-(2-hydroxyphenyl)prop-1-enyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 20ch

Following the general procedure, diazabicyclic olefin (50 mg, 0.1866 mmol), o-vinylphenol (33 mg, 0.2426 mmol), $[RhCl_2Cp^*]_2$ (3 mol%) and NaOAc (1.5 equiv.) in 2 mL CH_3CN at 80 ^oC under argon atmosphere for 16 h gave the product the product as a coloueless viscous liquid in 61% (46 mg) yield.

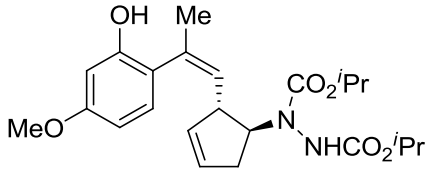


R_f : 0.63 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.18 (brs, 1H), 6.94-6.89 (m, 3H), 5.62 (brs, 2H), 5.48-5.40 (m, 2H), 4.94-4.91 (m, 2H), 4.86-4.72 (m, 1H), 3.21 (brs, 1H), 2.55-2.35 (m, 2H), 1.99 (s, 3H), 1.27-1.19 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 155.4, 136.9, 136.2, 132.5, 130.556127.9, 118.9, 117.9, 114.7, 70.6, 69.7, 64.3, 46.8, 35.3, 25.1, 21.9 ppm. **HRMS (ESI):** calcd for $C_{22}H_{30}N_2NaO_5$ $(M+Na)^+$: 425.20524; found 425.20624.

Diisopropyl 1-((2-((Z)-2-(2-hydroxy-5-methylphenyl)prop-1-enyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 20ci

Following the general procedure, diazabicyclic olefin (50 mg, 0.1866 mmol), o-vinylphenol (36 mg, 0.2426 mmol), $[RhCl_2Cp^*]_2$ (4 mg, 0.0062 mmol) and NaOAc (23 mg, 0.2799 mmol) in 2 mL CH_3CN at 80 ^oC under argon atmosphere for 16 h gave the product as a coloueless viscous liquid in 69% (54 mg) yield.



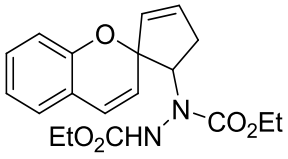
R_f : 0.58(7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 6.95-6.94 (m, 1H), 6.83-6.81 (m, 2H), 6.45 (brs, 1H), 6.31 (brs, 1H), 5.89-5.88 (m, 1H), 5.67 (brs, 1H), 5.09-4.98 (m,3H), 4.77 (s, 1H), 3.83 (s, 4H). 2.78-2.65 (m, 2H), 2.17 (s, 1H), 1.29=1.21 (m, 12H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ 153.1, 144.7, 141.5, 135.1, 129.6, 129.3, 124.5, 120.9, 119.0, 70.3, 69.7, 55.9, 45.97, 36.0, 21.9 ppm. **HRMS (ESI):** calcd for $C_{23}H_{32}N_2NaO_5$ $(M+Na)^+$: 455.21581; found. 455.21012.1

4.6.3. General Experimental Procedure for Rhodium/Copper Catalyzed C-H Activation/Annulation of Diazabicyclic Olefins *via* C-H Activation of *o*-Vinylphenols

A mixture of diazabicyclic olefin (1 equiv.), o-vinylphenol (1.3 equiv.), $[RhCl_2Cp^*]_2$ (3 mol%) and $Cu(OAc)_2 .H_2O$ (3.0 equiv.) were weighed in a Schlenk tube and degassed for 10 minutes. Dry acetonitrile (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at 80 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the spiroannulated product *via* C-H activation.

Diethyl 1-(spiro[chromene-2,1'-cyclopent[2]ene]-5'-yl)hydrazine-1,2-dicarboxylate 21ba

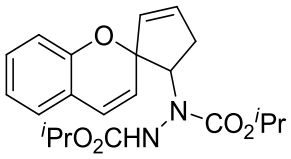
Following the general procedure procedure diazabicyclic olefin (50 mg, 0.2083 mmol), o-vinylphenol (33 mg, 0.2708 mmol), $[RhCl_2Cp^*]_2$ (4 mg, 0.0062 mmol)and $Cu(OAc)_2 .H_2O$ (124 mg, 0.6249 mmol) in 2 mL acetonitrile were allowed to stir at 80 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the spiro annulated product *via* C-H activation in 48% (36 mg) yield as a mixture of diastereomers (1:1.3 ratio).



R_f : 0.78 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.09 (t, J= 8 Hz, 2H), 6.98-6.95 (m, 2H), 6.87-6.84 (m, 2H), 6.76-6.75 (m, 2H), 6.58-6.53 (m, 2H), 6.43-6.37 (m, 2H), 5.98-5.93 (m, 2H), 5.77 (s, 2H), 5.64 (d, J= 10 Hz, 1H), 5.49 (J= 9.5 Hz, 1H), 5.01-4.97 (m, 1H), 4.79 (s, 1H), 4.20-3.74 (m, 8H), 2.71-2.68 (m, 4H), 1.33-1.02 (m, 12H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 159.9, 156.6, 156.3, 156.1, 152.5, 152.5, 133.9, 132.9, 132.2, 129.7, 129.5, 129.1, 127.1, 126.5, 123.4, 122.8, 121.4, 114.9, 89.36, 89.2, 65.4, 63.7, 62.7, 62.6, 61.9, 33.7, 32.6, 14.6, 14.4, 14.3, 14.1 ppm. **HRMS (ESI):** calcd for $C_{19}H_{22}N_2NaO_5$ $(M+Na)^+$: 381.14264; found 381.14236.

Diisopropyl 1-(spiro[chromene-2,1'-cyclopent[2]ene]-5'-yl)hydrazine-1,2-dicarboxylate 21ca

Following the general procedure, diazabicyclic olefin (1 equiv.), o-vinylphenol (1.3 equiv.), $[RhCl_2Cp^*]_2$ (3 mol%) and $Cu(OAc)_2 .H_2O$ (3.0 equiv.) in 2 mL acetonitrile were allowed to stir at 80 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the spiroannulated product *via* C-H activation in 48 % (36 mg) yield as a mixture of diastereomers (1:1.3 ratio).

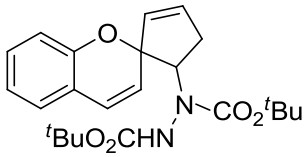


R_f : 0.82 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.08 (t, J =8 Hz, 1H), 6.97-6.92 (m, 2H), 6.85-6.82 (m, 2H), 6.75 (d, J = 8Hz, 2H), 6.49-6.43 (m, 4H), 5.98-5.91 (m, 2H), 5.77-5.76 (m, 2H), 5.64-5.62 (m, 2H), 5.48 (d, *J* =9.5 Hz, 1H), 4.98-4.94 (m,

4H), 4.78-4.72 (m, 1H), 2.71-2.68 (m, 4H), 1.29-1.21 (m,24H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.6, 156.4, 156.1, 155.9, 152.4, 152.3, 135.9, 135.7, 135.4, 133.7, 132.8, 132.0, 131.89, 131.7, 129.5, 129.1, 129.0, 128.6, 128.5, 128.3, 128.2, 128.0, 127.7, 127.8, 127.5, 127.4, 126.9, 126.8, 126.6, 126.4, 123.5, 122.9, 121.5, 121.1, 120.3, 115.4, 115.0, 89.2, 89.1, 68.0, 67.6, 65.4, 64.0, 33.5, 32.7 ppm. **HRMS (ESI):** calcd for $C_{19}H_{22}N_2NaO_5$ $(M+Na)^+$: 409.17394; found 409.17393.

Di-tert-butyl 1-(spiro[chromene-2,1'-cyclopent[2]ene]-5'-yl)hydrazine-1,2-dicarboxylate 21da

Following the general procedure diazabicyclic olefin (50 mg, 0.1677 mmol), o-vinylphenol (26 mg, 0.2181 mmol), $[RhCl_2Cp^*]_2$ (3 mg, 0.0050 mmol) and $Cu(OAc)_2 .H_2O$ (101 mg, 0.5064 mmol) in 2 mL acetonitrile were allowed to stir at 80 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the spiroannulated product *via* C-H activation.in 41% (23 mg) yield yield as a mixture of diastereomers (1:1.3 ratio).



R_f : 0.85 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.08-7.06 (m, 2H), 6.94-6.92 (m, 2H), 6.82-6.74 (m, 4H), 6.39-6.28 (m, 2H), 6.03-5.98 (m, 2H), 5.75 (s, 2H), 5,614 (d, *J* = 10 Hz, 1H), 5.46(d, *J* =9.5 Hz, 1H), 4.97-4.95 (m, 1H), 4.73-4.70 (m, 1H), 2.69-2.63 (m, 2H), 1.48-1.26 (m, 36H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 155.6, 155.5, 155.4, 130.6, 130.3, 128.0, 127.9, 121.3, 121.2, 119.7, 116.8, 89.2, 89.0, 81.9, 81.6, 59.4, 59.1, 30.3, 28.4, 28.1 ppm. **HRMS (ESI):** calcd for $C_{23}H_{30}N_2NaO_5$ $(M+Na)^+$: 437.20524; found 437.20541.

Dibenzyl 1-(spiro[chromene-2,1'-cyclopent[2]ene]-5'-yl)hydrazine-1,2-dicarboxylate 21ea

Following the general procedure diazabicyclic olefin (50 mg, 0.1373 mmol), o-vinylphenol (21 mg, 0.1785 mmol), $[RhCl_2Cp^*]_2$ (4 mg, 0.0062 mmol) $Cu(OAc)_2 .H_2O$ (82 mg, 0.4119 mmol) in 2 mL acetonitrile were allowed to stir at 80 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the spiroannulated

product *via* C-H activation in 35 % (23 mg) yield yield as a mixture of diastereomers (1:1.3 ratio).

R_f : 0.75 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.39 (m, 20H), 6.84-6.83 (m, 4H), 6.73-6.67 (m,4H), 6.41 (d, J= 10 Hz, 2H), 5.96-5.87 (m, 2H), 5.77-5.72 (m,2H), 5.64-5.60 (m, 1H), 5.37 (d, J= 10 Hz, 1H), 5.21-5.09 (m, 4H), 5.03-4.95 (m, 4H), 4.81 (t, J= 6 Hz, 1H), 4.73 (brs, 1H), 2.71-2.69 (m, 4H). 2.71-2.69(m, 4H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$): δ** 156.6, 156.4, 156.1, 155.9, 152.4, 152.3, 135.9, 135.7, 135.4, 133.9, 133.74, 133.2, 132.8, 132.4, 132.3, 131.9, 131.68, 129.5, 129.1, 129.0, 128.6, 128.5, 128.3, 128.2, 128.0, 127.7, 127.5, 127.6, 126.9, 126.8, 126.6, 126.4, 124.29, 123.5, 122.9, 122.3, 121.5, 121.2, 121.1, 120.6, 120.3, 118.1, 115.4, 115.0, 89.21, 89.1, 68.5, 68.0, 67.7, 67.6, 65.35, 64.0, 33.5, 32.7 ppm. **HRMS (ESI):** calcd for $C_{29}H_{26}N_2NaO_5$ $(M+Na)^+$: 505.17394; found 505.17205.

Diethyl 1-(6-methylspiro[chromene-2,1'-cyclopent[2]ene]-5'-yl)hydrazine-1,2-dicarboxylate 21bb

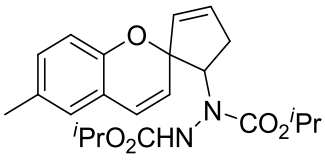
Following the general procedure diazabicyclic olefin (50 mg, 0.2083mmol), o-vinylphenol (36 mg, 0.2708mmol), $[RhCl_2Cp^*]_2$ (4 mg, 0.0062 mmol) and $Cu(OAc)_2$ .H_2O (124 mg, 0.6244 mmol) in 2 mL acetonitrile were allowed to stir at 80 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the spiroannulated product *via* C-H activation in 60% (46 mg) yield yield as a mixture of diastereomers (1:1.2 ratio).

R_f : 0.73 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.23-7.15 (m, 2H), 6.88 (d, *J* =7.5 Hz, 2H), 6.78-6.74 (m, 2H), 6.64 (d, *J* = 8 Hz, 2H), 6.56-6.49 (m, 2H), 6.37-6.31 (m, 2H), 5.96-5.91 (m, 2H), 5.76 (s, 2H), 5.62 (d, *J* = 9.5 Hz, 2H), 5.46 (d,

J = 9.5 Hz, 2H), 4.98-4.94 (m, 1H), 4.77 (s, 1H), 4.21-3.79 (m, 8H), 2.69-2.67 (m, 4H), 1.33-1.11 (m, 24H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ 156.9, 156.6, 156.4, 156.1, 150.3, 133.9, 133.3, 132.9, 131.9, 130.9, 130.6, 129.7, 129.4, 127.2, 126.9, 123.6, 123.0, 120.6, 120.6, 115.1, 114.9, 114.6, 89.2, 89.1, 65.3, 63.8, 63.7, 62.7, 62.6, 61.9, 61.8, 30.9, 20.5, 14.6, 14.1. **HRMS (ESI):** calcd for $C_{20}H_{24}N_2NaO_5$ $(M+Na)^+$: 395.15829; found 395.15990.

Diisopropyl 1-(6-methylspiro[chromene-2,1'-cyclopent[2]ene]-5'-yl)hydrazine-1,2-dicarboxylate 21cb

Following the general procedure diazabicyclic olefin (50 mg, 0.1866 mmol o-vinylphenol (33 mg, 0.2426 mmolv.), $[RhCl_2Cp^*]_2$ (4 mg, 0.0062 mmol) and $Cu(OAc)_2 .H_2O$ (111 mg, 0.5592 mmol) in 2 mL acetonitrile were allowed to stir at 80 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the spiroannulated product *via* C-H activation in 56% (42 mg) yield yield as a mixture of diastereomers (1:1.1 ratio).



R_f : 0.80 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 6.87-6.73 (m, 2H), 6.77-6.73 (m, 2H), 6.65 (d, *J* =8 Hz, 2H), 6.43-6.27 (m, 4H), 5.96-5.89 (m,2H), 5.75-5.74 (m, 2H), 5.61(d, *J* =9.5 Hz, 1H), 5.46 (d, *J* =10 Hz, 1H), 4.98-4.94 (m, 4H), 4.76-4.72 (m, 2H), 2.69-2.66 (m, 2H), 2.22 (s, 6H), 1.29-1.15 (m, 24H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ 156.5, 156.0, 155.9, 150.5, 150.3, 133.9, 132.8, 132.0, 131.9, 130.5, 129.8, 129.6, 129.4, 127.3, 126.9, 123.4, 122.9, 115.2, 114.7, 114.5, 88.9, 70.7, 70.0, 69.5, 69.4, 64.9, 63.5, 33.6, 32.8, 32.5, 30.9, 29.7, 22.0, 21.9, 21.8, 21.8, 21.8, 21.4, 20.5, ppm. **HRMS (ESI):** calcd for $C_{22}H_{28}N_2NaO_5$ $(M+Na)^+$: 423.18959; found 423.18894.

Diethyl 1-(8-methylspiro[chromene-2,1'-cyclopent[2]ene]-5'-yl)hydrazine-1,2-dicarboxylate 21bj

Following the general procedure diazabicyclic olefin (50 mg, 0.2083mmol), o-vinylphenol (36 mg, 0.2708mmol), $[RhCl_2Cp^*]_2$ (4 mg, 0.0062 mmol) and $Cu(OAc)_2 .H_2O$ (124 mg, 0.6244 mmol) in 2 mL acetonitrile were allowed to stir at 80 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the spiroannulated product *via* C-H activation in 62 (48 mg) yield yield as a mixture of diastereomers (1:1.2 ratio).

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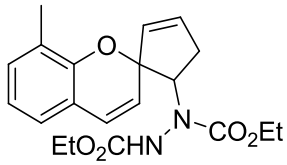
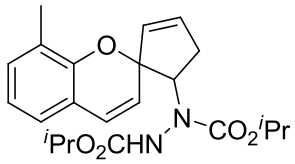


R_f : 0.75 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 6.98-6.97 (m, 2H), 6.84-6.75 (m, 4H), 6.64-6.55 (m, 2H), 6.42-6.36 (m, 2H), 5.92-5.89 (m, 2H), 5.78 (s, 2H), 5.64 (d, *J* = 9.5 Hz, 1H), 5.48 (d, *J* = 9.5 Hz, 1H), 5.02-4.97 (m, 2H), 4.81 (s, 1H), 4.22-3.84 (m, 8H), 2.72-2.69 (m, 4H), 1.30-1.03 (m, 12H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.8, 156.4, 156.0, 150.5, 150.4, 133.3, 132.9,132.4, 132,3, 131.1, 130.8, 130.7, 126.5, 126.4, 126.1, 124.6, 124.4, 124.1, 123.7, 123.1, 120.8, 120.7, 119.8, 89.2, 89.0, 63.8, 63.7, 62.7, 62,6, 61.9, 61.8, 33.6, 32.7, 32,6, 14.6, 14.5, 14.4, 14.3 ppm. **HRMS (ESI):** calcd for $C_{20}H_{24}N_2NaO_5$ $(M+Na)^+$: 395.15829; found 395.15997.

Diisopropyl 1-(8-methylspiro[chromene-2,1'-cyclopent[2]ene]-5'-yl)hydrazine-1,2-dicarboxylate 21cj

Following the general procedure diazabicyclic olefin (50 mg, 0.1866 mmol o-vinylphenol (33 mg, 0.2426 mmol.), $[RhCl_2Cp^*]_2$ (4 mg, 0.0062 mmol) and $Cu(OAc)_2$ .H_2O (3.0 equiv.) in 2 mL acetonitrile were allowed to stir at 80 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the spiroannulated product *via* C-H activation in 59% (44 mg) yield yield as a mixture of diastereomers (1:1.1 ratio).

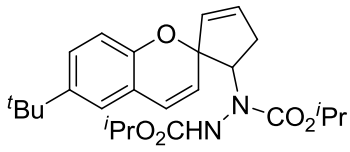


R_f : 0.70 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ6.98-6.97 (m, 2H), 6.83-6.74 (m, 4H), 6.48-6.28 (m, 4H), 5.94-5.87 (m, 2H), 5.78-5.77 (m, 2H), 5.62 (d, *J* = 10 Hz, 1H), 5.48 (d, *J* = 10 Hz, 1H), 5.02-4.94 (m, 3H), 4.81-4.78 (m, 2H), 2.72-2.2.68 (m, 4H), 1.29-1.08 (m, 24H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.5, 150.1, 133.4, 133.2, 132.4, 131.9, 130.7, 128.7, 126.5, 125.1, 124.1, 123.6, 121.0, 120.6, 84.6, 70.2, 69.7, 69.5, 69.3, 65.7, 63.6, 39.0, 32.8, 30.2, 29.7, 21.9, 21.8 ppm. **HRMS (ESI):** calcd for $C_{22}H_{28}N_2NaO_5$ $(M+Na)^+$: 423.18959; found 423.18914.

Diisopropyl 1-(6-tert-butylspiro[chromene-2,1'-cyclopent[2]ene]-5'-yl)hydrazine-1,2-dicarboxylate 21cd

Following the general procedure diazabicyclic olefin (50 mg, 0.1866 mmol o-vinylphenol (43 mg, 0.2426 mmolv.), $[RhCl_2Cp^*]_2$ (4 mg, 0.0062 mmol) and Cu $Cu(OAc)_2$ .H_2O (111

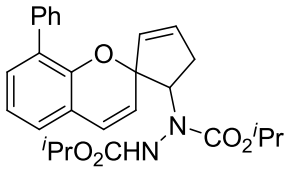
mg, 0.5592 mmol) in 2 mL acetonitrile were allowed to stir at 80 ^{o}C for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the spiroannulated product *via* C-H activation in 58% yield (48 mg) yield yield as a mixture of diastereomers (1:1.6 ratio).



R_f : 0.76 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.10-.09 (m, 2H), 6.95-6.91 (m, 2H), 6.69-6.66 (m, 2H), 6.44-6.28 (m, 4H), 5.97-5.88 (m, 2H), 5.75 (s, 2H), 5.61 (d, *J* = 10 Hz, 1H), 5.45 (d, *J* = 10 Hz, 1H), 4.99-4.93 (m, 3H), 4.76-4.67 (m, 2H), 2.70-2.66 (m, 4H), 1.29-1.00 (m, 4H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 155.9, 148.9, 148.6, 148.0, 143.3, 142.6, 136.4, 133.5, 132.9, 132.4, 132.0, 128.3, 126.9, 126.1, 125.4, 124.2, 123.7, 123.1, 121.9, 88.3, 87.9, 87.8, 70.3, 70.18, 69.7, 69.4, 69.21, 64.5, 63.4, 59.4, 35.0, 34.7, 31.5, 30.3, 29.9, 29.8, 29.7, 21.9 ppm. **HRMS (ESI):** calcd for $C_{22}H_{28}N_2NaO_5$ $(M+Na)^+$: 465.23654 ; found 465.23694.

Diisopropyl 1-(8-phenylspiro[chromene-2,1'-cyclopent[2]ene]-5'-yl)hydrazine-1,2-dicarboxylate 21cl

Following the general procedure diazabicyclic olefin (50 mg, 0.1866 mmol), o-vinylphenol (48 mg, 0.2425 mmol), $[RhCl_2Cp^*]_2$ (4 mg, 0.00662 mmol) and $Cu(OAc)_2 .H_2O$ (124 mg, 0.6244 mmol) in 2 mL acetonitrile were allowed to stir at 80 ^{o}C for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the spiroannulated product *via* C-H activation in 43% (45 mg) yield yield as a mixture of diastereomers (1:1.6 ratio).



R_f : 0.86 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.47-7.34 (m, 2H), 7.16 (d, *J* = 7.5 Hz, 2H), 7.01-6.92 (m, 2H), 6.46-6.42 (m, 2H), 5.92-5.79 (m, 4H), 5.66 (d, *J* = 9.5 Hz, 1H), 5.79 (m, 4H), 5.57 (d, *J* = 9.5 Hz, 1H), 5.05-4.73 (m, 5H), 2.77-2.52 (m,

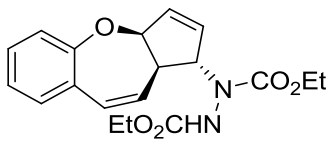
4H), 1.27-1.07 (m, 24H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.5, 155.9, 149.8, 137.8, 137.5, 132.9, 131.5, 131.4, 130.5, 130.2, 129.6, 129.3, 129.1, 128.9, 128.7, 128.5, 128.5, 128.2, 128.2, 127.5, 127.3, 127.2, 126.2, 125.9, 122.9, 121.7, 121.2, 88.8, 70.7, 69.9, 68.9, 68.8, 64.4, 63.1, 38.2, 33.9, 33.5, 29.7, 22.1, 21.9, 21.9 ppm. **HRMS (ESI)):** calcd for $C_{27}H_{30}N_2NaO_5$ $(M+Na)^+$: 485.20524; found 485.20464.

4.6.4. General Experimental Procedure for Palladium Catalyzed Intramolecular Cyclization of the Ring Opened Product 20

A mixture of ring opened product (1 equiv.), $[Pd(OAc)_2$ (5 mol%) and $Cu(OAc)_2$ (1.0 equiv.) and 1,10-phenanthroline (10 mol%) were weighed in a pressure. Dry DCE (2 mL) was added allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the benzoxepine fused cyclopentene.

Diethyl 1-(3a,10a-dihydro-1H-benzo[b]cyclopenta[f]oxepin-1-yl)hydrazine-1,2-dicarboxylate 22bb

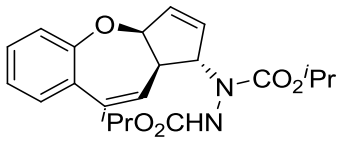
Following the general procedure, mixture of ring opened product (25 mg, 0.0694 mmol), $[Pd(OAc)_2$ (8 mg, 0.0357 mmol), $Cu(OAc)_2$ (13 mg, 0.0694 mmol) and 1,10-phenanthroline (2 mg, 0.0111 mmol) in 2 mL DCE were weighed in a pressure. Dry DCE (2 mL) was added and the reaction mixture was allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the benzoxepine fused cyclopentene in 60% (15 mg) yield.



R_f : 0.62 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.16-7.09 (m, 2H), 6.95 (d, *J* =8.5 Hz, 1H), 6.37-6.19 (m, 4H), 5.60-5.30 (m, 2H), 4.81 (s, 1H), 4.23-4.22 (m, 4H), 2.96 (s, 1H), 1.29-1.28 (m, 6H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 155.9, 151.0, 137.4, 134.2, 131.7, 130.6, 129.5, 128.8, 128.5, 127.8, 126.9, 125.3, 123.81, 122.9, 86.7, 68.7, 62.4, 49.2, 14.5, 14.4 ppm. **HRMS (ESI):** calcd for $C_{19}H_{21}ClN_2NaO_5$ $(M+Na)^+$: 381.14264; found 381.14304.

Diisopropyl 1-(3a,10a-dihydro-1H-benzo[b]cyclopenta[f]oxepin-1-yl)hydrazine-1,2-dicarboxylate 22ca

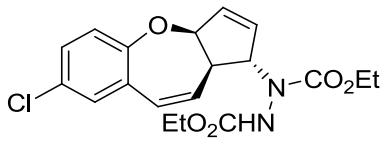
Following the general procedure, mixture of ring opened product (25 mg, 0.0644 mmol), [$Pd(OAc)_2$ (7 mg, 0.0313 mmol), $Cu(OAc)_2$ (12 mg, 0.0644 mmol) and 1,10-phenanthroline (1 mg, 0.0056 mmol) in 2 mL DCE were weighed in a pressure. Dry DCE (2 mL) was added and the reaction mixture was allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the benzoxepine fused cyclopentene in 57% (14 mg) yield.



R_f : 0.80 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.19-7.16 (m, 2H), 7.07-7.02 (m, 2H), 6.41 (d, *J* = 11.5 Hz, 1H), 6.21 (brs, 3H), 5.33-5.53-5.34 (m, 2H), 5.01-4.96 (m, 2H), 4.84 (s, 1H), 2.95 (s, 1H), 1.28-1.26 (m, 12 H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 157.5, 131.3, 128.1, 126.3, 123.9, 121.6, 86.5, 70.2, 68.1, 49.2, 31.9, 31.6, 29.7, 29.4, 14.1 ppm. **HRMS (ESI):** calcd for $C_{19}H_{22}N_2NaO_5$ $(M+Na)^+$: 409.17394; found 409.17469.

Diethyl 1-(7-chloro-3a,10a-dihydro-1H-benzo[b]cyclopenta[f]oxepin-1-yl)hydrazine-1,2-dicarboxylate 22be

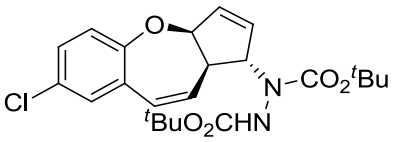
Following the general procedure, mixture of ring opened product (30 mg, 0.0761 mmol.), [$Pd(OAc)_2$ (9 mg, 0.0402 mmol), $Cu(OAc)_2$ (14 mg, 0.0761,) and 1,10-phenanthroline (1 mg, 0.0056 mmol) in 2 mL DCE were weighed in a pressure. Dry DCE (2 mL) was added and the reaction mixture was allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the benzoxepine fused cyclopentene in 63% (19 mg) yield.



R_f : 0.85 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.16-7.09 (m, 2H), 6.95 (d, *J* =8.5 Hz, 1H), 6.37-6.19 (m, 4H), 5.60-5.30 (m, 2H), 4.81 (s, 1H), 4.23-4.22 (m, 4H), 2.96 (s, 1H), 1.29-1.28 (m, 6H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 155.9, 151.0, 137.4, 134.18, 131.7, 130.6, 129.2, 128.1, 128.1, 127.0, 126.3, 125.3, 123.1, 122.9, 86.7, 68.7, 62.4, 49.2, 14.5, 14.5 ppm. **HRMS (ESI):** calcd for $C_{19}H_{21}ClN_2NaO_5$ $(M+Na)^+$: 415.10367; found 415.10465.

Di-tert-butyl 1-(7-chloro-3a,10a-dihydro-1H-benzo[b]cyclopenta[f]oxepin-1-yl)hydrazine-1,2-dicarboxylate 22de

Following the general procedure, mixture of ring opened product (28 mg, 0.0622 mmol), [$Pd(OAc)_2$ (7 mg, 0.0313 mmol), $Cu(OAc)_2$ (11 mg, 0.0622 mmol) and 1,10-phenanthroline (1 mg, 0.0056 mmol) in 2 mL DCE were weighed in a pressure. Dry DCE (2 mL) was added and the reaction mixture was allowed to stir at 110 ^oC for 12 hours. The crude reaction mixture on silica gel (100-200 mesh) column chromatography yielded the benzoxepine fused cyclopentene in 50% (14 mg) yield.



R_f : 0.80 (7:3 hexane/EtOAc). **^{1}H NMR (500 MHz, $CDCl_3$, TMS):** δ 7.17-7.09 (brs, 1H), 6.96-6.94 (m, 1H), 6.78-6.77 (m, 1H), 6.32-6.17 (m, 4H), 5.48-5.30 (m, 1H), 4.81 (s, 1H), 2.94 (s, 1H), 1.49-1.46 (m, 18H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$):** δ 156.0, 154.8, 137.9, 131.8, 130.5, 128.7, 127.7, 125.0, 122.9, 116.0, 114.8, 86.9, 85.0, 81.48, 68.7, 68.4, 55.6, 49.3, 28.2 ppm. **HRMS (ESI):** calcd for $C_{23}H_{29}ClN_2NaO_5$ $(M+Na)^+$: 471.16627; found 471.16721.

4.7. References

1. (a) Zhang, B.; Studer, A.; Zhang, B. *Chem. Soc. Rev.* **2015**, *44*, 3505.

2. Kaur, P.; Arora, R.; Gill, N.S. *Indo Am. J. Pharm. Res.* **2013**, *3*, 9067.

3. (a) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (b) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. (c) Hyster, T. K.; Knörr, L.; Ward, T. R.; Rovis, T. *Science* **2012**, *338*, 500.

4. Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788.

5. (a) Davies, H. M. L.; Morton, D. *J. Org. Chem.* **2016**, *81*, 343. (b) Yu, J.-T.; Pan, C. *Chem. Commun.* **2016**, *52*, 2220.

6. Huang, C.; Chattopadhyay, B.; Gevorgyan, V. *J. Am. Chem. Soc.* **2011**, *133*, 12406.

7. Liu, B.; Jiang, H. Z.; Shi, B. F. *J. Org. Chem.* **2014**, *79*, 1521.

8. Kuram, M. R.; Bhanuchandra, M.; Sahoo, A. K. *Angew. Chem. Int. Ed.* **2013,** *52*, 4607.

9. Sharma, U.; Naveen, T.; Maji, A.; Manna, S.; Maiti, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 12669.

10. Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, *62*, 4564.

11. Shi, Z.; Schröder, N.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51* , 8092.

12. (a) Seoane, A.; Casanova, N.; Quiñones, N.; Mascareñas, J. L.; Gulías, M. *J. Am. Chem. Soc.* **2014**, *136*, 834. (b) Seoane, A.; Casanova, N.; Quiñones, N.; Mascareñas, J. L.; Gulías, M. *J. Am. Chem. Soc.* **2014**, *136*, 7607. (c) Casanova, N.; Seoane, A.; Mascareñas, J. L.; Gulías, M. *Angew. Chem. Int. Ed.* **2015**, *54* , 2374.

13. Saranya, S.; Chand, S.; Gopalan, G.; Jijitha, V.; Radhakrishnan, K. *Synthesis.* **2018**, *50*, 184.

14. Wang, Y. F.; Chen, H.; Zhu, X.; Chiba, S. *J. Am. Chem. Soc.* **2012**, *134* , 11980.

15. Nechab, M.; Mondal, S.; Bertrand, P. *Chem. Eur. J.* **2014**, *20*, 16034.

16. Doveston, R. G.; Steendam, R.; Jones, S.; Taylor, R. J. K. *Org. Lett.* **2012**, *14* , 1122.

17. Hill, R. A. *Annu. Reports Sect. Organic Chem.* **2012**, *108*, 131.

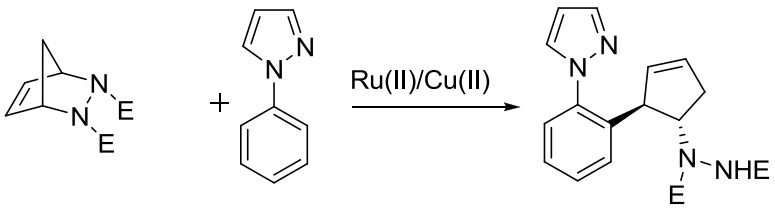
18. (a) Gu, Z. Y.; Wang, X.; Cao, J. J.; Wang, S. Y.; Ji, S. J. *European J. Org. Chem.* **2015**, *21*, 4699. (b) Hoberg, J. O. *J. Org. Chem.* **1997**, *62* , 6615.

Summary

The thesis entitled "**Desymmetrization of Diazabicyclic Olefins *via* Transition Metal Catalyzed sp^2 C-H Activation: Access to Functionalized Cyclopentenes**" describes the results of the investigations carried out towards novel carbon-carbon and carbon-heteroatom bond formation *via* synthetic transformations of diazabicyclic olefins by exploring aromatic C-H activation strategy. Transition metal catalyzed carbon–carbon bond formation via cleavage of inert C–H bonds represents a proficient, atom-economical, and environmentally friendly strategy in organic synthesis. The thesis is divided into four chapters, which consists of detailed discussion on the synthesis of carbocyclic and heterocyclic compounds, *via* transition metal catalyzed desymmetrization of diazabicyclic and olefins.

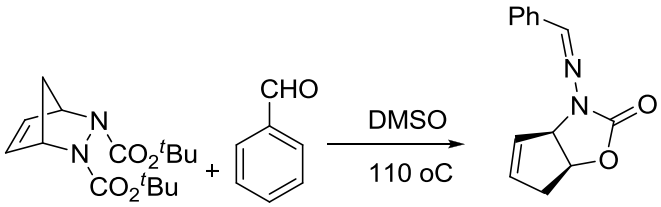
Chapter 1 gives an overview on synthetic utility of strained systems with an emphasis to diazabicyclic olefins. Various acid and transition metal catalyzed synthetic transformations of diazabicyclic olefins are discussed here. Definition of the research problem has also been incorporated in the chapter.

Chapter 2 is divided into two parts. First part describes a ruthenium catalyzed redox-neutral C–H activation of phenylazoles toward the ring-opening of diazabicyclic olefins for the first time (Scheme 1). Incorporation of biologically relevant cyclopentene ring to these heteroaromatics expands the biological applications.



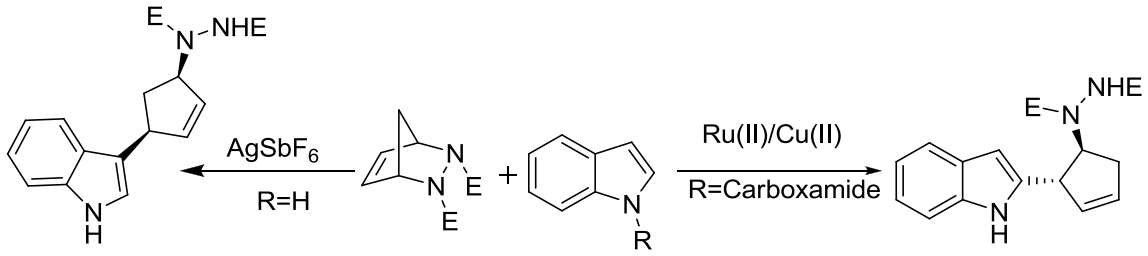
Scheme 1

The second part deals with thermal rearrangement of diazabicyclic olefins and sequential imine formation exclusively in DMSO (Scheme 2). The reaction explains the thermal rearrangement of Boc protected diazabicyclic olefin in the absence of any metal catalysts. The reaction doen't require any Lewis acid as well as transition metal catalysts.



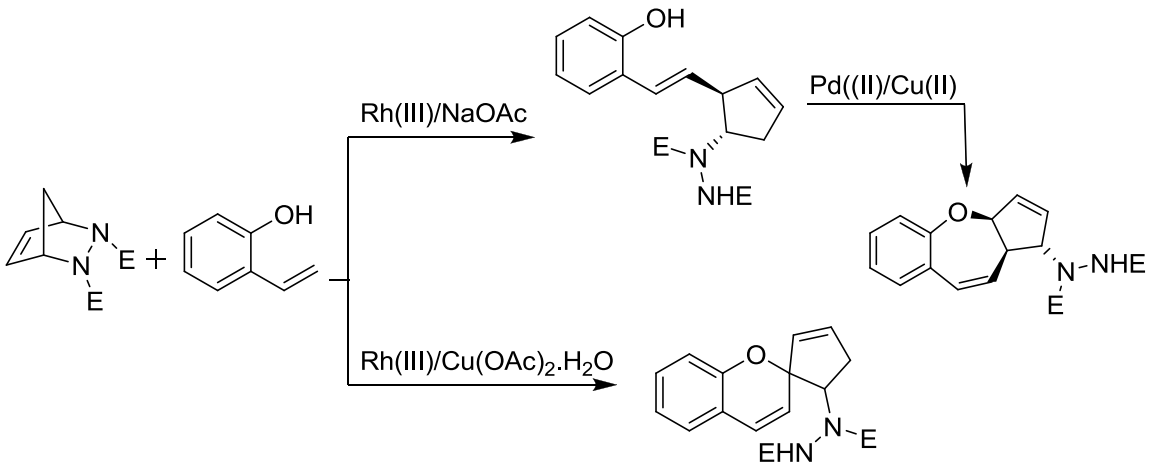
Scheme 2

In Chapter 3, regioselective C-2/C-3 activation of indoles with diazabicyclic olefins is discussed. It includes, a ruthenium (II) catalyzed stereoselective C-N bond cleavage of diazabicyclic olefins through C-H bond activation of suitably protected indoles and $AgSbF_6$ catalyzed mild C-3 cyclopentenylation of indoles with diazabicyclic olefins. The strategy provides an efficient access to biologically important *trans*- 3,4 as well as cis- 3,5 difunctionalized cyclopentenes (Scheme 3).



Scheme 3

We have also developed a ring opening and annulation of diazabicyclic olefins with *o*-vinylphenols by Rh(III)/Cu(III) co-catalysis which is discussed in Chapter 4 (Scheme 4). The reactions were controllable with respect to the additive added. In addition to this palladium catalyzed intramolecular cyclization of the ring opened product is also demonstrated. The methodology enables the synthesis of cyclopentene fused spiropyrans and oxepines along with the ring opened product.



Scheme 4

In conclusion, we have developed one pot strategies for the synthesis of biologically important carbocycles and heterocycles by desymmetrization of diazabicyclic olefins. It is to be noted that we have achieved desymmetrization of diazabicyclic olefins by C–H bond functionalization of aromatic compounds in a more atom economic way mainly *via* C-H activation strategy.

List of Publications

1. Prakash, P.; Jijy, E.; Shimi, M.; Aparna, P. S.; Suresh, E.; Radhakrishnan, K. V., Mild rhodium(I) catalyzed ring opening of cyclopropane appended spirotricyclic olefins through C-H activation

of arylboronic acids. *Rsc Adv* **2013**, *3*, 19933-19936.

2. Prakash, P.; Jijy, E.; Aparna, P. S.; Viji, S.; Radhakrishnan, K. V., Rhodium(III) catalyzed synthesis of isoquinolone fused azabicycles through C-H activation of N-pivaloyloxy benzamides. *Tetrahedron Lett* **2014**, *55*, 916.

3. Prakash, P.; Aparna, P. S.; Jijy, E.; Santhini, P. V.; Varughese, S.; Radhakrishnan, K. V., Rhodium(III)-Catalyzed C-H Activation of Phenylazoles toward C-N Bond Cleavage of Diazabicyclic Olefins: A Facile Access to Mono- and Biscyclopentenyl-Functionalized Aza-Heteroaromatics. *Synlett* **2014**, *25*, 275.

4. Aparna, P. S.; Prabha, B.; Prakash, P.; Jijy, E.; Varma, R. L.; Radhakrishnan, K. V., Ruthenium catalyzed desymmetrization of diazabicyclic olefins to access heteroaryl substituted cyclopentenes through C-H activation of phenylazoles. *Tetrahedron Lett* 2014, *55*, 865.

5. Aparna, P. S.;Vijayan A.; Raveendran S.P.; Varma, R. L.; Radhakrishnan, K. V., Ruthenium/Iridium-Catalyzed C-2 Activation of Indoles with Bicyclic Olefins: An Easy Access to Functionalized Heterocyclic Motifs. *Synlett*, 2017, *28*, 572.

6. Aparna, P. S.;.; Varma, R. L.; Radhakrishnan, K. V., Rh(III)/Cu(II) Catalyzed Simultaneous Ring Opening & Annulation Of Diazabicyclic Olefins with o-Vinylphenols: Access to cyclopentene fused oxacycles. (*to be communicated*)

7. Aparna, P. S.;.; Varma, R. L.; Radhakrishnan, K. V., Thermal Rearrangement of Diaza-bicyclic Olefins and Sequential Imine Formation in DMSO. (*to be communicated*)

Papers Presented at Conferences

1. Rh(III)/Ru(II) Catalyzed C-H Activation of Phenylazoles through C-N Bond Cleavage of Diazabicyclic Olefins, Aparna, P. S.; Prabha, B.; Prakash, P.; Jijy, E.; Varma, R. L.; Radhakrishnan, K. V a poster presented at National Symposium on Transcending Frontiers in Organic Chemistry (TFOC 2014) held at CSIR-NIIST, Trivandrum, October, **2014**.

2. Rh(III)/ Ru(II) Catalyzed C-H Activation of Phenylazoles via C-N bond Cleavage of Diazabicyclic Olefins, Aparna P S, Praveen P, Prabha B, R Luxmi Varma and Radhakrishnan K. V.; a poster presented at international conference on international conference on Nascent Developments in ChemicalSciences: Opportunities for Academia-Industry Collaboration, BITS Pilani, Rajasthan, October, **2015**.

3. 3. C-2 Functionalization of Indoles with Diazabicyclic Olefins : Different Aspects of Ru & Ir Catalysis, Aparna P. S., Ajesh Vijayan and K. V. Radhakrishnan, 53rd Annual Convention of Chemist conference at GITAM University, Visakhapatnam, December, **2016**.