Transition Metal Catalyzed Transformations of Pentafulvenes and Its Derivatives: Facile Strategies Toward Carbocycles and Heterocycles

Thesis Submitted to the University of Kerala for the Award of the

Degree of **Doctor of Philosophy in Chemistry** under the Faculty of

Science

By

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Under the Supervision of

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2017

...To My Family

DECLARATION

I hereby declare that the Ph.D. thesis entitled "**Transition Metal Catalyzed Transformations of Pentafulvenes and Its Derivatives: Facile Strategies Toward Carbocycles and Heterocycles**" is an independent work carried out by me at the Organic Chemistry Section of National Institute for Interdisciplinary Science and Technology (CSIR), Thiruvananthapuram, under the supervision of **Dr. K. V. Radhakrishnan** and it has not been submitted anywhere else for any other degree, diploma or title.

Preethanuj Preethalayam

Thiruvananthapuram

July, 2017.

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CERTIFICATE

This is to certify that the work embodied in the thesis entitled "**Transition Metal Catalyzed Transformations of Pentafulvenes and Its Derivatives: Facile Strategies Toward Carbocycles and Heterocycles**" has been carried out by **Preethanuj Preethalayam** under my supervision and guidance at the Organic Chemistry Section of National Institute for Interdisciplinary Science and Technology (CSIR), Thiruvananthapuram and the same has not been submitted elsewhere for any other degree.

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ABBREVIATIONS

Ac : acetyl

AcOH: acetic acid

ADDM: azodicarbonyldimorpholide

AIBN : azobisisobutyronitrile

APT : attached proton test

Ar : aryl

bmim : 1-butyl-3 methylimidazolium

Bn : benzyl

Boc : tertiary butyloxycarbonyl

bs : broad singlet

^{t}Bu : tertiary butyl

CA : cycloaddition

calcd : calculated

CCDC : Cambridge Crystallographic Data Centre

cod : 1,5-cyclooctadiene

COSY : correlated spectroscopy

Cp : cyclopentadienyl

Cp* : pentamethylcyclopentadienyl

Cy : cyclohexyl

CPD : cyclopentadiene

d : doublet

dba : dibenzylidene acetone

DCE : dichloroethane

DCM : dichloromethane

dd : doublet of a doublet

dr : diastereomeric ratio

DIBAL-H: diisobutylaluminium hydride

DIEPA: N,N-diisopropylethylamine

DMF : dimethyl formamide

DMSO: dimethyl sulfoxide

DPF : diphenylfulvene

PPh_3 : triphenylphosphine

dppe : bis(diphenylphosphino)ethane

dppb : 1,4-Bis(diphenylphosphino) butane

dppf : bis(diphenylphosphino)ferrocene

dppm : bis(diphenylphosphino)methane

EDG : electron donating group

ee : enantiomeric excess

equiv. : equivalent

ESI : electron spray ionization

esp : α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid

Et : ethyl

EWG : electron withdrawing group

FT : Fourier transform

h : hour

HIV : human immunodeficiency virus

HOMO: Highest Occupied Molecular Orbital

HRMS : high resolution mass spectrometry

Hz : Hertz

IR : infrared

IMDA : intramolecular Diels-Alder

J : coupling constant

LA : Lewis acid

LAH : lithium aluminium hydride

LUMO: Lowest Unoccupied Molecular Orbital

m : meta

m : multiplet

max : maximum

mp : melting point

mCPBA: *meta*-chloroperoxybenzoic acid

Me : methyl

MHz : mega hertz

mg : milligram

mL :millilitre

min : minutes

M : mesomeric effect

MS : molecular sieves

MW : micro wave

n : normal

NHC : N-heterocyclic carbine

NMP : N-methyl-2-pyrrolidone

NMO : N-Methylmorpholine N-oxide

NMR : nuclear magnetic resonance

NOESY: nuclear overhauser effect spectroscopy

Nu : nucleophile

OTf : triflate

o : ortho

p : para

PG : protecting group

Ph : phenyl

PMB : 4-Methoxybenzyl ether

PPTS : Pyridinium *p*-toluenesulfonate

ppm : parts per million

^{i}Pr : isopropyl

^{n}Pr : propyl

PTSA : *p*-toluene sulfonic acid

q : quartet

rac : racemic

R_f : retention factor

rt : room temperature

s : singlet

t : triplet

TBAF : tetra-n-butylammonium fluoride

TBD : 1,5,7-Triazabicyclo[4.4.0]dec-5-ene

TBDMS: *tert*-Butyldimethylsilyl ethers

tert : tertiary

Tf : triflyl(trifluoromethane sulfonyl)

TFA : trifluoroacetic acid

TBHP : *tert*-Butyl hydroperoxide solution

THF : tetrahydrofuran

[Ti] : titanocene dichloride

TLC : thin layer chromatography

TMEDA: Tetramethylethylenediamine

TMS : trimethyl silyl

TMSI : trimethylsulfoxonium iodide

Ts : tosyl

UV : ultra violet

[Zr] : Zirconocene Chloride

PREFACE

Over the past few decades, a wide range of versatile synthetic protocols has been developed for the construction of carbocycles and heterocycles. These scaffolds are the key composites for various natural products, pharmaceuticals and biologically active compounds. There exist many deep-rooted approaches in the toolbox of a modern organic chemist's for the construction of carbocycles and heterocycles. However, the syntheses of these scaffolds are much more challenging, and certainly will attract much devotion in the future.

The utilization of pentafulvene and its derivatives for the construction of complex carbocycles and heterocycles continues to mesmerize our research group because of their excellent internal synthetic potential. Transition metal catalysed strain releases of diazanorbornenes have been extensively explored with some of mono and bicentered nucleophiles. These protocols delivered disubstituted cyclopentenes; cyclopentene fused heterocycles, carbocycles, etc. However, the reactivity of many more nucleophiles and effect of inherent nucleophilicity within the system remains uncharted and design of new methodologies for the construction of carbocycles and heterocycles is also challenging. The thesis entitled "**Transition Metal Catalyzed Transformations of Pentafulvenes and Its Derivatives: Facile Strategies Toward Carbocycles and Heterocycles**" predominantly focuses on our inquiries in developing strategies towards the synthesis of carbocycles from bicyclic olefins using transition metal catalysts.

The thesis is organized into four chapters. Each chapter of the thesis is presented as an independent entity and therefore the structural schemes, formulae and figures are numbered chapter wise. Relevant references are given at the end of the thesis.

A comprehensive review on pentafulvene and their derivatives with a special focus on fundamental properties, synthesis, cycloaddition profiles and their metal catalysed reactions are presented in the first chapter of the thesis. The definition of the current research problem is also unified in this chapter.

The second chapter explains our investigation on the titanium and zirconium catalyzed regioselective synthesis of five membered carbocycles. This section has been divided into two parts. Part A, describes a titanium catalyzed hydroalumination of various

spirocyclopentadienes with different aromatic aldehydes towards the methodology for the generation of the functionalized spiro appended cyclopentenyl homoallylic alcohols. A simple protocol towards the synthesis of a new class of substituted 1,2-dihydrofulvenes constitutes part B of the second chapter.

Our exertions towards the Lewis acid mediated ring opening of pentafulvene derived diazanorbornenes and subsequent trapping of the generated transient species with aliphatic and aromatic alcohols towards the synthesis of various aryl and alkyl cyclopentenyl ethers are presented in the third chapter.

A general and efficient methodology for the synthesis of tetrahydrocyclopenta[b]pyrans and indoline derivatives from hydroxy group tethered diazabicyclic olefins through a sequential Lewis acid-palladium mediated transformation is described in the last chapter.

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

CHAPTER 1

Pentafulvene and Its Derivatives: An Overview

1.1. Introduction

Aromaticity is one of the exciting features that attract chemists towards the world of organic compounds [von Schleyer 1996]. It describes the cyclic delocalization of π-electrons across a molecule, closely associated with conjugation as well as resonance; terms which were coined after the discovery of benzene in 1825 [Faraday 1825]. The concept of aromaticity has a well-defined role in predicting the physical, chemical and structural features of organic compounds [Alonso 2010]. In actual sense, the term is associated with the ground-state properties of cyclic π-electron compounds which (i) are more stable than their open-chain analogues, (ii) have bond lengths between those typical of the single and double ones, and (iii) have a π-electron ring current that is produced when the system is shown to external magnetic fields, leading to increased values of the magnetic susceptibility and specific values of ^{1}H NMR chemical shifts. From the chemical reactivity perspectives, aromatic compounds prefer substitution to addition, and hence, they exhibit a tendency to retain their π-electron structure. Even though there exist so many definitions; aromaticity is essentially an "excess property," *i.e.*, a deviation from an additive scheme. Cyclic cross conjugated systems that possess an *exo*-methylene unit in the ring system is generally termed *fulvenes* [Radhakrishnan 2017].

1.2. Fulvenes - Structure and Nomenclature

Fulvenes are stable isomers of benzene, that exhibit numerous physical and chemical properties, and have received tremendous attention from the synthetic community. The name fulvene has its origin from the Latin word "fulvus" meaning 'yellow', and not surprisingly most of the members in the family are yellow in color. The fulvenes were first prepared and

named by Thiele in 1900 [Thiele 1900, Thiele 1906], through the condensation of aldehydes and ketones with cyclopentadiene in the presence of alkoxides, however in low yields. Based on the size of the ring skeleton, they are classified as tria-, penta-, hepta-, and nona-fulvenes [Neuenschwander 1989].

The nomenclature of fulvenes follows the basic rules of chemical abstracts and the Beilstein numbering systems [Radhakrishnan 2017]. Currently, the most common numbering of pentafulvene is based on the *Chemical Abstracts format* (Figure 1.1a), where they are named simply by noting the name and position of substituents to the structure, in the usual fashion. However, this cannot be considered as a general pattern since articles appearing in German usually use the Beilstein numbering, which is depicted in figure **1.1b**. Occasionally fulvenes are named as cyclopentadiene derivatives also, for example dimethylfulvene is often referred as isopropylidenecyclopentadiene.

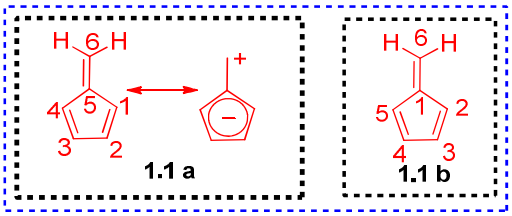


Figure 1.1: Dipolar structure and numbering of the parent pentafulvene

1.2.1. Fundamental Properties of Pentafulvene

Pentafulvenes are renowned isomers of benzene; however, they exhibit exceptional reactivities when compared to the latter due to the relatively high polarization of the exocyclic olefin and the resulting electropositive character at the exocyclic carbon atom. The color of pentafulvenes is due to their cross conjugation and varies with substitution. The color darkens while substituting with arenes, heteroatoms or cyano groups [Day 1953]. The substitution of an aromatic group directly on to the ring is less effective in deepening the color compared to the introduction of groups onto the exocyclic carbon. The bond lengths of fulvenes strongly alternate between those of open chain olefins and delocalized aromatic systems, the two extremes.

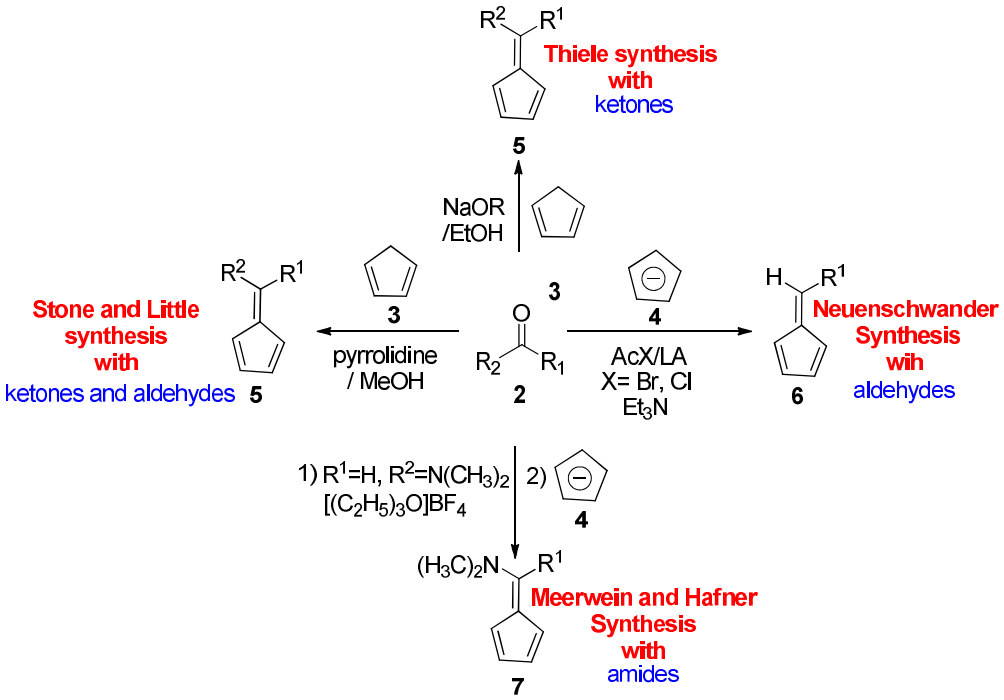
Pentafulvenes were considered as non-alternant hydrocarbons for a long time and are often taken as a model for studying the aromaticity of that class of compounds. In such cases, the π- density is shifted from the exocyclic olefins to the endocyclic aromatic five membered ring. The proton chemical shift values of the planar pentafulvene are in the olefinic region. The vicinal H,H coupling constants of the ring protons are strongly alternating for pentafulvene [Neuenschwander 1986, Neuenschwander 2015], thus indicating a strong alternation in the C-C bond lengths also. This phenomenon was confirmed using microwave data [Baron 1972]; and by the UV spectra, where the bathochromic shift of the longest wavelength absorption from triafulvene to pentafulvene corresponds to the extension of the conjugative system [Day 1952]. However, the infrared spectrum was not informative in deciding the aromaticity of fulvenes [Brown 1970a]. In short, spectroscopic data clearly indicate the non-aromatic character of pentafulvene and its analogues, which was further supported through theoretical calculations. With increase in the electron donating ability of the substituents at C-6 position, the formal double bonds are lengthened where as the formal single bonds are shortened. In contrast, introducing electron-withdrawing groups in the exocyclic position leads to an inversion of polarity at the exocyclic double bond. These findings clearly show that even though the parent pentafulvene has non-aromatic character, substitution at the exocyclic position can change the aromaticity of fulvenes significantly.

1.2.2. Synthesis of Pentafulvenes

Suitably substituted fulvenes have a critical role in synthetic organic chemistry. Till date a large number of procedures are employed for the synthesis of pentafulvene core following the preliminary report of Thiele *et al.* in 1900 [Thiele 1900, Thiele 1906]. This classical procedure was based on a simple condensation of the cyclopentadiene with aldehydes/ketones in the presence of sodium ethoxide in alcohol (Scheme 1.1). However, the yield depended on the reactivity of the carbonyl compound as well as on the stability of the fulvene formed. Even though the method was found to be suitable for reactions involving aliphatic and alicyclic ketones, the yield was poor in the case of diaryl, aryl alkylketones and aliphatic aldehydes.

Thiele's procedure was modified by Stone and Little in 1984 [Little 1984]. They introduced a more general method for the synthesis of pentafulvenes using pyrrolidine as the

base, but failed in the case of bulky ketones such as diaryl ketones. The problem with aliphatic, α,β-unsaturated and most aromatic aldehydes was solved by Neuenschwander's procedure [Neuenschwander 1965]. Here the Lewis acid mediated reaction of an acyl halide with the aldehyde produce 1-Acetoxy-1-halomethanes, which then reacted with cyclopentadiene in the presence of a tertiary amine like triethylamine afforded the fulvene. Later Meerwein and Hafner devised the first synthetic route to electron rich diaminopentafulvenes from dimethylformamide diethylacetals and cyclopentadiene (Scheme 1.1) [Meerwein 1961, Hafner 1964].



Scheme 1.1: Conventional methods for fulvene synthesis

An efficient catalytic method for the synthesis of pentafulvenes was described by Erden and Coskun using catalytic amounts of pyrrolidine in MeOH/H_2O [Erden 2011]. This method allows the use of lesser amounts of cyclopentadiene and base, compared to the conventional syntheses, and interestingly even low molecular-weight fulvenes such as 6-methyl and 6-ethylfulvene can be synthesised in high yields. Despite the wide range of literature reports, the conventional methods established by Thiele, Little and Erden are still considered as the most common methods for the preparation of pentafulvenes.

1.2.3. Reactivity Profile of Pentafulvenes

Fulvenes display a wide spectrum of reactivity patterns. They undergo reaction with various electrophiles, nucleophiles, bases, transition metals and participate in a number of cycloaddition reactions.

1.2.3.1. Substituent Effects and the General Reactivity Patterns

The substitution effect on the aromaticity of pentafulvene is a subject matter of interest since the parent fulvene is known to be non-aromatic (Figure 1.2). Early experimental works and measured dipole moments of substituted fulvenes indicate that the substitution can considerably increase the π-delocalization, hence the corresponding derivatives may occupy an intermediate position between the non-aromatic and aromatic molecules [Hafner 1963, Yates 1968]. Therefore a variation in the substitution can cause a change in π-delocalization and charge distribution without contributing much to the steric factors. In the case of pentafulvene, electron donating substituents at the exocyclic carbon enhances the above properties and the effect can be directly followed, by X-ray [Norman 1961], MW data [Baron 1972] and indirectly by the NMR spectra [Neuenschwander 1986, Radhakrishnan 2017].

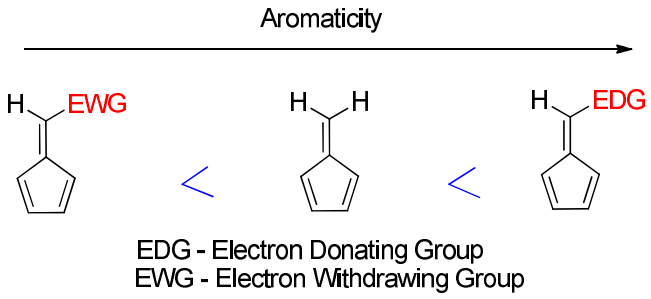


Figure 1.2: Order of aromaticity of pentafulvenes

1.2.3.2. Reactivity of Pentafulvenes with Electrophiles, Nucleophiles and Bases

Most of the fulvenes react readily with electrophiles and nucleophiles. A better insight into the reactivity of fulvenes can be obtained from the frontier orbital considerations

[Fleming 1976, Houk 1979]. Pentafulvene, when compared with its isomer benzene, has high energy HOMO (Highest Occupied Molecular Orbital) and comparably low energy LUMO (Lowest Unoccupied Molecular Orbital), as evident from the long wavelength absorption of fulvene and its color. One of the frontier orbitals of fulvene has a nodal plane passing through the exocyclic bond, so that energy of that molecular orbital remains unaltered by the exocyclic substituent (Figure 1.3a). This difference in the HOMO and LUMO accounts for the reactivity, electronic nature, as well as the low thermal stability of the fulvenes when compared to other aromatics.

Electrophiles usually have a low energy LUMO and actively interact with the HOMO of the pentafulvene, while nucleophiles possessing a high energy HOMO are expected to have a strong binding interaction with the LUMO of the pentafulvene. The exocyclic substituent has a strong influence on the LUMO of the pentafulvenes. –M substituent lowers the energy of LUMO and the effect is just opposite if the substituent has +M effect (Figure 1.3b). In fact, by considering the LUMO of pentafulvene, the C6 has the largest Huckel coefficient, and nucleophile will attack at the exocyclic position. But in the case of the HOMO of pentafulvene, electrophiles are expected to react predominantly at the C1/C4 position (Figure 1.3c) [Radhakrishnan 2017].

The Frontier orbital consideration also gives an idea about the cycloaddition profile of pentafulvenes. The dienophiles with low energy LUMO are expected to have a strong interaction with HOMO of pentafulvene. Substituent at the exocyclic position will determine the energy of LUMO, and that will decide in which manner the pentafulvene will act in their cycloaddition profile [Neuenschwander 2015]. Pentafulvenes bearing alkyl substituents in the exocyclic position can be easily converted into the corresponding vinyl cyclopentadienyls using strong bases. This transformation has been well utilized in the cycloaddition as well as organometallic reactions involving fulvenes, and subsequently expanded the scope of pentafulvene chemistry.

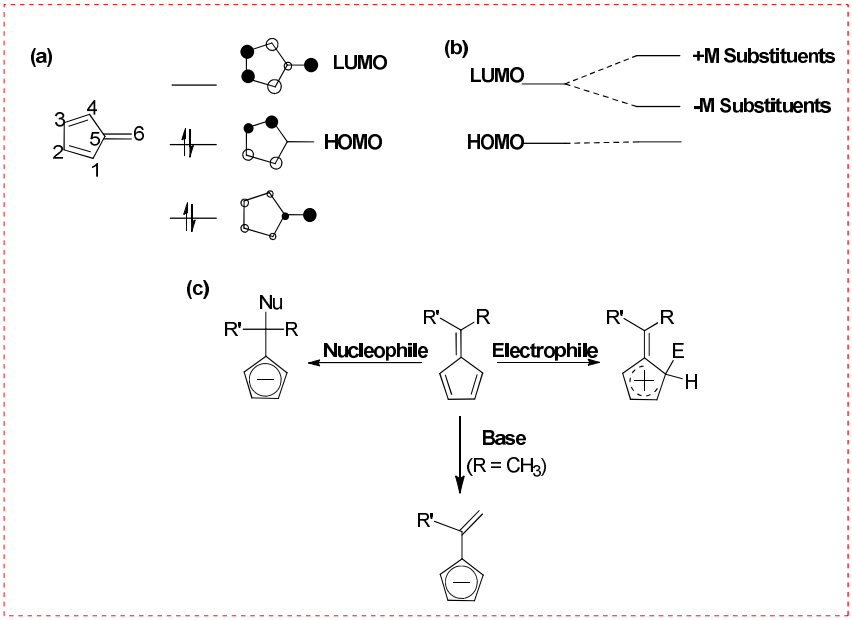


Figure 1.3: (a) HOMO-LUMO representation of pentafulvene. (b) Influence of substituents on the energy of frontier orbitals. (c) Reactivity of pentafulvenes towards nucleophiles, electrophiles and base [Radhakrishnan 2017].

1.2.4. Pentafulvenes in Cycloaddition

Cycloaddition reactions occupy a prominent place in the toolbox of synthetic chemists and are among the most dependable chemical transformations available to date [Trost 1991]. The development of pentafulvenes as versatile scaffolds immensely expanded the scope of cycloaddition reactions, attributed to the multiple reaction profiles displayed by them and the diversity of the reaction products. Pentafulvenes perform flexibly as 2π, 4π or 6π candidates (Figure 1.4) and have been recognized as the eminent building unit of many fused complex ring systems through intra and intermolecular cycloaddition reactions. The periselectivity of these reactions is controlled by the substituents on the fulvene.

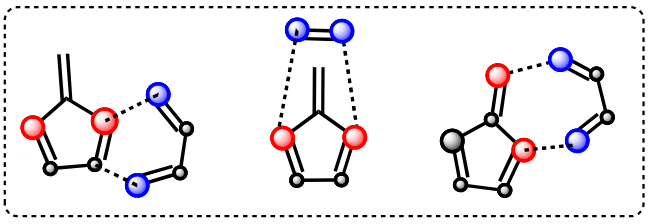
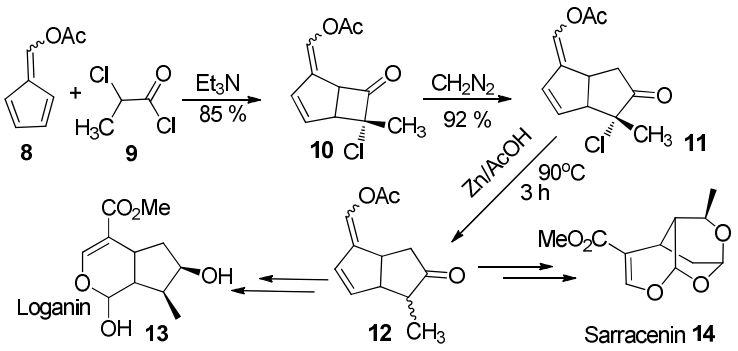


Figure 1.4: Pentafulvene as 2π, 4π and 6π partners in cycloaddition reactions

1.2.4.1. Pentafulvene as 2π Component

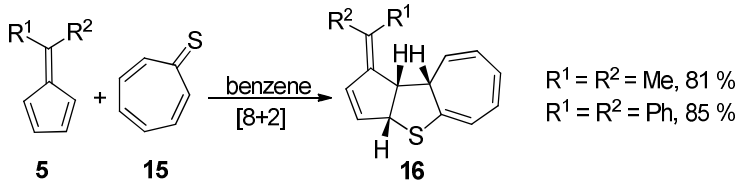
Pentafulvenes behave as 2π components with electron deficient dienes. As per the selection rules, a thermal [2+2] cycloaddition is not expected from pentafulvenes due to symmetry reasons. Surprisingly, one such reactivity of pentafulvenes with ketenes was developed into a general and robust approach towards the synthesis of polycyclic systems. The reaction with ketenes proceeds *via* suprafacial- antarafacial pathway and is thermally allowed.

An interesting example of the [2+2] cycloaddition of pentafulvene was reported by Chang and co-workers. They utilized a protocol similar to the one proposed by Imafuku *et al.* for the preparation substituted tropolone derivatives through a [2+2] cycloaddition between 2-alkyl-6,6-dimethyl fulvene and dichloroketene. Chang *et al.* have extended their strategy towards the total synthesis of Iridoid natural products such as Loganin and Sarracenin. The key intermediate **10** in the report was derived from the diquinane obtained by the [2+2] cycloaddition reaction of 6-acetoxy fulvene and methyl chloroketene (Scheme 1.2) [Chang 1999].



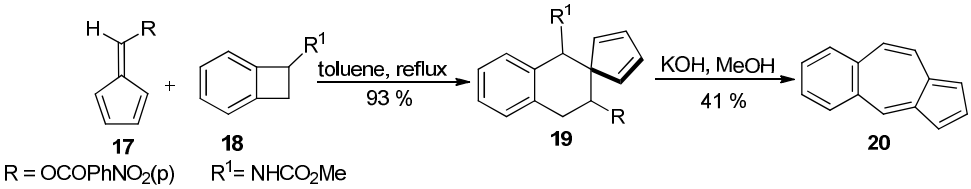
Scheme 1.2: Total synthesis of Iridoid natural product Loganin and Sarracenin

Machiguchi *et al.* found that fulvene can act as a 2π component with tropothione **15**, in which the latter serves as the 8π component. But this observation is in contrast with that of Houk *et al*., who found that fulvene acted as a 4π module with the tetraene system of tropone affording a double [6+4] type adduct [Machiguchi 1993]. These examples emphasize the difference in reactivity pattern of pentafulvene with various cycloaddition partners (Scheme 1.3).



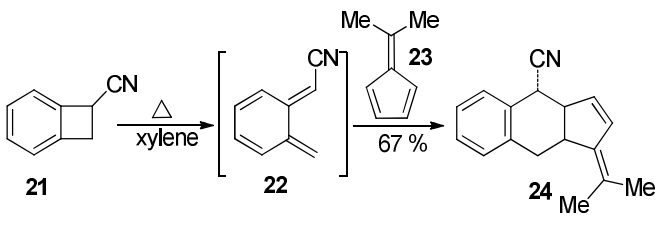
Scheme 1.3: [8+2] Cycloaddition between pentafulvene and tropothione

It is interesting to note that the exocyclic double bond of pentafulvene is reluctance to participate as a 2π component during the cycloaddition reactions. But, an exciting report on the cycloadditions of *o*-xylylenes to pentafulvenes came from Houk *et al*. They found that the electron-deficient *o*-xylylenes react in a [4+2] manner to the endocyclic double bond of fulvene, whereas electron-rich ones add primarily in the same fashion to the exocyclic double bond. The presence of electron withdrawing substituents on the C-6 position of fulvene further stimulates the exocyclic double bond in cycloaddition reactions. For example, the reaction of fulvene with [(methoxycarbonyl)amino]benzocyclobutene afforded the spiro adduct **19** (93 % yield) which can be transformed to benzoazulene **20** (Scheme 1.4) [Houk 1983a].



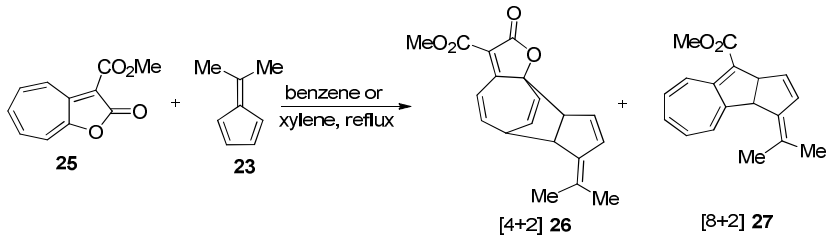
Scheme 1.4: Reaction of pentafulvene with [(methoxycarbonyl)amino]benzocyclobutene

On the contrary, the reaction of cyanobenzocyclobutene with excess dimethyl fulvene resulted in cycloaddition at the endocyclic double bond of fulvene and afforded a single [4+2] adduct in 67 % of yield (Scheme 1.5).



Scheme 1.5: Reaction of cyanobenzocyclobutene with excess dimethylfulvene

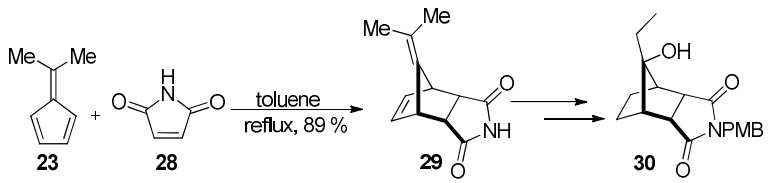
Yasunami *et al.* have studied the effect of solvent on the cycloaddition mode of pentafulvenes by following the reaction between 6,6-dimethylfulvene and 3-methoxycarbonyl-*2H*-cyclohepta[*b*]furan-2-one in different solvents [Deslongchamps 1992]. The reaction may proceed either through a [4+2] or [8+2] cycloaddition pathway depending on the solvent. The [4+2] cycloadduct was the major product in ethanol or benzene together with a minor [8+2] adduct**,** while the latter was the exclusive product in xylene (Scheme 1.6).



Scheme 1.6: [4+2] or [8+2] Cycloaddition of pentafulvenes with 3-alkoxycarbonyl-*2H*-cyclohepta[*b*]furan-2-one

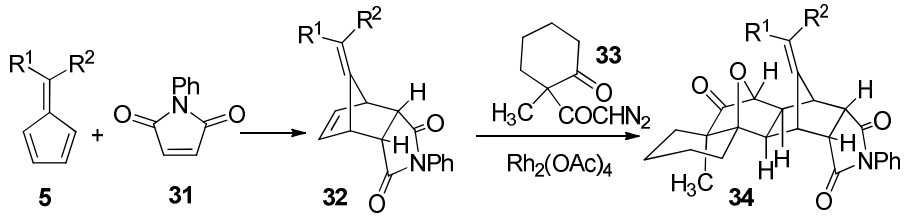
1.2.4.2. Pentafulvene as 4π Component

The existing literature on the cycloaddition reactions of fulvenes and various dienophiles clearly depicts that pentafulvenes can act as extremely reactive dienes. The Diels-Alder reaction of pentafulvenes with dienophiles such as maleimide and maleic anhydride proved a well suited key synthetic route to many supramolecular frameworks [Deslongchamps 1996]. For example, maleimide reacted with 6,6-dimethylfulvene in refluxing toluene affording [4+2] cycloadducts as an 8:1 mixture of *exo* and *endo* isomers. The major *exo* isomer was readily converted into the structure **30**, for the rapid assembly of abiotic receptors toward neutral organic guest molecules. The simple structure and the capability of the stiff carbobicyclic framework to introduce the hydroxyl group *cis* to the latent imide group made them more attractive for molecular recognition (Scheme 1.7).



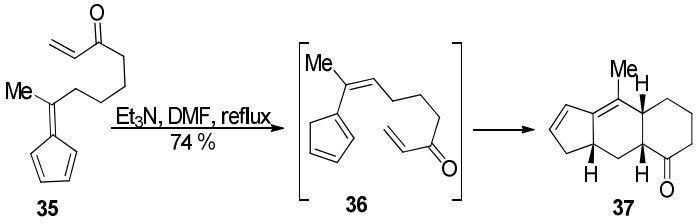
Scheme 1.7: Reaction of 6,6-dimethylfulvene with maleimide

Muthusamy *et al.* developed an efficient and stereoselective protocol for the construction of *syn*-facially bridged norbornane frameworks from pentafulvene derivatives *via* reactions with rhodium carbenoids produced from diazo ketones (Scheme 1.8) [Muthusamy 2002].



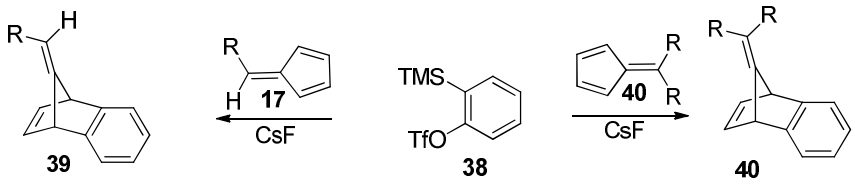
Scheme 1.8: Construction of *syn*-facially bridged norbornane frameworks

The intramolecular Diels-Alder (IMDA) reaction involving fulvenes as 4π components is a powerful strategy for the creation of polycyclic systems and has been effectively applied to the synthesis of various natural products [Craig 1987]. Later, an efficient IMDA of simple acyclic fulvene molecules towards the creation of polycyclic skeletons present in various pharmaceutical agents such as SP 18904, treprostinil and kigelinol was established by Hong and co-workers [Hong 2005]. They also exemplified that the length of the chain and the diversity of the substituents on the fulvene can dictate the nature of the cycloaddition pathway (Scheme 1.9).



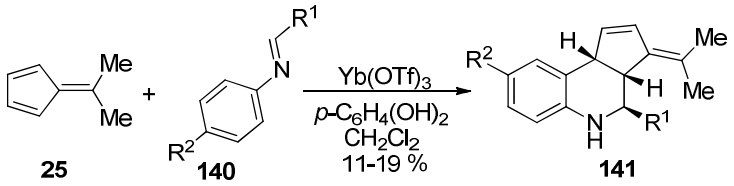
Scheme 1.9: Intramolecular [4+2] cycloadditon of a simple acyclic fulvene

A convenient, versatile and at the same time high-yielding procedure for the Diels-Alder reaction of pentafulvenes with arynes under mild reaction conditions is reported. For example, the arynes produced by the fluoride prompted 1,2-elimination of 2-(trimethylsilyl)aryl triflates underwent efficient cycloaddition with 6-substituted and 6,6-disubstituted pentafulvenes and afforded novel benzonorbornadiene derivatives (Scheme 1.10) [Biju 2012].



Scheme 1.10: Diels-Alder reaction of pentafulvene with arynes

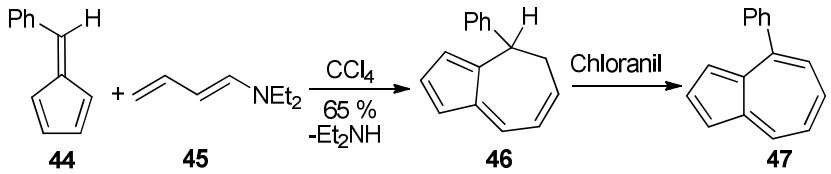
In 2014, Molchanov *et al.* reported a Lewis acid catalyzed formal aza-Diels–Alder (Povarov) reaction involving fulvenes and aromatic imines for the first time. However, the reaction was restricted to dimethyl fulvene and also the yield was low due to polymerization (Scheme 1.11) [Stepakov 2014].



Scheme 1.11: Lewis acid catalysed formal aza- Diels- Alder (Povarov) reactions involving fulvenes and aromatic imines

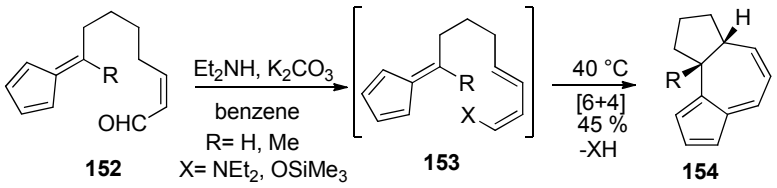
1.2.4.3. Pentafulvene as 6π Component

The pioneering work by Houk and co-workers established that pentafulvene can also be utilized as 6π components in cycloaddition reactions. In this direction, they have developed an efficient protocol for azulene synthesis *via* the [6+4] cycloaddition of pentafulvenes and electron rich amino butadienes [Houk 1976]. For example, the cycloaddition of 6-phenyl fulvene with 1-diethylamino butadiene, followed by the elimination of diethylamine resulted in hydrazulene derivative **46** which on aromatization with chloranil afforded phenyl substituted azulene (Scheme 1.12).



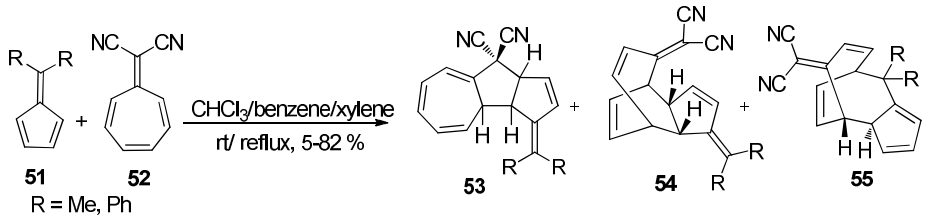
Scheme 1.12: [6+4] Cycloaddition of pentafulvenes and electron-rich aminobutadiene

Subsequently, the same group developed an intramolecular version of the reaction by resorting to an extremely selective intramolecular [6+4] cycloaddition of aminodienylfulvenes leading to tricyclic systems (Scheme 1.13) [Houk 1983b].



Scheme 1.13: Intramolecular [6+4] cycloaddition of aminodienylfulvenes

In contrast to intramolecular cycloaddition reactions comprising higher-order π systems (*vide supra*) intermolecular versions endure from the loss of regioselectivity, *endo/exo* selectivity, and diastereofacial selectivity. Liu and Ding verified this information by investigating the cycloadditions of pentafulvenes with the higher homologue of the fulvenoid family, heptafulvene [Liu 1992]. Multiple cycloaddition profiles were observed and the reactions proceed with low yields and low periselectivity, afforded a mixture of [6+4], [8+2] and/or [4+2] adducts depending on the reaction conditions (Scheme 1.14).



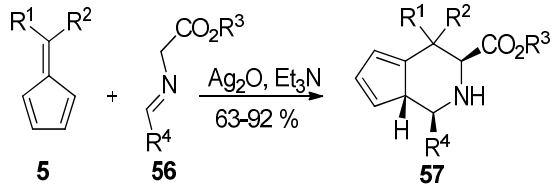
Scheme 1.14: Multiple cycloaddition profiles shown by the reaction of pentafulvenes with heptafulvene

To stimulate pentafulvene as a 6π component, either the cycloaddition partner or the pentafulvene itself must be electron rich. Naturally, these restrictions limited the scope of this cycloaddition mode which is evident from the limited number of reports in the last two decades. However, the recent enhancement observed in the chemistry of electron rich fulvenes and metal-mediated cycloadditions along with the launch of various electron rich dipoles as partners, established the reactivity of pentafulvene as a 6π component and made the approach an efficient strategy for the construction of impressive organic structures.

1.2.4.4. Pentafulvenes in Dipolar Cycloaddition Reactions

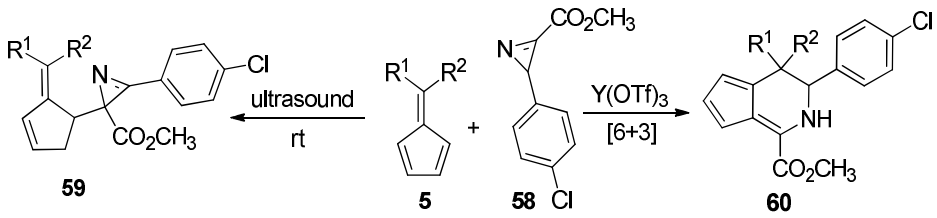
1,3-Dipolar cycloaddition offers a high-yielding, efficient, regio- and stereocontrolled method for the synthesis of numerous carbocyclic and heterocyclic compounds [Crabb 1984]. Considering the potential features achievable through the chemistry of pentafulvenes, there was a general acceptance of the latter in the zone of dipolar cycloaddition reactions. Mesoionic ring systems are extensively recognized 1,3-dipolar species and are employed as the synthons for rendering a variety of heterocycles [Newton 1982]. One of the earliest attempts to couple the attractive dipolar chemistry of pentafulvenes with mesoionic compounds came from Kato and co-workers [Kato 1997]. Afterwards, numerous mesoionic compounds have been studied with pentafulvene derivatives, affording [4+2] and [4+6] cycloadducts, which under suitable reaction conditions undergo fragmentation, elimination or isomerization leading to a variety of heterocycles isoelectronic with azulene.

In 2003, Hong and co-workers established the [6+3] cycloaddition reaction of azomethine ylides generated *in situ* from glycine-N-benzylidene ethyl ester with a series of pentafulvenes leading to biologically relevant [2]pyrindine systems (Scheme 1.15) [Hong 2003].



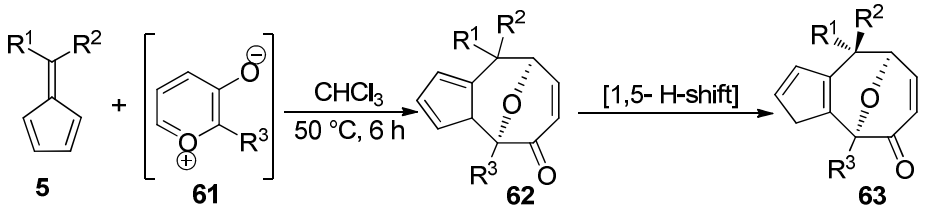
Scheme 1.15: [6+3] Cycloaddition reactions of azomethine ylides with pentafulvene

One year later, the same group uncovered a unique dual reactivity pattern of pentafulvenes with *2H*-azirines. In the presence of a Lewis acid, 2H-azirine reacted with fulvenes *via* a formal regioselective [6+3] cycloaddition reaction and developed an efficient synthetic route to [2]pyrindine derivatives. Contrarily, under ultrasound conditions, the reaction afforded alkylated fulvene azirines through an unexpected rearrangement of the initial Diels-Alder cycloadduct (Scheme 1.16) [Hong 2004].



Scheme 1.16: Dual reactivity of pentafulvenes and *2H*-azirine

In view of the advancements in pentafulvene chemistry, our research group had a reasonable quest to explore the untouched reactivity modes of pentafulvenes. Through our systematic efforts in this direction, we have unravelled a simple but efficient [6+3] cycloaddition reaction of pentafulvenes with 3-oxidopyrylium betaines and the approach presented a valuable protocol for the synthesis of 5-8 fused cyclooctanoids [Radhakrishnan 2005]. The similar chemistry was effectively prolonged to a number of pentafulvenes with various alkyl, aryl and cycloalkyl substituents (Scheme 1.17).



Scheme 1.17: [6+3] Cycloaddition reactions of pentafulvenes with 3-oxidopyrylium betaines

1.2.5. Miscellaneous Reactions of Pentafulvenes

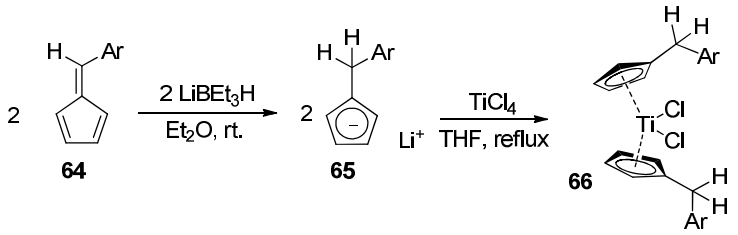
1.2.5.1. Pentafulvenes in Metallocene Chemistry

Besides being served as interesting models for cycloaddition reactions, aromaticity studies and photophysical investigations, etc. [Radhakrishnan 2017], fulvenes also found their own place in organometallic chemistry. They serve either as easy-to-handle precursors for a large variety of the ubiquitous cyclopentadienyl ligands or as versatile ligands for a variety of transition metal complexes, providing numerous coordination and reactivity patterns. Furthermore, fulvenes are interesting substrates for organic transformations using organometallic reagents.

1.2.5.1.1. Formation of Metallocenes

1.2.5.1.1.1. Reductive Complexation

Many of the fulvene-metallocene complexes exhibit very good anti-proliferative activity profile against several cancer cell lines. The beginning of fulvene metallocene chemistry dates back to 1990, attributed to the original preparation of lithium cyclopentadienyl reagents by the reduction of fulvenes with LAH [Day 1952]. After relying on the transmetallation reactions with $FeCl_2$ and $ReBr(CO)_3$ [Hopf 2002], the field has now witnessed the discovery of a powerful super-hydride reagent $LiBEt_3H$ which has been successfully applied to a large variety of 6-arylfulvenes (Scheme 1.18). This method readily gives access to the corresponding lithium cyclopentadienyl precursors for direct use in the synthesis of titanocene [Tacke 2008], zirconocene [Tacke 2007], vanadocene [Tacke 2009a], niobocene [Tacke 2009b], molybdocene [Vinklárek 2014] and tin [Tacke 2010] complexes. Fulvenes with different electronic, steric and solubility properties can be employed in the reactions.



Scheme 1.18: Synthesis of titanocene dichloride complexes by reduction of 6 arylfulvene followed by transmetallation

1.2.5.1.1.2. Carbometalation Reaction

The addition of organometallic reagents onto the exocyclic double bond of fulvenes readily gives access to diversely substituted cyclopentadienyl metal precursors which can be further employed in salt metathesis reactions and several studies related to this area are published already. Various titanocene complexes reported by Tacke exhibited high cytotoxicity which may arise from the stabilization of mono- or dications through intramolecular coordination from the N,N-dimethylamino groups (Figure 1.5) [Tacke 2008]. Jaouen used this approach for the synthesis of Cp ligands containing steroid groups, which

were employed for the synthesis of non-radioactive Re-complexes [Jaouen 2006]. Several research groups have contributed to this area over the last 25 years [Kirillov 2010, Bercaw 2006, Halterman 2001, Kaminsky 2003].

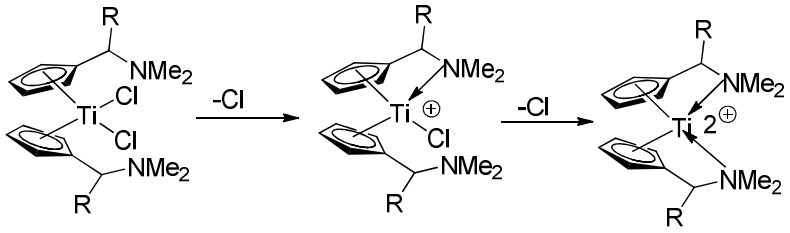
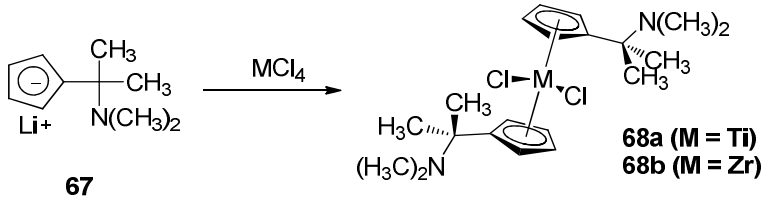


Figure.1.5: Stabilisation of the mono- or dications of dimethylaminofunctionalised titanocenes

Erker *et al.* studied the addition of alkyllithium reagents to dialkylaminofulvenes which provided, after transmetallation, group 4 metallocenedichloride complexes (Scheme 1.19) [Erker 2006]. Addition of methyl or phenyllithium to 6-alkylsubstituted fulvenes and transmetallation with $ZrCpCl_3$ yielded new zirconocene dichloride complexes which were investigated for ethylene and propylene polymerization [Prashar 2007].



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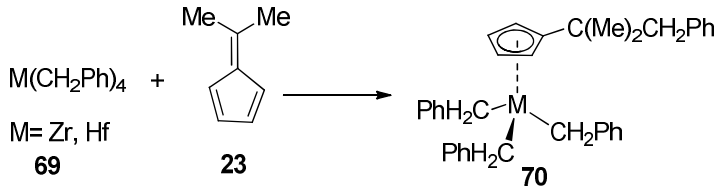
Scheme 1.19: Formation of metallocene with zirconium and titanium

Zirconium and hafnium tetrabenzyl complexes react smoothly with 6,6-dimethyl fulvene to afford selectively mono $CpM(benzyl)_3$ complexes, whereas in the case of 6,6-DPF only Hf yielded a clean reaction [Bazan 1999]. Interestingly, no proton abstraction from the methyl group on the C-6 position was observed (Scheme 1.20).



Scheme 1.20: Synthesis of monocyclopentadienyl zirconium and hafnium tris(benzyl) complexes

1.2.5.1.2. Fulvenes as Ligands in Organometallic Complexes

Due to their unique cross-conjugated system, fulvenes display a wide array of coordination modes to metals (Figure 1.6). Often these binding patterns are subject to discussions and present extreme situations, with the reality being found in-between the different possibilities [Radhakrishnan 2017].

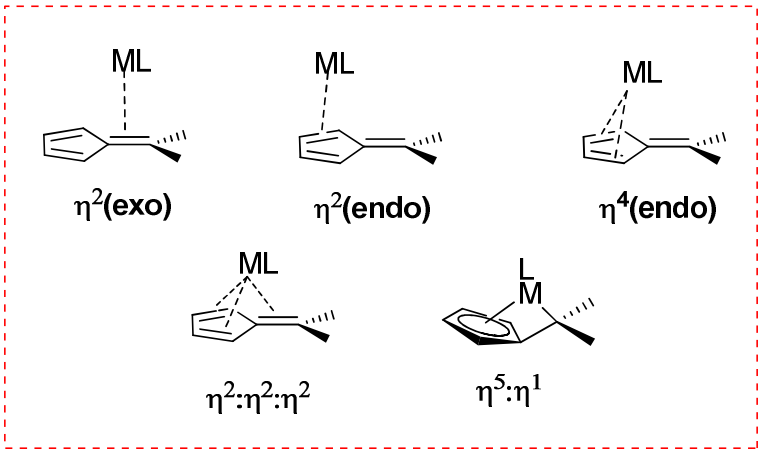


Figure 1.6: Various binding modes of transition metals to pentafulvene

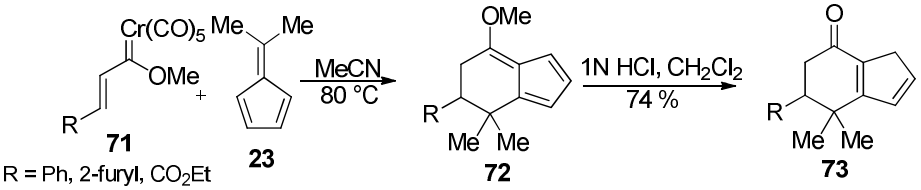
1.2.5.2. Transformation of Pentafulvene *via* Metal Catalyzed Reactions

1.2.5.2.1. Unusual Cycloaddition Partners of Pentafulvenes: Fischer-Carbene Complexes

Organometallic chemistry in the current era has witnessed the introduction of a novel reactivity pattern of pentafulvenes with Fischer carbene complexes and its rapid development as a general protocol for the synthesis of substituted indenes and annulated cyclopentanones. The effort to integrate the chemistry of pentafulvenes with Fischer carbene complexes was attributed to the efforts taken by Barluenga. Heteroatom stabilized carbene complexes have been proved to be useful organometallic reagents for carbo- and heterocyclization reactions [Sierra 2000]. Depending on the type of carbene complex used, it is possible to create versatile carbon synthons for organic synthesis.

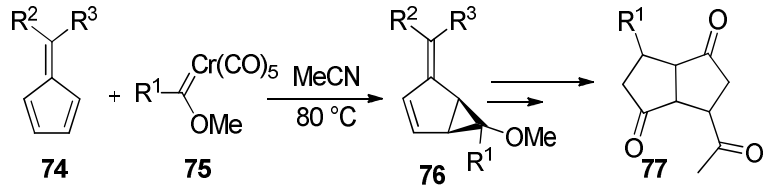
While investigating the reactivity of the alkenyl carbene complex **71** with dimethyl fulvene **23,** Barluenga *et al.* observed the formation of substituted indene **72** *via* a [6+3] cycloaddition [Barluenga 2001]. This is considered as the earliest report on the [6+3] cycloaddition of metal carbene complexes and offered an unusual approach for the indene synthesis. The protocol provides a unique benzannulation of the fulvene system instead of the

cyclopentene annulation onto the benzo ring. The reaction was found to be applicable to various alkyl and alkenyl fulvenes and afforded substituted indanones and indenes in a regioselective way (Scheme 1.21).



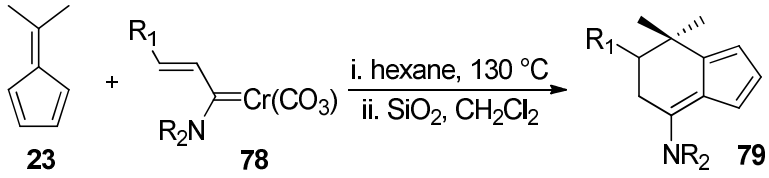
Scheme 1.21: [6+3] Cycloaddition of alkenyl carbene complexes with dimethylfulvene

A systematic carry-over of the above strategy yielded the most primitive cyclopropanation and cycloheptannulation of the pentafulvene system with Fischer carbene complexes. The cyclopropanation of pentafulvenes was accomplished *via* a [2+1] cyclization with alkyl or aryl(methoxy) carbene complex. A logical extension of this method provided access to more complex cyclopentane frameworks (Scheme 1.22) [Barluenga 2002].



Scheme 1.22: [2+1] Cyclization of pentafulvene with alkyl or aryl(methoxy) carbene complexes

A rapid synthesis of amino indenes was established *via* a regioselective [6+3] cycloaddition reaction of alkenylaminocarbene complex with pentafulvenes (Scheme 1.23) [Barluenga 2005].



Scheme 1.23: [6+3] Cycloaddition of alkenylaminocarbene complexes with a pentafulvene

It is notable that the pentafulvene-Fischer carbene combination offers an exceptional protocol for the construction of substituted indenes and various annulated cyclopentanoids. Another attractive feature of the strategy is that the newly formed indenes preserve a reactive fulvene unit and are promising candidates for the synthesis of diverse polycyclic systems.

1.3. Synthetic Utility of Pentafulvene Derived Systems

1.3.1. Pentafulvene Derived Diazabicyclic Olefins

The synthetic potential of pentafulvenes can also be utilized for the diverse synthesis of cyclopentanoids by transforming them into the corresponding diazanorbornene. Desymmetrization of *meso* compounds is renowned as a potent method for accessing biologically significant molecular skeletons in a limited number of steps. In this context, heterobicyclic olefins play a vital role due to its high ring strain character originating from the unfavorable bond angles and eclipsing interactions [Goddard 2009, Cheng 2007, Goddard 2004, Hall 1973]. The strain of norbornene (27kcal/mol) is comparable to other strained olefins. The ring strain increases further if an electronegative atom is incorporated. Relieving the strain through ring opening reactions provides an entry into otherwise inaccessible acyclic variants with several stereocentres in a single step. In addition to ring strain, its unique geometry also plays a significant role in its reactivity. It's exclusive facial selectivity and reactivity as a diene is also due to the two distinct faces of the cup-shaped [2.2.1] bicycle including a convex *exo* face and a concave *endo* face. Steric considerations in an unsubstituted molecule dictate that the *exo* face is more accessible to reactants. The homoconjugation (the phenomenon of interactions of the π-orbitals through space) of norbornadiene derivatives in spite of the isolated double bonds is evident from their photoelectron spectrum. Extensive research has been dedicated toward the synthetic transformations of oxa-, aza- and diaza-norbornenes/ norbornadienes for the synthesis of a broad range of carbocycles and heterocycles in a single step as well as in a stereo- and chemoselective manner. The desymmetrization protocols for the pentafulvene derived azabicyclic olefins developed from our research group (Figure 1.7) are presented in the following section.

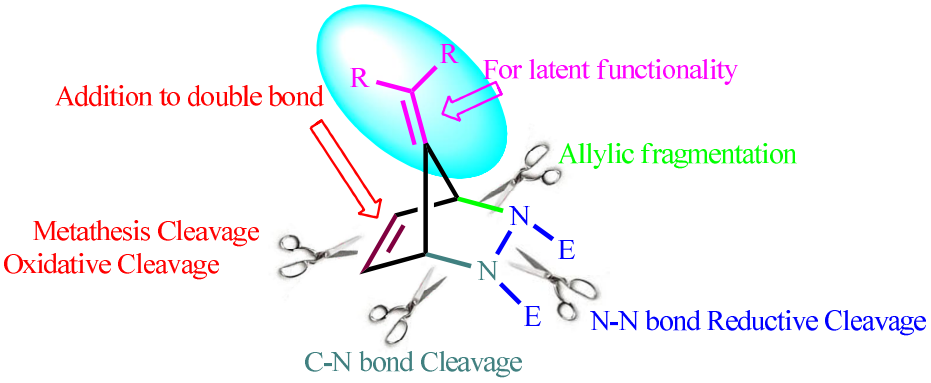


Figure 1.7: Functionalisation protocols for pentafulvene derived diazabicyclic olefins

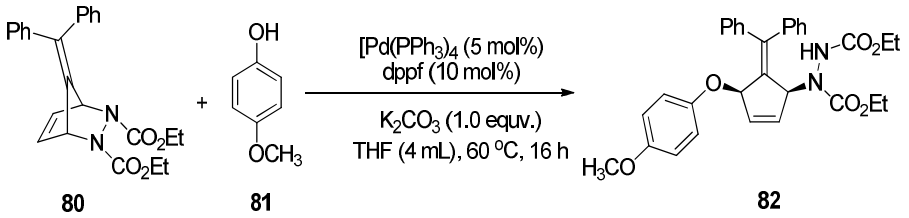
The *meso* diazanorbornenes obtained by the Diels-Alder cycloaddition of fulvenes with dialkylazodicarboxylates, exhibit a unique bicyclic olefinic structure as well as versatile reactivity patterns. Their exceptional ability to control chemoselectivity/regioselectivity and at the same time allowing otherwise difficult complexity-building transformations elevate their chemistry [Cheng 2007]. The synthetic potential of these bicyclic adducts can be attributed to (1) the efficient ring fragmentations of adducts *via* nitrogen–nitrogen bond reduction, carbon–carbon oxidative cleavage or ring-opening metathesis or allylic carbon–nitrogen cleavage; (2) skeletal rearrangements involving carbocationic intermediates [Micouin 2009, Radhakrishnan 2009] and (3) desymmetrization reactions leading to enantioenriched products.

1.3.1.1. Chemical Reactivity of Pentafulvene Derived Diazabicycic Olefins

1.3.1.1.1. Reaction with Soft Nucleophiles: Trost Approach

The acid mediated rearrangement of diazanorbornenes derived from diazodicarboxylates was introduced by Micouin *et al.*in 2003 [Micouin 2003]. They have generated and trapped the allylic reactive species formed during rearrangement, using palladium as catalyst, thereby achieving the desymmetrization of the diazanorbornene in a completely regio- and diastereoselective manner. Due to our interest in the area, we have investigated the ring opening of pentafulvene derived bicyclic hydrazines under palladium catalysis [Radhakrishnan 2010]. The desymmetrization of fulvene derived azabicyclic olefin

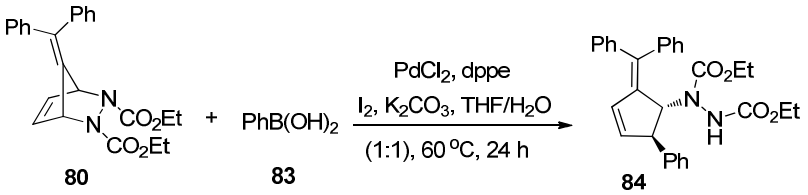
with 4-methoxyphenol afforded *cis*-3,5-disubstituted alkylidenecyclopentene in good yields and as a single diastereomer (Scheme 1.24).



Scheme 1.24: Synthesis of *cis*-3,5-disubstituted alkylidenecyclopentene

1.3.1.1.2. Reactions with Organoboranes

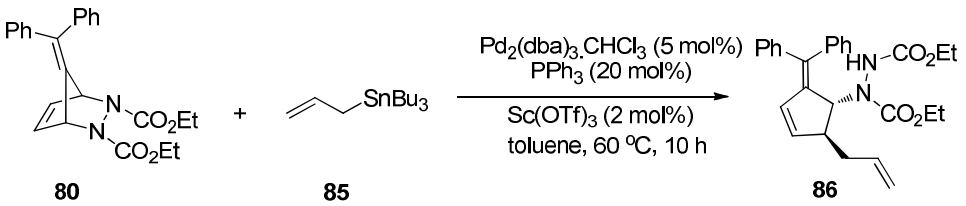
A major breakthrough in the field the palladium catalyzed cross coupling of organoboronic acid and 2,3-diazanorbornenes came from our group in 2006 [Radhakrishnan 2006]. The reaction resulted in the stereoselective formation of *trans*-3,4-disubstituted cyclopentenes. The strategy was further extended to afford highly functionalized alkylidenecyclopentenes *via* pentafulvene derived diazanorbornenes and tricyclic olefins derived from triazoline (Scheme 1.25) [Radhakrishnan 2007].



Scheme 1.25: Stereoselective formation of *trans*-3,4-disubstituted cyclopentenes

1.3.1.1.3. Reactions with Organostannanes

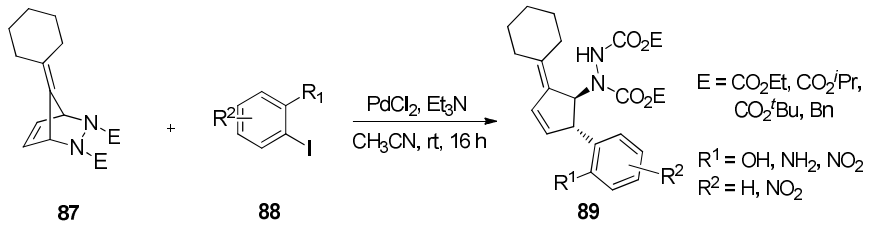
The first report on the ring opening of bicyclic olefins towards 3,4-disubstituted cyclopentenes by the application of organostannanes as nucleophiles came from our group in 2006 [Radhakrishnan 2006]. Following a similar protocol, we successfully synthesized the allyl substituted alkylidenecyclopentene from fulvene derived azabicyclic olefins (Scheme 1.26) [Radhakrishnan 2008].



Scheme 1.26: Ring opening of bicyclic olefins by organostannanes

1.3.1.1.4. Reaction with Aryl Iodides

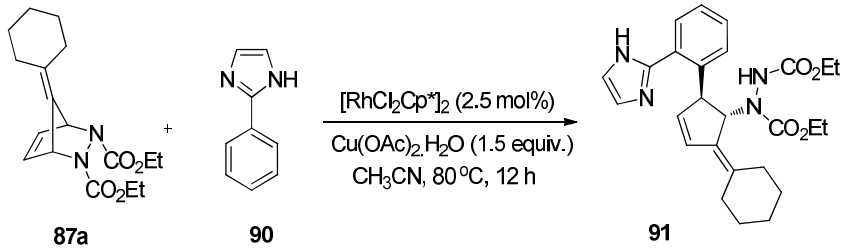
The successful incorporation of the Heck chemistry to the stereoselective ring opening reactions of fulvene derived diazabicyclic olefins with various aryl iodides was reported by our group (Scheme 1.27) [Radhakrishnan 2013b].



Scheme 1.27: Heck strategy towards the ring opening reactions

1.3.1.1.5. Ring Opening *via* C-H Activation

A Rh catalysed stereoselective C-N bond cleavage of pentafulvene derived diazabicyclic olefins *via* C-H bond activation of phenylazoles was our most recent achievement in the area [Radhakrishnan 2014]. The Rh catalysed coupling afforded the corresponding alkylidene cyclopentenyl derivative in 40% yield (Scheme 1.28).



Scheme 1.28: C-H bond activation strategy towards the ring opening reactions of fulvene derived diazabicyclic olefin

1.4. Conclusion and Background of the Present Work

Even if we consider these impressive array of transition metal catalyzed transformations of pentafulvene and pentafulvene derived systems, still there exist enough opportunities for researchers to develop various synthetic protocols for the construction of carbocycles and heterocycles. The literature surveys included in Chapter 1 mostly cover the available synthetic routes to fulvenes and a selected portion of the reactivity of pentafulvene and pentafulvene derived systems. In line with this, the thesis is entirely focused on methodology development based on the transition metal mediated transformations of pentafulvene derived systems.

Compared to the theoretical as well as cycloaddition chemistry/organometallic profile of pentafulvene, the endocyclic activation of the system remained the least explored, till our efforts on the hydroalumination of pentafulvene using a titanium complex as the catalyst. In light of the impressive initial results, we have extended this approach towards the chemistry of simple spirocyclopentadienes and different fulvene derived spirocyclopentadienes and the details are presented in the beginning of the second chapter of the thesis (Part A). The part B of the second chapter deals with selective functionalization of the endocyclic C-C double bond by hydrozirconation, which was then developed into a simple method towards the synthesis of a new class of substituted 1,2-dihydrofulvenes. The successful extension of the new methodology towards complex cyclopentanols with multiple stereocenters is also presented towards the end of the second chapter.

Development of efficient procedures for the direct creation of carbon-oxygen bonds in complex systems using commercially available and inexpensive chemicals is always a matter of concern in synthesis. In this direction, we have attempted the synthesis of various aryl and alkyl cyclopentenyl ethers from pentafulvene derived diazabicyclic olefins by exploiting the desymmetrization concept. The results and the related chemistry constitute the subject matter of the third chapter.

Our research group has developed general and efficient methodologies for the stereoselective synthesis of indoline derivatives from diazabicyclic olefins through a one-pot ring opening/ring closing mechanism. As a continuation of our interest in the chemistry of

pentafulvene and its derivatives, we developed a sequential Lewis acid-palladium mediated transformation of hydroxy tethered diazanorbornene towards novel cyclopentene fused indoline, pyrazolidine and 1,3-oxazinan-2-one skeletons, the details of the study forms the crux of the final chapter.

CHAPTER 2

Titanium and Zirconium Catalyzed Regioselective Synthesis of Five Membered Carbocycles

PART A

Regiocontrolled Functionalization of Spiro Cyclopentadienes: Facile Synthesis of 4, 7-Dihydrospiro[2.4] hepta-5-ene

2.1. Introduction

Stereocontrol in acyclic systems have been a stern concern in modern organic chemistry and a large number of beneficial protocols have been developed for the stereo-regulated synthesis of conformationally non-rigid complex molecules, such as, macrolides and polyether antibiotics [Corcoran 1977, Yamamoto 1993]. In this context, special emphasis has been laid upon aldol reactions [Figure 2.1(a)], which constitute one of the vital bond construction strategies in synthesis. The reaction of allylic organometallic reagents with aldehydes [Figure 2.1(b)] is synthetically equivalent to the aldol addition of metal enolates, since the subsequent homoallylic alcohol can be effortlessly converted to the aldol [Hoffmann 1982, Yamamoto 1987, Marek 2004]. This methodology has some advantages over the latter due to its versatility for further synthetic transformations such as cycloaddition, dihydroxylation, epoxidation, hydroboration, hydroformylation, hydrogenation, hydration, olefin metathesis, ozonolysis, *etc.* In the past two decades, the allylation of carbonyl derivatives has received particular interest in carbon-carbon bond-forming reactions due to the versatility of homoallylic alcohols as synthetic intermediates [Yamamoto 1993].

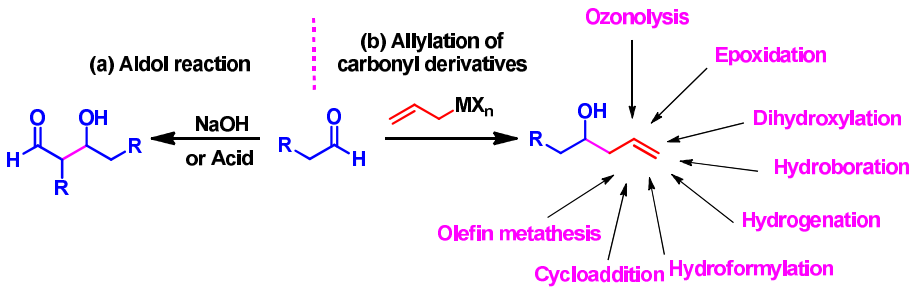


Figure 2.1: Importance of allylation of carbonyl derivatives

Among the reported protocols for the allylation of carbonyl compounds, the most renowned method is Barbier-type allylation in which an allyl halide and a carbonyl compound in the presence of magnesium, aluminium, zinc, indium, tin or its salts generates primary, secondary or tertiary alcohol [Blomberg 1977]. Over the past few decades, a number of organometallic reagents such as Grignard reagents [Kang 1984, Ren 2014], organolithium [Seyferth 1977], organosilanes [Esterbauer 1992], organozinc [Knochel 1998, Montgomery 2002], organoboranes [Zaidlewicz 1998, Horino 2015] and organostannanes [Yamamoto 1984] have been developed. Wada and co-workers [Akiba 1985, Akiba 1986] reported an allylation of aldehydes, using allyl bromide and metallic bismuth [Bi(0)]/ bismuth(III) chloride in the presence of metallic species such as Zn(0)/ Fe(0)/ Al(0). However, the allylation using bismuth(III) chloride failed in the absence of Al(0) and Al(0) alone did not lead to the desired products. Later on, Mukaiyama *et al.* [Mukaiyama 1986] investigated the proficient allylation of aldehydes using allyldiethylaluminum, in which the organoaluminum was formed *via* the reaction of diethylaluminum chloride with allylmagnesium chloride. However, only a limited number of reports are available on the generation of allylaluminium reagent using titanium and zirconium complexes. Thus, it would be attractive to develop an efficient allylation method for a wide variety of substrates with organoaluminum compounds *via* a Grignard-type addition, since aluminum is an inexpensive and convenient alternative to traditionally used metals, such as magnesium and zinc [Tanaka 1999].

Because of the prevalence of the cyclopropane motif in biologically relevant compounds [Silva-Júnior 2015] (Figure 2.2), their synthesis has been the subject of extensive research within the scientific community. In this context, we introduce spiro

cyclopentadienes derived from pentafulvene as a fascinating group of conjugated molecules and their regiospecific functionalization into 4,7-dihydrospiro[2.4]hepta-5-ene. Before going into the details, a brief history of the regiocontrolled functionalization of unsaturated systems *via* titanium and zirconium reagents is presented in the following section.

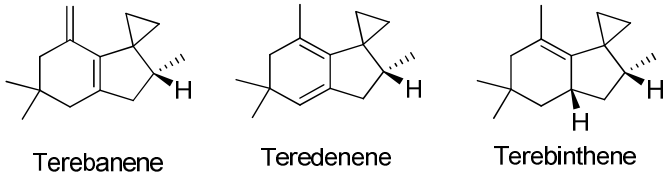


Figure 2.2: Biologically important compounds containing cyclopropane motif

2.2. Regiocontrolled Functionalization of Unsaturated Systems *via* Titanium and Zirconium Reagents

The scientific world has always been engaged in the investigation of the transition metal catalysed hydroalumination of alkenes and dienes, using less expensive and more easily accessible systems that have been available so far. Numerous unsaturated systems, including internal and terminal alkenes, alkynes, as well as nonconjugated dienes have been explored. In contrast, reports on the transition metal catalysed hydroalumination of conjugated dienes are scarce and no reactivity studies toward electrophiles other than protolysis have been reported. In this context, we have attempted to provide a systematic account of the reactivity of unsaturated systems with mild titanium and zirconium reagents such as titanocene and zirconocene dichloride. These are organo titanium and zirconium complex with general formula $(\eta^5\text{-}C_5H_5)_2MCl_2$, where 'M' is titanium or zirconium. These are 16 electron species with metal in the +4 oxidation state, usually denoted as Cp_2MCl_2. These metals are relatively economical and generally harmless elements, has been rather underutilized in organic synthesis.

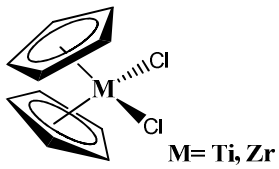
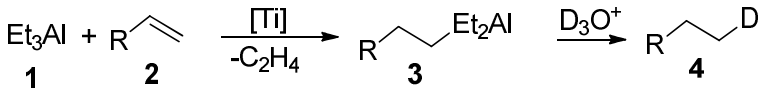


Figure 2.3. Structure of metalocene dichloride

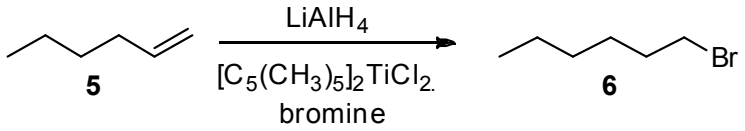
2.2.1. Alkenes

lbragimov and co-workers have reported the synthesis of (alkyl)diethylalanes from α-olefins with triethylaluminum in the presence of titanocene dichloride as catalyst [Ibragimov 1998]. The reaction was found to be working with α-olefins as well as cyclic and acyclic unsaturated compounds containing disubstituted double bonds. (Scheme 2.1).



Scheme 2.1: Synthesis of (alkyl)diethylalanes from α-olefins

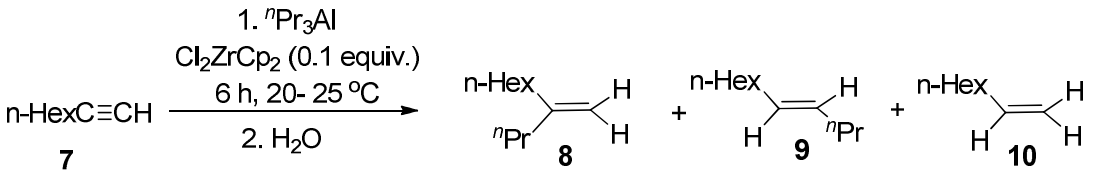
In 2005, Lee *et al*. developed a rapid and convenient procedure for the regioselective hydroalumination of alkenes using $LiAlH_4$ in the presence of $[C_5(CH_3)_5]_2TiCl_2$ [Lee 2005]. The reaction involves anti-Markovnikov addition, proceeds quickly with high regioselectivity and afforded products in excellent yields (Scheme 2.2). The reaction of alkynes gave preferentially monoaluminated products and in the case of internal alkynes, *cis*-alkenes predominate in the initial stage.



Scheme 2.2: Regioselective hydroalumination of alkenes with $LiAlH_4$ in the presence of $[C_5(CH_3)_5]_2TiCl_2$

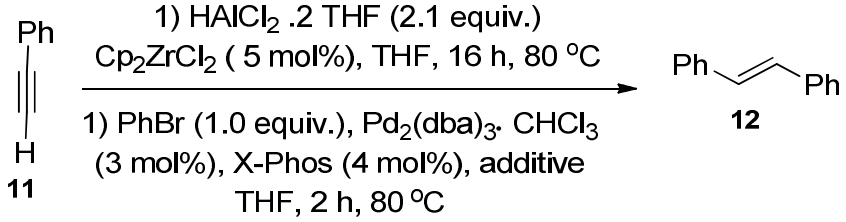
2.2.2. Alkynes

In 1980, Negishi *et al*. reported a novel chemoselective hydroalumination of alkynes using zirconocene dichloride as a catalyst. Interestingly, the corresponding reaction of diisobutylaluminum hydride (DIBAL-H) with 1-octyne in the presence of a catalytic amount (10 mol %) of Cp_2ZrCl_2 does not proceed to any detectable extent (< 1-2%) even after 6 hour at O ^oC (Scheme 2.3) [Negishi 1980].



Scheme 2.3: Chemoselective hydroalumination of alkynes

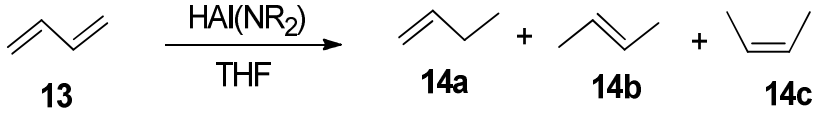
In 2013, Woodward and co-workers developed an efficient catalytic procedure using metallocene dichlorides of zirconium/titanium and dichloroalane ($HAlCl_2$) toward an exceptional chemo-, regio- and stereoselective hydroalumination of terminal alkynes [Woodward 2013] (Scheme 2.4).



Scheme 2.4: Hydroalumination of terminal alkynes

2.2.3. Acyclic Conjugated System

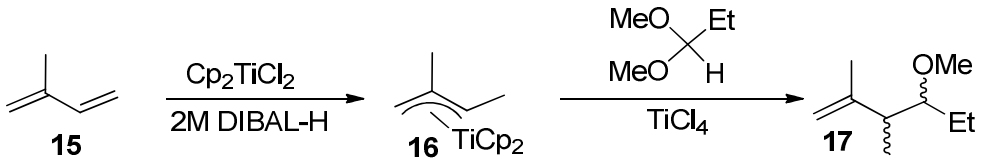
In 1979, Ashby *et al.* developed an efficient catalytic system for the hydrogenation of dienes *via* hydrometallation, which consists of a bis(dialkylamino)alane [$HAl(NR_2)$], as the hydrometallation agent with a catalytic amount of the transition metal halide [Ashby 1979] (Scheme 2.5).



Scheme 2.5: Hydrometallation of dienes

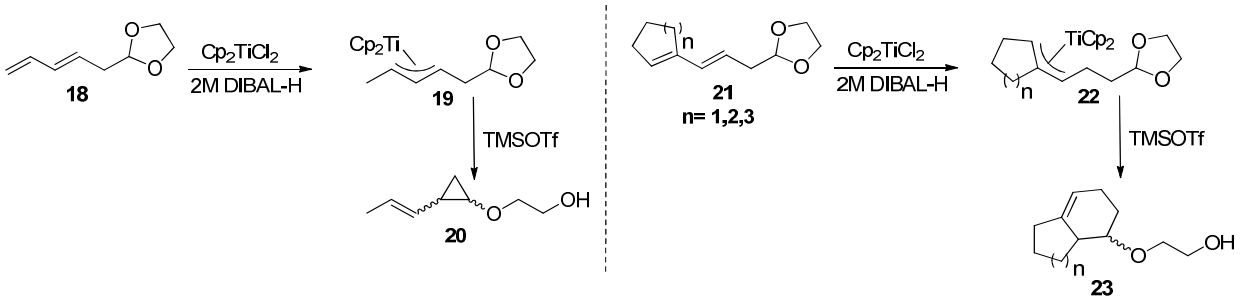
In this context, Szymoniak and co-workers generated homoallylic ethers from the reaction of η^3-crotyltitanocene reagents with acetals in the presence of a Lewis acid. The allyltitanium reagent **16** was prepared *in situ* at room temperature by the reaction of Cp_2TiCl_2

with two moles of DIBAL-H and isoprene [Szymoniak 1999] (Scheme 2.6). The reaction was found to be general for aliphatic and aromatic acetals by using TMSOTf as an inductor.



Scheme 2.6: Generation of homoallylic ethers from η^3-crotyltitanocene

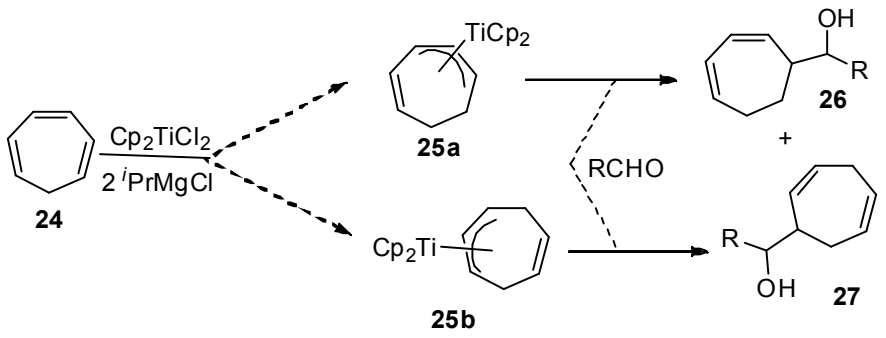
Subsequently in 2000, they extended the scope of the reaction to the tethered dienyl acetals. Here they demonstrated a Lewis acid induced inter- and intramolecular coupling of η^3-crotyltitanocenes with acetals [Szymoniak 2000] (Scheme 2.7). This method delivered a new synthetically useful protocol for the preparation of small- and medium-sized vinylcycloalkanes, and also offered an opportunity to create versatile entries into fused bicyclic compounds.



Scheme 2.7: Protocol for the preparation of small- and medium-sized vinyl cycloalkanes

2.2.4. Cyclic Conjugated System

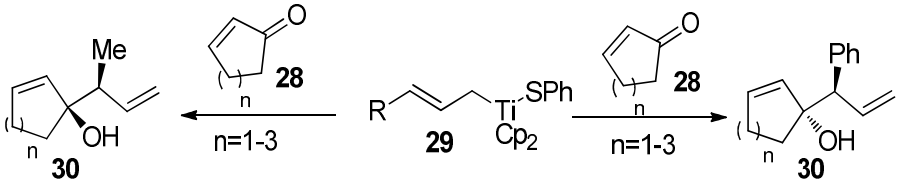
In 1994, Szymoniak and co-workers generated cycloheptenyl- η^3-allyltitanium species *via* the reaction of titanium dichloride and an alkyl Grignard reagent with cycloheptatriene [Szymoniak 1994] (Scheme 2.8). The striking feature of these species is that, they readily get added to the electrophile in a highly regio- and stereocontrolled fashion. This was the first report on the use of alkenyl-η^3-allyltitocenes as nucleophile reagents. Later, they extended this methodology towards various other electrophiles and open chain trienes.



Scheme 2.8: Generation of cycloheptenyl- η^3-allyltitanium

2.2.5. *α, β* -Unsaturated Systems

In 2012, Takeda *et al.* reported the first regio- and diastereo selective addition of allylmetals to cyclic enones [Takeda 2012] (Scheme 2.9). The reaction was found to be highly regioselective and the formation of 1,4-addition product was not observed. This methodology provides a useful route towards the synthesis of stereochemically defined cycloalkenols.

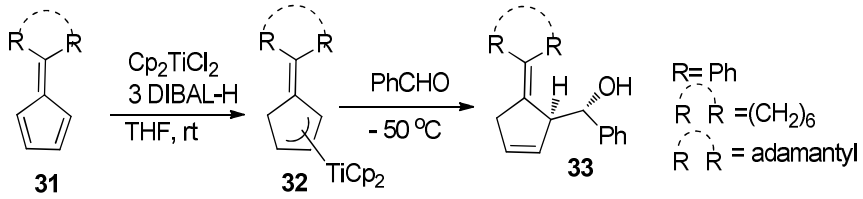


Scheme 2.9: Diastereo selective addition of allylmetals to cyclic enones

2.2.6. Cross-Conjugated System

Until recently, the reactivity of organometallic reagents with pentafulvenes was mainly concentrated on the nucleophilic addition reactions to the exocyclic position. In contrast, one of our main interest remained the search of methods for the selective activation of the endocyclic double bonds of fulvenes. This prompted us to couple the allyl metal chemistry with these cross conjugated scaffolds. Moreover, there are only a few transition metal mediated reactions employing pentafulvenes as substrates including the elegant work of Barluenga *et al*. [Barluenga 2001, Barluenga 2002, Barluenga 2005] regarding chromium Fischer carbene complexes and a few isolated reports on copper and rhodium carbenes.

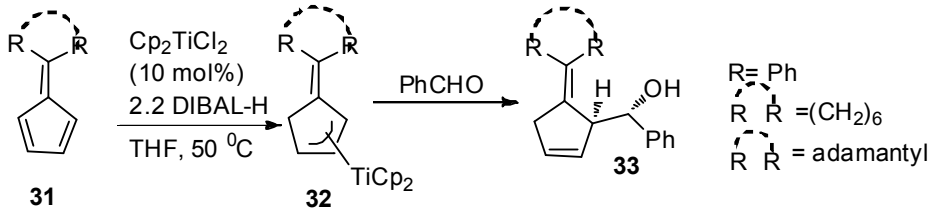
In this scenario, we developed an efficient method for the synthesis of pentafulvene-derived η^3-allyltitanocenes (Scheme 2.10), which on reaction with aldehydes afforded the corresponding homoallylic alcohols with excellent diastereoselectivity, albeit in moderate yields. The synthetic potential of the methodology was exemplified *via* the diastereoselective synthesis of highly substituted cyclopentanones [Szymoniak 2013].



Scheme 2.10: Synthesis of pentafulvene derived η^3-allyltitanocenes

2.3. Background of the Present Work

Survey of the pertinent literature reveals that the transition metal catalyzed hydroalumination of unsaturated carbon–carbon bonds has gained wide interest. So we attempted the hydroalumination of pentafulvenes using a catalytic amount of the titanium reagent. Afterward, it was found that a catalytic amount of titanium is sufficient to direct the reaction towards the desired outcome. The finding of new reaction conditions made the transformation of mono-substituted pentafulvenes and the successive trapping with carbonyl compounds more straightforward to access homoallylic alcohols [Szymoniak 2014] (Scheme 2.11).



Scheme 2.11: Titanium catalyzed hydroalumination of pentafulvene

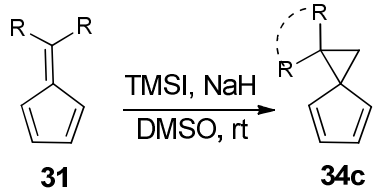
Working on the hypothesis that cyclized dienes also possess the same reactivity, we chose substituted spirocyclopentadiene as our initial substrate. Structures containing a cyclopropane skeleton have gained paramount interest due to their existence in many

biologically active molecules and not surprisingly, the discovery of novel synthetic protocols to this vital class of compounds requires special consideration. These facts prompted us to check the reactivity of pentafulvene derived spirocyclopentadienes and simple spirocyclopentadienes toward titanium-catalyzed hydroalumination instead of simple fulvenes.

2.4. Results and Discussion

2.4.1. Preparation of Pentafulvene Derived Spirocyclopentadiene

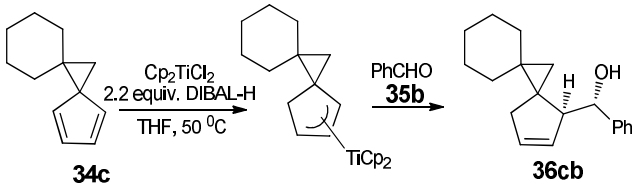
Substituted pentafulvene derived spirocyclopentadiene were synthesized from corresponding pentafulvene by trimethyl sulfoxonium iodide in DMSO solvent at room temperature (Scheme 2.12) [Leighton 2007].



Scheme 2.12: Synthesis of pentafulvene derived spirocyclopentadiene

2.4.2. Titanium Catalyzed Hydroalumination of Various Spirocyclopentadienes with Different Aromatic Aldehydes

With the above plan in mind, we treated 1.5 equiv. of pentafulvene derived spirocyclopentadiene with 10 mol% Cp_2TiCl_2 and 2.2 equiv. of DIBAL-H and 1 equiv. of aldehyde at 50 ^oC. The reaction afforded spiro appended cyclopentenyl homoallylic alcohol in 18 % yield (Scheme 2.13).



Scheme 2.13: Synthesis of spiro appended cyclopentadienyl homoallylic alcohol

The structure of the product **36cb** was elucidated by spectroscopic analyses. The IR spectrum showed characteristic hydroxyl absorption at 3735 cm^{-1}. In the ^1H NMR spectrum (Figure 2.4), the aromatic protons appeared as a doublet at δ 7.95 ppm and a multiplet in the

region δ 7.51-7.40 ppm. The proton attached to the carbon bearing -OH resonated as doublet of doublet at δ 3.80 ppm. The olefinic protons were found to resonate as a multiplet in the region δ 5.74- 5.73 ppm and δ 5.57- 5.55 ppm respectively. The proton on the ring junction appeared as a multiplet in the region δ 2.95- 2.93 ppm. All other signals were in good agreement with the proposed structure. The relative stereochemistry of the product was established by referring to our previous report [Szymoniak 2013].

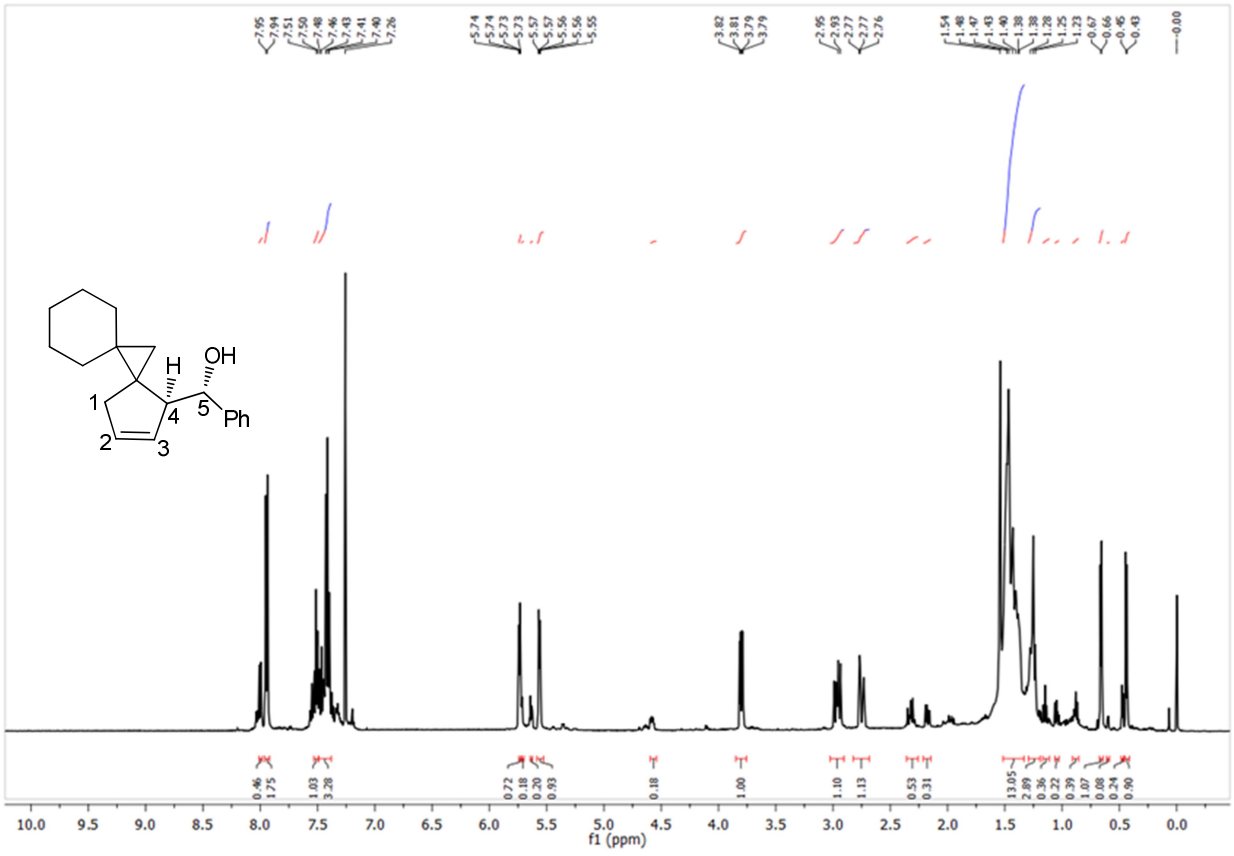


Figure 2.4: ^{1}H NMR spectrum of compound **36cb**

^{13}C NMR spectroscopy of **36cb** (Figure 2.5) positioned the signals of the olefinic carbons at δ 135.3 ppm and δ 132.6 ppm. The carbon bearing the -OH, C-5 was spotted at δ 77.1 ppm, ring junction carbon at C-4 was observed at δ 47.2 ppm. Further evidence for the structure was obtained from the mass spectral analysis which showed the molecular ion peak at *m/z* 290.15977 $[M+Na-1]^{+}$.

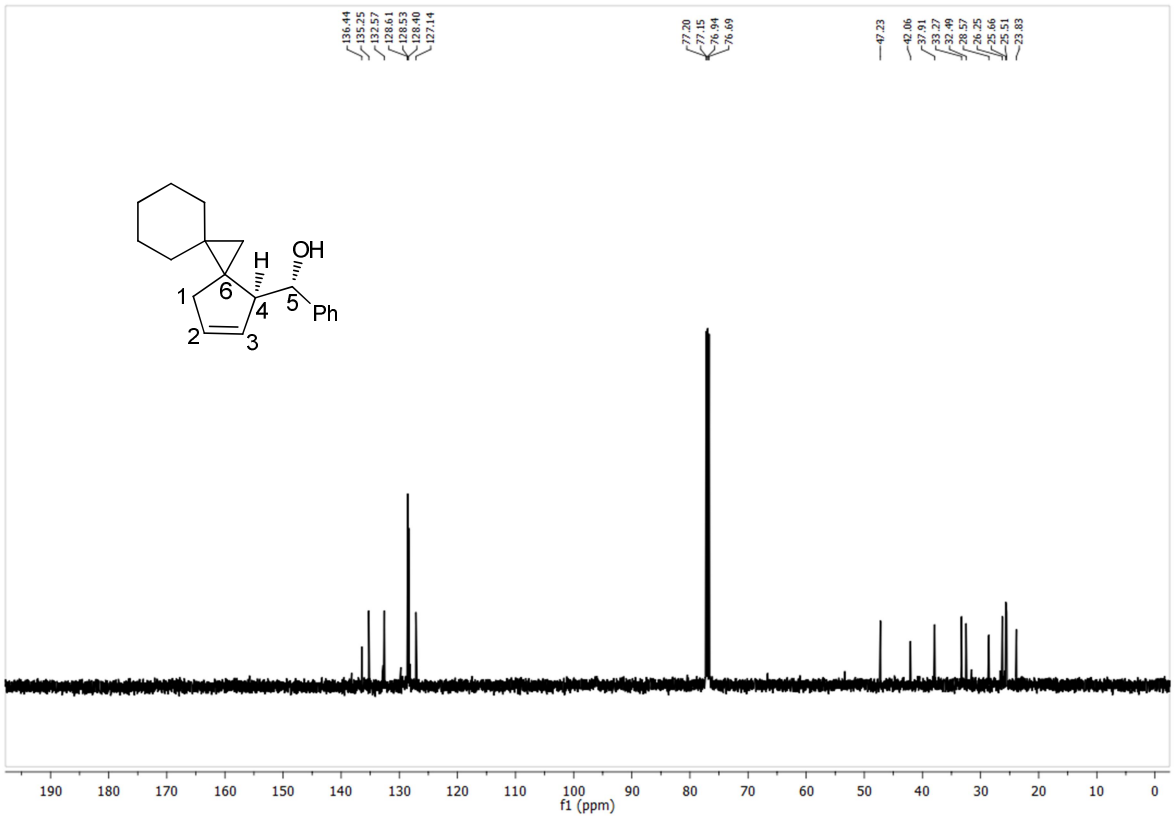


Figure 2.5: ^{13}C NMR spectrum of compound **36cb**

The determination of the relative stereochemistry of the observed product using the coupling constant is comparatively difficult due to the presence of bulky cyclohexane moiety. To solve this issue, we took the COSY spectrum of one of the derivative **36ab**. From the spectrum, it is clear that the protons at C_4 and C_5 are adjacent to each other (Figure 2.6) and the coupling constant for the proton C_5 is J = 6.0 Hz. Hence the protons attached to these carbons are *trans* to each other [Friebolin 2010]. Also the proton at C_4 and –OH at C_5 are down with respect to the cyclopentene moiety. The structure and relative stereochemistry were further confirmed by single crystal X- ray analysis of one of the derivative **36ac** (Figure 2.7).

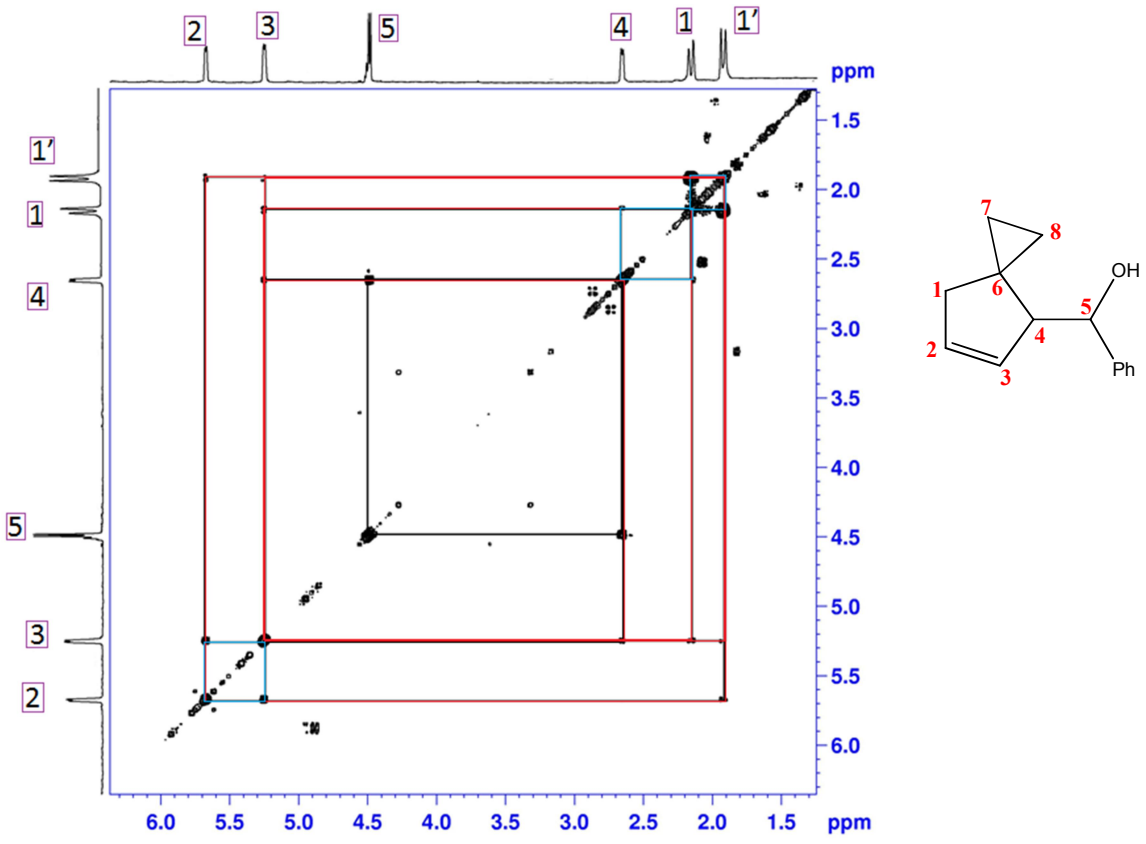


Figure 2.6: COSY spectrum of compound **36ab**

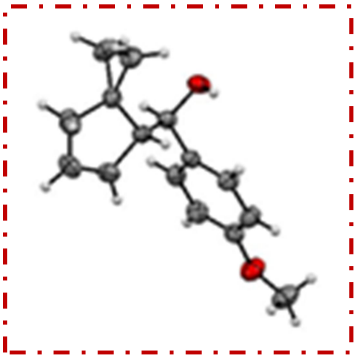
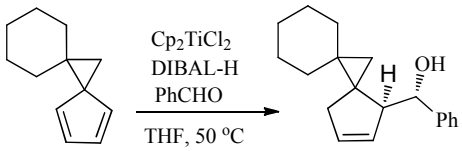


Figure 2.7: Single crystal X-ray structure of compound **36ac**

Considering the availability of substrates, the new method appears to be not competent in terms of the yield of the desired product and in order to find out the optimum conditions, we screened various reaction parameters (Table 2.1). Performing the reaction with 15 mol% of the catalyst (entry 13), didn't improve the yield. Upon increasing the concentration of the substrate, the yield improved slightly with 2.2 equiv of DIBAL-H. The yield increased notably when 3 equiv. of DIBAL-H was added. From the detailed

optimization study, use of DIBAL-H (3.0 equiv.) ,spiro[2.4]heptane (4.0 equiv.), [Cp_2TiCl_2] (10 mol%), benzaldehyde (1.0 equiv.) and 50 ^oC was found to be the best condition for this reaction.

Table 2.1: Screening of various reaction parameters for the best reaction condition

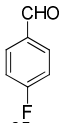
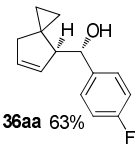
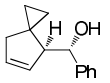
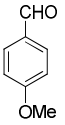
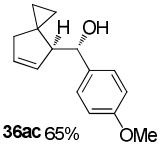
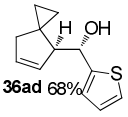
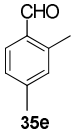
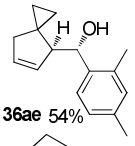
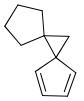
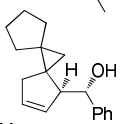
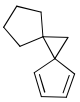
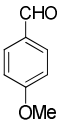
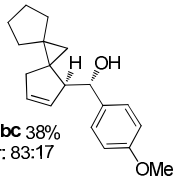
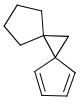
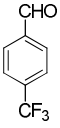
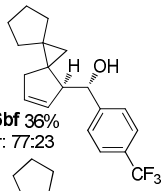
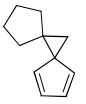
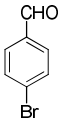
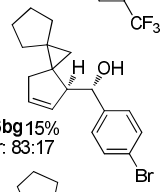
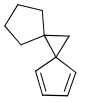
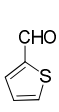
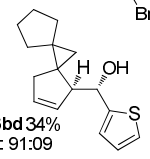


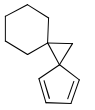
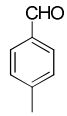
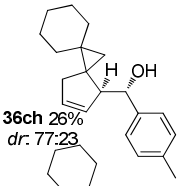
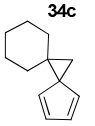
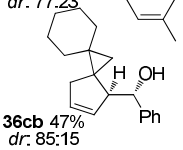
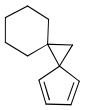
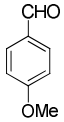
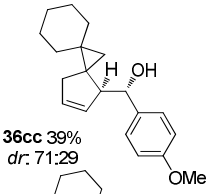
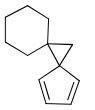
Entry	Spiro CPD (Equiv.)	Cp_2TiCl_2 (mol %)	DIBAL-H (Equiv.)	Solvent (mL)	Yield[a]
1	1.5	10	2.2	THF	18%
2	1.5	10	2.2	Toluene	5%
3	2.0	10	2.2	THF	20%
4	3.0	10	2.2	THF	22%
5	4.0	10	2.2	THF	25%
6	4.0	10	2.0	THF	20%
7	4.0	10	2.6	THF	27%
8	4.0	10	2.9	THF	39%
9	4.0	10	3.0	THF	48%
10	4.0	10	3.2	THF	43%
11	4.0	10	3.5	THF	36%
12	4.0	10	4.0	THF	20%
13	4.0	15	3.0	THF	46%

Reaction conditions: spiro[2.4]hepta-4,6-diene (4 equiv.), Cp_2TiCl_2 (10 mol %) DIBAL-H (3 equiv.), aldehyde (1 equiv.),THF (5 mL), 50 ^oC, 5 h
[a] isolated

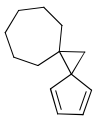
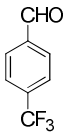
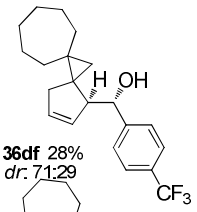
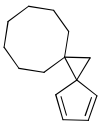
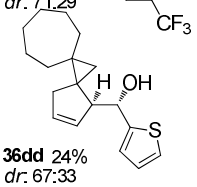
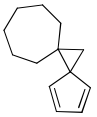
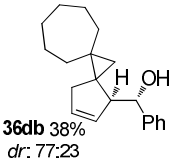
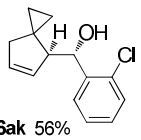
With the optimal reaction conditions in hand, we explored the titanium catalyzed hydroalumination of various spirocyclopentadienes with different electrophiles. Generality of the method was tested by performing the reaction with electrophiles such as substituted benzaldehydes bearing electron donating as well as electron withdrawing groups such as OMe, Me, CF_3, Br, F and thiophene-2-carboxaldehyde. Further, we extended our methodology to pentafulvene derived spirocyclopentadienes and it was also noted that the new approach is also applicable to simple spirocyclopentadienes. The corresponding functionalized spiro appended cyclopentenyl homoallylic alcohols were formed in moderate to good yields through the hydroalumination catalyzed by titanium (Table 2.2).

Table 2.2: Reaction of spirocyclopentadienes with various aromatic aldehydes

Entry	Spiro[2.4]hepta-4,6-diene	Aldehyde	Products -Yield[a]
1	 **34a**	 **35a**	 **36aa** 63%
2	 **34a**	 **35b**	 **36ab** 75%
3	 **34a**	 **35c**	 **36ac** 65%
4	 **34a**	 **35d**	 **36ad** 68%
5	 **34a**	 **35e**	 **36ae** 54%
6	 **34b**	 **35b**	 **36bb** 43% *dr*: 92:08
7	 **34b**	 **35c**	 **36bc** 38% *dr*: 83:17
8	 **34b**	 **35f**	 **36bf** 36% *dr*: 77:23
9	 **34b**	 **35g**	 **36bg** 15% *dr*: 83:17
10	 **34b**	 **35d**	 **36bd** 34% *dr*: 91:09

Entry	Spiro[2.4]hepta-4,6-diene	Aldehyde	Products -Yield[a]
11	 **34c**	 **35h**	 **36ch** 26% *dr*: 77:23
12	 **34c**	 **35b**	 **36cb** 47% *dr*: 85:15
13	 **34c**	 **35c**	 **36cc** 39% *dr*: 71:29
14	 **34c**	**35d**	**36cd** 28% *dr*: 71:29
15	**34c**	**35f**	**36cf** 29% *dr*: 92:08
16	**34c**	**35g**	**36cg** 21% *dr*: 77:23
17	**34c**	**35i**	**36ci** 20% *dr*: 91:09
18	**34c**	**35j**	**36cj** 18% *dr*: 91:09
19	**34d**	**35h**	**36dh** 16% *dr*: 50:50
20	**34d**	**35c**	**36dc** 32% *dr*: 71:29

Reaction conditions: spiro[2.4]hepta-4,6-diene (4 equiv.), Cp_2TiCl_2 (10 mol %) DIBAL-H (3 equiv.), aldehyde (1 equiv.),THF (5 mL), 50 °C, 5 h, [a] Isolated yield

Entry	Spiro[2.4]hepta-4,6-diene	Aldehyde	Products -Yield [a]
21	 **34d**	 **35f**	 **36df** 28% *dr*: 71:29
22	 **34d**	 **35d**	 **36dd** 24% *dr*: 67:33
23	 **34d**	 **35b**	 **36db** 38% *dr*: 77:23
24	 **34a**	 **35k**	 **36ak** 56%

Reaction conditions: spiro[2.4]hepta-4,6-diene (4 equiv.), Cp_2TiCl_2 (10 mol %) DIBAL-H (3 equiv.), aldehyde (1 equiv.),THF (5 mL), 50 °C, 5 h, [a] Isolated yield.

We suspected that the low yield and diastereomeric ratio of the substituted spiro cyclopentadiene might be attributed to the steric hindrance over the cyclopropane moiety as shown in Figure 2.8. Both regio- and stereochemistry of the reaction of pentafulvene derived spirocyclopentadiene is reliable on six-membered chair-like transition state**.** It normally forms two transition states, out of which, six-membered chair-like transition state with the metal part located at the less-crowded C_3 position ie the intermediate **II** might be the major one.

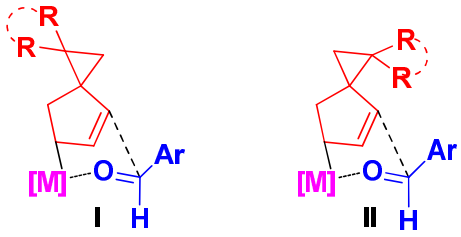
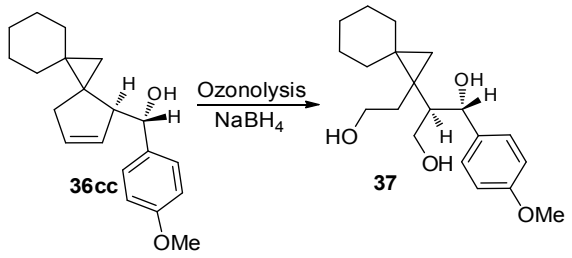


Figure 2.8: Six-membered chair-like transition state

2.4.3. The Scope of Spirocyclopentenyl Homoallylic Alcohol: Access to Cyclopropane

Having developed an efficient method for the construction of spiro appended cyclopentenyl homoallylic alcohol; we focused our attention on exploring the possibility for further synthetic transformation of synthesized molecule. The spirocyclopentenyl homoallylic alcohol was converted into substituted cyclopropanes by ozonolysis followed by $NaBH_4$ reduction (Scheme 2.14).



Scheme 2.14: Scope of the new compound

The structure of the product **37** was elucidated by spectroscopic analysis. The IR spectrum showed three characteristic hydroxyl absorption at 3744, 3648 and 3619 cm^{-1}. In the ^1H NMR spectrum (Figure 2.9), the aromatic protons appeared as two doublets at δ 7.98 ppm and δ 6.94 ppm. The proton attached to the carbon bearing -OH resonated as a multiplet in the region δ 3.69- 3.67 ppm. The $-OCH_3$ protons were found to resonate as a singlet at δ 3.89 ppm. The $-CH_2-$ protons attached to -OH group resonated as a multiplet in the region δ 3.88- 3.80 ppm. The proton in the cyclopropane ring resonated as two separate doublet at δ 0.30 ppm and 0.22 ppm respectively. All other signals were in agreement with the proposed structure.

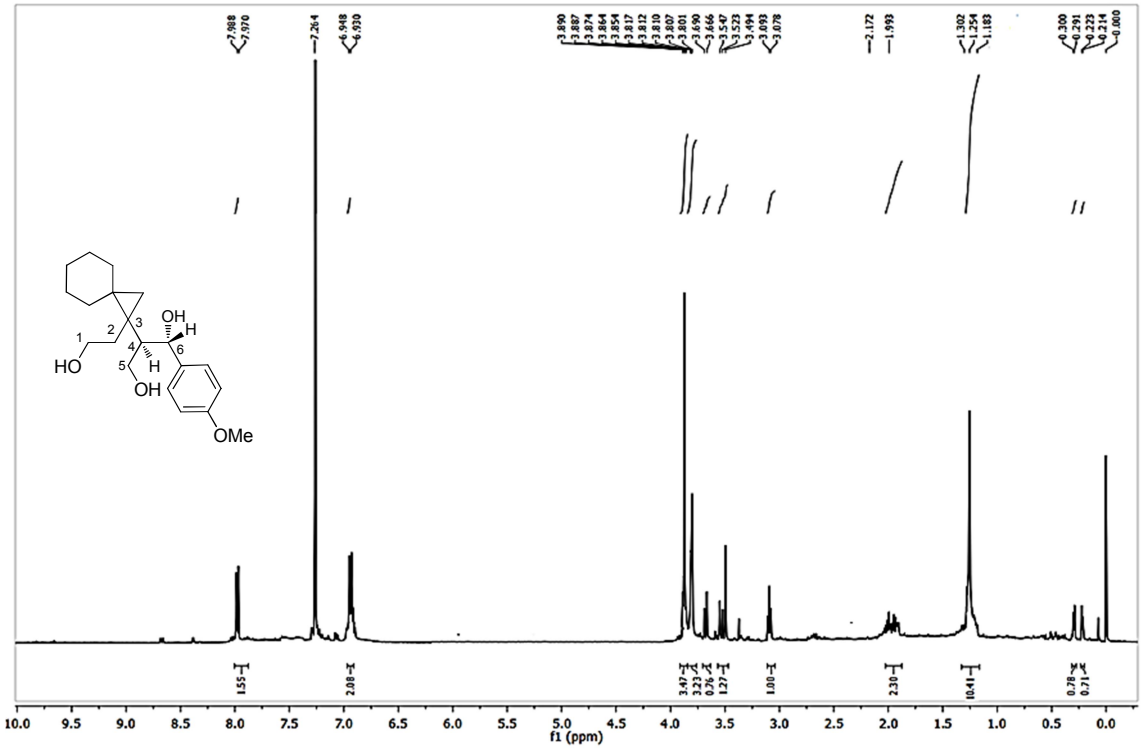


Figure 2.9: ^1H NMR spectrum of compound **37**

^{13}C NMR spectroscopy of **37** (Figure 2.10) positioned the signals of the olefinic carbons at δ 130.5 and δ 113.7 ppm. The carbon bearing the -OH C-6 was spotted at δ 65.4 ppm, carbons at C-2 was observed at δ 36.3 ppm. The carbon in the OCH_3 group resonated at δ 55.5 ppm. Further evidence for the structure was obtained from mass spectral analysis which showed the molecular ion peak at m/z 357.20418 $[M+Na]^+$.

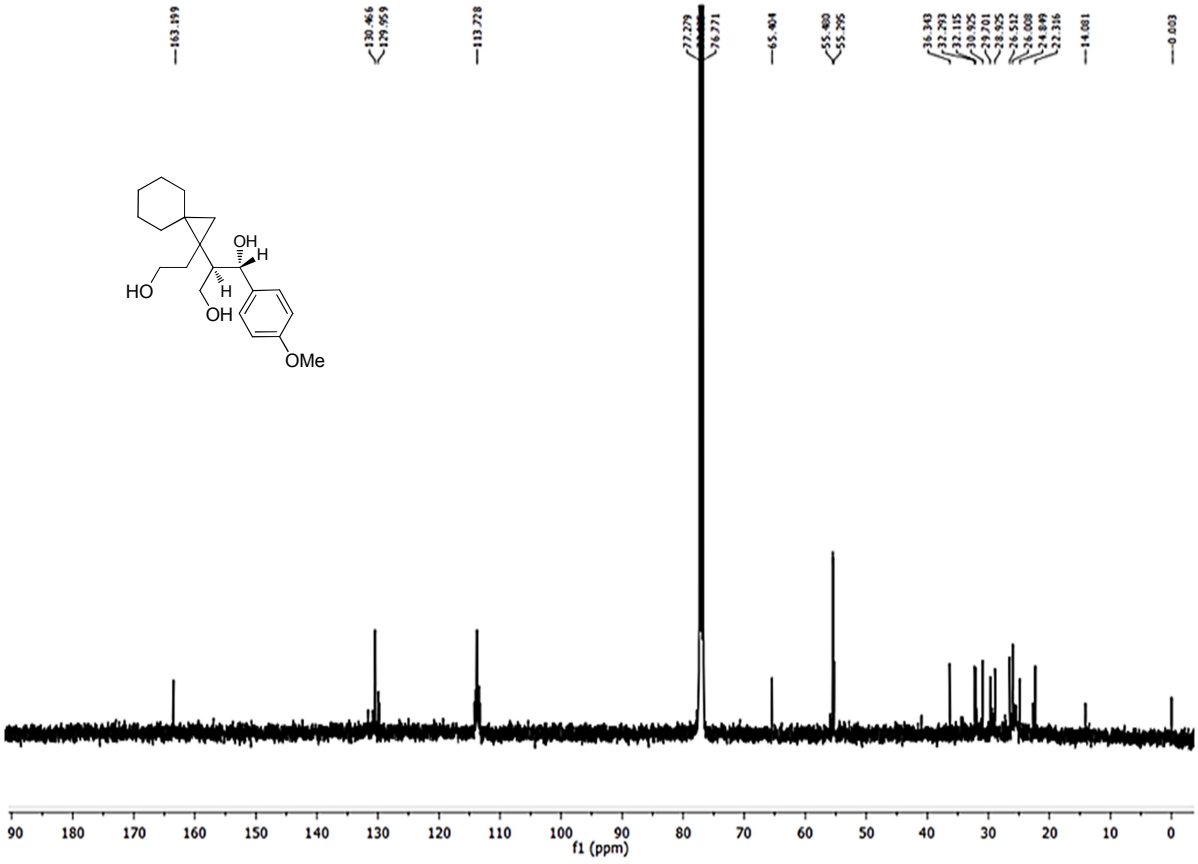
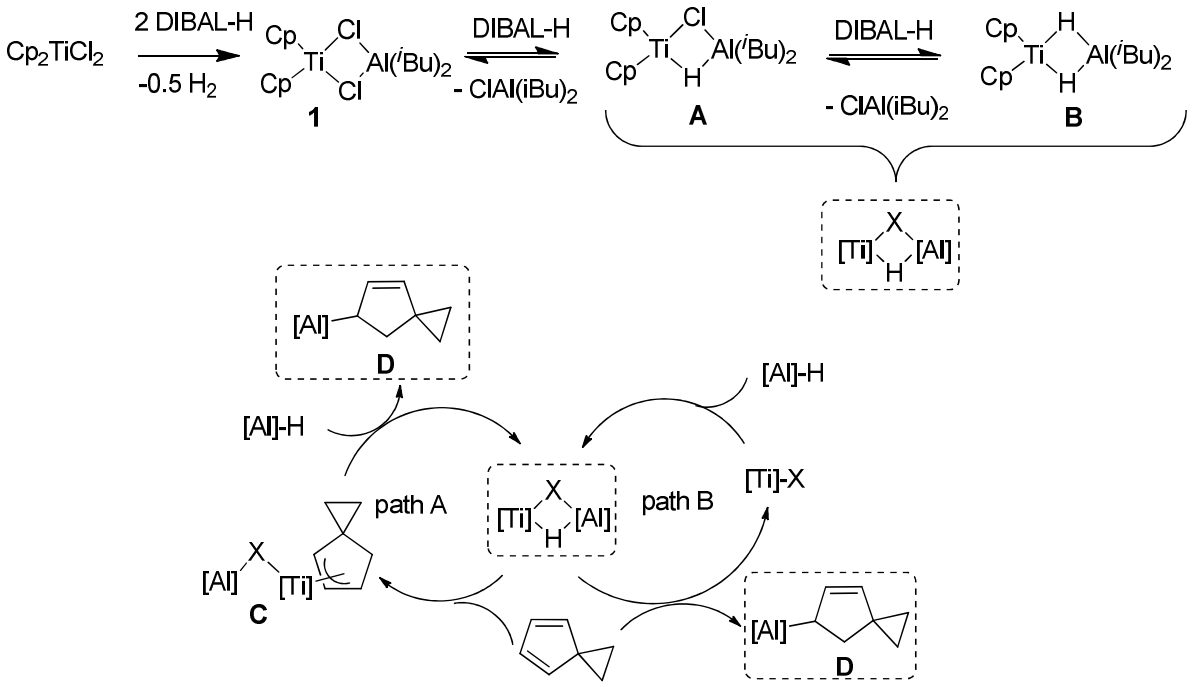


Figure 2.10: ^{13}C NMR spectrum of compound **37**

2.5. Plausible Mechanism

The currently accepted mechanism is shown in the Scheme 2.15. Starting from the initially formed trivalent complex $[Cp_2Ti(\mu\text{-}Cl)_2Al(^iBu)_2]$ (1), followed by chloride to hydride exchange could generate two bivalent intermediates **A** and **B**. These complexes act as spiro-CPD hydrometallation agent to give the allyl titanocene **C** which on transmetallation produce allylaluminium **D** and generate the catalytically active hydride (path **A**). Alternatively complexes **A** and **B** can undergo direct hydroalumination to yield **D** (path **B**)



Scheme 2.15: Proposed mechanism for the hydroalumination of spirocyclopentadiene

2.6. Conclusion

In conclusion, we have unraveled a facile method for the generation of the functionalized spiro appended cyclopentenyl homoallylic alcohols *via*, a titanium catalyzed hydroalumination of various spirocyclopentadienes with different aromatic aldehydes. The generality of the methodology was established by various pentafulvene derived spirocyclopentadienes. A variety of functional groups on the aromatic aldehydes were well tolerated under the reaction conditions.

2.9. Experimental Details

2.9.1. General Methods

All reactions were carried out in oven dried glasswares under inert atmosphere. All commercially available chemicals used were of the best grade and were used without further purification. All solvents used for the experiments were purified and dried according to the literature methods. Progress of the reactions was monitored by thin layer chromatography, which was performed on precoated plates (Silica gel 60 F_{254}, 0.25 mm, Merck) and visualized with UV light. Gravity column chromatography was performed using 60 -120, 100

-200 and 230-400 mesh silica gel and appropriate mixtures of hexane-ethyl acetate were used for elution.

Melting points were determined using a Fisher Johns melting point apparatus and were uncorrected. IR spectra were recorded on Bruker FT-IR spectrometer. Proton Nuclear magnetic resonance spectra were recorded at 250, 300 and 500 MHz on a Bruker AMX 250, 300, 500 Spectrophotometer. Carbon nuclear magnetic resonance spectra were recorded at 62.5, 75.0 and 125 MHz on a Bruker AMX 250, 300, 500 Spectrophotometer. Chemical shifts for ^{1}H NMR spectra were reported as δ in units of parts per million (ppm) with $SiMe_4$ (δ 0.0) as the internal standard and relative to the signal of chloroform-d (δ 7.25, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (double doublet) and m (multiplet). Coupling constants are reported as *J* values in Hz. ^{13}C NMR spectra are also reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). Mass spectra were recorded under ESI/HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer.

2.8.2. General Procedure for the Preparation of Pentafulvene Derived Spirocyclope ntadiene

The pentafulvene was synthesized by base catalyzed condensation between corresponding aldehydes and ketones with cyclopentadiene. The ketone (1 equiv.) was dissolved in methanol and cooled in an ice bath. Cyclopentadiene (2 equiv.) was added initially followed by slow addition of pyrrolidine (1.8 equiv.). The reaction mixture was stirred for 4 h at 0 ^{o}C– rt. The excess base was neutralized by adding acetic acid drop wise to the ice-cooled reaction mixture. Then cold water was added and the pentafulvene was extracted with diethyl ether. The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated with the aid of a rotary evaporator. The crude pentafulvene was purified by silica gel column chromatography using hexane as the eluent.

NaH (60 % suspension in mineral oil, 2.5 equiv.) was washed twice with dry pentane, dried under a stream of dry nitrogen, agitated into a free flowing powder, and suspended in DMSO (20 mL). Trimethyl sulfoxonium iodide (2.4 equiv.) was added in portions over the course of 30 minutes. Then a solution of fulvene (1.0 equiv.) in DMSO (10 mL) was added

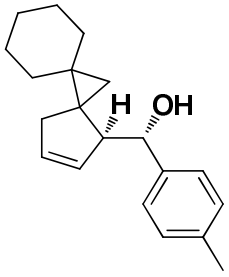
by way of an addition funnel over 20 min. After 8 h, the mixture was poured into an addition funnel containing CH_2Cl_2 (200 mL) and the mixture was washed with water (2 × 40 mL). The organic layer was dried with Na_2SO_4, filtered through a short silica pad, and concentrated. The residue was purified by column chromatography on silica [Leighton 2007]

2.8.3. General Procedure for the Preparation of Spiro Appended Cyclopentenyl Homoallylic Alcohol

DIBAL-H (0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (1.0 mmol) and [Cp_2TiCl_2] (10 mol%) at 50 ^oC. After stirring for 4 h at the same temperature, aldehyde (0.25 mmol) was added at the same temperature and the reaction was continued for 1 h. Basic workup (aqueous $NaHCO_3$) resulted in the exclusive formation of spiro appended cyclopentenyl homoallylic alcohol

Preparation of Compound 36ch

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (160 mg, 1.0 mmol), [Cp_2TiCl_2] (7 mg, 0.025 mmol) and tolualdehyde (26.5 mg, 0.25 mmol) at 50 ^oC yielded **36ch** (19 mg, 26 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.43 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3740, 2925, 2851, 1673, 1605, 1560, 1542, 1454, 1341, 1275, 1180, 1016, 749 cm^{-1}.

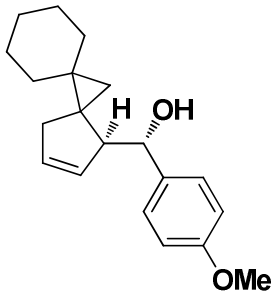
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.85 (d, J = 10.0 Hz, 2H), 7.21(d, J = 10.0 Hz, 2H), 5.74-5.72 (m, 1H), 5.59-5.56 (m, 1H), 3.79 (dd, J_1 = 10.0 Hz, , J_2 = 5.0 Hz, 1H), 2.97-2.92 (m, 1H), 2.76-2.71 (m, 1H), 2.40 (s, 3H), 1.58-1.24 (m, 11H), 0.65 (d, J = 5.0 Hz, 1H), 0.44 (d, J = 5.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 143.2, 135.2, 134.0, 129.2, 129.1, 128.7(2), 127.2, 47.1, 42.1, 38.0, 33.3, 32.5, 28.6, 26.3, 25.7, 25.5, 23.8, 21.6 ppm.

HRMS-ESI: m/z $[M]^+$ Calcd for $C_{20}H_{26}O$: 282.19837; Found: 282.19301.

Preparation of Compound 36cc

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (160 mg, 1.0 mmol), [Cp_2TiCl_2] (7 mg, 0.025 mmol) and anisaldehyde (34 mg, 0.25 mmol) at 50 ^oC yielded **36cc** (29 mg, 39 %) as pale yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.33 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}**:** 3739, 3060, 2925, 2848, 1669, 1598, 1571, 1457, 1313, 1261, 1169, 1026, 846, 769 cm^{-1}.

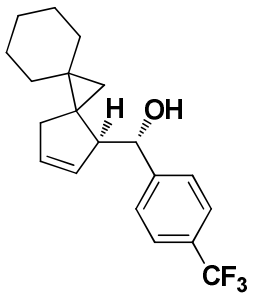
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.94 (d, *J* = 10.0 Hz, 2H), 6.89 (d, *J* = 10.0 Hz, 2H), 5.75-5.72 (m, 1H), 5.57-5.50 (m, 1H), 3.86 (s, 3H), 3.77-3.74 (m, 1H), 2.98-2.92 (m, 1H), 2.77-2.72 (m, 1H), 1.6-1.25 (m, 11H), 0.64 (d, *J* = 5.0 Hz, 1H), 0.44 (d, *J* = 5.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 163.1, 135.3, 130.8, 129.3, 127.2, 113.7, 55.3, 47.1, 42.3, 38.2, 33.3, 32.4, 28.6, 26.3, 25.7, 25.5, 23.9 ppm.

HRMS-ESI: m/z $[M-H]^+$ Calcd for $C_{20}H_{25}O_2$: 297.18546; Found: 297.18480.

Preparation of Compound 36cf

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (160 mg, 1.0 mmol), [Cp_2TiCl_2] (7 mg, 0.025 mmol) and trifluomethyl benzaldehyde (44 mg, 0.25 mmol) at 50 ^oC yielded **36cf** (24 mg, 29 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane)



R_f: 0.55 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3737, 3063, 2929, 2853, 1679, 1614, 1582, 1511, 1448, 1409, 1324, 1169, 1035, 1014, 954 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.00 (d, *J* = 10.0 Hz, 2H), 7.62 (d, *J* = 5.0 Hz, 2H), 5.70-5.68 (m, 1H), 5.53-5.51 (m, 1H), 3.69-3.66 (m, 1H), 2.95-2.90 (m, 1H), 2.70-2.65 (m,

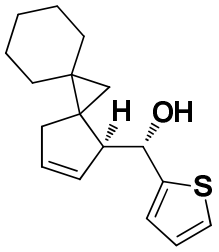
1H), 1.46-1.18 (m, 11H), 0.60 (d, J = 5.0 Hz, 1H), 0.33(d, J = 5.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 135.3, 128.9, 127.2, 125.5, 125.4, 48.2, 42.0, 37.6, 33.2, 32.3, 28.7, 26.2, 25.6, 25.5, 23.9 ppm.

HRMS-ESI: m/z $[M]^+$ Calcd for $C_{20}H_{23}F_3O$: 336.17010; Found: 336.17477.

Preparation of Compound 36cd

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (160 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and 2- thiophenecarboxaldehyde (28 mg, 0.25 mmol) at 50 ^oC yielded **36cd** (19 mg, 28 %) as yellow viscous liquid upon purification by column chromatography (5 % ethyl acetate-hexane)



R_f: 0.38 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3737, 3064, 2926, 2850, 1653, 1515, 1446, 1413, 1356, 1272, 1236, 1157, 1057, 1031, 962, 855 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.75 (d, J = 5.0 Hz, 1H), 7.59 (d, J = 5.0 Hz, 1H), 7.08 (d, J = 5.0 Hz, 1H), 5.75-5.73 (m, 1H), 5.55-5.53 (m, 1H), 3.64 (dd, J_1 = 10.0 Hz, , J_2 = 5.0 Hz, 1H), 2.97-2.96 (m, 1H), 2.86-2.85 (m, 1H), 1.50-1.40 (m, 11H), 0.65 (d, J = 5.0 Hz, 1H), 0.50 (d, J = 5.0 Hz, 1H) ppm.

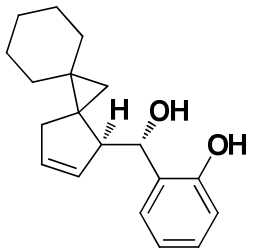
^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 142.7, 137.6, 134.1, 132.1, 130.7, 130.2, 126.9, 126.2, 126.0, 98.9, 47.4, 41.2, 37.3, 32.2, 31.4, 27.7, 25.2, 24.6, 24.4, 22.9 ppm.

HRMS-ESI: m/z $[M-H]^+$ Calcd for $C_{17}H_{21}OS$: 273.13131; Found: 273.13152.

Preparation of Compound 36cj

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (160 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and salicylaldehyde (28 mg, 0.25 mmol) at 50 ^oC yielded **36cj** (13 mg, 18

%) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.48 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3739, 2927, 2854, 1651, 1577, 1458, 1394, 1363, 1314, 1268, 1156, 1118, 753 cm^{-1}.

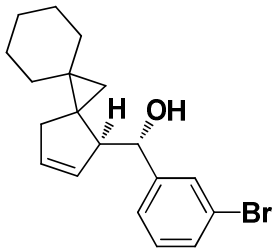
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.75 (s, 1H), 7.14-7.11 (m,1H), 6.88-6.79 (m, 3H), 5.82-5.80 (m, 1H), 5.44-5.40 (m, 1H), 4.89 (s, 1H), 2.69-2.65 (m, 1H), 2.58-2.55 (m, 1H), 1.56-1.39 (m, 11H), 0.75 (d, J = 5.0 Hz, 1H), 0.70 (d, J = 5.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.4, 134.3, 130.7, 128.4, 126.8, 124.3, 119.5, 117.4, 43.5, 39.5, 33.2, 32.6, 32.5, 28.8, 26.2, 25.7, 25.5, 20.7 ppm.

HRMS-ESI: m/z $[M+H]^+$ Calcd for $C_{19}H_{25}O_2$: 285.18546; Found: 285.18426.

Preparation of Compound 36ci

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (160 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and 3-bromo benzaldehyde (46 mg, 0.25 mmol) at 50 ^oC yielded **36ci** (17 mg, 20 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.48 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3751, 3061, 2925, 2850, 1679, 1564, 1445, 1417, 1341, 1264, 1203, 1066, 1028, 748 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.09-8.07 (m, 1H), 7.88 (d, J = 5.0 Hz, 1H), 7.64 (d, J = 10.0 Hz, 1H), 7.29 (t, J = 10.0 Hz, 1H), 5.76-5.74 (m, 1H), 5.59-5.57 (m, 1H), 3.75-3.72 (dd, J_1 = 10.0 Hz, , J_2 = 5.0 Hz, 1H), 3.00-2.95 (m, 1H), 2.75-2.71 (m, 1H), 1.49-1.38 (m, 11H), 0.68 (d, J = 5.0 Hz, 1H), 0.41 (d, J = 5.0 Hz, 1H) ppm.

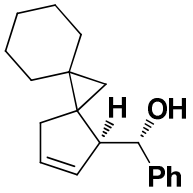
^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 138.1, 135.4, 131.7,

130.0, 127.1, 127.0, 123.0, 47.7, 42.0, 37.7, 33.2, 32.4, 28.7, 26.2, 25.6, 25.5, 23.9 ppm.

HRMS-ESI: m/z $[M-H]^+$ Calcd for $C_{19}H_{22}BrO$: 345.08540; Found: 345.08566.

Preparation of Compound 36cb

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (160 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and benzaldehyde (27 mg, 0.25 mmol) at 50 ^oC yielded **36cb** (32 mg, 47 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.50 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3735, 3061, 2928, 2850, 1678, 1596, 1448, 1343, 1272, 1214, 1172, 1108, 1022, 755, 701 cm^{-1}.

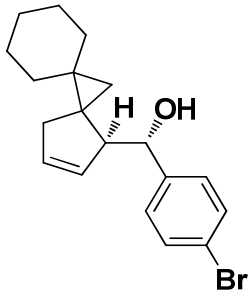
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.95 (d, J = 10.0 Hz, 1H), 7.51-7.46 (m, 2H), 7.43-7.40 (m, 2H), 5.74-5.73 (m, 1H), 5.57-5.55 (m, 1H), 3.80 (dd, J_1 = 10.0 Hz, , J_2 = 5.0 Hz, 1H), 2.95-2.93(m, 1H), 2.77-2.76 (m, 1H), 1.48-1.38 (m, 11H), 0.67 (d, J = 5.0 Hz, 1H), 0.44 (d, J = 5.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 136.4, 135.3, 132.6, 128.6, 128.4, 127.1, 77.1, 47.2, 42.0, 37.9, 33.3, 32.5, 28.6, 26.3, 25.7, 25.5, 23.8 ppm.

HRMS-ESI: m/z $[M+Na-H]^+$ Calcd for $C_{19}H_{23}ONa$: 290.16466; Found: 290.15977.

Preparation of Compound 36cg

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (160 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and 4-bromobenzaldehyde (46 mg, 0.25 mmol) at 50 ^oC yielded **36cg** (41 mg, 47 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.53 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3738, 3061, 2927, 2853, 1676, 1589, 1485, 1447, 1398, 1268, 1171, 1093, 1015, 845, 802, 760 cm^{-1}.

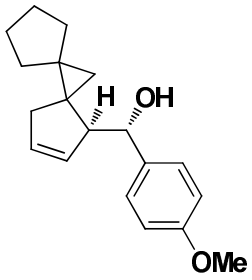
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.82 (d, *J* = 10.0 Hz, 2H), 7.55 (d, *J* = 10.0 Hz, 2H), 5.75-5.73 (m, 1H), 5.57-5.56 (m, 1H), 3.71 (dd, J_1 = 10.0 Hz, , J_2 = 5.0 Hz, 1H), 2.96-2.94 (m, 1H), 2.75-2.71 (m, 1H), 1.43-1.37 (m, 11H), 0.64 (d, *J* = 5.0 Hz, 1H), 0.39 (d, *J* = 5.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 135.3, 134.8, 131.9, 131.7, 131.2, 130.1, 127.8, 127.3, 127.2, 65.8, 47.8, 42.1, 37.8, 33.2, 32.3, 30.8, 28.6, 26.2, 25.6, 23.9 ppm.

HRMS-ESI: m/z $[M+Na-H]^+$ Calcd for $C_{19}H_{22}BrONa$: 368.07517; Found: 368.07523.

Preparation of Compound 36bc

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (146 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and anisaldehyde (34 mg, 0.25 mmol) at 50 ^oC yielded **36bc** (27 mg, 38 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.25 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3734, 3053, 2948, 2858, 1711, 1668, 1599, 1570, 1458, 1422, 1312, 1260, 1171, 1114, 1028, 846, 752 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.97-7.91 (m, 2H), 6.90-6.88 (m, 2H), 6.03-6.01 (m, 1H), 5.76-5.74 (m, 1H), 4.22 (s, 1H), 3.86 (s, 3H), 2.59-2.55 (m, 2H), 1.75-1.68 (m, 9H), 0.50 (d, *J* = 5.0 Hz, 1H), 0.46 (d, *J* = 5.0 Hz, 1H) ppm.

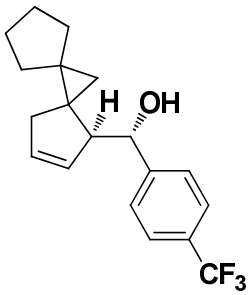
^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 136.0, 133.9, 130.9, 130.8, 130.6, 127.1, 113.5, 65.8, 57.4, 55.3, 40.0, 33.3, 30.8, 26.1, 26.0 ppm.

HRMS-ESI: m/z $[M+Na-H]^+$ Calcd for $C_{19}H_{23}O_2Na$:

306.15957; Found: 306.15444.

Preparation of Compound 36bf

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (146 mg, 1.0 mmol), [Cp_2TiCl_2] (7 mg, 0.025 mmol) and trifluomethyl benzaldehyde (44 mg, 0.25 mmol) at 50 ^oC yielded **36bf** (29 mg, 36 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.48 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3746, 3058, 2949, 2863, 1684, 1513, 1450, 1409, 1324, 1170, 1131, 1067, 1015, 858, 763 cm^{-1}.

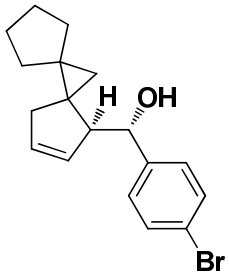
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.06-8.03 (m, 2H), 7.69 (d, J = 10.0 Hz, 2H), 5.75-5.73 (m, 1H), 5.41-5.40 (m, 1H), 3.75 (dd, J_1 = 10.0 Hz, , J_2 = 5.0 Hz, 1H), 3.00-2.94 (m, 1H), 2.82-2.78 (m, 1H), 1.76-1.24 (m, 9H), 0.74 (d, J = 5.0 Hz, 1H), 0.52 (d, J = 5.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 139.3, 136.1, 128.9, 128.8, 127.1, 125.4, 58.8, 48.4, 40.9, 37.6, 33.1, 33.0, 32.9, 26.3, 26.1, 25.3 ppm.

HRMS-ESI: m/z $[M-H]^+$ Calcd for $C_{19}H_{20}F_3O$: 321.14662; Found: 321.14641.

Preparation of Compound 36bg

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (146 mg, 1.0 mmol), [Cp_2TiCl_2] (7 mg, 0.025 mmol) and 4-bromobenzaldehyde (46 mg, 0.25 mmol) at 50^oC yielded **36bg** (13 mg, 15 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane)



R_f: 0.45 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3737, 2946, 2860, 1706, 1686, 1581, 1524, 1457, 1398, 1323, 1273, 1170, 1067, 1013, 760 cm^{-1}.

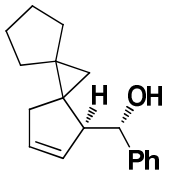
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.81 (d, J = 10.0 Hz, 2H), 7.56 (d, J = 10.0 Hz, 2H), 5.74-5.72 (m, 1H), 5.39-5.37 (m, 1H), 3.72 (dd, J_1 = 10.0 Hz, , J_2 = 5.0 Hz, 1H), 2.97-2.92 (m, 1H), 2.81-2.77 (m, 1H), 1.75-1.66 (m, 9H), 0.72 (d, J = 5.0 Hz, 1H), 0.52 (d, J= 5.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 136.0, 135.3, 131.7, 130.1, 127.8, 127.0, 65.8, 48.0, 41.0, 37.8, 33.1, 33.0, 32.9, 26.3, 26.1, 25.3, 15.3 ppm.

HRMS-ESI: m/z $[M+ Na]^+$ Calcd for $C_{18}H_{21}BrONa$: 355.06735; Found: 355.06514.

Preparation of Compound 36bb

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (146 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol)and benzaldehyde (27 mg, 0.25 mmol) at 50 ^oC yielded **36bb** (28 mg, 43 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane)



R_f: 0.45 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3736, 3059, 2944, 2859, 1674, 1602, 1448, 1344, 1269, 1215, 1174, 1115, 1023, 740, 700 cm^{-1}.

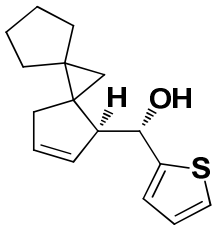
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.96-7.93 (m, 2H), 7.53-7.52 (m, 1H), 7.45-7.41 (m, 2H), 5.75-5.73 (m, 1H), 5.39-5.38 (m, 1H), 3.84 (dd, J_1 = 10.0 Hz, J_2 = 5.0 Hz, 1H), 2.93-2.91 (m, 1H), 2.83-2.82 (m, 1H), 1.77-1.65 (m, 7H), 1.38-1.23 (m, 2H), 0.74 (d, J = 10.0 Hz, 1H), 0.57 (d, J = 5.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 136.9, 136.0, 132.7, 128.6, 128.5, 127.1, 47.3, 41.0, 37.9, 33.2, 32.9, 26.4, 26.1, 25.2 ppm.

HRMS-ESI: m/z $[M+H]^+$ Calcd for $C_{18}H_{23}O$: 255.17489; Found: 255.17426.

Preparation of Compound 36bd

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (146 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and 2-thiophenecarboxaldehyde (28 mg, 0.25 mmol) at 50 ^oC yielded **36bd** (22 mg, 34 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.23 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3745, 3048, 2948, 2559, 1695, 1657, 1597, 1446, 1302, 1167, 1037, 997, 853, 751, 699 cm^{-1}.

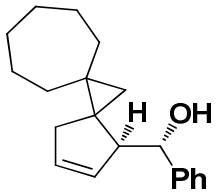
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.26-7.24 (m, 1H), 6.98-6.97 (m, 2H), 5.74-5.72 (m, 1H), 5.58-5.57 (m, 1H), 4.83 (d, *J* =10.0 Hz, 1H), 3.36-3.31 (m, 1H), 2.13-2.08 (m, 1H), 1.66-1.64 (m, 7H), 1.31-1.22 (m, 2H), 0.70 (d, *J* = 5.0 Hz, 1H), 0.51 (d, *J* = 5.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 148.1, 139.9, 127.9, 126.6, 124.4, 123.8, 74.2, 53.3, 36.7, 33.5, 33.0, 32.9, 32.7, 27.9, 26.4, 26.1 ppm.

HRMS-ESI: m/z $[M+ Na]^+$ Calcd for $C_{16}H_{20}OSNa$: 283.11326; Found: 283.11272.

Preparation of Compound 36db

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (174 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and benzaldehyde (27 mg, 0.25 mmol) at 50 ^oC yielded **36db** (27 mg, 38 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.38 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3741, 3059, 2922, 3852, 1676, 1451, 1280, 1210, 1119, 1063, 1022, 756, 698 cm^{-1}.

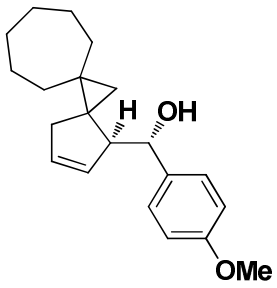
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.96-7.92 (m, 2H), 7.52-7.50 (m, 1H), 7.44-7.40 (m, 2H), 5.75-5.73 (m, 1H), 5.55-5.53 (m, 1H), 3.88 (dd, J_1 = 10.0 Hz, J_2 = 6.0 Hz, 1H), 2.99-2.94 (m, 1H), 2.75-2.70 (m, 1H), 1.58-1.45 (m, 13H), 0.69 (d, J = 5.0 Hz, 1H), 0.48 (d, J = 5.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 136.1, 132.6, 128.5, 128.4, 126.9, 77.1, 47.5, 43.2, 37.9, 35.7, 35.2, 30.0, 28.7, 28.1, 26.4, 25.9 ppm.

HRMS-ESI: m/z $[M+H]^+$ Calcd for $C_{20}H_{27}O$: 283.20619; Found: 283.20673.

Preparation of Compound 36dc

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (174 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and anisaldehyde (34 mg, 0.25 mmol) at 50 ^oC yielded **36dc** (25 mg, 32 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.30 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3739, 3055, 2920, 2850, 1671, 1599, 1514, 1458, 1312, 1218, 1170, 1028, 847, 736 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.94-7.91 (m, 2H), 6.89-6.86 (m, 2H), 5.75-5.73 (m, 1H), 5.55-5.53 (m, 1H), 3.86 (s, 3H), 3.83 (dd, J_1 = 10.0 Hz, J_2 = 4.0 Hz, 1H), 2.99-2.92 (m, 1H), 2.75-2.71 (m, 1H), 1.56-1.45 (m, 13H), 0.66 (d, J = 5.5 Hz, 1H), 0.48 (d, J = 5.5 Hz, 1H) ppm.

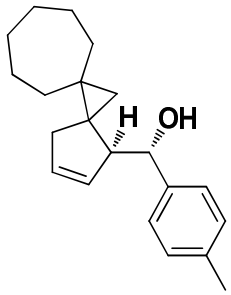
^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 163.1, 136.1, 131.0, 130.8, 129.5, 127.0, 113.3, 77.1, 55.3, 47.4, 43.4, 38.1, 35.7, 35.1, 30.0, 28.7, 28.2, 26.4, 25.9 ppm.

HRMS-ESI: m/z $[M]^+$ Calcd for $C_{21}H_{28}O_2$: 312.20893;

Found: 312.20406.

Preparation of Compound 36dh

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (174 mg, 1.0 mmol), [Cp_2TiCl_2] (7 mg, 0.025 mmol) and tolualdehyde (26.5 mg, 0.25 mmol) at 50 ^oC yielded **36dh** (12 mg, 16 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.40 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3735, 3054, 2923, 2853, 1684, 1668, 1606, 1448, 1407, 1322, 1289, 1223, 1202, 1180, 1117, 1017, 972, 844, 732 cm^{-1}.

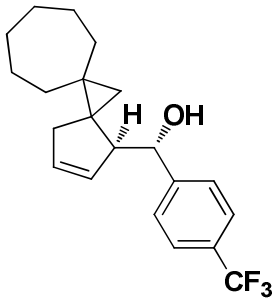
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.86-7.83 (m, 2H), 7.20 (d, J = 8.0 Hz, 2H), 5.74-5.72 (m, 1H), 5.54-5.52 (m, 1H), 4.32 (s, 1H), 3.86 (dd, J_1 = 10.0 Hz, J_2 = 4.5 Hz, 1H), 2.98-2.93 (m, 1H), 2.74-2.70 (m, 1H), 2.40 (s, 3H), 1.58-1.47 (m, 13H), 0.67 (d, J = 5.5 Hz, 1H), 0.47 (d, J = 5.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 143.1, 136.1, 133.7, 130.6, 129.1, 129.0, 128.8, 128.6, 126.9, 77.1, 47.3, 43.3, 38.0, 35.0, 33.6, 30.0, 29.3, 28.7, 28.3, 26.4, 26.0 ppm.

HRMS-ESI: m/z $[M+H]^+$ Calcd for $C_{21}H_{29}O$: 297.22184; Found: 297.22134.

Preparation of Compound 36df

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (174 mg, 1.0 mmol), [Cp_2TiCl_2] (7 mg, 0.025 mmol) and trifluomethyl benzaldehyde (44 mg, 0.25 mmol) at 50 ^oC yielded **36df** (24 mg, 28 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.53 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3745, 3060, 2924, 2855, 1683, 1452, 1408, 1170, 1132, 1068, 1014, 973, 747, 686 cm^{-1}.

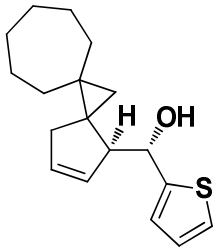
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.07-8.04 (m, 2H), 7.69 (d, J = 8.5 Hz, 2H), 5.77-5.75 (m, 1H), 3.85 (dd, J_1 = 10.0 Hz, J_2 = 4.5, 1H), 3.03-2.98 (m, 1H), 2.75-2.71 (m, 1H), 1.57-1.46 (m, 13H), 0.71 (d, J = 5.5 Hz, 1H), 0.44 (d, J = 5.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 136.1, 128.8, 127.0, 125.8, 125.5, 77.2, 48.3, 43.2, 37.6, 35.6, 35.1, 30.1, 28.6, 28.1, 26.4, 25.8 ppm.

HRMS-ESI: m/z $[M+H]^+$ Calcd for $C_{20}H_{26}F_3O$: 351.19358; Found: 351.19347.

Preparation of Compound 36dd

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (174 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and 2-thiophenecarboxaldehyde (28 mg, 0.25 mmol) at 50 ^oC yielded **36dd** (17 mg, 24 %) as yellow viscous liquid upon purification by column chromatography (5 % ethyl acetate-hexane).



R_f: 0.33 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3741, 3058, 2921, 2852, 1653, 1515, 1450, 1412, 1354, 1279, 1235, 1207, 1163, 1059, 858, 721 cm^{-1}.

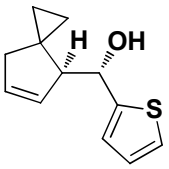
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.75 (dd, J_1 = 3.5 Hz, J_2 = 1.0 Hz, 1H), 7.61-7.59 (m, 1H), 7.10-7.09 (m, 1H), 5.76-5.74 (m, 1H), 5.55-5.53 (m, 1H) , 3.76-3.73 (dd, J_1 = 10.0 Hz, J_2 = 6.0 Hz, 1H), 3.01-2.96 (m, 1H), 2.83-2.73 (m, 1H), 1.56-1.49 (m, 13H), 0.69 (d, J = 5.5 Hz, 1H), 0.54 (d, J = 5.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 143.9, 136.0, 133.5, 131.4, 128.1, 127.0, 77.2, 46.7, 43.5, 38.4, 35.6, 35.2, 30.1, 28.7, 28.1, 26.4, 25.8 ppm.

HRMS-ESI: m/z $[M+H]^+$ Calcd for $C_{18}H_{25}OS$: 289.16261; Found: 289.16260.

Preparation of Compound 36ad

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (92 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and 2-thiophenecarboxaldehyde (28 mg, 0.25 mmol) at 50 ^oC yielded **36ad** (35 mg, 68 %) as yellow viscous liquid upon purification by column chromatography (5 % ethyl acetate-hexane).



R_f: 0.20 (hexane/ethyl acetate = 95:5).

IR (Neat) ν_{max}: 3731, 3069, 2922, 1708, 1655, 1517, 1414, 1358, 1312, 1263, 1236, 1025, 854, 704 cm^{-1}.

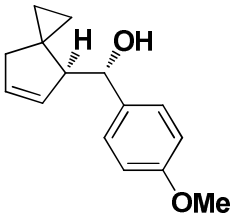
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.25-7.20 (m, 1H), 6.97-6.94 (m, 2H), 5.87 (d, J = 5.0 Hz, 1H), 5.53 (d, J = 4.0 Hz, 1H), 4.86 (d, J = 3.5 Hz, 1H), 2.84 (d, J = 5.0 Hz, 1H), 2.36-2.31 (m, 1H), 2.17-2.07 (m, 1H), 1.16-1.12 (m, 1H), 0.89-0.82 (m, 1H), 0.63-0.46 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 147.4, 133.1, 131.4, 126.3, 124.6, 124.2, 72.8, 58.3, 43.9, 22.7, 16.2, 8.8 ppm.

HRMS-ESI: m/z $[M+H]^+$ Calcd for $C_{12}H_{15}OS$: 207.08436; Found: 207.08466.

Preparation of Compound 36ac

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (92 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and anisaldehyde (34 mg, 0.25 mmol) at 50 ^oC yielded **36ac** (38 mg, 65 %) as yellow viscous liquid upon purification by column chromatography (5 % ethyl acetate-hexane).



R_f: 0.35 (hexane/ethyl acetate = 90:10).

IR (Neat) ν_{max}: 3735, 3060, 2955, 2921, 2844, 1709, 1645, 1607, 1509, 1455, 1279, 1249, 1173, 1029, 825, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.28-7.26 (m, 2H), 6.86 (d, J =8.5 Hz, 2H), 5.81 (d, J = 4.0 Hz, 1H), 5.40 (d, J =

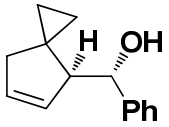
3.5 Hz, 1H), 4.60 (d, *J* = 6.5 Hz, 1H), 3.82 (s, 3H), 2.77 (d, *J* = 6.5 Hz, 1H), 2.26 (d, *J* = 16.0 Hz, 1H), 2.02 (d, *J* = 16.5 Hz, 1H), 1.72 (s, 1H), 1.27-1.24 (m, 1H), 0.62-0.60 (m, 1H), 0.51 (s, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 135.7, 134.5, 132.8, 131.6, 127.9, 113.3, 76.5, 58.1, 55.1, 43.6, 37.9, 23.3, 16.4, 8.1 ppm.

HRMS-ESI: m/z $[M+H]^+$ Calcd for $C_{15}H_{19}O_2$: 231.13850; Found: 231.13746.

Preparation of Compound 36ab

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (92 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and benzaldehyde (27 mg, 0.25 mmol) at 50 ^oC yielded **36ab** (38 mg, 75 %) as yellow viscous liquid upon purification by column chromatography (5 % ethyl acetate-hexane)



R_f: 0.35 (hexane/ethyl acetate = 90:10).

IR (Neat) ν_{max}: 3742, 3064, 2994, 2862, 1678, 1603, 1493, 1451, 1385, 1283, 1197, 1044, 1013, 964, 915, 750, 703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.37-7.32 (m, 5H), 5.67 (d, *J* = 5.5 Hz, 1H) , 5.41-5.36 (m, 1H), 4.57 (d, *J* = 6.0 Hz, 1H), 3.33-3.28 (m, 1H), 2.04 (bs, 1H), 1.98-1.87 (m, 1H), 1.67 (dd, J_1 =13.0 Hz, J_2 = 5.0 Hz, 1H), 0.91(d, *J* = 6.5 Hz, 1H), 0.66-0.59 (m, 2H) ppm.

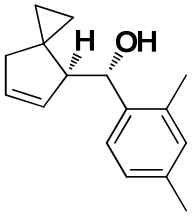
^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 143.7, 140.6, 128.6, 128.3, 127.3, 126.2, 77.8, 53.2, 36.4, 28.7, 13.4, 13.3 ppm.

HRMS-ESI: m/z $[M+H]^+$ Calcd for $C_{14}H_{17}O$: 201.12794; Found: 201.12742.

Preparation of Compound 36ae

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (92 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and 2,4 dimethyl benzaldehyde (34 mg, 0.25 mmol) at 50 ^oC yielded **36ae**

(31 mg, 54 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.28 (hexane/ethyl acetate = 95:05).

IR (Neat) ν_{max}: 3738, 3059, 2997, 2919, 2843, 1614, 1501, 1453, 1378, 1295, 1202, 1114, 1014, 822, 775, 702 cm^{-1}.

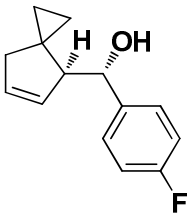
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.30 (d, J = 6.5 Hz, 1H), 7.03(d, J = 6.5 Hz, 1H), 6.93(s, 1H), 5.77(d, J = 4.5 Hz, 1H), 5.11-5.10 (m, 1H), 4.83 (d, J = 9.0 Hz, 1H), 2.75 (d, J = 8.5 Hz, 1H), 2.58-2.55 (m, 1H), 2.32 (s, 3H), 2.29 (s, 3H), 2.22-2.18 (m, 1H), 1.49-1.46 (m, 1H), 0.70-0.66 (m, 1H), 0.56-0.48 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 139.5, 136.6, 134.6, 132.2, 131.9, 130.9, 127.0, 126.3, 72.7, 58.1, 43.9, 24.2, 21.0, 19.6, 15.4, 8.9 ppm.

HRMS-ESI: m/z $[M+H]^+$ Calcd for $C_{16}H_{21}O$: 229.15924; Found: 229.15850.

Preparation of Compound 36aa

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (92 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and 4-fluoro benzaldehyde (31 mg, 0.25 mmol)at 50 ^oC yielded **36aa** (34 mg, 63 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.25 (hexane/ethyl acetate = 95:05).

IR (Neat) ν_{max}: 3736, 3063, 2924, 2854, 1710, 1661, 1600, 1511, 1458, 1267, 1225, 1045, 841, 740 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.33-7.26 (m, 2H), 7.03-6.97 (m, 2H), 5.62 (dd, J_1 = 5.5 Hz, J_2 = 2.0 Hz, 1H), 5.39 (dd, J_1 = 6.0 Hz, J_2 = 2.0 Hz, 1H), 4.55 (t, J = 5.5 Hz, 1H), 3.28-3.24 (m, 1H), 1.99 (d, J = 4.5 Hz, 1H), 1.93-1.86 (m,1H), 1.66-1.63 (m, 1H), 0.67-055 (m, 3H) ppm.

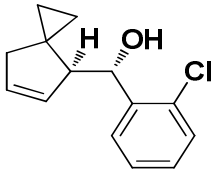
^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 161.1, 140.9, 128.1,

127.8, 127.7, 114.8, 77.1, 53.8, 53.2, 43.5, 36.3, 28.6, 12.9 ppm.

HRMS-ESI: m/z $[M+H]^+$ Calcd for $C_{14}H_{16}FO$: 219.11852; Found: 219.11196.

Preparation of Compound 36ak

Following the general procedure (Section 2.8.3), DIBAL-H (0.75 mL, 0.75 mmol) was added to a THF solution of spiro[2.4]hepta-4,6-diene (92 mg, 1.0 mmol), $[Cp_2TiCl_2]$ (7 mg, 0.025 mmol) and 2-chloro benzaldehyde (35 mg, 0.25 mmol) at 50 ^oC yielded **36ak** (33 mg, 56 %) as yellow viscous liquid upon purification by column chromatography (3 % ethyl acetate-hexane).



R_f: 0.25 (hexane/ethyl acetate = 95:05).

IR (Neat) ν_{max}: 3740, 3064, 2921, 2853, 1710, 1677, 1655, 1541, 1465, 1275, 1039, 753740 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.47(d, J = 7.5 Hz, 1H), 7.32(d, J = 7.5 Hz, 1H), 7.29-7.27 (m, 1H), 7.19 (t, J = 7.0 Hz, 1H), 5.49-5.48 (m, 1H), 5.45 (d, J = 4.5 Hz, 1H), 3.43-3.42 (m, 1H), 2.13-2.06 (m, 2H), 1.80 (dd, J_1 = 13.5 Hz, J_2 = 4.5 Hz, 1H), 0.89 (d, J = 6.5 Hz, 1H), 0.68(d, J = 6.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 143.5, 129.4, 128.2, 127.4, 127.2, 126.7, 73.4, 51.1, 36.5, 28.8, 13.6, 13.5 ppm.

HRMS-ESI: m/z $[M+H]^+$ Calcd for $C_{14}H_{16}ClO$: 235.08897; Found: 235.08869.

Preparation of Compound 37

O_3 was bubbled through a solution of **36cc** (45 mg, 0.15 mmol) in CH_2Cl_2 (4 mL) at -78 °C until a blue color persists. The stirring was continued for 45 min, then, the solution was degassed with a flow of N_2. Me_2S (0.5 mL) was added and the reaction mixture was slowly warmed to room temperature, then the crude reaction mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (5 mL), then $NaBH_4$ (10 mg, 0.25 mmol) was added. The mixture was stirred for 1h, then, water (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic phases were combined,

dried over Na_2SO_4, filtered and concentrated under reduced pressure yielded **37** (23 mg, 46 %) as a pale yellow oil after purification by column chromatography on silica gel eluting with 18 % petroleum ether and ethyl acetate.

R_f: 0.20 (hexane/ethyl acetate = 75:25).

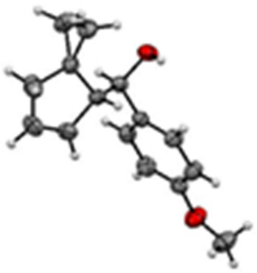
IR (Neat) ν_{max}: 3744, 3648, 3619, 2926, 2852, 1710, 1601, 1511, 1451, 1275, 1309, 1039, 1257, 1172, 1108, 840, 764 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.98 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 3.89-3.80 (m, 6H), 3.69-3.67 (m, 1H), 3.55-3.49 (m, 1H), 3.09-3.08 (m, 1H), 2.17-1.99 (m, 2H), 1.30- 1.18 (m, 10H), 0.30 (d, *J* = 4.5Hz, 1H), 0.22 (d, *J* = 4.5Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 163.2, 130.5, 130.0, 113.7, 65.4, 55.5, 55.3, 36.3, 32.3, 32.1, 30.9, 29.7, 28.9, 26.5, 26.0, 24.8, 22.3, 14.0 ppm.

HRMS-ESI: m/z $[M+H]^+$ Calcd for $C_{20}H_{31}O_4$: 335.22223; Found: 335.21856 .

X-ray crystal data of Compound 36ac



CCDC Number: 1553606

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chemical_formula_sum	'C15 H18 O2'
chemical_formula_weight	230.29

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 '-x, -y, -z'
 'x, -y-1/2, z-1/2'

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cell_length_b                 5.184(3)
cell_length_c                 20.618(12)
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cell_angle_beta               106.349(8)
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CHAPTER 2

Titanium and Zirconium Catalyzed Regioselective Synthesis of Five Membered Carbocycles

PART B

Hydrozirconation as a Versatile Tool for the Regioselective Isomerization of 1, 4 Dihydrofulvenes

2.10. Introduction

Transition metal catalyzed reactions have been extensively used as a potential tool for the construction of carbon-carbon and carbon-heteroatom bonds [Stoltz 2017]. Consequently the chemistry of transition metal complexes as reagents for organic synthesis has gained considerable attention. Among these reagents, transition metal hydrides shows good efficiency in the synthetic transformation and found use as catalysts for reactions of unsaturated hydrocarbons such as hydrogenation, hydroformylation, hydrosilation, and isomerization, *etc*. [Muetterties 1971, Teets 2016]. To improve the scope of transition metal hydride chemistry for a better general applicability, it is now challenging to find reactivity of these hydrides with ordinary "unactivated" alkenes or alkynes. Therefore, the chemistry involved in the formation of transition metal-carbon σ-bonds by *β*-hydride addition to unsaturated organic molecules, has attracted the scientific community all over the world.

In line with our efforts to develop a new methodology for the hydrometalation–isomerization of internal olefin, our group disclosed a C=C migration strategy from a non-conjugated system to access 1,2 dihydropentafulvene, the details of which form the subject matter of the present chapter. In order to provide an idea about the metal

mediated activation of unactivated alkenes/alkynes, a brief introduction about hydrozirconation is presented in the following section.

2.11. Hydrozirconation

Hydrozirconation is a process allowing the selective conversion of unactivated alkenes and alkynes into a variety of organic products through isolable σ-bonded organozirconium intermediates [Schwartz 1976b]. The σ-bound allylzirconocenes can readily add diastereoselectively to aldehydes and ketones to yield homoallylic alcohols. Even though the hydrometallation is possible through other metals like niobium (III) and tantalum(III), cleavage of this organometallic intermediate was found to be non-specific with d^2 metals. However, by using d^0systems like zirconium (IV), specific C-M cleavage as well as specific activation of an olefin or an acetylene, could be achieved. Even though a large variety of zirconium (IV) reagents are available, only a few of these like Schwartz reagent found extensive use as a reagent in organic synthesis. The zirconium hydride $Cp_2Zr(H)C1$ (Schwartz's reagent) was first prepared by Wailes *et al*. from Cp_2ZrC1_2 and $LiAIH_4$ [Wailes 1970]. It can also be easily prepared by the treatment of zirconium dichloride in tetrahydrofuran with a stoichiometric amount of $NaAIH_2(OR)_2$. Compared to the hydrometallation with aluminium and boron, hydrozirconation is widely accepted mainly due to the simple reaction conditions and efficient conversion [Marek 2006]. Schwartz reagent is a 16 electron organo zirconium species with metal in the $^+4$ oxidation state. The unsaturated systems normally bind weakly to the vacant d orbital on zirconium *via* σ-donation there by forming 18 electron d^0 species with zirconium (IV) (Figure 2.11).

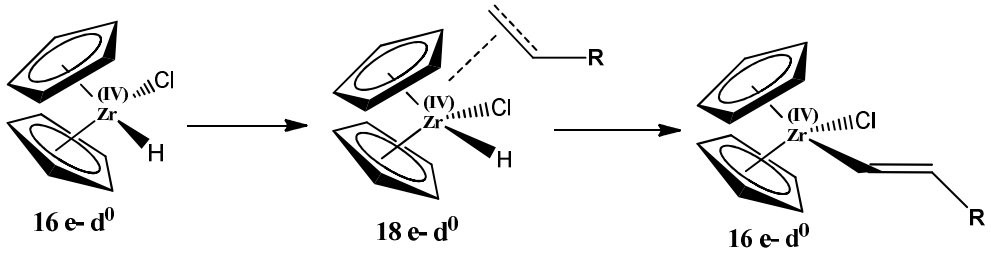


Figure 2.11: Hydrozirconation pattern

2.11.1. Hydrozirconation of Alkenes

During the hydrozirconation of olefins, the zirconium moiety, adds to the least sterically hindered position of the olefin chain. The formation of the observed product occurs either *via* a regiospecific addition of Zr-H to the terminal double bond or the Zr-H addition to an internal double bond, followed by a rapid rearrangement *via* Zr-H elimination. The re-addition occurs in each case at the less hindered position of the alkyl chain [Schwartz 1974]. The isomerisation happens probably through the reversible β-hydride elimination and re-addition. In the case of alkylzirconium(IV) complexes prepared from Schwartz reagent, the migration of the metallic moiety happens rapidly at room temperature than the other analogues. Relative rates for hydrozirconation with the Schwartz reagent can be illustrated as α-olefin > *cis* internal olefin ~ *trans* olefin > exocyclic functionalized olefin > cyclic olefin, which may be generalized as terminal olefins > disubstituted olefins > trisubstituted olefins (Scheme 2.12). The tetrasubstituted olefins such as tetramethylethylene failed to react with the hydride even after many hours of reaction at room temperature.

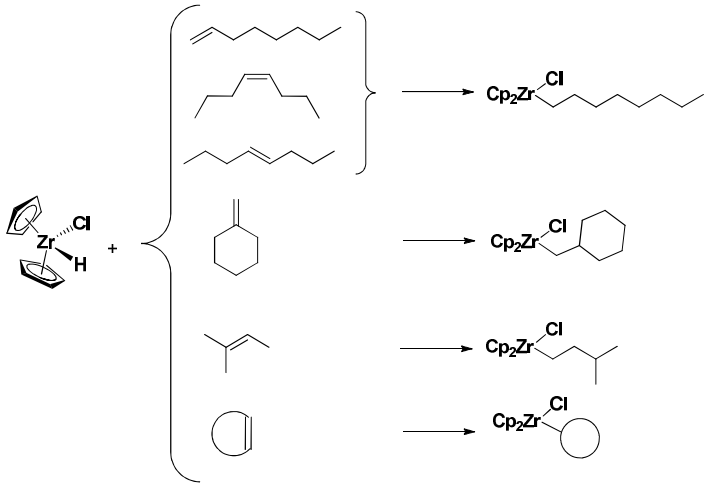
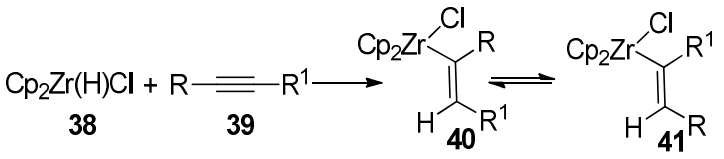


Figure 2.12: Hydrozirconation of alkenes

2.11.2. Hydrozirconation of Alkynes

The hydrozirconation of terminal alkynes proceeds with the addition of zirconium at the terminal carbon atom to get (C=C) *cis*-stereochemistry [Schwartz

1975]. In the case of unsymmetrically substituted alkynes, mixtures of alkenylzirconium derivatives are formed in which the relative steric bulk of the alkyl substituents on the alkyne C-C bond decide the preferred sight for Zr-H *cis-β* addition (Scheme 2.15). Since both the metal hydride addition as well as the elimination occur in a *cis* fashion stereo specifically, there is no loss of (C=C) stereochemistry in the isomerization process.



Scheme 2.15: Hydrozirconation of alkynes

2.11.3. Hydrozirconation of 1,3-Dienes

The hydrozirconation of a variety of 1,3-dienes proceeds by 1,2-addition to the sterically less hindered double bond to give *γ, δ* - unsaturated alkyl complexes in high yield (Scheme 2.13)[Schwartz 1976a]. But in the case of boron and aluminium, hydrides often doubly metalate 1,3- dienes or give a mixture of products, or to most transition metal hydrides which undergo 1,4- or 1,2-addition to yield corresponding allylic complexes [Wilkinson 1971].

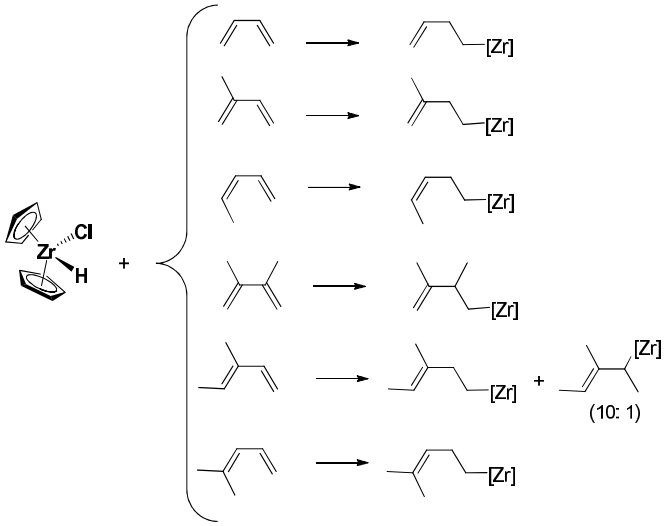
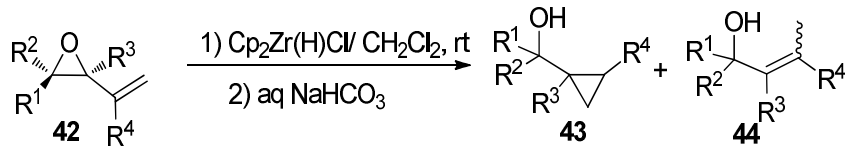


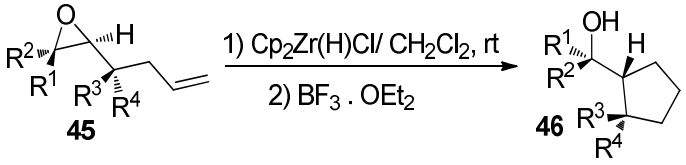
Figure 2.13: Hydrozirconation of 1,3-dienes

2.11.4. Hydrozirconation of Oxiranes

The hydrozirconation of oxiranes with vinyl substitution followed by an intramolecular nucleophilic attack of the alkylzirconocene results in the formation of cyclopropyl carbinol derivatives [Hanzawa 1997, Hanzawa 1998]. The methodology can be extended for the preparation of cyclopentyl derivatives from (l-butenyl)oxirane through a chemoselective hydrozirconation reaction with Cp_2ZrHCl. The ring formation was stereospecific and continued with the inversion of the configuration at the reacting oxirane carbon.



Scheme 2.16. Hydrozirconation of oxiranes with vinyl substitution



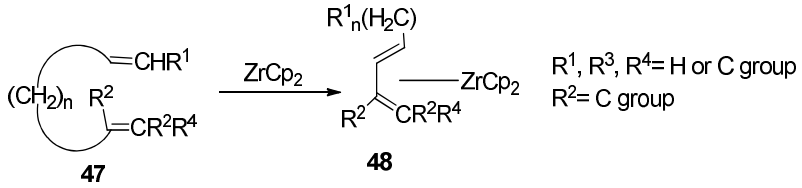
Scheme 2.17: Hydrozirconation of (l-butenyl)oxirane

2.11.5. Derivatives of Schwartz reagents for Hydrozirconation

In the last few decades huge efforts were taken to achieve good regioselectivity on terminal alkylzirconium. In 1987, Gibson reported hydrozirconation of aromatic olefins to give mixtures of benzylic and terminally substituted alkyl zirconiums [Gibson 1987]. In contrast to the simple acyclic olefins, movement of the zirconium to the end of the chain is sluggish and incomplete. At moderate temperatures, the benzylic product predominates. In 1989, Erker *et al.* improved the reactivity of Schwartz reagent by preparing derivatives of hydrozirconium reagent [Erker 1989]. Later Annby and co-workers compared the activity of different hydrozirconium reagents and their studies found $Cp^*CpZrCl_2$ as the efficient reagent for hydrozirconation [Annby 1990].

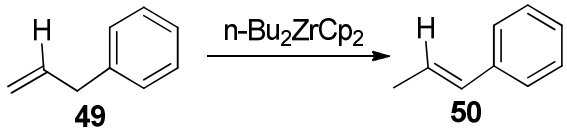
2.11.5.1. Regioisomerization (Hydrozirconation of Non-Conjugated Systems)

Zirconocene η- complex with alkene containing allylic hydrogen can further undergo regioisomerization in which alkene and Cp_2Zr moieties migrate along the carbon chain. The reaction of nonconjugated dienes having two vinyl (-CH=CH_2) groups linked by more than two carbon atom appended with $ZrCp_2$ equivalents has been used to produce the corresponding dienes. However, this type of reactivity was not studied extensively and only a limited number of reports are available. In 1993, Negishi and coworkers established a new reactivity of zirconocene derivatives [Negishi 1993a, Negishi 1993b, Annby 1993]. A non-conjugated diene containing terminal alkene moieties on reaction with hydrozirconation reagents afforded a conjugated diene with a number of carbon atoms through a multipositional regioisomerization.



Scheme 2.18: Hydrozirconation of non-conjugated systems

Later in 1995, the same group extended the scope of the reaction *via* studies regarding the isomerization of 1-substituted alkene to 2-substituted alkene [Negishi 1995].



Scheme 2.19: Hydrozirconation of 1-substituted alkene

2.12. Background to the Present Work

As mentioned earlier, Negishi reported an elegant low valent zirconocene mediated conversion of non-conjugated dienes to conjugated ones through the selective migration of the less sterically hindered unsaturated fragment [Negishi 1993, Negishi 1993, Annby 1993, Negishi 1995] (Figure. 2.14). In our lab, we were interested in the titanium catalyzed allylalumination of fulvene, leading to the formation of 1,4- dihydrofulvene, in which the exocyclic and the endocyclic double bonds remain non conjugated. Although significant progress has been made toward developing regioisomerization protocols, the selective endocyclic regioisomerization of the 1,4-dihydropentafulvenes has not been studied yet. This observation prompted us to investigate the effect of zirconium reagents on 1,4-dihydropentafulvenes foreseeing the formation of 1,2-dihydropentafulvene.

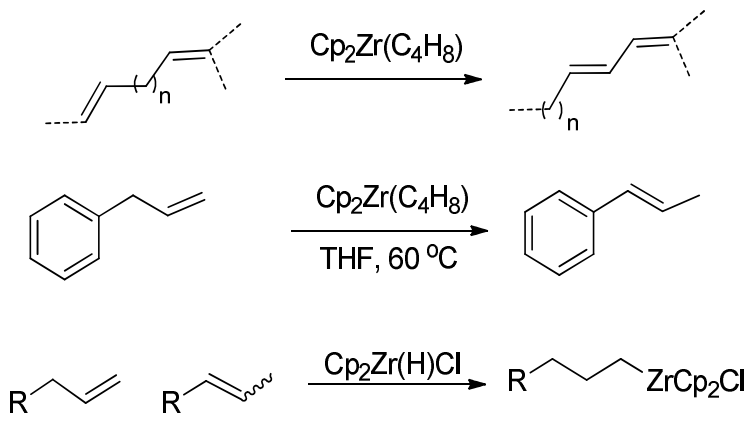
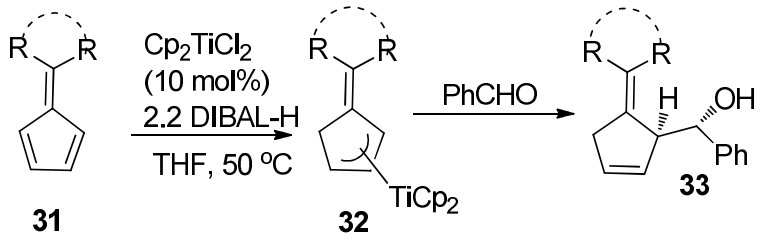


Figure 2.14: Regioisomerization

2.13. Results and Discussion

2.13.1. Synthesis of 1,4-Dihydrofulvenes

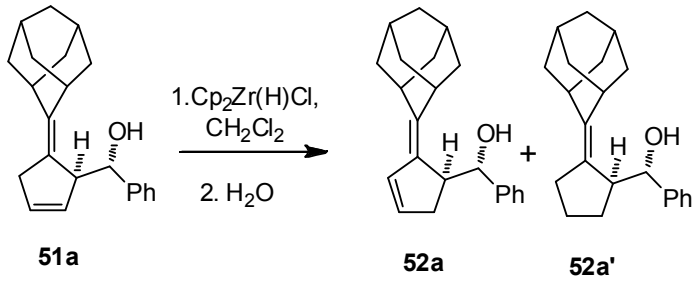
Pentafulvene derived homoallyllic alcohols were synthesized from corresponding pentafulvene by the reaction of aromatic aldehyses, in presence of Cp_2TiCl_2 and DIBAL-H in THF at at 50 ^oC (Scheme 2.20) [Szymoniak 2014].



Scheme 2.20: Synthesis of 1,4- dihydrofulvenes

2.13.2. Synthesis of 1,2-Dihydrofulvenes

In a typical experiment, the Schwartz reagent was added to a solution of adamantylfulvene derived dienic alcohol **51a** in DCM and stirred till complete dissolution (almost 2 h), followed by the addition of water. Under these conditions, a mixture of two new products, **52a** and **52a'**, were isolated in a 2:1 ratio in 60 % yield (Scheme 2.21).



Scheme 2.21: Synthesis of 1,2- dihydrofulvenes

The structure of the product **52a** was elucidated by spectroscopic analysis. In the ^{1}H NMR spectrum (Figure 2.15), the aromatic protons appeared as a multiplet in the region δ 7.32- 7.17 ppm. The proton attached to the carbon bearing -OH resonated as doublet at δ 4.27 ppm. The olefinic protons were found to resonate as multiplets in the region δ 6.18- 6.16 and δ 5.67- 5.65 ppm. The proton on ring junction C-4 appeared as a triplet at δ 3.18 ppm. All other signals are in quite agreement with the proposed structure. The proton NMR of **51a** is shown as inset in the Figure 2.15 for distinguishing the spectral pattern of the two structures.

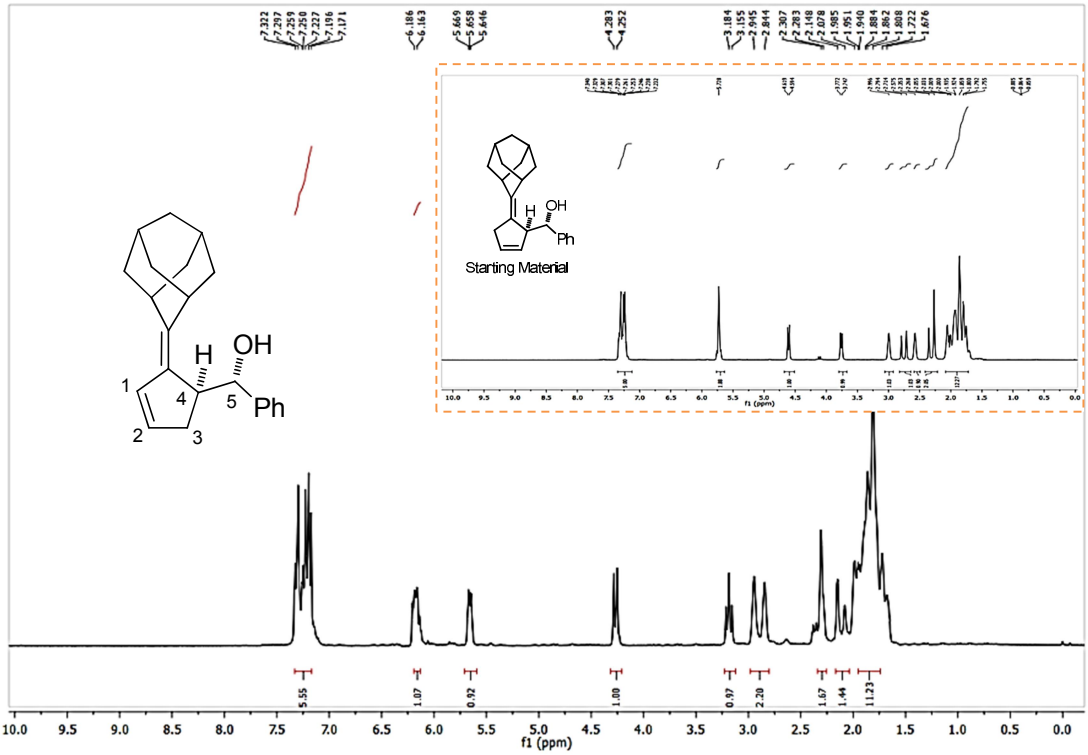


Figure 2.15: ^{1}H NMR spectrum of compound **52a**

Attached Proton Test (APT) is a 1D ^{13}C NMR experiment that is used as a method to assign 1^{o}, 2^{o}, 3^{o} and quaternary carbon. This shows methine (-CH-) and methyl (-CH_3) signals positive and quaternary (C) and methylene (-CH_2-) signals negative. When compared to DEPT, it is less sensitive but a single test gives all carbon signals at once unlike DEPT that didn't give quaternary carbons. In the ^{13}C APT NMR spectra of **52a** (Figure 2.16), the signals of the olefinic carbons were found at δ 129.9 and δ 133.3 ppm. The carbon bearing the -OH was spotted at δ 76.3 ppm while signal for the ring junction carbon C-4 was observed at δ 46.5 ppm. Further evidence for the structure was obtained from mass spectral analysis which showed the molecular ion peak at *m/z* 329.18816 $[M+ Na]^{+}$.

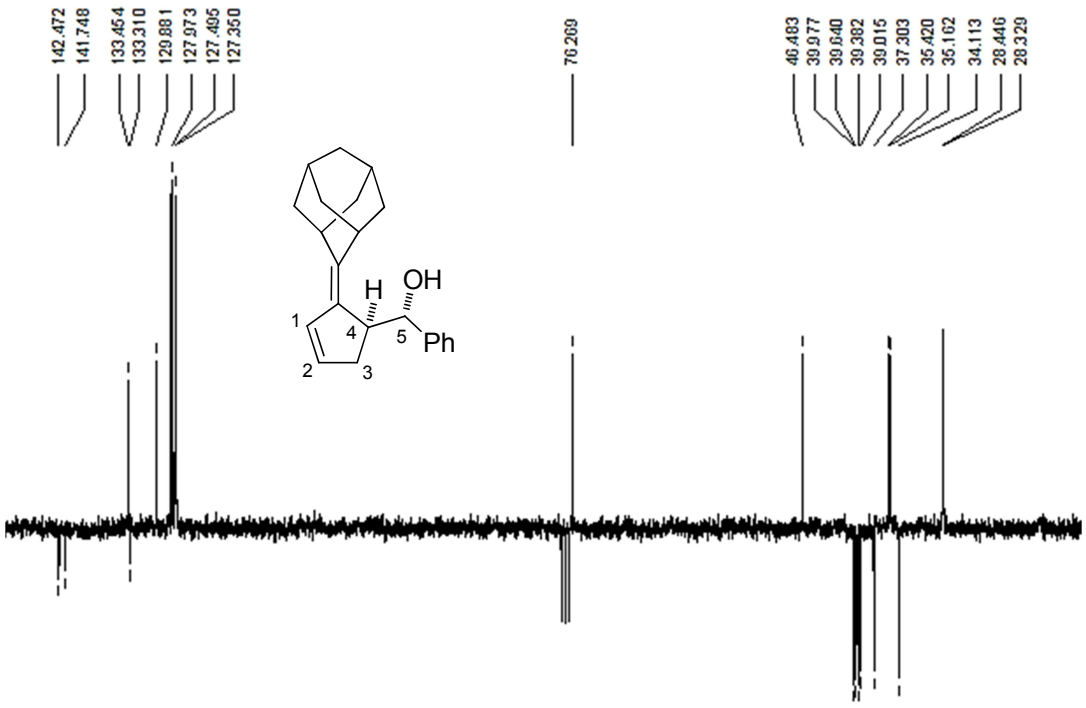
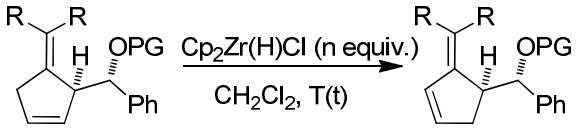


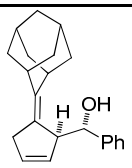
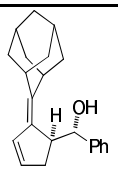
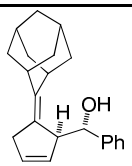
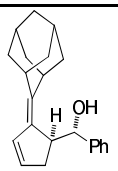
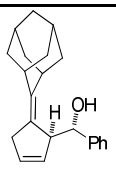
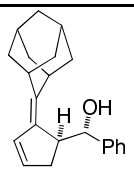
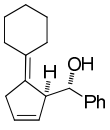
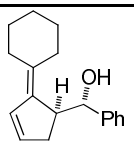
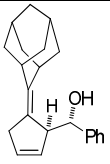
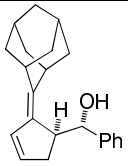
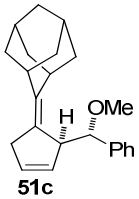
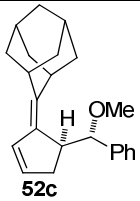
Figure 2.16: ^{13}C APT NMR spectrum of compound **52a**

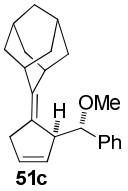
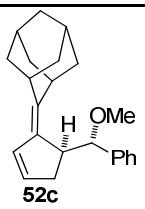
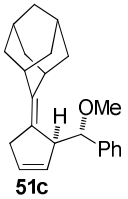
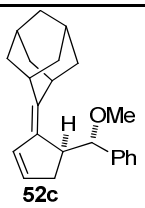
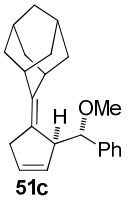
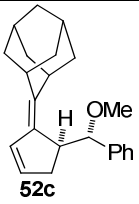
This result encouraged us to optimize the formation of the conjugated diene **52a**. Initially, the reaction proceeded to near completion after a prolonged reaction time (12 h) (Table 2.3, entry 1) or by heating at 40 °C for 2 h (entry 2). In addition, the substituents on the exocyclic double bond were found to have an effect on the kinetics of the reaction (entries 3 and 4).

More interestingly, when the analogous methyl ether was used as the substrate, the Schwartz reagent loading could be reduced to 50 % for obtaining a near complete conversion with 78 % yield (entry 6). Further reduction in the loading to 0.30 equiv. resulted in the formation of 75 % of the corresponding product (entry 7), suggesting a catalytic process. After screening a series of reaction conditions, we were pleased to find that the yield was increased to 77 % by using only 0.25 equiv. of Schwartz reagent in dichloromethane at 40 ^{o}C for 2 hours (entry 8).

Table 2.3: Optimization of the reaction



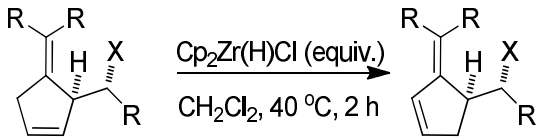
Entry	Starting material	T (t)	Solvent	$Cp_2Zr(H)Cl$ (equiv.)	compound	Yield (%)
1	 **51a**	rt (12 h)	DCM	2	 **52a**	70
2	 **51a**	rt (12 h)	THF	2	 **52a**	40
3	 **51a**	40 °C (2 h)	DCM	2	 **52a**	85
4	 **51b**	40 °C (2 h)	DCM	2	 **52b**	83
5	 **51a**	40 °C (2 h)	DCM	1.25	 **52a**	86
6	 **51c**	40 °C (2 h)	DCM	1	 **52c**	78

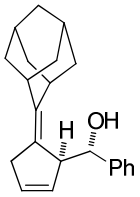
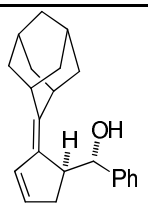
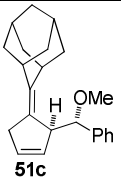
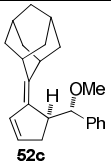
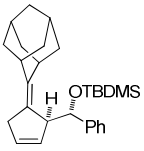
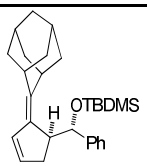
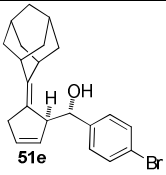
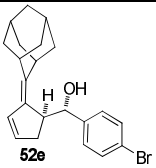
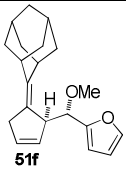
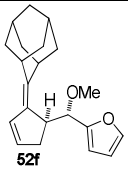
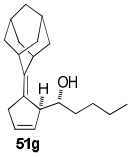
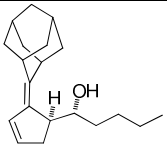
7	 51c	40 °C (2 h)	DCM	0.3	 52c	75
8	 51c	40 °C (2 h)	DCM	0.25	 52c	77
9	 51c	40 °C (2 h)	DCM	0.2	 52c	76

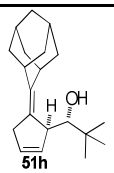
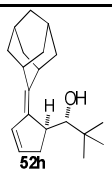
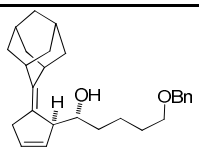
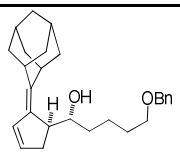
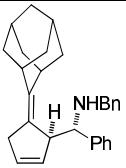
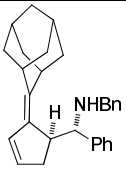
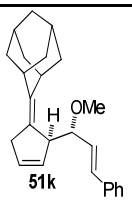
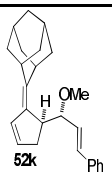
Reaction conditions: Starting material (1 equiv.), Cp_2ZrCl_2 (0.25 equiv.), DCM (2.5 mL), 40 ^oC, 2 h

With these conditions in hand, a series of adamantylfulvene derived dienic alcohols were tested (Table 2.4). The reaction appears to be quite general allowing the formation of dienic alcohols or ethers containing aryl (entries 1-4), heteroaryl (entry 5), linear alkyl (entry 6), bulky alkyl (entry 7) or even a chain incorporating a protected hydroxy group (entry 8). The reaction conditions are also found to be compatible for an unprotected secondary amine (entry 9). Surprisingly, the reaction proceeded with excellent chemoselectivity in the presence of a cinnamyl unit (entry 10).

Table 2.4: Reaction of series of adamantylfulvene-derived dienic alcohols, ethers and amines with Schwartz reagent.

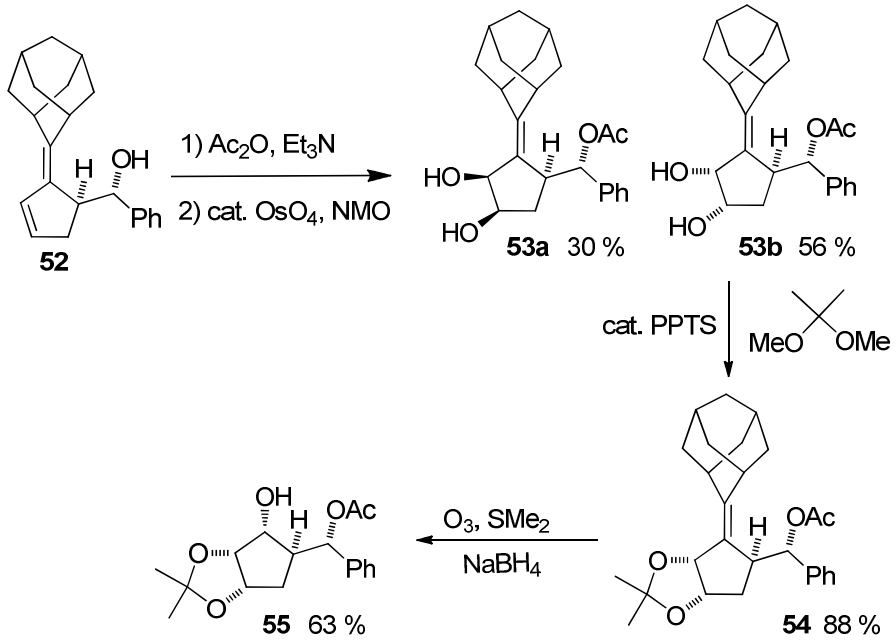


Entry	Starting Material	$Cp_2Zr(H)Cl$ (equiv.)	Compound	Yield (%)
1	 **51a**	1.25	 **52a**	86
2	 **51c**	0.25	 **52c**	77
3	 **51d**	0.25	 **52d**	83
4	 **51e**	1.25	 **52e**	79
5	 **51f**	0.25	 **52f**	73
6	 **51g**	1.25	 **52g**	69

7	 **51h**	1.25	 **52h**	77
8	 **51i**	1.25	 **52i**	74
9[b]	 **51j**	0.25	 **52j**	87
10	 **51k**	0.25	 **52k**	85

[b] = in THF

Motivated by these pleasing results, we went on to explore the synthetic utility of the new methodology by attempting further transformations of the dienic alcohols. In a preliminary experiment, alcohol **52a** was acylated and selectively dihydroxylated to afford the corresponding diols **53a** and **53b**. Eventhough we observed a low diastereoselectivity, the major isomer **53b** was isolated in the pure form. Subsequent protection and ozonolysis gave the ketone which was immediately reduced using $NaBH_4$ to the corresponding cyclopentanol **55** with good diastereoselectivity in 63 % yield.



Scheme 2.22: Synthesis of cyclopentanol

The structure of the product **55** was elucidated by spectroscopic analysis. In the ^{1}H NMR spectrum (Figure 2.17), the aromatic protons appeared as a multiplet in the region δ 7.35- 7.26 ppm. The proton attached to the carbon bearing -OAc group resonated as doublet at δ 5.93 ppm with a coupling constant $J_{1,6}$ = 7.25 Hz. The proton at C_1 carbon resonated at δ 3.57 ppm as a doublet of doublet with coupling constant $J_{1,5}$ = 10.0 Hz and $J_{1,2}$ = 5.7 Hz. The proton on the carbon C_2 resonated as a multiplet in the range δ 2.48- 2.40 ppm. The ring junction protons were found to resonate as two triplets in the region δ 4.50- 4.38 ppm. The methoxy protons appeared as a singlet at δ 2.10 ppm. In most of the cyclopentanes, the *cis* proton will have an H-C-C-H dihedral angle close to 0^o, while in the case of *trans*, it is near 120^o. Hence *cis* coupling (8-10 Hz) is usually larger than *trans* coupling (2-9 Hz) [Friebolin 2010]. With these evidents, we assigned the stereochemistry of the prepared compound. All other signals were in good agreement with the proposed structure.

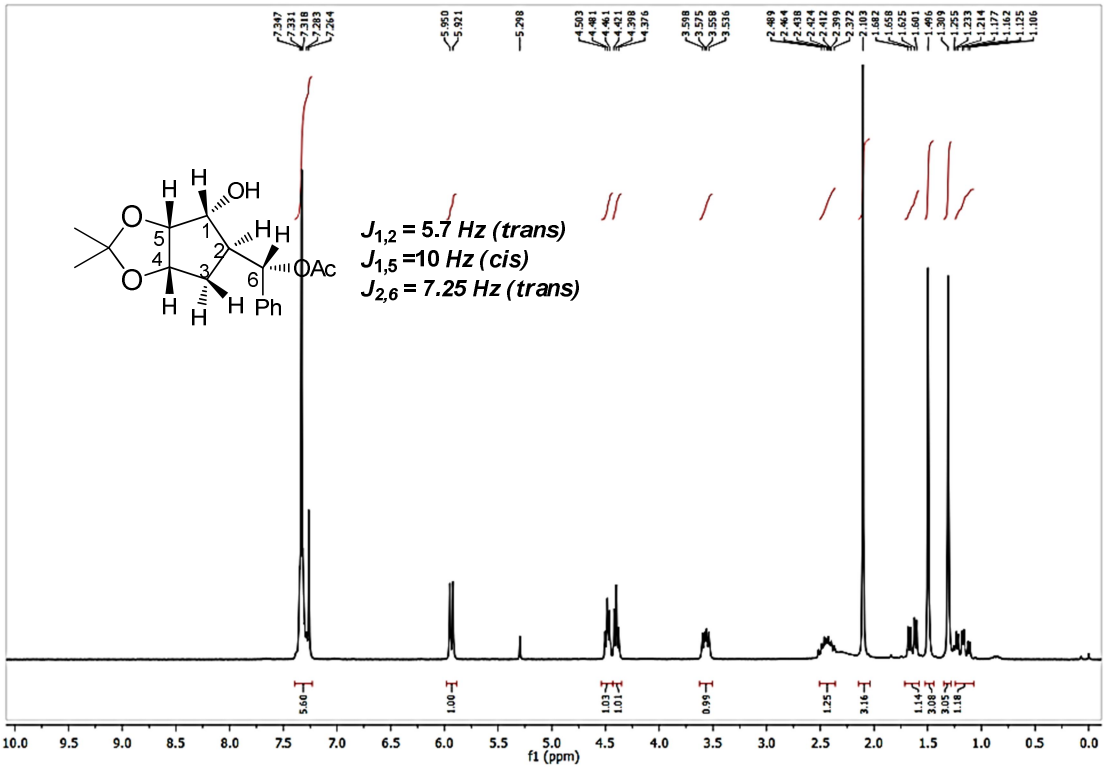


Figure 2.17: ^{1}H NMR spectrum of compound **55**

^{13}C APT NMR spectroscopy of **55** (Figure 2.18) positioned the signals of the CH_3 carbons at δ 26.3 and δ 24.5 ppm. The carbon bearing the acetyl group was spotted at δ 77.2 ppm, ring junction carbons were observed at δ 79.1 and 75.6 ppm respectively. Further evidence for the structure was obtained from mass spectral analysis which showed the molecular ion peak at *m/z* 327.1327 $[M+ Na]^{+}$.

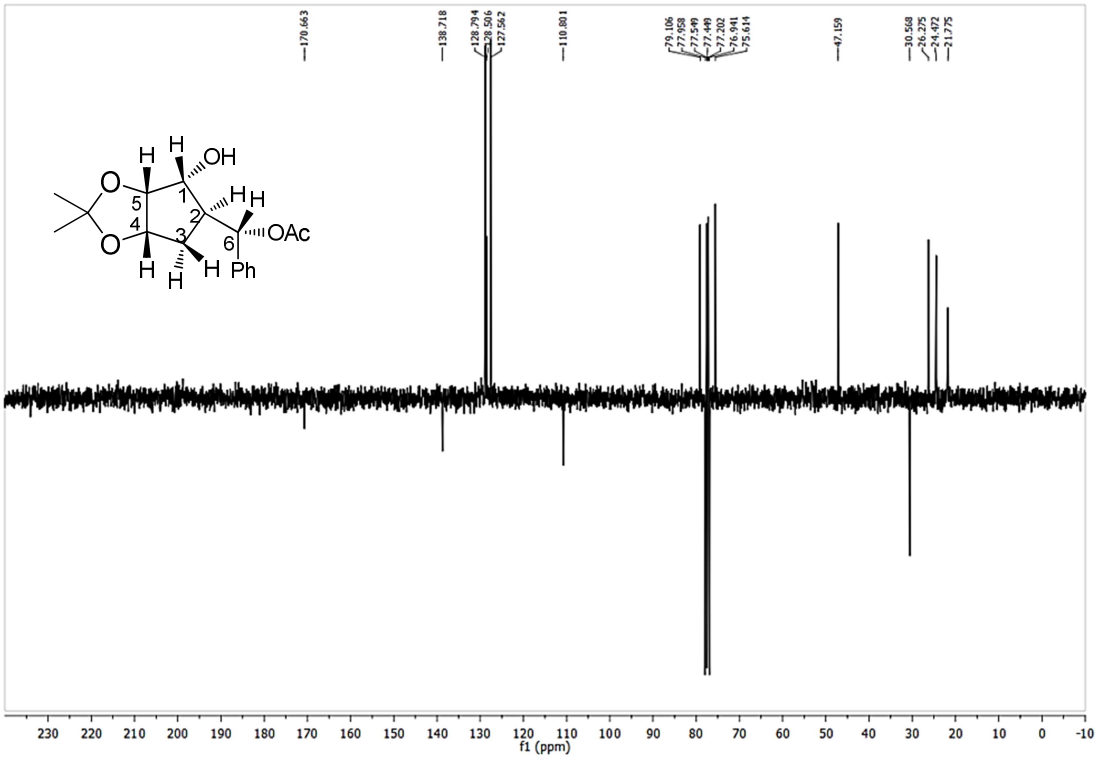


Figure 2.18: ^{13}C APT NMR spectrum of compound **55**

2.14. Mechanistic Pathway

To account for the catalytic activity of the zirconium hydride, the stereoselectivity aspects are omitted for the sake of simplicity (Figure 2.19). Initially, the hydrozirconation of **1** would reversibly lead to zirconocene **I**. In a first approximation, one may assume that owing to steric hindrance considerations, **I** is the major adduct, however the reversible formation of the regioisomer may also be considered. At this stage, **I** would competitively switch irreversibly to complex **II**. Finally, hydride transfer from **II** to **1** would give the conjugated diene **2** and zirconocene **I** to complete the catalytic cycle.

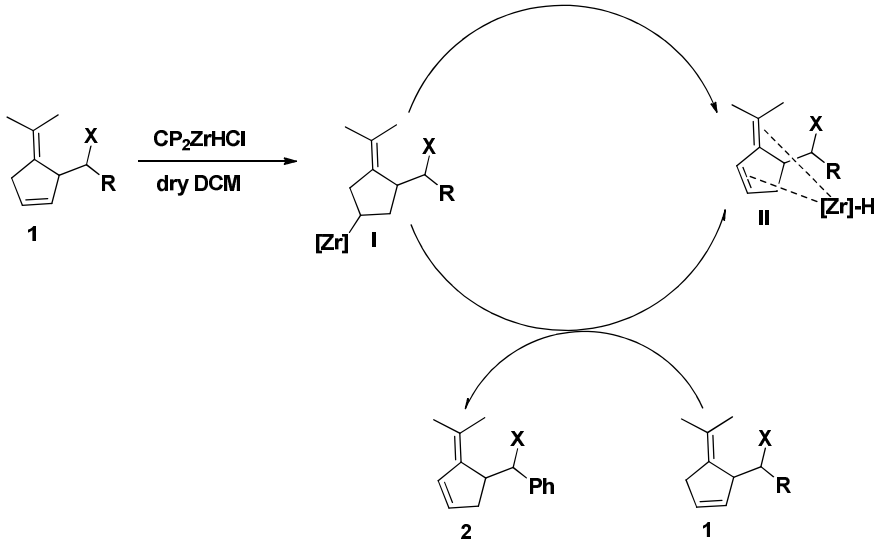


Figure 2.19: Mechanistic Pathway

2.15. Conclusion

In summary, we selectively functionalized the endocyclic C=C double bond *via* hydrozirconation and developed a facile method for the synthesis of a new class of substituted cyclopent-3-enyl (phenyl) methanols. Afterwards we exploited the promising synthetic potential of the method by preparing a complex cyclopentanol with more number of stereocenters in the endocyclic ring by a simple synthetic transformation. Our strategy is promising since the substituted cyclopentanols are the key intermediates in the synthesis of a number of biologically active molecules. The widespread occurrence and interesting biological activities of substituted cyclopentanol derivatives makes them important targets for synthesis.

2.16. Experimental Details

General information about the experiments is given in section 2.9.1 of Chapter 2a.

2.16.1. General Procedure for Homoallylic Alcohols Derived from Fulvenes and Aldehydes/Ketones

A standard Schlenk tube with magnetic stir bar was charged with fulvene (0.75 mmol) and Cp_2TiCl_2 (12.5 mg, 0.05 mmol). The system was evacuated and back filled

with argon (3 times). Dry THF was added (5 mL) followed by slow addition of DIBAL-H (1M in THF, 1.1 mL) at room temperature. When the addition of DIBAL-H was completed, the reaction vessel was inserted into a preheated oil bath at 50 ^{o}C. After 4 h at the same temperature, the mixture was cooled to -50 ^{o}C and aldehyde/ketone (0.5 mmol) was added. The reaction was continued for 1 h at the same temperature and then quenched by adding a saturated aqueous solution of $NaHCO_3$. The mixture was further diluted with ether (25 mL) and stirred for another 2 h. The organic phase was separated and concentrated under reduced pressure. The residue was purified by column chromatography to give the corresponding homoallylic alcohol.

2.16.2. General Procedure for the C=C Double Bond Migration.

2.16.2.1. In the case of Homoallylic Alcohols.

To a solution of homoallylic alcohol (1 mmol) in CH_2Cl_2 (5 mL), $Cp_2Zr(H)Cl$ (322 mg, 1.25 mmol) was added at rt. The mixture was stirred for 5 min and keeps it for 2 h at 40 °C. 5 mL of water was added followed by Et_2O (2.5 mL) and the biphasic mixture was vigorously stirred for 1 h. The organic layer was washed with an aqueous solution of HCl (1M, 2 x 1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography silica gel eluting with PE: Et_2O (95:5) to give corresponding product.

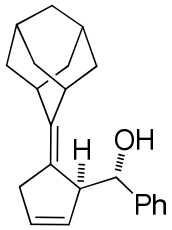
2.16.2.2. In the case of Homoallylic Ether and Amine

To a solution of homoallylic ether or amine **51** (1 mmol), in CH_2Cl_2 (2.5 mL) $Cp_2Zr(H)Cl$ (65 mg, 0.25 mmol) was added at rt. The mixture was stirred for 5 min and then keeps it for 2 h at 40 °C. 5 mL of water was added followed by Et_2O (2.5 mL) and the biphasic mixture was vigorously stirred for 1 h. The organic layer was washed with an aqueous solution of HCl (1 M, 2 x 1 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with PE: Et_2O (95:5 to 90:10) to give **52**.

Preparation of Compound 51a

Following the general procedure (Section 2.16.1), the reaction of fulvene (147

mg, 0.75 mmol), Cp_2TiCl_2 (12.5 mg, 0.05 mmol) and DIBAL-H (1M in THF, 1.1 mL) with benzaldehyde (53 mg, 0.5 mmol) yielded **51a** (209 mg, 92 %) as a pale yellow semisolid after purification by column chromatography on silica gel by eluting with 5 % petroleum ether/Et_2O.



R_f : 0.25 (PE: Et_2O = 95:05).

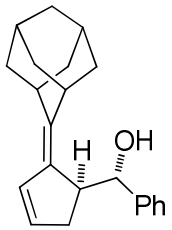
^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.34- 7.23 (m, 5H), 5.73 (bs, 2H), 4.61 (d, *J* = 6.3 Hz, 1H), 3.76 (d, *J* = 6.3 Hz, 1H), 3.00 (bs, 1H), 2.79- 2.71 (m, 1H), 2.58 (s, 1H), 2.35- 2.27 (m, 2H), 2.07- 1.76 (m, 12H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 141.9, 141.6, 140.0, 130.5, 127.4, 127.1, 127.1, 125.1, 77.2, 39.3, 38.95, 38.5, 38.4, 37.1, 35.1, 35.0, 34.4, 28.2, 28.1 ppm.

HRMS-ESI: m/z $[M+Na]^+$ calcd. for $C_{22}H_{26}NaO$: 329.18814; found: 329.18817.

Preparation of Compound 52a

Following the general procedure (Section 2.16.2.1), the addition of $Cp_2Zr(H)Cl$ (113 mg, 0.44 mmol) to a solution of homoallylic alcohol **51a** (109 mg, 0.35 mmol) in CH_2Cl_2 (2.5 mL) for 2 h at 40 °C yielded **52a** (94 mg, 86 %) as a pale yellow oil after purification by column chromatography on silica gel by eluting with 5 % PE: Et_2O .



R_f : 0.28 **(**PE: Et_2O = 95:05)**.**

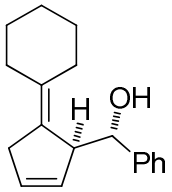
^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.32-7.17 (m, 5H), 6.18- 6.16 (m, 1H), 5.67- 5.65 (m, 1H), 4.27 (d, J_1 = 7.7, 1H), 3.18 (t, *J* = 7.3 Hz, 1H), 2.95 (bs, 1H), 2.84 (bs, 1H), 2.31-2.28 (m, 2H), 2.14 (d, *J* = 17.5 Hz, 1 H), 2.06 - 1.68 (m, 11H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 142.5, 141.7, 133.4, 133.3, 129.9, 128.0, 127.5, 127.3, 76.3, 46.5, 40.0, 39.6, 39.4, 39.0, 37.3, 35.4, 35.2, 34.1, 28.4, 28.3 ppm.

HRMS-ESI: m/z $[M+Na]^+$ calcd. for $C_{19}H_{24}NaO$: 329.18814; found: 329.1883.

Preparation of Compound 51b

Following the general procedure (Section 2.16.1), the reaction of fulvene (110 mg, 0.75 mmol) Cp_2TiCl_2 (12.5 mg, 0.05 mmol) and DIBAL-H (1M in THF, 1.1 mL) with benzaldehyde (53 mg, 0.5 mmol) yielded **51b** (48 % ,91 mg) as a pale yellow semisolid upon purification by column chromatography on silica gel eluting with 5 % petroleum ether/Et_2O .



R_f : 0.43 (PE: Et_2O = 95:05).

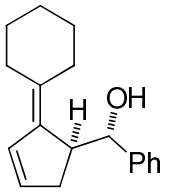
^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.48 (bs, 5H), 5.97 (m, 2H), 4.99 (d, *J* = 6.3 Hz, 1H), 3.96 (bs, 1H), 3.00 - 2.38 (m, 4H), 1.86-1.79 (m, 8H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 141.9, 135.8, 132.9, 131.9, 127.4, 127.1, 126.9, 125.1, 76.5, 55.3, 33.1, 32.5, 30.5, 29.5, 28.0, 27.1 ppm.

HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{18}H_{23}O$: 255.17489; found: 255.17456.

Preparation of Compound 52b

Following the general procedure (Section 2.16.2.1), the addition of $Cp_2Zr(H)Cl$ (184 mg, 0.71 mmol) to a solution of homoallylic alcohol **51b** (145 mg, 0.57 mmol) in CH_2Cl_2 (2.5 mL) for 2 h at 40 °C yielded **52b** (120 mg, 83 %) as a pale yellow oil after purification by column chromatography on silica gel by eluting with 3 % PE: Et_2O .



R_f : 0.45 **(**PE: Et_2O = 95:05).

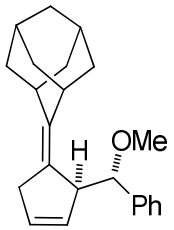
^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.30- 7.17 (m, 5H), 6.21 (ddd, J_1 = 5.6 Hz, J_2 =2.4 Hz, J_3 =1.3 Hz, 1H), 5.71 (dt, J_1 = 5.7 Hz, J_2 = 2.8 Hz, 1H), 4.24 (d, *J* = 8.0 Hz, 1H), 3.19 (t, *J* = 7.4 Hz, 1H), 2.38-2.19 (m, 6H), 2.09 (d, *J* = 17.7 Hz, 1H), 1.58-1.49 (m, 6H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS): δ142.4, 137.2, 133.8, 133.6, 130.1, 127.9, 127.4, 127.2, 76.4, 46.8, 34.2, 32.6, 31.9, 28.2, 28.0, 26.7 ppm.

HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{18}H_{23}O$: 255.17489; found: 255.17656.

Preparation of Compound 51c

NaH (60 mg, 2.5 mmol) was added to a solution of homoallylic alcohol **51a** (384 mg, 1.25 mmol) in THF (2 mL). After 30 min. of stirring, MeI (0.19 mL, 3 mmol) was added. After 1 h of stirring, yielded **51c** in 92 % (370 mg) as a pale yellow oil after purification by column chromatography on silica gel eluting with 5 % petroleum ether/Et_2O.



R_f : 0.38 (PE: Et_2O = 95:05).

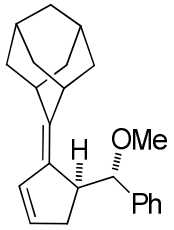
^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.32- 7.21 (m, 5H), 5.77 (dq, J_1 = 6.1 Hz, J_2 = 2.1 Hz, 1H), 5.63 (dq, J_1 = 6.0 Hz, J_2 =1.6 Hz, 1H), 4.27 (d, J = 5.1 Hz, 1H), 3.89 (bs, 1H), 3.25 (s, 3 H), 2.99 (s, 1H), 2.59 (dt, J_1 = 20.0 Hz, J_2 = 2.0 Hz, 1H), 2.48 (bs, 1H), 2.08-2.03 (m, 3H), 1.97-1.66 (m, 10H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS): δ 140.2, 138.9, 132.1, 130.3, 128.2, 126.9, 124.9, 86.3, 56.8, 52.6, 39.1, 38.8, 38.5, 38.4, 37.2 ; 35.2 ; 34.9, 34.2, 28.3, 28.1 ppm.

HRMS-ESI: m/z $[M+Na]^+$ calcd. for $C_{23}H_{28}NaO$: 343.20379; found: 343.20378.

Preparation of Compound 52c

Following the general procedure (Section 2.16.2.2), the addition of $Cp_2Zr(H)Cl$ (22 mg, 0.09 mmol) to a solution of homoallylic alcohol **51c** (110 mg, 0.34 mmol) in CH_2Cl_2 (2.5 mL) for 2 h at 40 °C yielded **52c** (85 mg, 77 %) as a pale yellow oil after purification by column chromatography on silica gel by eluting with 2 % PE: Et_2O .



R_f : 0.13 (PE: Et_2O = 98:02).

^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.31-7.21 (m, 5H), 6.02 (dt, J = 5.8 Hz, J_2 =1.8 Hz, 1H), 5.46 (dt, J_1 = 5.7 Hz, J_2 = 2.9 Hz, 1H), 4.14 (d, J = 5.4 Hz, 1H), 3.41 (q , J = 5.0 Hz, 1H), 3.25 (s, 3H), 2.97 (m, 1H), 2.83 (bs, 1H), 2.40 (dt, J_1 = 4.4 Hz, J_2 =2.2 Hz, 2H), 2.06-1.73 (m, 12H) ppm.

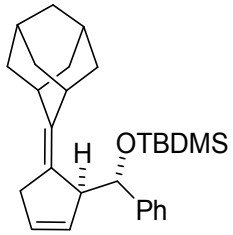
^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 139.3, 139.1, 133.3, 113.0, 130.2, 127.5, 127.3, 127.0, 85.2, 56.9, 44.1,

39.5, 39.3, 39.0, 38.9, 37.3, 35.0, 34.9, 32.6, 28.5, 28.4 ppm.

HRMS-ESI: m/z $[M+Na]^+$ calcd. for $C_{23}H_{28}NaO$: 343.20379; found: 343.20374.

Preparation of Compound 51d

TBDMSCl (211 mg, 1.45 mmol) was added to a solution of homoallylic alcohol **51a** (420 mg, 1.37 mmol) and imidazole (231 mg, 3.4 mmol) in DMF (5 mL), and the resulting mixture was stirred at rt overnight. Water (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 x 5 mL). The organic phases were combined, washed with water (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with PE to yielded **51d** in 27 % (155 mg) as a pale yellow oil upon purification by column chromatography on silica gel eluting with PE



R_f : 0.55 **(**PE: Et_2O = 100:00).

^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.21-7.06 (m, 5H), 5.82 (dq, J_1 = 5.9 Hz, J_2 =2.0 Hz, 1H), 4.79 (d, J = 4.5 Hz, 1H), 4.50 (ddd, J_1 = 5.9 Hz, J_2 =2.2 Hz, J_3 = 0.5 Hz, 1H), 3.69 (bs, 1H), 2.84 (s, 1H), 2.53-2.36 (m, 2H), 2.01-1.62 (m, 13 H), 0.84 (s, 9H), 0.00 (s, 3H), -0.16 (s, 3H) ppm.

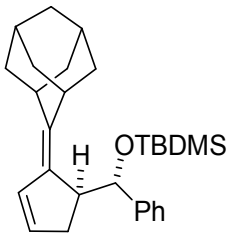
^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 142.1, 139.6, 131.7, 130.6, 127.5, 126.4, 126.3, 125.4, 76.8, 55.7, 39.1, 38.6, 38.40, 38.35, 37.2, 35.6, 35.0, 34.6, 28.4, 28.2, 25.8, 18.2, -4.8, -4.9 ppm.

HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{28}H_{40}ONaSi$: 443.2746; found: 443.2748.

Preparation of Compound 52d

Following the general procedure (Section 2.16.2.2), the addition of $Cp_2Zr(H)Cl$ (14 mg, 0.05 mmol) to a solution of homoallylic alcohol **51d** (90 mg, 0.21 mmol) in CH_2Cl_2 (2.5 mL) for 2 h at 40 °C yielded **52d** (75 mg, 83 %) as a pale yellow oil after purification by column chromatography on silica gel by eluting with

PE.



R_f : 0.58 **(**PE: Et_2O = 100:00).

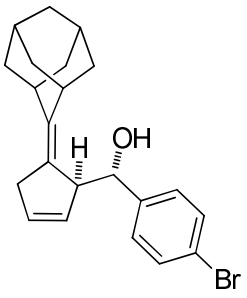
^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.40 (bs , 2H), 7.23-7.21 (m, 3H), 5.97 (dt, J = 5.5, 1.8 Hz, 1H), 5.45 (dt, J_1 = 5.5 Hz, J_1 =2.4 Hz, 1H), 4.87 (d, J = 4.2 Hz, 1H), 3.34 (dd, J_1 = 6.6 Hz, J_2 =4.3 Hz, 1H), 2.98 (s, 1H), 2.90 (bs, 1H), 2.63 (d, J = 18.1 Hz, 1H), 2.44 (ddt, J_1 = 18.1 Hz, J_2 = 7.5 Hz, J_3 =2.3 Hz, 1H), 2.22-1.80 (m, 13H), 0.98 (s, 9H), 0.12 (s, 3H), 0.00 (s, 3H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 141.5, 138.0, 133.95, 133.90, 130.1, 126.9, 126.6, 126.4, 75.1, 46.8, 39.3, 39.2, 38.9, 38.8, 37.3, 34.8, 31.7, 28.5, 28.3, 25.9, 18.2, -4.8, -4.9 ppm.

HRMS-ESI: m/z $[M+Na]^+$ calcd for $C_{28}H_{40}ONaSi$: 443.2746; found: 443.2744.

Preparation of Compound 51e

Following the general procedure (Section 2.16.1), the reaction of fulvene (147 mg, 0.75 mmol), Cp_2TiCl_2 (12.5 mg, 0.05 mmol) and DIBAL-H (1M in THF, 1.1 mL) with 4-bromo benzaldehyde (53 mg, 0.5 mmol) yielded **51e** (247 mg, 87 %) as colorless oil after purification by column chromatography on silica gel by eluting with 3 % petroleum ether/Et_2O.



R_f : 0.28 (PE: Et_2O = 95:05).

^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.36 (m, 2H), 7.16 (bs, 2H), 5.71 (bs, 2H), 4.58 (d, J = 6.1 Hz, 1H), 3.72 (bs, 1H), 2.92 (s, 1H), 2.72 (d, J = 20.2 Hz, 1H), 2.54-2.51 (m, 1H), 2.19 (bs, 2H), 1.83-1.72 (m, 12H) ppm.

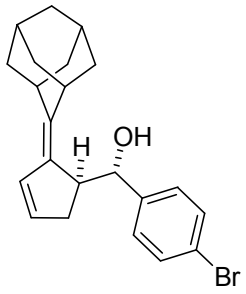
^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 141.7, 140.7, 132.4, 130.3, 129.9, 128.8, 124.7, 120.9, 76.4, 54.2, 39.2, 38.9, 38.5, 38.3, 37.0, 35.1, 35.0, 34.3, 28.1, 28.0 ppm.

HRMS-ESI: m/z $[M+Na]^+$ calcd. for $C_{22}H_{25}BrNaO$:

407.0986; found: 407.0983.

Preparation of Compound 52e

Following the general procedure (Section 2.16.2.1), the addition of $Cp_2Zr(H)Cl$ (150 mg, 0.58 mmol) to a solution of homoallylic alcohol **51e** (180 mg, 0.46 mmol) in CH_2Cl_2 (2.5 mL) for 2 h at 40 °C yielded **52e** (142 mg, 79 %) as a pale yellow oil after purification by column chromatography on silica gel by eluting with 10 % PE: Et_2O.



R_f : 0.60 **(**PE: Et_2O = 80:20).

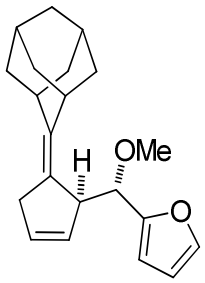
^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2 H), 6.22 (m, 1H), 5.71 (dt, J_1 = 5.7 Hz, J_2 = 2.4 Hz, 1H), 4.33 (d, *J* = 7.4 Hz, 1H), 3.21 (t, *J*= 7.2 Hz, 1H), 2.96 (s, 1H), 2.90 (bs, 1H), 2.46-2.34 (m, 2H), 2.15 (d, *J* = 17.6 Hz, 1H), 2.06-1.73 (m, 12H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 141.7, 141.2, 133.3, 133.0, 130.9, 129.8, 128.8, 121.2, 75.4, 46.3, 39.8, 39.4, 38.9, 37.1, 35.3, 35.0, 33.7, 28.3, 28.2 ppm.

HRMS-ESI : *m/z* $[M+Na]^+$ calcd for $C_{22}H_{25}BrONa$: 407.0986; found: 407.0980.

Preparation of Compound 51f

MeI (0.54 mL, 0.87 mmol) was added to a solution of homoallylic alcohol (85 mg, 0.29 mmol) and NaH (18 mg, 0.73 mmol) in THF (2 mL) yielded **51f** (77 mg, 90 %) as brownish oil after purification by column chromatography on silica gel eluting with 5 % PE: Et_2O.



R_f : 0.46 **(**PE: Et_2O = 95:05).

^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.33 (dd, J_1 = 1.6 Hz, J_2 =0.7 Hz, 1H), 6.29 (dd, J_1 = 3.1 Hz, J_2 =1.8 Hz, 1H), 6.16 (d, *J* = 2.8 Hz, 1H), 5.86-5.75 (m, 2H), 4.26 (d, *J* = 6.2 Hz, 1H), 3.91 (d, *J* = 6.1 Hz, 1H), 3.25 (s, 3H), 2.88 (s, 1H), 2.77 (dt, J_1 = 20.1 Hz, J_2 = 1.9 Hz, 1H), 2.48 (bs, 1H), 2.39 (d, *J* = 20.1 Hz, 1H), 2.00-1.62 (m, 12H) ppm.

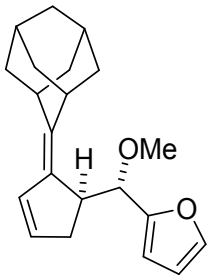
^{13}C NMR (62.5 MHz, $CDCl_3$, TMS): δ 153.4, 141.6,

141.1, 132.1, 130.4, 123.8, 109.9, 108.0, 56.9, 51.0, 38.95, 38.90, 38.2, 37.2, 35.3, 35.0, 34.4, 28.3, 28.1 ppm.

HRMS-ESI : *m/z* $[M+Na]^+$ calcd for $C_{21}H_{26}NaO_2$: 333.18305; found: 333.18312.

Preparation of Compound 52f

Following the general procedure (Section 2.16.2.2), the addition of $Cp_2Zr(H)Cl$ (15 mg, 0.06 mmol) to a solution of homoallylic alcohol **51f** (69 mg, 0.22 mmol) in CH_2Cl_2 (2.5 mL) for 2 h at 40 °C yielded **52f** (51 mg, 73 %) as a brownish oil after purification by column chromatography on silica gel by eluting with 2 % PE: Et_2O .



R_f : 0.20 **(**PE: Et_2O = 98:02).

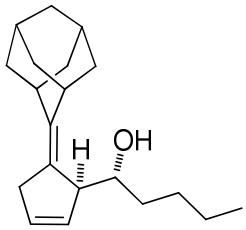
^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.33 (dd, J_1 = 1.6 Hz, J_2 =0.9 Hz, 1H), 6.28 (dd, J_1 = 3.1 Hz, J_2 =1.8 Hz, 1H), 6.18 (d, J = 2.8 Hz, 1H), 6.14 (dt, J_1 = 5.7 Hz, J_2 = 2.0 Hz, 1H), 5.68 (dt, J_1 = 5.7 Hz, J_2 =2.4 Hz, 1H), 4.11 (d, J = 6.4 Hz, 1H), 3.43 (td, J = 5.9, 3.7 Hz, 1H), 3.25 (s, 3H), 2.86 (bs, 1H), 2.80 (s, 1H), 2.53-2.49 (m, 2 H), 2.01-1.72 (m, 12H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) :δ 153.1, 153.0, 141.8, 140.0, 132.7, 132.4, 129.7, 109.6, 108.4, 79.3, 57.0, 42.6, 39.3, 39.2, 39.1, 37.3, 35.1, 34.9, 33.7, 28.4, 28.3 ppm.

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{21}H_{26}O_2Na$: 333.1831; found: 333.1827.

Preparation of Compound 51g

Following the general procedure (Section 2.16.1), the reaction of fulvene (147 mg, 0.75 mmol), Cp_2TiCl_2 (12.5 mg, 0.05 mmol) and DIBAL-H (1M in THF, 1.1 mL) with nbutyl carboxaldehyde (43 mg, 0.5 mmol) yielded **51g** (128 mg, 61 %) as a colorless oil after purification by column chromatography on silica gel by eluting with 3 % petroleum ether/Et_2O.



R_f : 0.30 **(**PE: Et_2O = 95:05).

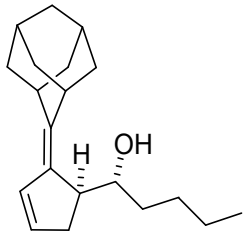
^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 5.94 (bs, 1H), 5.83-5.81 (m, 1H), 3.53-3.50 (m, 2H), 2.95 (bs, 2H), 2.79 (bs, 1H), 2.59 (bs, 1H), 1.83 (bs, 12H), 1.39 (bs, 6H), 0.89 (t, *J* = 6.7 Hz, 3H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 141.2, 131.6, 130.8, 125.0, 74.5, 53.6, 39.2, 39.0, 38.8, 38.2, 37.0, 35.7, 35.0, 34.3, 32.1, 28.5, 28.2, 28.0, 22.7, 14.0 ppm.

HRMS-ESI: m/z $[M+Na]^+$ calcd. for $C_{20}H_{30}NaO$: 309.2194; found: 309.2198.

Preparation of Compound 52g

Following the general procedure (Section 2.16.2.1), the addition of $Cp_2Zr(H)Cl$ (71 mg, 0.28 mmol) to a solution of homoallylic alcohol **51g** (63 mg, 0.22 mmol) in CH_2Cl_2 (2.5 mL) for 2 h at 40 °C yielded **52g** (44 mg, 69 %) as a pale yellow oil after purification by column chromatography on silica gel by eluting with 10 % PE: Et_2O.



R_f : 0.54 **(**PE: Et_2O = 90:10).

^{1}H NMR (250 MHz, $CDCl_3$, TMS) :δ 6.34 (ddd, J_1 = 5.7 Hz, J_2 =2.3 Hz, J_3 =1.6 Hz, 1H), 5.88 (ddd, J_1 = 5.7 Hz, J_2 =2.8 Hz, J_3 =2.4 Hz, 1H), 3.42 (t, *J* = 6.9 Hz, 1H), 3.01 (t, *J* = 6.9 Hz, 1H), 2.87 (s, 1H), 2.76 (bs, 1H), 2.53 (ddt, J_1 = 17.7 Hz, J_2 =7.4 Hz, J_3 =2.4 Hz, 1H), 2.29 (d, *J* = 17.7 Hz, 1H), 1.99-1.71 (m, 13H), 1.52-1.21 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H) ppm.

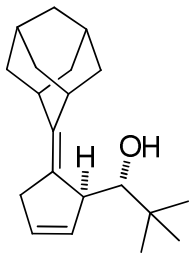
^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 140.7, 133.5, 130.3, 73.6, 45.2, 39.6, 39.5, 39.3, 37.2, 35.05, 34.95, 33.90, 31.8, 28.8, 28.3, 22.7, 14.0 ppm.

HRMS-ESI: m/z $[M+Na]^+$ calcd. for $C_{20}H_{30}NaO$: 309.2194; found: 309.2195.

Preparation of Compound 51h

Following the general procedure (Section 2.16.1), the reaction of fulvene (147 mg, 0.75 mmol), Cp_2TiCl_2 (12.5 mg, 0.05 mmol) and DIBAL-H (1M in THF, 1.1 mL)

with *t*-butyl carboxaldehyde (43 mg, 0.5 mmol) yielded **51h** (161 mg, 76 %) as a colorless oil after purification by column chromatography on silica gel by eluting with 5 % petroleum ether/Et_2O.



R_f : 0.28 **(**PE: Et_2O = 95:05).

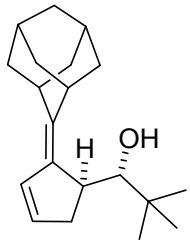
^{1}HNMR (250 MHz, $CDCl_3$, TMS) : δ 6.13 (bs, 1H), 5.78 (s, 1H), 3.71 (bs, 1H), 3.33 (s, 1H), 2.94 (bs, 2H), 2.71 (s, 1H), 2.58 (bs, 1H), 1.77 (bs, 13H), 0.98 (s, 9H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 139.0, 135.0, 129.6, 128.1, 83.2, 48.4, 38.9, 38.7, 38.6, 38.3, 37.1, 36.2, 35.7, 34.9, 33.8, 28.1, 28.0, 26.9 ppm.

HRMS-ESI: m/z $[M+Na]^+$ calcd. for $C_{20}H_{30}NaO$: 309.2194; found: 309.2194.

Preparation of Compound 52h

Following the general procedure (Section 2.16.2.1), the addition of $Cp_2Zr(H)Cl$ (74 mg, 0.29 mmol) to a solution of homoallylic alcohol **51h** (65 mg, 0.23 mmol) in CH_2Cl_2 (2.5 mL) for 2 h at 40 °C yielded **52h** (50 mg, 77%) as a pale yellow oil after purification by column chromatography on silica gel by eluting with 3% PE: Et_2O .



R_f : 0.33 **(**PE: Et_2O = 95:05).

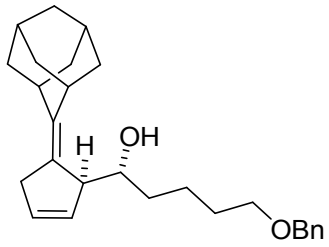
^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ6.38 (dt, J_1 = 5.8 Hz, J_2 = 2.2 Hz, 1H), 5.86 (dt, J_1 = 5.8 Hz, J_2 = 2.7 Hz, 1H), 3.32 (d, J = 3.8 Hz, 1H), 3.10 (dd, J_1 = 7.9 Hz, J_2 =1.0 Hz, 1H), 2.67-2.57 (m, 2H), 2.81 (s, 1H), 2.34 (ddt, J_1 = 17.7 Hz, J_2 =8.1 Hz, J_3 =2.5 Hz, 1H), 1.92-1.66 (m, (13H), 0.90 (s, 9H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) :δ138.9, 137.0, 135.0, 130.9, 84.0, 39.4, 39.3, 39.15, 39.10, 37.2, 35.7, 35.0, 34.3, 32.8, 28.3, 28.2, 27.1 ppm.

HRMS-ESI: m/z $[M+Na]^+$ calcd. for $C_{20}H_{30}NaO$: 309.2194; found: 309.2192

Preparation of Compound 51i

Following the general procedure (Section 2.16.1), the reaction of fulvene (127 mg, 0.64 mmol), Cp_2TiCl_2 (12.5 mg, 0.05 mmol) and DIBAL-H (1M in THF, 1.1 mL) with 5-(benzyloxy)pentanal (154 mg, 0.64 mmol) yielded **51i** (133 mg, 53 %) as a pale yellow oil after purification by column chromatography on silica gel by eluting with 15 % petroleum ether/AcOEt.



R_f : 0.53 **(**PE: Et_2O = 80:20**).**

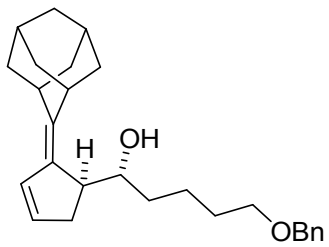
^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.33-7.25 (m, 5H), 5.93 (d, J = 6.0 Hz, 1H), 5.81 (dq, J_1 = 6.0 Hz, J_2 =1.9 Hz, 1H), 4.48 (s, 2 H), 3.53 (bs, 2H), 3.46 (t, J = 6.1 Hz, 2H), 2.95 (dt, J_1 = 20.3 Hz, J_2 =1.8 Hz, 1H), 2.89-2.75 (m, 2H), 2.58 (s, 1H), 1.95-1.58 (m, 19H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 141.2, 138.5, 131.6, 130.8, 128.3, 127.6, 127.4, 125.0, 74.4, 72.8, 70.3, 53.6, 39.2, 39.0, 38.8, 38.2, 37.0, 35.7, 35.0, 34.3, 32.2, 29.6, 28.1, 28.0, 23.0 ppm.

HRMS-ESI : *m/z* $[M+H]^+$ calcd for $C_{27}H_{36}O_2Na$: 415.2613; found: 415.2607.

Preparation of Compound 52i

Following the general procedure (Section 2.16.2.1), the addition of $Cp_2Zr(H)Cl$ (90 mg, 0.35 mmol) to a solution of homoallylic alcohol **51i** (110 mg, 0.28 mmol) in CH_2Cl_2 (2.5 mL) for 2 h at 40 °C yielded **52i** (81 mg, 74 %) as a pale yellow oil after purification by column chromatography on silica gel by eluting with PE: Et_2O (95:5-80:20).



R_f : 0.55 **(**PE: Et_2O = 80:20**).**

^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.34-7.32 (m, 5H), 6.34 (dt, J_1 = 5.7 Hz, J_2 =1.9 Hz, 1H), 5.88 (ddd, J_1 = 5.7 Hz, J_2 =2.9 Hz, J_3 =2.3 Hz, 1H), 4.49 (s, 2H), 3.53-3.39 (m, 3H), 3.00 (t, J = 6.9 Hz, 1H), 2.87 (s, 1 H), 2.75 (bs, 1H), 2.52 (ddt, J_1 = 17.7 Hz, J_2 =7.5 Hz, J_3 =2.4 Hz, 1H),

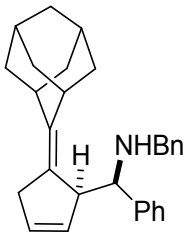
2.26 (d, J = 17.7 Hz, 1H), 1.98-1.55 (m, 19H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 140.8, 138.6, 133.5, 133.1, 130.3, 128.3, 127.6, 127.4, 73.5, 72.8, 70.4, 45.2, 39.6, 39.4, 39.2 (2 C), 37.1, 35.0, 34.9, 33.9, 31.9, 29.7, 28.2, 23.2 ppm.

HRMS-ESI : *m/z* $[M+H]^+$ calcd for $C_{27}H_{36}O_2Na$: 415.2613; found: 415.2610

Preparation of Compound 51j

Following the general procedure (Section 2.16.1), the reaction of fulvene (110 mg, 0.55 mmol), Cp_2TiCl_2 (12.5 mg, 0.05 mmol) and DIBAL-H (1M in THF, 1.1 mL) with N-benzylidene-1-phenylmethanamine (105 mg, 0.54 mmol) yielded **51j** (103 mg, 48 %) as a pale yellow oil after purification by column chromatography on silica gel by eluting with 25 % petroleum ether/AcOEt.



R_f : 0.46 **(**PE: Et_2O = 70:30).

^{1}H NMR (250 MHz, $CDCl_3$, TMS) :δ 7.37-7.15 (m, 10H), 5.94 (ddd, J_1 = 6.0 Hz, J_2 =2.2 Hz, J_3 =1.8 Hz, 1H), 5.59 (ddd, J_1 = 6.0 Hz, J_2 = 2.2 Hz, J_3 =2.0 Hz, 1H), 3.92 (d, J = 3.1 Hz, 1H), 3.77 (d, J = 13.6 Hz, 1H), 3.58 (bs, 1H), 3.44 (d, J = 13.6 Hz, 1H), 2.98 (bs, 2H), 2.88 (s, 1H), 2.59 (bs, 1H), 1.89-1.61 (m, 13H) ppm.

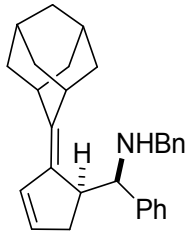
^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) :δ 143.1, 141.0, 140.9, 131.6, 130.3, 128.3, 127.3, 126.7, 125.9, 65.1, 54.6, 51.7, 39.0, 38.9, 38.5, 38.2, 37.2, 36.9, 35.3, 34.2, 28.3, 28.1 ppm.

HRMS-ESI: *m/z* $[M+H]^+$ calcd for $C_{29}H_{34}N$: 396.2691; found: 396.2691.

Preparation of Compound 52j

Following the general procedure (Section 2.16.2.2), the addition of $Cp_2Zr(H)Cl$ (25 mg, 0.10 mmol) to a solution of homoallylic amine **51j** (150 mg, 0.38 mmol) in CH_2Cl_2 (3.5 mL) for 2 h at 40 °C yielded **52j** (130 mg, 87 %) as a pale yellow oil after

purification by column chromatography on silica gel by eluting with 20 % PE: Et_2O.



R_f : 0.48 (PE: Et_2O = 75:25).

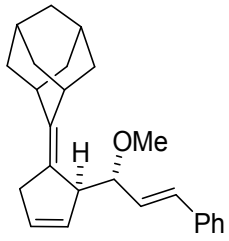
^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.47 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.29-7.13 (m, 6H), 6.39 (dt, J_1 = 5.6 Hz, J_2 =1.9 Hz, 1H), 5.96 (ddd, J = 5.6, 2.8, 2.4 Hz, 1H), 3.89 (d, J = 2.2 Hz, 1H), 3.75 (d, J = 13.7 Hz, 1H), 3.41 (d, J = 13.7 Hz, 1H), 3.11 (d, J = 8.7 Hz, 1H), 2.87 (bs, 2H), 2.73 (d, J = 17.8, 1H), 2.14 (ddt, J_1 = 17.8 Hz, J_1 =8.5 Hz, J_1 =2.3 Hz, 1H), 1.94-1.62 (m, 13H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 142.8, 140.8, 140.0, 135.1, 134.2, 130.4, 128.2 (3 C), 127.5, 126.60, 126.55, 64.6, 51.7, 45.8, 39.4, 39.2, 39.1, 39.0, 37.2, 35.0, 34.7, 31.9, 28.27, 28.23 ppm.

HRMS-ESI : *m/z* $[M+H]^+$ calcd for $C_{29}H_{34}N$: 396.2691; found: 396.2691.

Preparation of Compound 51k

MeI (0.52 mL, 0.84 mmol) was added to a solution of homoallylicalcohol (90 mg, 0.28 mmol) and NaH (14 mg, 0.56 mmol) in THF (2 mL) yielded **51k** (84 mg, 87 %) as a yellow oil after purification by column chromatography on silica gel by eluting with 3% petroleum ether/Et_2O. modify other procedures.



R_f : 0.45 **(**PE: Et_2O = 95:05).

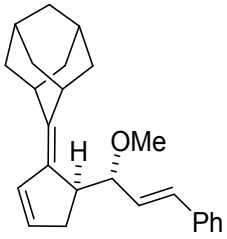
^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.31-7.20 (m, 5H), 6.47 (d, J = 15.9 Hz, 1H), 6.00 (ddt, J_1 = 15.9 Hz, J_2 = 7.9 Hz, J_3 = 2.2 Hz, 1H), 5.92 (s, 2H), 3.79 (bs, 1H), 3.34 (s, 3H), 2.86 (d, J = 20.0 Hz, 1H), 2.82 (bs, 1H), 2.65 (d, J = 20.0 Hz, 1H), 2.51 (s, 1H), 2.02-1.61 (m, 13H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 140.4, 137.2, 133.0, 131.8, 130.6, 128.5, 127.7, 127.4, 126.4, 124.6, 84.8, 56.4, 51.6, 39.2, 38.9, 38.2, 37.2, 35.8, 35.0, 34.3, 38.3, 28.1 ppm.

HRMS-ESI : *m/z* $[M+Na]^+$ calcd for $C_{25}H_{30}ONa$: 369.2194; found: 369.2198

Preparation of Compound 52k

Following the general procedure (Section 2.16.2.2), the addition of $Cp_2Zr(H)Cl$ (10 mg, 0.04 mmol) to a solution of homoallylic ether **51k** (55 mg, 0.16 mmol) in CH_2Cl_2 (1.0 mL) for 2 h at 40 °C yielded **52k** (47 mg, 85 %) as a pale yellow oil after purification by column chromatography on silica gel by eluting with 3 % PE: Et_2O



R_f : 0.48 **(**PE: Et_2O = 95:05).

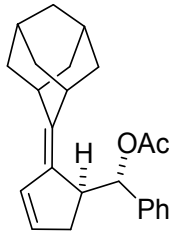
^{1}H NMR (250 MHz, $CDCl_3$, TMS): δ 7.33-7.18 (m, 5H), 6.51 (d, J = 15.9 Hz, 1H), 6.26 (dt, J_1 = 5.8 Hz, J_2 =1.8 Hz, 1H), 5.94 (dd, J_1 = 15.9 Hz, J_2 =7.0 Hz, 1H), 5.85 (ddd, J_1 = 5.7 Hz, J_2 =2.8 Hz, J_3 = 2.4 Hz, 1H), 3.77 (dd, J_1 = 6.3 Hz, J_2 =5.3 Hz, 1H), 3.38-3.31 (m, 1 H), 3.36 (s, 3 H), 2.81 (bs, 2H), 2.52 (bs, 1H), 2.04-1.68 (m, 13H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) :δ139.4, 137.3, 133.6, 133.1, 131.9, 130.7, 128.4, 127.2, 126.4, 83.9, 56.5, 42.5, 39.8, 39.2, 39.0, 37.2, 34.95, 34.90, 32.8, 28.4, 28.3 ppm.

HRMS-ESI : *m/z* $[M+Na]^+$ calcd for $C_{25}H_{30}ONa$: 369.2194; found: 369.2208

[2-(2-Adamantan-2-ylidene)cyclopent-3-enyl](phenyl)methyl acetate

Ac_2O (0.15 mL, 1.5 mmol) was added to a solution of homoallylic alcohol (335 mg, 1.1 mmol), Et_3N (0.31 mL, 2.2mmol) and DMAP (12 mg, 0.1 mmol) in CH_2Cl_2 (10 mL), and the resulting mixture was stirred for 4 h at room temperature, then Water (10 mL) was added. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography yielded (360 mg, 94 %) as pale yellow oil after purification by column chromatography on silica gel eluting with 5 % PE and Et_2O.



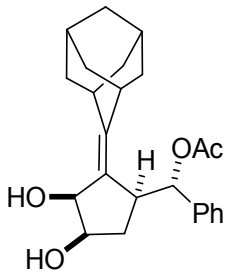
R_f : 0.33 **(**PE: Et_2O = 95:05).

^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.27-7.14 (m, 5H), 5.95 (dt, J_1 = 5.6 Hz, J_2 =1.6 Hz, 1H), 5.69 (d, J = 5.2 Hz, 1H), 5.39 (ddd, J_1 = 5.6 Hz, J_2 =2.9 Hz, J_3 = 2.4 Hz, 1H), 3.36 (dd, J_1 = 9.1 Hz, J_2 =4.9 Hz, 1H), 3.03 (bs, 1H), 2.77 (bs, 1H), 2.37 (bs, 2H), 2.04 (s, 3H), 2.05-1.65 (m, 12H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 170.2, 140.3, 137.6, 132.7, 130.4, 127.3, 127.0, 76.8, 43.0, 39.5, 39.3, 39.0, 38.8, 37.2, 34.7, 32.6, 28.30, 28.25, 21.5 ppm.

Preparation of Compound 53a and 53b

To a solution of the above ester (288 mg, 0.83 mmol) in a 10: 1 acetone / water mixture (30 mL), OsO_4 (4 % in H_2O, 0.5 mL) and NMO (200 mg, 1.7 mmol) were added. The mixture was stirred for 6 h then, sodium sulfite was added then the mixture for 1 h. The residue on purification by flash column chromatography yielded diols **53a** (95 mg, 30 %) and **53b** (177 mg, 56 %). as pale yellow oil after purification by column chromatography on silica gel eluting with mixture of PE and AcOEt (70:30 to 40:60)

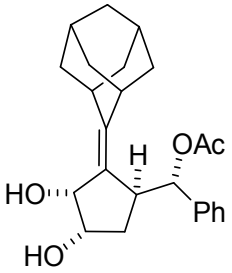


[3,4-Dihydroxy-2-(adamantan-2-ylidene)cyclopentyl](phenyl) methyl acetate 53a

R_f : 0.38 **(**PE: Et_2O = 60:40).

^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.37-7.24 (m, 5H), 5.98 (d, J = 9.1 Hz, 1H), 4.40 (d, J = 5.3 Hz, 1H), 3.94 (dd, J_1 = 11.3 Hz, J_2 =5.4 Hz, 1H), 3.07 (td, J_1 = 8.5 Hz, J_2 =4.2 Hz, 1H), 2.92 (bs, 2H), 2.59 (bs, 2H), 2.01 (s, 3H), 1.96-1.53 (m, 14H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$) : δ 171.5, 151.0, 138.8, 128.3, 128.1, 127.5, 79.0, 72.0, 71.3, 43.8, 39.8, 39.4, 38.8, 38.5, 36.8, 34.7; 34.6, 34.0, 28.0, 27.7, 22.0 ppm.



[3,4-Dihydroxy-2-(adamantan-2-ylidene) cyclopentyl](phenyl) methyl acetate 53b

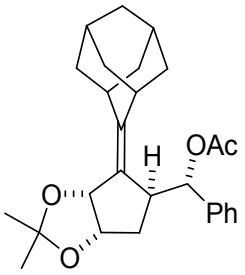
R_f : 0.35 **(**PE: Et_2O = 60:40**).**

^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ: 7.24-7.19 (m, 5H), 5.66 (d, J = 4.7 Hz, 1H), 3.98 (d, J = 5.5 Hz, 1H), 3.22 (dd, J_1 = 8.4 Hz, J_2 = 4.7 Hz, 1H), 3.04 (bs, 1H), 2.88 (bs, 1H), 2.58 (dt, J_1 = 10.9 Hz, J_2 =6.2 Hz, 1H), 2.35 (bs, 1H), 2.06 (s, 3H), 2.01-1.72 (m, 14H), 1.51 (ddd, J_1 = 12.6 Hz, J_2 =11.5 Hz, J_3 =9.1 Hz, 1H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) δ: 170.0, 152.2, 138.2, 128.7, 128.2, 127.8, 126.3, 76.2, 71.4, 70.0, 43.0, 40.1, 39.2, 38.8, 38.5, 36.8, 35.6, 34.5, 32.7, 27.95, 27.85, 21.4 ppm.

[3,4-Dihydroxy-3,4-isopropylidene-2-(adamantan-2-ylidene) cyclopentyl](phenyl) methyl acetate 54

PPTS (12 mg, 0.04 mmol) was added to a mixture of diol **3** (192 mg, 0.45 mmol) and DMP (0.62 mL, 10 mmol) in CH_2Cl_2 (2 mL), after stirring for 3h yielded **54** (167 mg, 88 %) as a pale yellow oil after purification by column chromatography on silica gel by eluting with 20 % PE and Et_2O .



R_f : 0.58 **(**PE: Et_2O = 75:25).

^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ7.30 (m, 5H), 5.68 (d, J = 4.5 Hz, 1H), 4.41 (d, J = 6.4 Hz, 1H), 3.56-3.45 (m, 2H), 3.03 (m, 1H), 2.94 (m, 1H), 2.21 (dd, J_1 = 14.0 Hz, J_2 = 7.4 Hz, 1H), 2.12 (s, 3H), 2.04-1.68 (m, 13H), 1.36 (s, 3H), 1.15 (s, 3H) ppm.

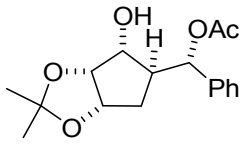
^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 170.0, 149.9, 138.1, 128.1, 127.8, 126.7, 125.6, 111.3, 79.5, 76.7, 47.1, 39.3, 39.1, 38.9, 38.6, 37.1, 35.3, 34.8, 33.0, 28.1, 28.0, 25.7, 21.4 ppm.

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{27}H_{34}O_4Na$:

445.23553; found: 445.2341.

Phenyl[2,3,4-trihydroxycyclopentyl-3-4-isopropylidene) methyl acetate 55

O_3 was bubbled through a solution of **54** (65 mg, 0.15 mmol) in CH_2Cl_2 (4 mL) at -78 °C until a blue color persists. The stirring was continued for 45 min, then, the solution was degassed under a flow of N_2. Me_2S (0.5 mL) was added and the reaction mixture was slowly warmed to rt, then the crude reaction mixture was concentrated under reduced pressure. The residue was dissolved in MeOH (5 mL), then $NaBH_4$ (10 mg, 0.25 mmol) was added. The mixture was stirred for 1h, then, water (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure yielded **55** (29 mg, 63 %) as a pale yellow oil after purification by column chromatography on silica gel by eluting with 18 % PE and Et_2O.



R_f : 0.23 **(**PE: Et_2O = 80:20).

^{1}H NMR (250 MHz, $CDCl_3$, TMS) : δ 7.35-7.26 (m, 5H), 5.94 (d, J = 7.3 Hz, 1H), 4.48 (t, J = 5.2 Hz, 1H), 4.40 (t, J = 5.7 Hz, 1H), 3.57 (dd, J_1 = 10.0 Hz, J_2 =5.7 Hz, 1H), 2.49-2.37 (m, 1H), 2.30 (bs, 1H), 2.10 (s, 3H), 1.64 (dd, J_1 = 14.1 Hz, J_2 =6.0 Hz, 1H), 1.50 (s, 3H), 1.31 (s, 3H), 1.17 (ddd, J_1 = 14.0 Hz, J_2 =13.1 Hz, J_3 = 4.8 Hz, 1H) ppm.

^{13}C NMR (62.5 MHz, $CDCl_3$, TMS) : δ 170.6, 138.7, 128.7, 128.5, 127.6, 110.8, 79.1, 77.6, 77.2, 75.6, 47.1, 30.5, 26.3, 24.5, 21.8 ppm.

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{17}H_{22}O_5Na$: 329.1365; found: 329.1360.

CHAPTER 3

Lewis Acid Catalyzed Desymmetrization of Pentafulvene Derived Diazanorbornenes: An Efficient Access to Aryl and Alkyl Cyclopentenyl Ethers

3.1. Introduction

Developing a novel methodology for the direct carbon-oxygen bond formation from commercially available and economically viable chemicals is a matter of serious concern in organic synthesis [Larock 1991, Yamamoto 1999, Togni 2001]. Nucleophilic addition reactions of aromatic and aliphatic alcohols to carbon carbon multiple bonds constitute one of the most remarkable transformations to generate the carbon-oxygen bond. Even though numerous methodologies were developed for this conversion, the use of organometallic catalysts remains less explored. In this scenario, the transition metal catalyzed addition of heteroatom-hydrogen (Het-H) bond across unsaturated systems is recognized as one of the most exciting and captivating subjects for further investigations. The nature of the hydrogen atom changes with electronegativity of the heteroatom, its oxidation state and the nature of the organic group attached. By considering these facts, the transition metal catalyzed addition system appears to be making a pronounced advancement in the synthesis of a wide variety of oxygen-containing heterocycles.

Ethers are the organic compounds having an oxygen atom attached to two similar or dissimilar alkyl or aryl groups. The general chemical formula for ethers is R-O-R, R-O-Ar or Ar-O-Ar, where R represents an alkyl group and Ar represents an aryl group. They are usually classified into two types based on substituents: symmetrical ethers (when two identical groups are appended to the oxygen atom) and unsymmetrical ethers (when two different groups are attached to the oxygen atom). Aryl alkyl ethers, aryl and alkyl ethers are present in many naturally occurring materials, medicinally important as well as pharmaceutically active compounds, and polymers [Czarnik 1996, Buchwald 2001].

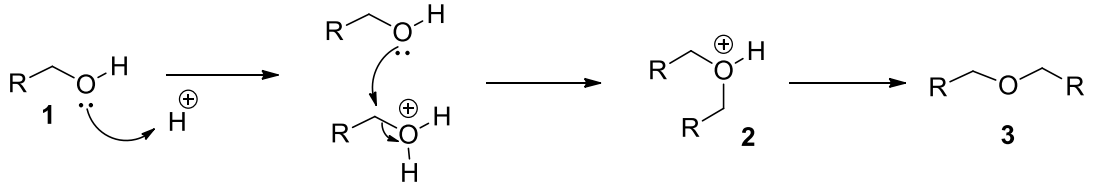
The conventional and most accepted method for the synthesis of ethers is the reaction between alcohols and alkyl or aryl halides. The direct coupling of alkenes with oxygen nucleophiles mediated either by bases or transition metal complexes is also accepted as a mild and efficient strategy for the preparation of various ethers. Over the past few decades, methods for the practical synthesis of diaryl ethers, alkyl aryl ethers and dialkyl ethers have attracted tremendous attention. As a notable advancement in this area, the present chapter discloses a facile methodology for the conversion of pentafulvene derived diazabicyclic olefins to aryl and alkyl cyclopentenyl ethers. Before going to the details, some of the conventional and transition metal catalyzed methods for the synthesis of ethers are briefly discussed in the following section.

3.2. General Methods for the Synthesis of Ethers

3.2.1. Conventional Methods of Preparation

3.2.1.1. Acid Catalyzed Condensation of Alcohols

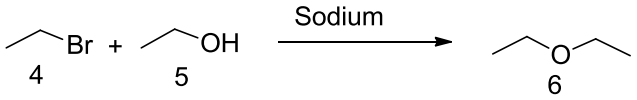
Nucleophilic addition of an alcohol to another alcohol in the presence of an acid like sulphuric acid at elevated temperature affords the corresponding ether [Traynelis 1964, Costa 1987, Tagliavini 1989]. This method is suitable only for the synthesis of symmetrical ethers and not for unsymmetrical ones. This is due to the fact that, two different alcohols will produce a mixture of products, causing their separation difficult (Scheme 3.1).



Scheme 3.1: Acid catalyzed condensation of alcohols

3.2.1.2. Williamson Ether Synthesis

In this method, initially the alcohol is treated with a strong base to form the alkoxide, which then react with an aliphatic compound having a good leaving group to afford the corresponding ether *via* an SN^2 reaction (Scheme 3.2). Suitable leaving groups (-X) include iodide, bromide, or sulfonates. However, this method is not suitable for the synthesis of aryl ethers from aryl halides [Williamson 1852, March 1995].



Scheme 3.2: Williamson ether synthesis

3.2.1.3. Alkoxymercuration Demercuration

Alkenes on reaction with alcohols in the presence of mercuric acetate produce the corresponding ethers thorugh alkoxymercuration [Brown 1970b] (Scheme 3.3). The reaction proceeds *via* the nucleophilic attack of the alcohol moiety on the initially fromed cyclic mercurinium ion. Finally, demercuration with sodium borohydride affords the final product.

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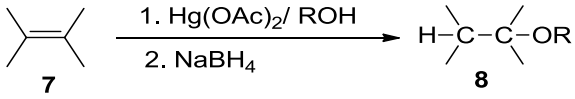
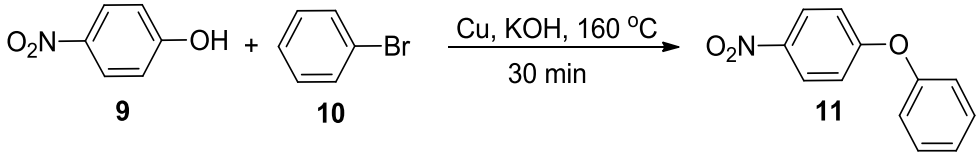


Scheme 3.3: Alkoxymercuration-demercuration

3.2.1.4. Ullmann Reaction

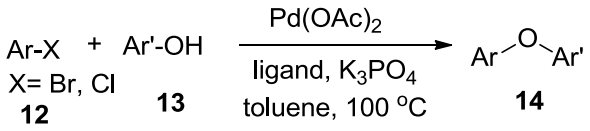
The Ullmann phenyl ether synthesis is a well-established methodology for ether synthesis, and is a variation of the classical Ullmann reaction [Lemaire 2002, Ma 2003, Stockland 2005, Chen 2006, Zhang 2011, Xu 2013]. The conventional method involves heating the aryl halides with potassium phenoxide at about 160-200 ^{o}C in the presence of a small quantity of copper powder and air (Scheme 3.4). Thereafter a large number of modifications were reported for the synthesis of ethers using transition metals including copper.



Scheme 3.4: Synthesis of ethers *via* Ullmann reaction

3.2.1.5. Buchwald Hartwig Coupling

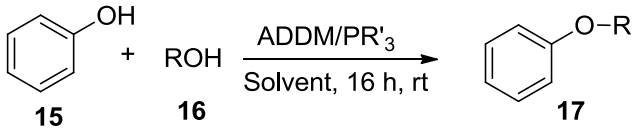
The Buchwald Hartwig coupling is a well-known strategy used for the synthesis of carbon–nitrogen bonds *via* the palladium catalyzed cross coupling of amines with aryl halides. A modified version of this coupling using aromatic alcohols instead of amines is reported and the method affords various aryl-aryl and aryl-alkyl ethers [Buchwald 1997, Buchwald 1999, Buchwald 2010] (Scheme 3.5).



Scheme 3.5: Synthesis of ethers *via* Buchwald Hartwig coupling

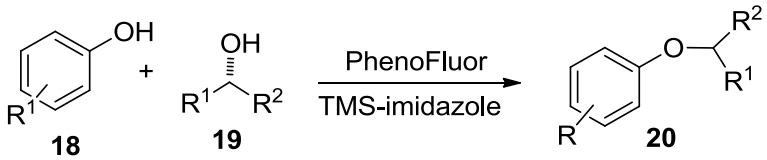
3.2.1.6. Mitsunobu Reaction

The substitution of primary or secondary alcohols with nucleophiles mediated by a redox combination of a trialkyl or triarylphosphine and a dialkyl azodicarboxylate is popularly known as the Mitsunobu reaction [Swamy 2009]. This reaction has been well employed in many synthetic procedures of organic chemistry and medicinal chemistry because of the scope, stereospecificity, and mild reaction conditions. However, the reaction is associated with one significant flaw: purification of the reaction mixture, as products are often contaminated with azo, hydrazide, and phosphine species from the co-reagents. In 2013, Fletcher *et al.* reported a modified version of Mitsunobu reaction using azodicarbonyldimorpholide as an effective and versatile Mitsunobu reagent for facilitating the dehydrative couplings of a variety of primary and secondary alcohols to afford corresponding ethers [Fletcher 2013] (Scheme 3.6).



Scheme 3.6: Synthesis of ethers *via* Mitsunobu reaction

As a successful modification of the conventional strategies of ether synthesis, Ritter and co-workers developed a new methodology for the synthesis of alkyl aryl ethers from phenols and primary/secondary alcohols using PhenoFluor (Scheme 3.7). This methodology has a large substrate scope and can produce ethers that are challenging to obtain with the conventional Mitsunobu reaction [Ritter 2015].



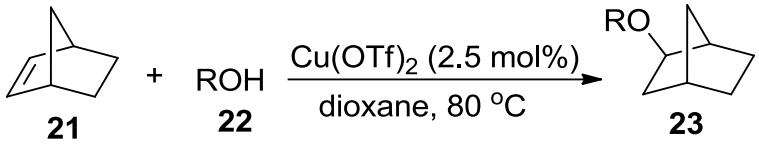
Scheme 3.7: Synthesis of ethers *via* improved Mitsunobu reaction

3.2.2. Transition Metal Catalyzed Reactions

The traditional copper-mediated Ullmann-type coupling requires stoichiometric amounts of copper, high temperature, and often proceeds with low/moderate yields which limited its application in industrial-scale synthesis. Therefore, significant efforts have been devoted in the past few decades towards the development of new methods for the preparation of diarylethers and aryl alkyl ethers under relatively mild conditions.

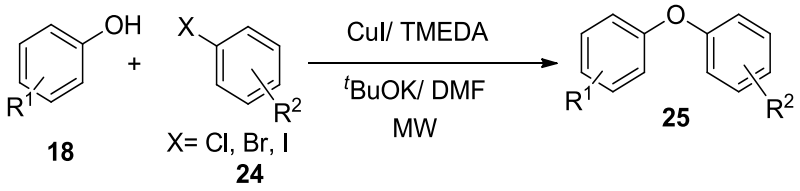
3.2.2.1. Copper Mediated Cross Coupling Reactions

In 2005, Hii and coworkers developed an efficient strategy for the addition of alcohols to norbornene catalyzed by $Cu(OTf)_2$ [Hii 2005] (Scheme 3.8). Here the catalyst is readily available, cheap, and does not require any pre-activation by silver salts. Both aromatic and aliphatic *O*-nucleophiles can be employed except sterically hindered alkyl alcohols. Later, an alternative method for this hydroalkoxylation was established by Zlotskii and co-workers by using HBeta Zeolite Catalyst [Raskil'dina 2015].



Scheme 3.8: Copper mediated cross coupling reaction

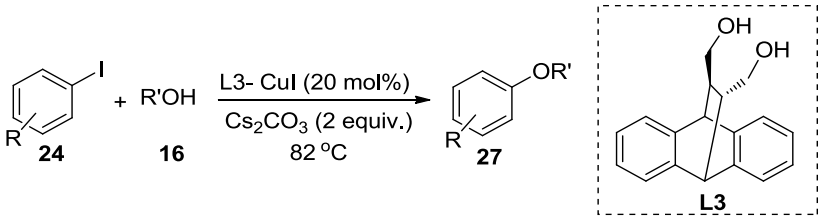
In 2007, Wan and co-workers reported a highly efficient method for the synthesis of diarylethers using CuI/TMEDA under microwave irradiation [Wan 2007] (Scheme 3.9). The reaction was found to be general for a wide range of activated and unactivated aryl bromides and iodides with phenols, by using cesium carbonate or potassium-*tertiary*-butoxide as base in anhydrous DMF or NMP.



Scheme 3.9: Efficient method for the synthesis of diarylether

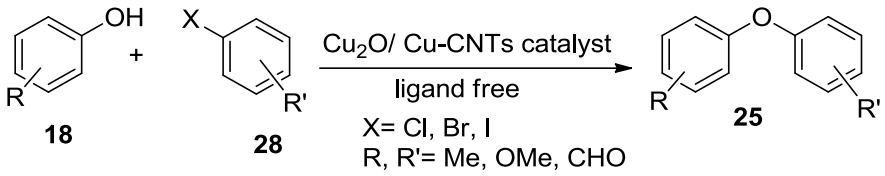
In 2009, Sekar and co-workers demonstrated the synthesis of diaryl ethers and alkyl aryl ethers from the corresponding aryl iodides/aryl bromides and phenols/alcohols *via* an Ullmann type coupling in the presence of a catalytic amount of (±)-diol L3-CuI complex

under very mild reaction condition [Sekar 2009] (Scheme 3.10). The presence of an electron donating group in phenol and electron-withdrawing group in aryl halide improved the yield of the coupling reaction.



Scheme 3.10: Synthesis of ethers from the corresponding aryl iodides/aryl bromides

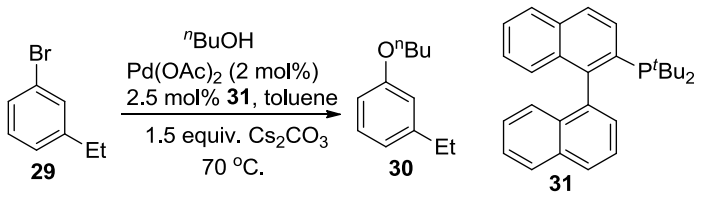
In 2013, Yang and co-workers reported the synthesis of various substituted diarylethers using heterogeneous reusable Cu_2O- and Cu-coated carbon nanotubes (Cu_2O/Cu-CNTs) as catalysts under ligand free conditions [Zhang 2013] (Scheme 3.11). The catalyst can be recovered by simple filtration of the reaction mixture and can be reused many times without any significant loss in catalytic activity.



Scheme 3.11: Synthesis of diarylethers using heterogeneous reusable Cu_2O- and Cu-coated carbon nanotubes

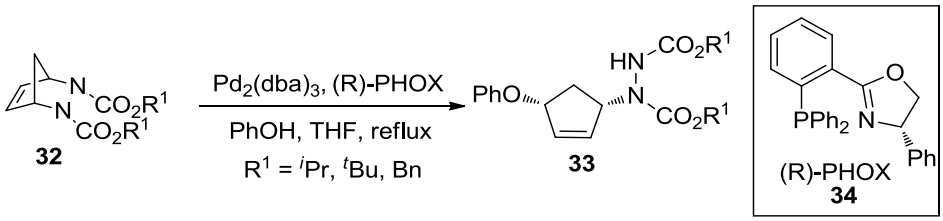
3.2.2.2. Palladium Catalyzed Cross Coupling Reactions

In 2001, Buchwald and co-workers demonstrated an efficient inter molecular palladium catalyzed reaction of aryl bromides and chlorides with primary alcohols affording corresponding aryl ethers [Buchwald 2001] (Scheme 3.12). The method works well for electron-deficient, neutral aryl halides and also for electron-rich aryl halides with an *ortho* alkyl substituent.



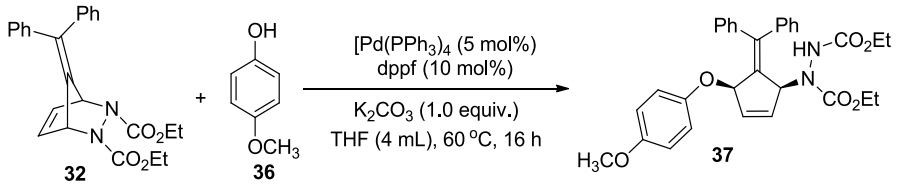
Scheme 3.12: Synthesis of ether *via* inter molecular palladium catalyzed reaction

In 2003, Micouin *et al.* reported the desymmetrisation of diazanorbornenes derived from diazodicarboxylates under acidic conditions by palladium catalyst in a totally regio- and diastereoselective manner [Micouin 2013]. They were successful in generating and trapping the allylic reactive species formed during rearrangement by using palladium (Scheme 3.13).



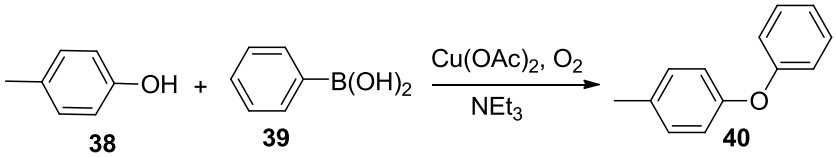
Scheme 3.13: Desymmetrisation of diazanorbornenes

Due to our interest in this area, we extended one of our protocols toward the ring opening of pentafulvene derived bicyclic hydrazines to access alkylidenecyclopentenes, a type of aryl ethers [Radhakrishnan 2010] (Scheme 3.14). For example, *cis*-3,5-disubstituted alkylidenecyclopentene **37** can be obtained by the palladium catalyzed desymmetrization of fulvene derived azabicyclic olefin with 4-methoxyphenol .



Scheme 3.14: Synthesis of *cis*-3,5-disubstituted alkylidenecyclopentene

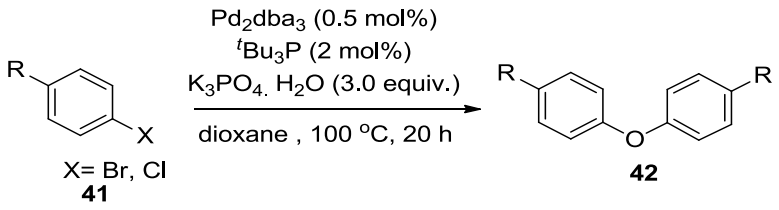
In 2006, Biffis *et al.* demonstrated that C–O coupling reactions between *p*-cresol and phenylboronic acid can be accomplished with a catalytic amount of $Cu(OAc)_2$ in presence of triethylamine under oxygen atmosphere [Biffis 2006] (Scheme 3.15).



Scheme 3.15: Reactions between *p*-cresol and phenylboronic acid

In 2007, Kwong *et al.* reported a simple synthesis of alkyl aryl ether *via* a one pot protocol from functionalized phenols and aryl halides by employing a commercially

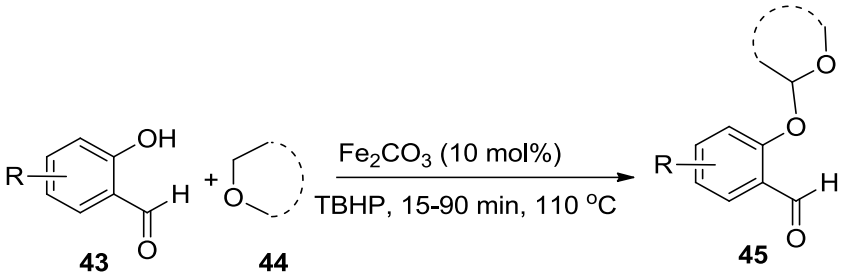
available palladium complex through the *in situ* formed phenoxide ion [Kwong 2007] (Scheme. 3.16). This new strategy delivered an improved alternative to etheration with the existing Pd-catalyzed coupling reactions



Scheme 3.16: Synthesis of alkyl aryl ether *via* a one pot protocol

3.2.2.3. Iron Catalyzed Cross Coupling Reactions

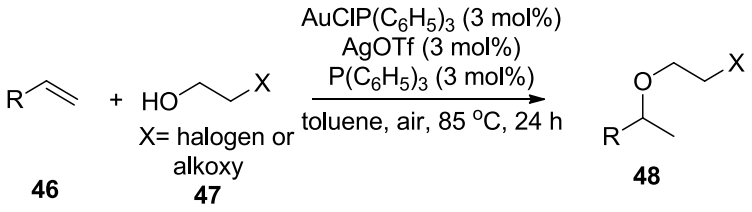
In 2014, Chang *et al.* reported a simple, efficient, and novel iron catalyzed protocol for the selective formation of ether linkage between salicylaldehydes and cyclic ethers without affecting the aldehyde group in the presence of a transition metal and an oxidant (Scheme 3.17) [Chang 2014]. This approach can be employed for the selective protection of hydroxyl groups by ethers.



Scheme 3.17: Iron catalyzed protocol for the selective formation of ether

3.2.2.4. Gold Catalyzed Cross Coupling Reactions

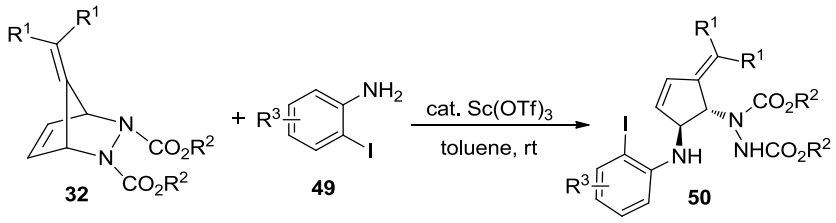
In 2009, Tokunaga and co-workers reported an intermolecular hydroalkoxylation of unactivated olefins catalyzed by gold(I) catalyst and electron deficient phosphine ligands [Tokunaga 2009] (scheme 3.18).



Scheme 3.18: Gold catalyzed protocol for the selective formation of ether

3.3. Background to the Present Work

Despite the availability of methods, synthesis of aryl and alkyl ethers often requires harsh reaction conditions and only a limited number of procedures have been reported under milder conditions. In 2013, our group reported the first Lewis acid catalyzed intermolecular ring opening of pentafulvene derived diazanorbornenes with aryl amines [Radhakrishnan 2013a]. Through this desymmetrization strategy, we have synthesized *trans*-3,4-diubstituted alkylidene cyclopentenes by trapping the transient allylic cation with 2-iodoanilines (Scheme 3.19). Encouraged by this result, we presumed that an appropriate extension of the current methodology would introduce varieties of functionalities to the alkylidene cyclopentene core. Thus by substituting 2-iodoaniline with other nucleophiles like aromatic/aliphatic alcohols etc. the method can provide access to various aryl/alkyl cyclopentenyl ethers and other analogs.



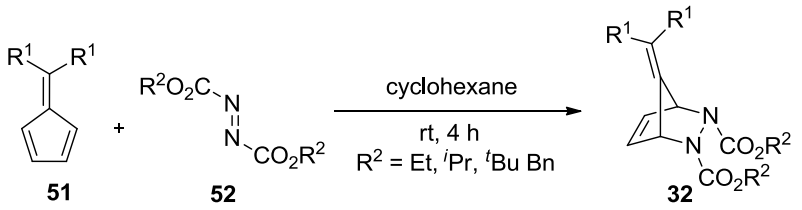
Scheme 3.19: Synthesis of alkylidene cyclopentene

Herein we discuss our efforts to synthesize aryl and alkyl cyclopentenyl ethers *via* a Lewis acid catalyzed ring opening of pentafulvene derived diazanorbornenes with aryl and aliphatic alcohols.

3.4. Results and Discussion

3.4.1. Synthesis of Pentafulvene Derived Diazanorbornenes

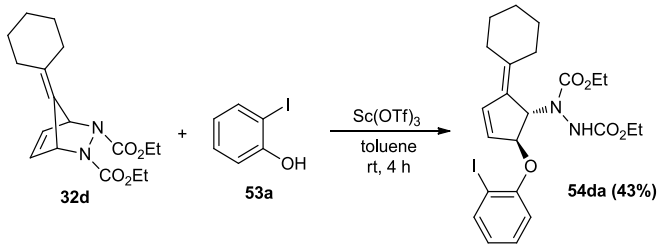
The Diels-Alder cycloaddition reaction [Diels 1925] of pentafulvene with dialkylazodicarboxylates furnished diazanorbornenes in excellent yields (Scheme 3.20).



Scheme 3.20: Synthesis of pentafulvene derived diazanorbornenes

3.4.2. Synthesis of Diazanorbornene Derived of Aryl Ethers

We initiated our studies using 2-iodo phenol as the nucleophile for the Lewis acid catalyzed ring opening reaction. In an initial attempt, the bicyclic alkene **32d** was treated with *o*-iodophenol **53a** in the presence of $Sc(OTf)_3$ in toluene at room temperature, under the optimized reaction conditions employed in the case of 2-iodoanilines [Radhakrishnan 2013a]. The reaction afforded the expected aryl cyclopentenyl ether **54da** in 43 % yield (Scheme 3.21).



Scheme 3.21: Synthesis of diazanorbornene derived of aryl ethers

The structure of the product **54da** was elucidated by various spectroscopic analyses. The IR spectrum showed a characteristic carbonyl absorption peak at 1718 cm^{-1} and an absorption indicative of the -NH stretching at 3385 cm^{-1}. In the ^1H NMR spectrum (Figure 4.4), the aromatic protons appeared separately as four signals in the region δ 7.74- 6.69 ppm. The -NH protons resonated as a singlet at δ 6.85 ppm. The olefinic protons were found to resonate as multiplet in the region δ 6.73- 6.69 and doublet at δ 5.95 ppm. The proton on ring

C-3 appeared as a doublet at δ 5.48 ppm. The proton on the carbon bearing the hydrazine moiety C-4 was spotted as broad singlet at δ 5.76 ppm. All other signals were in agreement with the proposed structure.

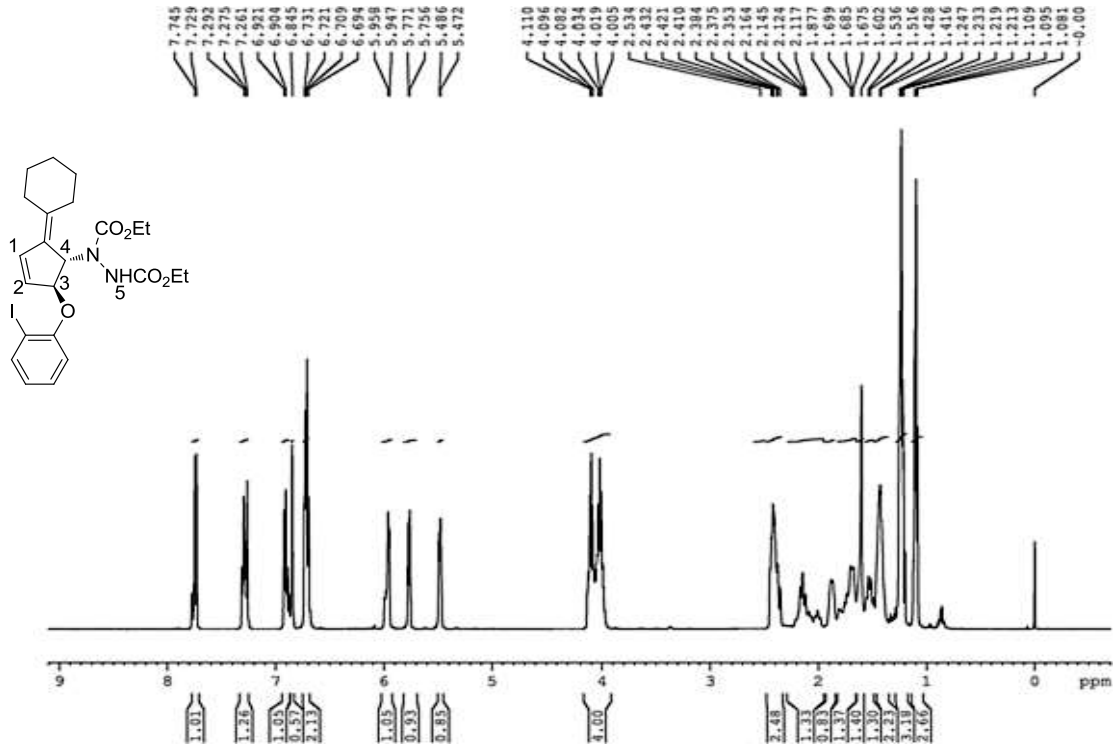


Figure 3.1: ^{1}H NMR spectrum of compound **54da**

^{13}C NMR spectroscopy of **54da** (Figure 4.5) positioned the carbonyl signals at δ 156.0 and 155.3 ppm. The signals of the olefinic carbons were found to resonate at δ 129.7 and δ 123.5 ppm. The carbon C-4 bearing the hydrazine moiety was spotted at δ 58.4 ppm, whereas the carbon on the ring at C-3 was observed at δ 80.6 ppm. The intense peaks at δ 14.4 and 14.6 ppm were assigned to methyl carbons of the carboethoxy group. Further evidence for the structure was obtained from mass spectral analysis which showed the molecular ion peak at *m/z* 563.10076 $[M+Na]^{+}$.

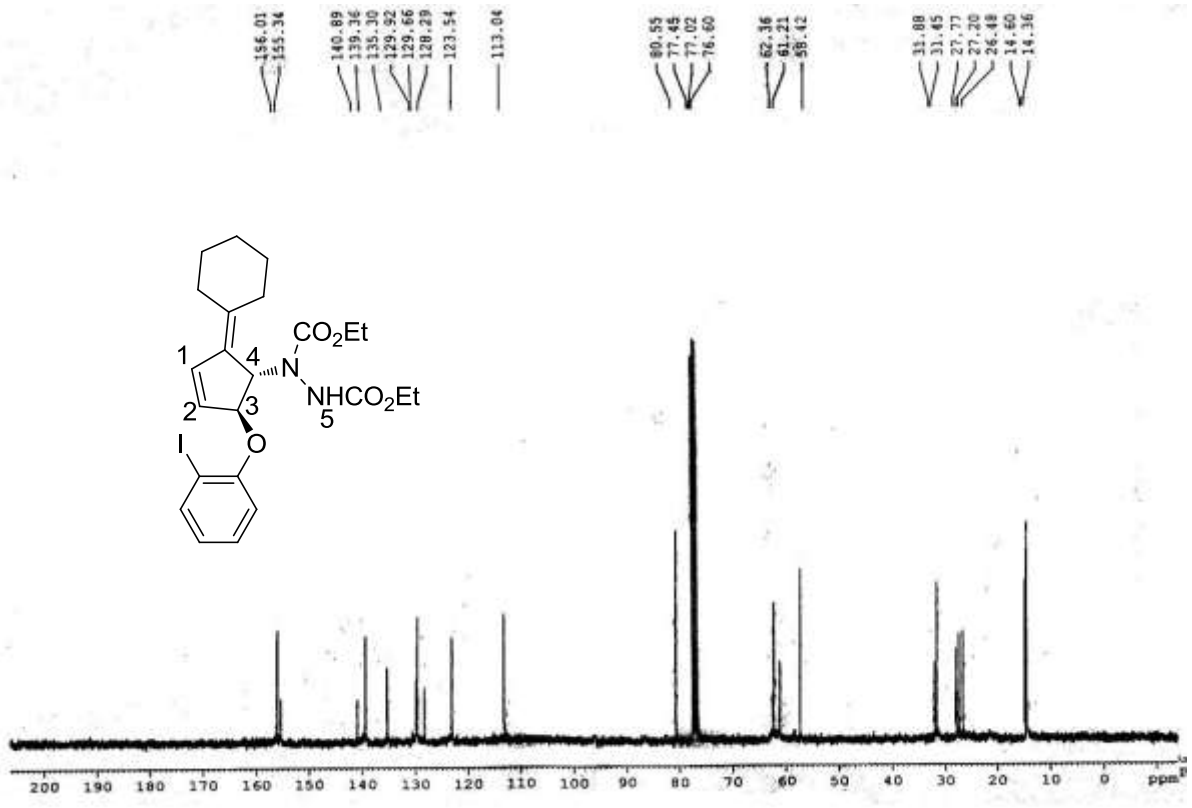
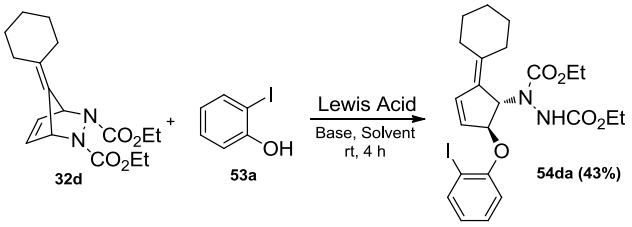


Figure 3.2: ^{13}C NMR spectrum compound **54da**

Table 3.1 summarizes our efforts toward optimizing various reaction parameters. AgOTf was found to be the most effective Lewis acid and acetonitrile as the suitable solvent for carrying out this chemistry. Further experiments revealed that the reaction gave better yields under basic conditions and Na_2CO_3 was found optimal compared to K_2CO_3, Cs_2CO_3 and Et_3N. (Table 3.1, entry 16). Gratifyingly, we optimized the reaction conditions as 3 equiv. alkene, 1 equiv. 2-iodophenol , 2 mol% Ag(OTf) and 1.5 equiv. Na_2CO_3 in CH_3CN at room temperature.

Table 3.1: Screening of various reaction parameters for the best reaction condition

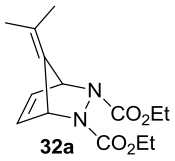
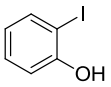
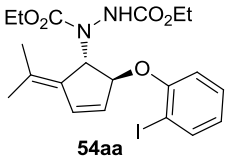
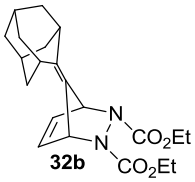
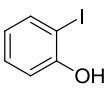
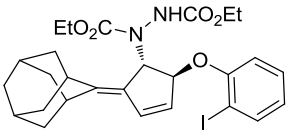
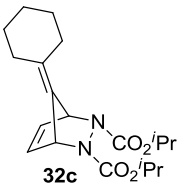
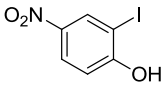
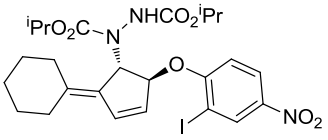
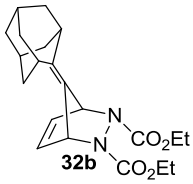
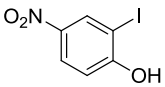
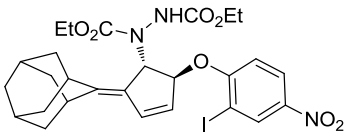
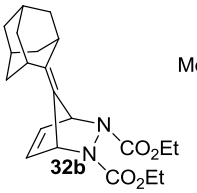
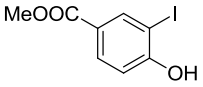
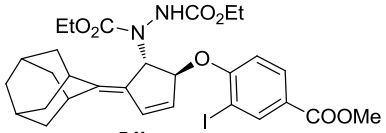
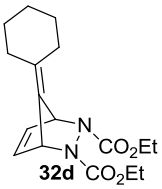
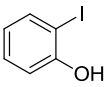
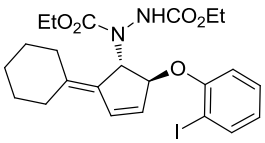
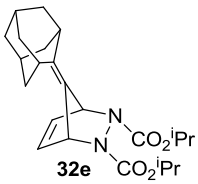
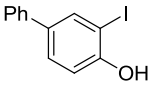
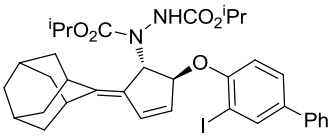


Entry	Lewis acid	Solvent	Base	Yield
1	$Sc(OTf)_3$	toluene	—	43%
2	$Yb(OTf)_3$	toluene	—	24%
3	$Cu(OTf)_2$	toluene	—	29%
4	$Sn(OTf)_2$	toluene	—	16%
5	$BF_3.Et_2O$	toluene	—	25%
6	$B(C_6F_5)_3$	toluene	—	18%
7	AgOTf	toluene	—	52%
8	AgOTf	DMF	—	20%
9	AgOTf	acetone	—	20%
10	AgOTf	DCM	—	17%
11	AgOTf	THF	—	37%
12	AgOTf	CH_3CN	—	54%
13	AgOTf	CH_3CN	Cs_2CO_3	20%
14	AgOTf	CH_3CN	K_2CO_3	52%
15	AgOTf	CH_3CN	Et_3N	30%
16	AgOTf	CH_3CN	Na_2CO_3	63%

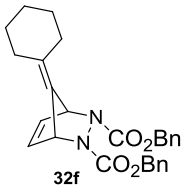
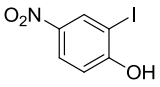
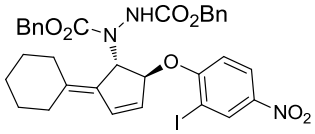
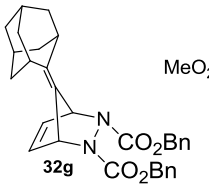
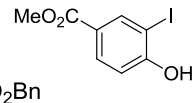
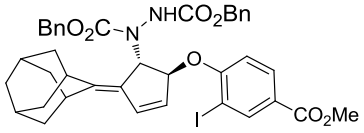
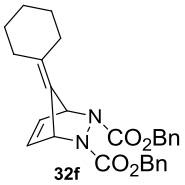
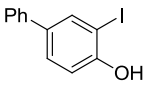
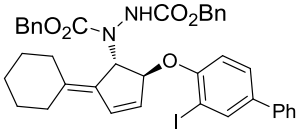
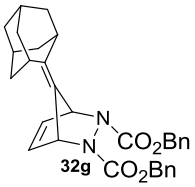
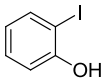
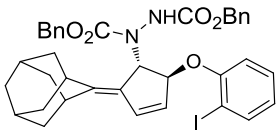
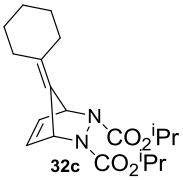
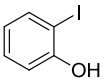
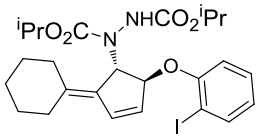
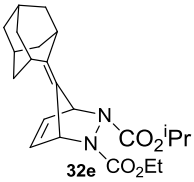
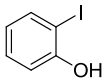
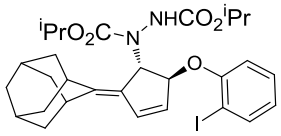
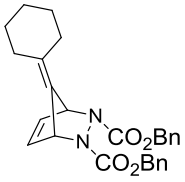
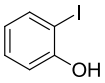
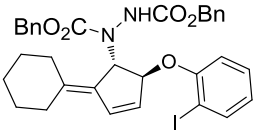
Reaction conditions: alkene (3 equiv.), 2-iodophenol (1 equiv.), catalyst (2 mol %), base (1.5 equiv.), solvent (2 mL), rt, 4 h

With the optimal reaction conditions in hand, we studied the Lewis acid catalyzed ring-opening of various pentafulvene derived diazabicyclic olefins with different 2-iodophenols (Table 3.2). It is to be noted that various 2-iodophenol bearing functional groups such as NO_2, CO_2Me and phenyl were successfully employed in the present strategy and the corresponding aryl cyclopentenyl ether or functionalized alkylidenecyclopentenes were formed in moderate to good yields.

Table 3.2: Generality of the methodology

Entry	Diazanorbornene	2-Iodophenol	Product	Yield (%)
1	 **32a**	 **53a**	 **54aa**	**55**
2	 **32b**	 **53a**	 **54ba**	**47**
3	 **32c**	 **53b**	 **54cb**	**45**
4	 **32b**	 **53b**	 **54bb**	**51**
5	 **32b**	 **53c**	 **54bc**	**46**
6	 **32d**	 **53a**	 **54da**	**63**
7	 **32e**	 **53d**	 **54ed**	**27**

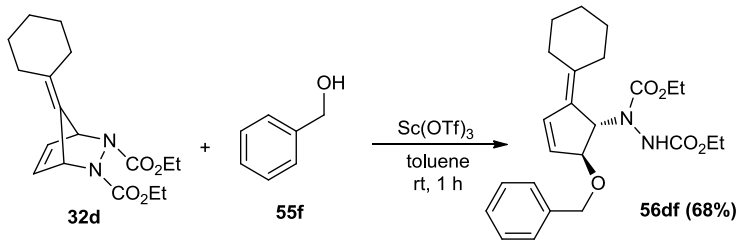
Reaction conditions: diazanorbornene (3 equiv.), 2-iodophenol (1 equiv.), AgOTf (2 mol%), Na_2CO_3 (1.5 equiv.), CH_3CN (2 mL), rt, 4 h

Entry	Diazanorbornene	2-Iodophenol	Product	Yield (%)
8	 **32f**	 **53b**	 **54fb**	42
9	 **32g**	 **53c**	 **54gc**	47
10	 **32f**	 **53d**	 **54fd**	40
11	 **32g**	 **53a**	 **54ga**	28
12	 **32c**	 **53a**	 **54ca**	56
13	 **32e**	 **53a**	 **54ea**	49
14	 **32f**	 **53a**	 **54fa**	52

Reaction conditions: diazanorbornene (3 equiv.), 2-iodophenol (1 equiv.), AgOTf (2 mol%), Na_2CO_3 (1.5 equiv.), CH_3CN (2 mL), rt, 4 h

3.4.3. Synthesis of Diazanorbornene Derived of Alkyl Ethers

In the next stage of our investigation, we examined the scope of the present strategy with nucleophiles such as benzylic and aliphatic alcohols. We initiated our studies with the reaction of diazabicyclic olefin **32d** and benzyl alcohol **55f** in the presence of $Sc(OTf)_3$ in toluene at room temperature for 1 hour and the reaction afforded the ring opened product **56df** in 68 % yield (Scheme 3.22).



Scheme 3.22: Synthesis of diazanorbornene derived of alkyl ether

The structure of the product **56df** was elucidated by different spectroscopic analyses. The IR spectrum showed characteristic carbonyl absorption at 1711 cm^{-1} and the absorption indicative of the -NH stretching at 3296 cm^{-1}. In the ^1H NMR spectrum (Figure 3.3), the -NH protons resonated as multiplet in the region δ 6.05- 5.94 ppm. The aromatic protons were resonated in the region δ 7.36- 7.24 ppm. The olefinic protons were found to resonate as two distinct peaks, a doublet at δ 6.60 and a singlet δ 5.84 ppm. The proton on the ring C-3, appeared as a multiplet in the range δ 5.24- 5.10 ppm. The proton on the carbon bearing the hydrazine C-4 appeared as a multiplet in the range δ 4.62- 4.60 ppm. All other signals were in agreement with the proposed structure.

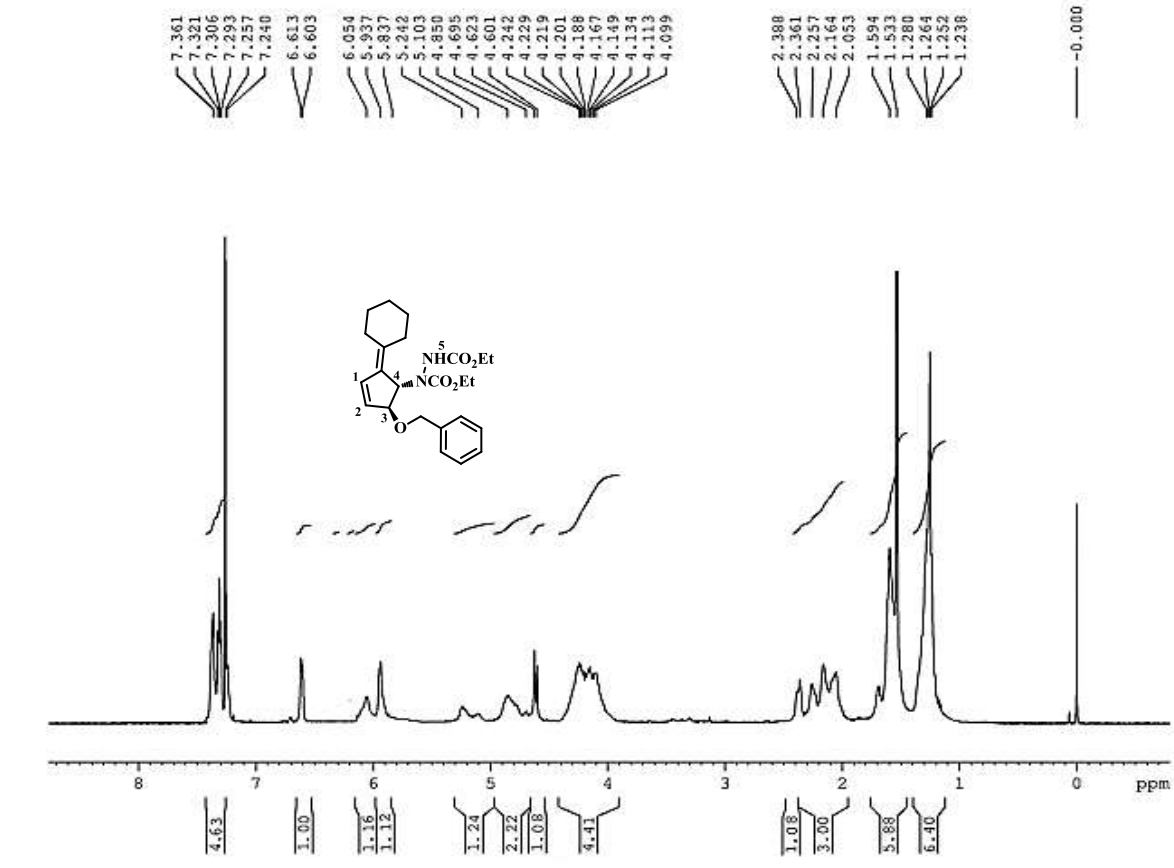


Figure 3.3: ^{1}H NMR spectrum of compound **56df**

^{13}C NMR spectroscopy of **56df** (Figure 3.4) positioned the carbonyl signals at δ 156.7 and 155.1 ppm. The signals of the olefinic carbons were found to resonate at δ 134.3 and δ 129.9 ppm. The carbon bearing the hydrazine C-4 was spotted at δ 53.3 ppm whereas the ring carbon at C-3 was observed at δ 88.1 ppm. The strong signal in the region δ 14.6- 14.4 ppm was assigned to the methyl carbons of the ester groups. Further evidence for the structure was obtained from mass spectral analysis which showed the molecular ion peak at *m/z* 451.22040 $[M+Na]^{+}$.

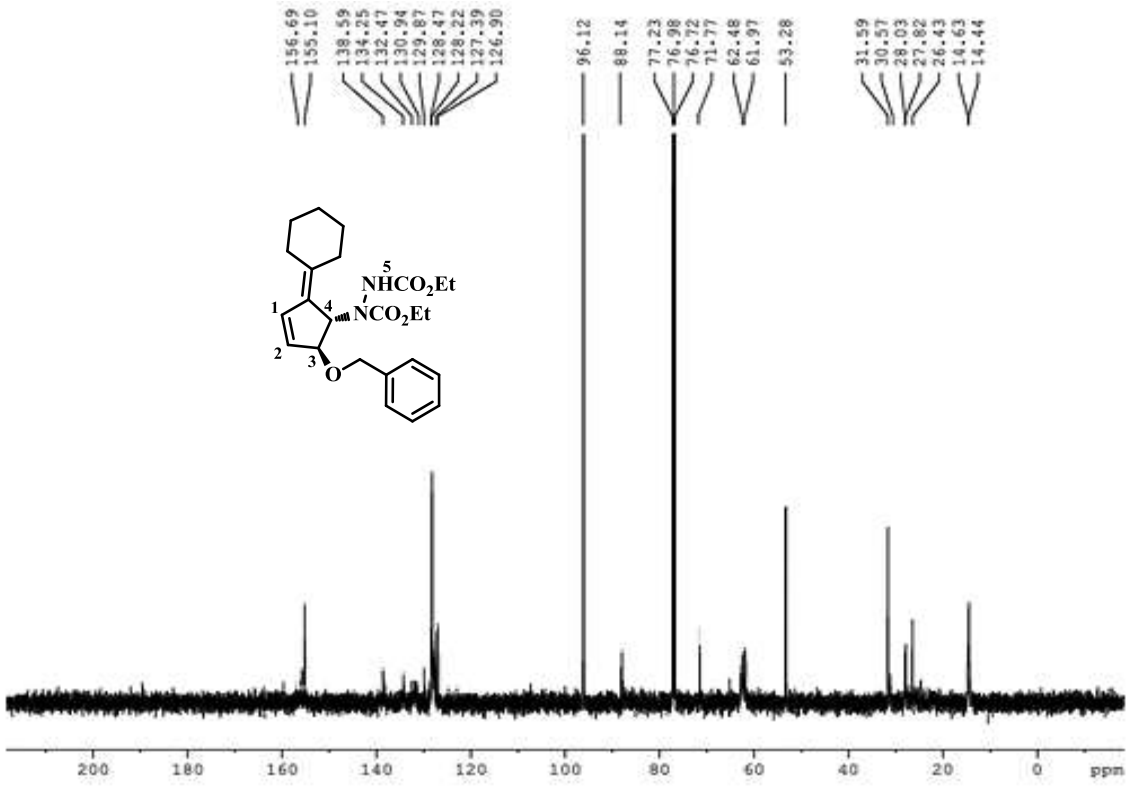
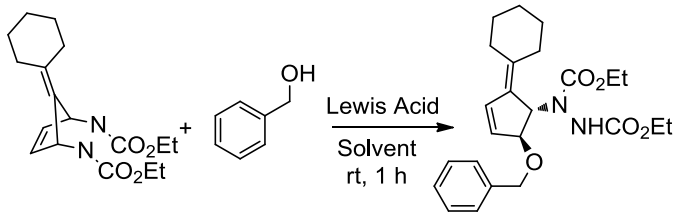


Figure 3.4: ^{13}C NMR spectrum of compound **56df**

After obtaining the exciting result with benzylic alcohol, we carried out detailed optimization studies with various Lewis acids, solvents and $Cu(OTf)_2$ in toluene was found to be the most suitable catalyst system for the ring-opening of bicyclic olefins with alcohols (entry 5).

Table 3.3: Optimization of the reaction conditions

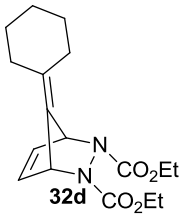
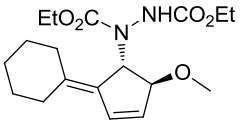
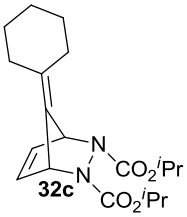
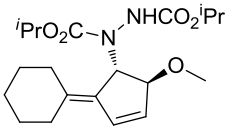
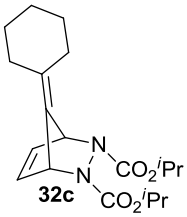
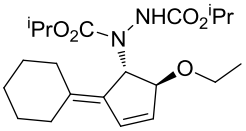
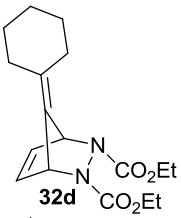
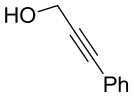
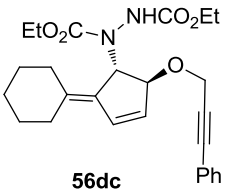
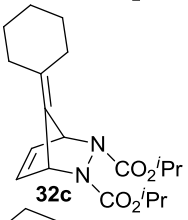
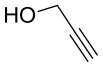
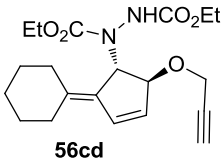
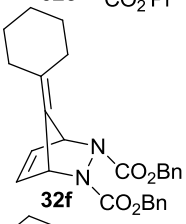
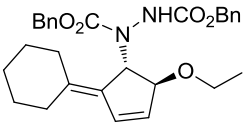
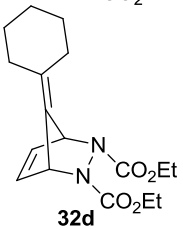
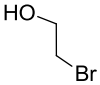
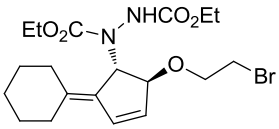


Entry	Lewis acid	Solvent	Yield (%)
1	$Sc(OTf)_3$	toluene	68
2	$Yb(OTf)_3$	toluene	33
3	$Zn(OTf)_2$	toluene	43
4	$La(OTf)_3$	toluene	66
5	$Cu(OTf)_2$	toluene	72
6	$Fe(OTf)_3$	toluene	35
7	Ag(OTf)	toluene	45
8	$Cu(OTf)_2$	THF	29
9	$Cu(OTf)_2$	CH_3CN	NR
10	$Cu(OTf)_2$	DCM	NR

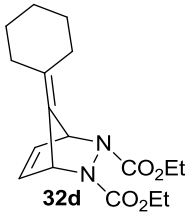
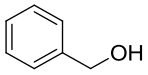
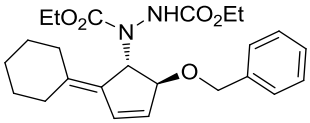
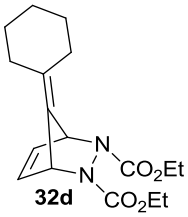
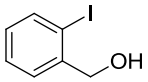
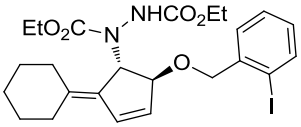
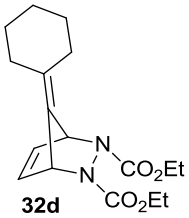
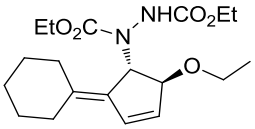
Reaction conditions: diazanorbornene (3 equiv.), alcohol (1 equiv.), $Cu(OTf)_2$ (5 mol%), toluene (2 mL), rt, 1 h

The reaction was found to be general for a variety of benzylic as well as aliphatic alcohols. The reaction with 2-iodobenzyl alcohol produced the desired alkylidenecyclopentene **56dg** in 55% yield. Under the optimized reaction condition, the reaction of bicyclic olefins proceeded smoothly with aliphatic alcohols such as methanol, ethanol and propargyl alcohol and the corresponding alkyl cyclopentenyl ether or alkylidenecyclopentene derivatives are obtained in moderate to good yields (Table 3.3).

Table 3.4: Reaction of aliphatic alcohols with bicyclic olefins

Entry	Diazanorbornene	Alcohol	Product	Yield (%)
1	 **32d**	H_3C-OH **55a**	 **56da**	**29**
2	 **32c**	H_3C-OH **55a**	 **56ca**	**31**
3	 **32c**	 **55b**	 **56cb**	**30**
4	 **32d**	 **55c**	 **56dc**	**27**
5	 **32c**	 **55d**	 **56cd**	**21**
6	 **32f**	 **55b**	 **56fb**	**75**
7	 **32d**	 **55e**	 **56de**	**26**

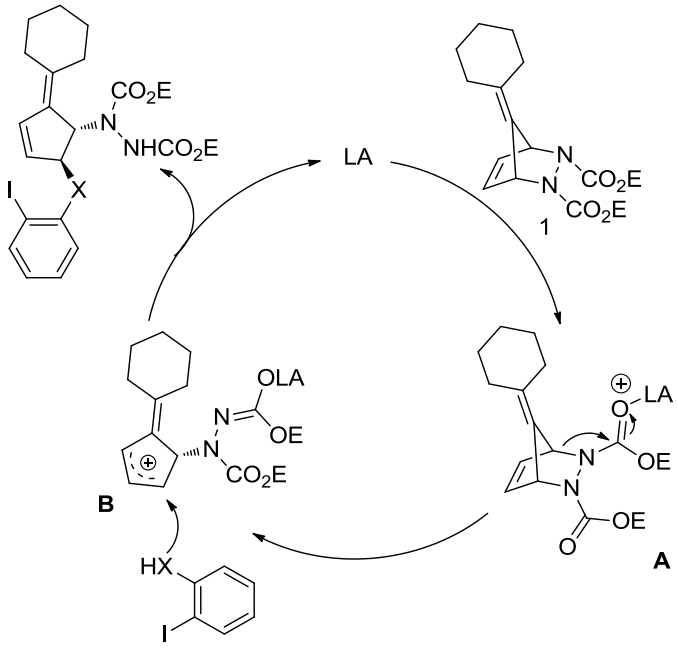
Reaction conditions: diazanorbornene (3 equiv.), alcohol (1 equiv.), $Cu(OTf)_2$ (5 mol%), toluene (2 mL), rt, 1 h

Entry	Diazanorbornene	Alcohol	Product	Yield (%)
8	 **32d**	 **55f**	 **56df**	**72**
9	 **32d**	 **55g**	 **56dg**	**55**
10	 **32d**	 **55b**	 **56db**	**24**

Reaction conditions: diazanorbornene (3 equiv.), alcohol (1 equiv.), $Cu(OTf)_2$ (5 mol%), toluene (2 mL), rt, 1 h

3.5. Mechanistic Consideration

Based on these results, we proposed a plausible mechanism for the Lewis acid catalyzed ring-opening of diazabicyclic olefins (Scheme 3.23). In the first step, Lewis acid is co-ordinated to the oxygen of the carbonyl group of diazabicyclic olefin. The subsequent cleavage of C-N bond leads to a transient allylic cation species **B**. Attack of the incoming nucleophile from the less hindered face furnished the corresponding product, *trans*-1,2-disubstituted alkylidenecyclopentene.



Scheme 3.23: Mechanistic Pathway

3.6. Conclusion

We have demonstrated a Lewis acid catalyzed stereoselective ring-opening of pentafulvene derived diazabicyclic olefins by using various substituted aromatic and aliphatic alcohols to access *trans*-1,2 disubstituted alkylidenecyclopentenes. We have proposed an easy way to synthesis aryl and alkyl cyclopentenyl ethers.

3.7. Experimental Details

General information about the experiments is given in section 2.9.1 of Chapter 2a.

3.7.1. General Procedure for the Preparation of Pentafulvene Derived Diazabicyclic Olefins

Pentafulvenes were synthesized by the base catalyzed condensation between the corresponding ketones and cyclopentadiene. The ketone (1 equiv.) was dissolved in methanol and cooled in an ice bath. cyclopentadiene (2 equiv.) was added, followed by the slow addition of pyrrolidine (1.8 equiv.). The reaction mixture was stirred for 4 h at 0 ^{o}C – rt. The excess base was neutralized by adding acetic acid drop wise to the ice-cooled reaction mixture. Cold water was then added and the product was extracted with diethyl ether. The

combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude pentafulvene was purified by silica gel column chromatography using hexane as the eluent.

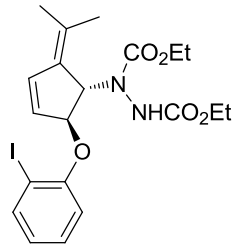
The pentafulvene (1.1 equiv.) was dissolved in cyclohexane at room temperature, followed by the addition of dialkylazodicarboxylate (1 equiv.). The reaction mixture was stirred for 3 h and the product was used for further reactions without purification.

3.7.2. General Procedure for the Lewis Acid Catalyzed Reaction of Pentafulvene Derived Bicyclic Hydrazines with *2*-Iodophenol

A mixture of pentafulvene derived diazabicyclic olefin (3.0 eqiuv.), *o*-iodophenol (1.0 equiv.), Ag(OTf) (2 mol%) and Na_2CO_3 (1.5 equiv) were weighed in a schlenk tube and degassed for 10 minutes. Dry acetonitrile (2 mL) was added and the reaction mixture was purged with argon and allowed to stir at room temperature for 4 hours. The solvent was evaporated *in vacuo* and the residue on silica gel (100-200 mesh) column chromatography yielded *trans*-3,4-disubstituted alkylidene cyclopentene.

Diethyl 1-2-(2-iodophenoxy)-5-(propan-2-ylidene) cyclopent-3-enyl)hydrazine-1,2-dicarboxylate (54aa)

Following the general procedure (Section 3.7.2), the reaction of pentafulvene derived diazanorbornene **32a** (189 mg, 0.68 mmol) and 2-iodophenol **53a** (50 mg, 0.23 mmol), in dry acetonirile (2 mL) in the presence of Ag(OTf) (1 mg, 0.005 mmol) and Na_2CO_3 (36 mg, 0.34 mmol) at room temperature for 4 h yielded **54aa** (63 mg, 55 %) as a yellow viscous liquid upon purification by column chromatography (15 % ethyl acetate-hexane).



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

IR (Neat) ν_{max}: 3357, 3064, 2958, 2921, 2854, 1715, 1578, 1467, 1411, 1379, 1307, 1280, 1236, 1167, 1122, 1058, 752 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.75 (d, *J* = 7.5 Hz, 1H), 7.30-7.27 (m, 1H), 6.93-6.87 (m, 2H), 6.73-6.68 (m, 2H), 5.95

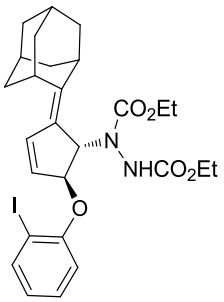
(d, *J* = 5.5 Hz, 1H), 5.74 (d, *J* = 7.0 Hz, 1H), 5.48 (d, *J* = 7.0 Hz, 1H), 4.12-4.02 (m, 4H), 1.95-1.84 (m, 3H), 1.84 (s, 3H), 1.24-1.11 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.1, 155.9, 139.3, 135.8, 133.3, 132.6, 129.6, 128.1, 123.0, 113.0, 80.6, 62.4, 61.2, 57.8, 21.7, 21.1, 14.5 ppm.

HRMS (ESI): Calcd for $C_{20}H_{25}IN_2O_5Na$ $[M+Na]^+$: 523.07058; Found: 523.07117.

Preparation of compound 54ba

Following the general procedure (Section 3.7.2), the reaction of pentafulvene derived diazanorbornene **32b** (262 mg, 0.68 mmol) and 2-iodophenol **53a** (50 mg, 0.23 mmol), in dry acetonirile (2 mL) in the presence of Ag(OTf) (1 mg, 0.005 mmol) and Na_2CO_3 (36 mg, 0.34 mmol) at room temperature for 4 h yielded **54ba** (65 mg, 47 %) as colourless viscous liquid upon purification by column chromatography (15 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3355, 3063, 2915, 2852, 1715, 1577, 1467, 1410, 1379, 1303, 1219, 1124, 1058, 1022, 73, 873, 746 cm^{-1}.

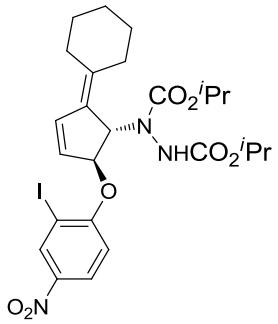
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.77-7.73 (m, 1H), 7.31-7.28 (m, 1H), 6.93- 6.88 (m, 1H), 6.85 (s, 1H), 6.73-6.70 (m, 2H), 5.93 (d, *J* = 5.5 Hz, 1H), 5.74 (d, *J* = 7.5 Hz, 1H), 5.49 (d, *J* = 7.0 Hz, 1H), 4.15-3.95 (m, 4H), 2.89 (d, *J* = 15.5 Hz, 2H), 2.43 (d, *J* = 12.0 Hz, 1H), 1.97-1.72 (m, 11H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.08 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 156.0, 155.1, 148.6, 139.3, 134.8, 129.6, 129.1, 127.8, 126.1, 123.0, 113.0, 80.8, 62.3, 61.1, 57.1, 40.1, 40.0, 38.2, 37.3, 37.2, 35.1, 35.0, 28.4, 28.0, 14.6, 14.3 ppm.

HRMS (ESI): Calcd for $C_{27}H_{33}IN_2O_5Na$ $[M+Na]^+$: 615.13318; Found: 615.13287.

Diisopropyl 1-(2-cyclohexylidene-5-(2-iodo-4-nitrophenoxy) cyclopent-3-enyl) hydrazine-1,2-dicarboxylate (54cb)

Following the general procedure (Section 3.7.2), the reaction of pentafulvene derived diazanorbornene **32c** (197 mg, 0.57 mmol) and 2-iodophenol **53b** (50 mg, 0.19 mmol), in dry acetonirile (2 mL) in the presence of Ag(OTf) (1 mg, 0.004 mmol) and Na_2CO_3 (30 mg, 0.29 mmol) at room temperature for 4 h yielded **54cb** (52 mg, 45 %) as yellow viscous liquid upon purification by column chromatography (15 % ethyl acetate-hexane)



R_f = 0.69 (hexane/ethyl acetate, 7:3).

IR (Neat) ν_{max}: 3376, 3062, 2921, 2853, 1757, 1710, 1657, 1577, 1517, 1468, 1411, 1380, 1341, 1305, 1267, 1216, 1119, 1037, 894, 740 cm^{-1}.

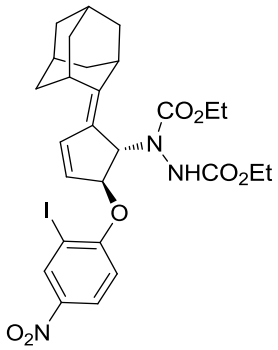
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 8.64 (d, J = 2.0 Hz, 1H), 8.24 (m, 1H), 6.99 (d, J = 9.5 Hz, 1H), 6.79 (d, J = 5.5 Hz, 1H), 6.53 (s, 1H), 5.94-5.91 (m, 1H), 5.81 (d, J = 7.0 Hz, 1H), 5.57 (d, J = 6.5 Hz, 1H), 4.85-4.82 (m, 1H), 4.73-4.70 (m, 1H), 2.45-2.43 (m, 2H), 1.90-1.42 (m, 8H), 1.29-1.16 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 160.9, 155.1, 154.8, 142.2, 141.9, 136.3, 134.8, 129.5, 126.9, 125.6, 111.7, 82.0, 70.1, 68.9, 56.8, 31.9, 31.5, 27.8, 27.2, 26.4, 22.1, 22.0, 21.8 ppm.

HRMS (ESI): Calcd for $C_{25}H_{32}IN_3O_7Na$ $[M+Na]^+$: 636.11826; Found: 636.11866.

Preparation of compound 54bb

Following the general procedure (Section 3.7.2), the reaction of pentafulvene derived diazanorbornene **32b** (211 mg, 0.57 mmol) and 2-iodophenol **53b** (50 mg, 0.19 mmol), in dry acetonirile (2 mL) in the presence of Ag(OTf) (1 mg, 0.004 mmol) and Na_2CO_3 (30 mg, 0.29 mmol) at room temperature for 4 h yielded **54bb** (63 mg, 51 %) as yellow viscous liquid upon purification by column chromatography (15 % ethyl acetate-hexane)



R_f = 0.69 (hexane/ethyl acetate, 7:3).

IR (Neat) ν_{max}: 3362, 2909, 2851, 1759, 1719, 1591, 1481, 1438, 1407, 1386, 1301, 1257, 1215, 1116, 1048, 875, 761, 668, 611, 556 cm^{-1}.

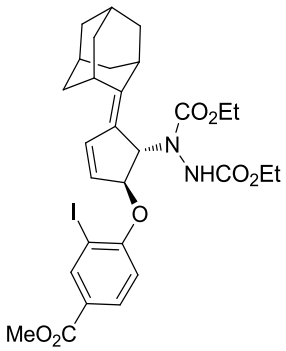
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 8.65 (s, 1H), 8.25 (d, *J* = 9.5 Hz, 1H), 6.99 (d, *J* = 9.0 Hz, 1H), 6.79 (d, *J* = 5.5 Hz, 1H), 6.62 (s, 1H), 5.89 (d, *J* = 5.5 Hz, 1H), 5.78 (d, *J* = 7 Hz, 1H), 5.58 (d, *J* = 7.0 Hz, 1H), 4.14-3.94 (m, 4H), 2.88 (s, 2H), 2.42 (d, *J* = 12.0 Hz, 1H), 1.98-1.80 (m, 11H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.08 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 160.4, 155.2, 153.2, 142.6, 140.4, 136.3, 134.9, 133.9, 126.3, 125.7, 82.1, 62.5, 61.4, 59.1, 57.1, 40.1, 38.6, 37.1, 35.2, 28.3, 27.9, 14.6, 14.3, 10.4 ppm.

HRMS (ESI): Calcd for $C_{27}H_{32}IN_3O_7Na$ $[M+Na]^+$: 660.11826; Found: 660.11799.

Preparation of compound 54bc

Following the general procedure (Section 3.7.2), the reaction of pentafulvene derived diazanorbornene **32b** (200 mg, 0.54 mmol) and 2-iodophenol **53c** (50 mg, 0.18 mmol), in dry acetonirile (2 mL) in the presence of Ag(OTf) (1 mg, 0.004 mmol) and Na_2CO_3 (29 mg, 0.27 mmol) at room temperature for 4 h yielded **54bc** (55 mg, 46 %) as colourless viscous liquid upon purification by column chromatography (12 % ethyl acetate-hexane)



R_f = 0.73 (hexane/ethyl acetate, 7:3).

IR (Neat) ν_{max}: 3370, 2913, 2850, 1760, 1719, 1591, 1567, 1480, 1439, 1407, 1385, 1301, 1256, 1214, 1117, 1046, 972, 942, 876, 838, 803, 760, 728, 698, 667 cm^{-1}**.**

^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 8.43 (d, *J* = 1.5 H z, 1H), 8.01-7.99 (m, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 6.76 (s, 2H), 5.91 (d, *J* = 6.0 Hz, 1H), 5.76 (d, *J* = 6.5 Hz, 1H), 5.56 (d, *J* = 7.0 Hz, 1H), 4.12-3.94 (m, 4H), 3.89 (s, 3H), 2.89 (s, 2H), 2.42 (d, *J* = 11.5 Hz, 1H), 1.97-1.72 (m, 11H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.08

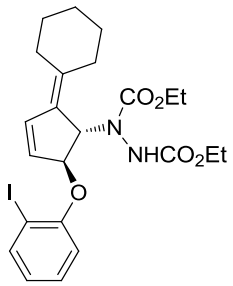
(t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$, TMS)**:** δ 165.1, 159.1, 156.1, 155.2, 140.9, 140.4, 131.7, 125.8, 124.9, 124.7, 114.6, 112.0, 81.1, 62.5, 61.4, 52.1, 40.1, 37.2, 35.2, 28.4, 28.0, 14.7, 14.4 ppm.

HRMS (ESI): Calcd for $C_{29}H_{35}IN_2O_7Na$ $[M+Na]^+$: 673.13866; Found: 673.13855.

Diethyl 1-(-2-cyclohexylidene-5-(2-iodophenoxy) cyclopent-3-enyl) hydrazine-1,2-dicarboxylate (54da)

Following the general procedure (Section 3.7.2), the reaction of pentafulvene derived diazanorbornene **32d** (235 mg, 0.68 mmol) and 2-iodophenol **53a** (50 mg, 0.23 mmol), in dry acetonirile (2 mL) in the presence of Ag(OTf) (1 mg, 0.005 mmol) and Na_2CO_3 (50 mg, 0.23 mmol) at room temperature for 4 h yielded **54da** (78 mg, 63 %) as yellow viscous liquid upon purification by column chromatography (15 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3385, 3052, 2925, 2855, 1763, 1718, 1596, 1478, 1462, 1409, 1379, 1309, 1277, 1218, 1129, 1097, 1065, 924, 838, 752 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.29-7.26 (m, 1H), 6.91(d, *J* = 8.5 Hz, 1H), 6. 85 (s, 1H), 6.73-6.69 (m, 2H), 5.95 (d, *J* = 5.5 Hz, 1H), 5.76 (d, *J* = 7.5 Hz, 1H), 5.48 (d, *J* = 7.0 Hz, 1H), 4.11-4.01 (m, 4H), 2.43-2.35 (m, 2H), 2.16-2.12 (m, 1H), 1.88-1.42 (m, 7H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.10 (t, *J* = 7.0 Hz, 3H) ppm.

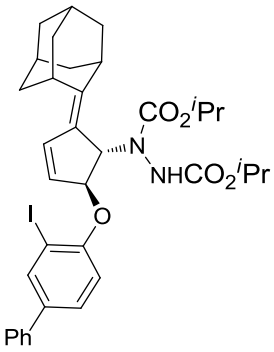
^{13}C NMR (75 MHz, $CDCl_3$, TMS)**:** δ 156.0, 155.3, 140.9, 139.4, 135.3, 129.9, 129.7, 128.3, 123.5, 113.0, 80.6, 62.4, 61.2, 58.4, 31.9, 31.5, 27.8, 27.2, 26.5, 14.6, 14.4 ppm.

HRMS (ESI): Calcd for $C_{23}H_{29}IN_2O_5Na$ $[M+Na]^+$: 563.10188; Found: 563.10076.

Preparation of compound 54ed

Following the general procedure (Section 3.7.2), the reaction of pentafulvene derived diazanorbornene **32e** (203 mg, 0.51 mmol) and 2-iodophenol **53d** (50 mg, 0.17

mmol), in dry acetonirile (2 mL) in the presence of Ag(OTf) (1 mg, 0.0034 mmol) and Na_2CO_3 (28 mg, 0.26 mmol) at room temperature for 4 h yielded **54ed** (32 mg, 27 %) as yellow viscous liquid upon purification by column chromatography (12 % ethyl acetate-hexane)



R_f = 0.73 (hexane/ethyl acetate, 7:3).

IR (Neat) ν_{max}: 3365, 3062, 3029, 2979, 2908, 2849, 1757, 1710, 1660, 1595, 1555, 1473, 1404, 1385, 1302, 1241, 1218, 1179, 1110, 1045, 974, 955, 921, 876, 808, 760, 739, 699, 664, 640, 603, 555 cm^{-1}.

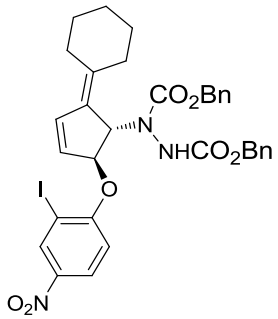
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.97 (s, 1H), 7.53-7.48 (m, 3H), 7.42-7.39 (m, 3H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.76-6.72 (m, 2H), 5.95 (d,*J* = 5.5 Hz, 1H), 5.78 (d, *J* = 7.0 Hz, 1H), 5.52 (d, *J* = 7.0 Hz, 1H), 4.88-4.84 (m, 1H), 4.74-4.69 (m, 1H), 2.94-2.89 (m, 3H), 2.43 (d, *J* = 12.0 Hz, 1H), 1.96-1.73 (m, 10H), 1.26-1.22 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 155.4, 154.8, 148.5, 139.2, 137.8, 136.4, 134.8, 128.8, 128.2, 127.9, 127.2, 126.7, 126.3, 113.0, 81.2, 69.9, 68.5, 56.9, 40.1, 38.3, 37.3, 35.1, 35.0, 28.4, 28.0, 22.1, 22.0 ppm.

HRMS (ESI): Calcd for $C_{35}H_{41}IN_2O_5Na$ $[M+Na]^+$:719.19579: Found: 719.19532.

Dibenzyl 1-(-2-cyclohexylidene-5-(2-iodo-4-nitrophenoxy) cyclopent-3enyl) hydrazine-1,2-dicarboxylate (54fb)

Following the general procedure (Section 3.7.2), the reaction of pentafulvene derived diazanorbornene **32f** (282 mg, 0.57 mmol) and 2-iodophenol **53b** (50 mg, 0.19 mmol), in dry acetonirile (2 mL) in the presence of Ag(OTf) (1 mg, 0.004 mmol) and Na_2CO_3 (30 mg, 0.29 mmol) at room temperature for 4 h yielded **54fb** (57 mg, 42 %) as yellow viscous liquid upon purification by column chromatography (15 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3360, 2910, 2854, 1759, 1715, 1598, 1479, 1438, 1405, 1387, 1298, 1257, 1215, 1118, 1045, 924, 836, 754 cm^{-1}.

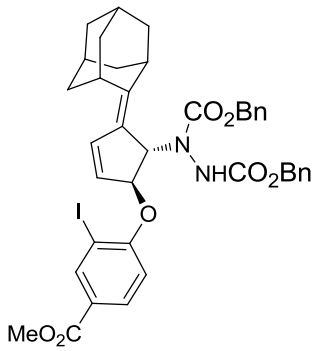
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 8.45 (d, *J* = 2.0 Hz, 1H), 8.14 (m, 1H), 7.32-7.14 (m, 10H), 6.89 (d, *J* = 9.0 Hz, 1H), 6.76-6.74 (m, 2H), 5.90 (d, *J* = 5.5 Hz, 1H), 5.82 (d, *J* =7.0 Hz, 1H), 5.52 (d, *J* = 7.0 Hz, 1H), 5.14-5.06 (m, 4H), 2.41-2.37 (m, 2H), 2.10-2.05 (m, 1H), 1.89-1.88 (m, 1H), 1.67-1.62 (m, 3H), 1.44-1.39 (m, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 160.6, 155.4, 155.0, 142.4, 142.2, 136.4, 136.3, 135.7, 134.9, 129.9, 129.6, 129.1, 128.5, 128.4, 128.3, 128.2, 128.1, 127.7 (2), 126.8, 125.5, 111.5, 81.8, 68.0, 66.9, 57.4, 31.9, 31.4, 27.7, 27.1, 26.4 ppm.

HRMS (ESI): Calcd for $C_{33}H_{32}IN_3O_7Na$ $[M+Na]^+$: 732.11826; Found: 732.11755.

Preparation of compound 54gc

Following the general procedure (Section 3.7.2), the reaction of pentafulvene derived diazanorbornene **32g** (267 mg, 0.54 mmol) and 2-iodophenol **53c** (50 mg, 0.18 mmol), in dry acetonirile (2 mL) in the presence of Ag(OTf) (1 mg, 0.004 mmol) and Na_2CO_3 (29 mg, 0.27 mmol) at room temperature for 4 h yielded **54gc** (66 mg, 47 %) as yellow viscous liquid upon purification by column chromatography (15 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3366, 2920, 2854, 1760, 1718, 1654, 1592, 1483, 1446, 1406, 1300, 1258, 1214, 1117, 1046, 756, 698, 611 cm^{-1}.

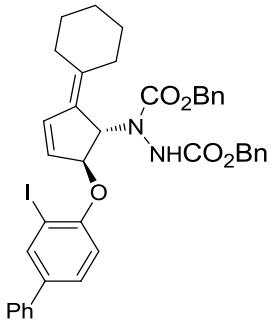
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 8.35 (s, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.32-7.21 (m, 10H), 6.99 (s, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.71 (d, *J* = 5.5 Hz, 1H), 5.89 (d, *J* = 6.0 Hz, 1H), 5.80 (d, *J* = 7.5 Hz, 1H), 5.55 (d, *J* = 6.5 Hz, 1H), 5.16-5.03 (m, 4H), 3.89 (s, 3H), 2.91-2.83 (m, 2H), 2.44 (d, *J* = 11.5 Hz, 1H), 1.95-1.68 (m, 11H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 165.1, 155.8, 155.0, 149.4, 140.9, 140.4, 136.4, 135.8, 135.5, 131.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.5, 127.4, 126.8, 125.5, 124.8, 111.8, 81.0, 67.9, 66.7, 57.2, 52.1, 40.0, 37.9, 37.1, 35.1(2), 28.3, 27.9 ppm.

HRMS (ESI): Calcd for $C_{39}H_{39}IN_2O_7Na$ $[M+Na]^+$: 797.16996; Found: 797.16933.

Dibenzyl 1-(-2-cyclohexylidene-5-(3-iodobiphenyl-4-yloxy) cyclopent-3-enyl) hydrazine-1,2-dicarboxylate (54fd)

Following the general procedure (Section 3.7.2), the reaction of pentafulvene derived diazanorbornene **32f** (225 mg, 0.51 mmol) and 2-iodophenol **53d** (50 mg, 0.17 mmol), in dry acetonirile (2 mL) in the presence of Ag(OTf) (1 mg, 0.004 mmol) and Na_2CO_3 (28 mg, 0.26 mmol) at room temperature for 4 h yielded **54fd** (50 mg, 40 %) as yellow viscous liquid upon purification by column chromatography (15 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3382, 3053, 2925, 2855, 1761, 1715, 1596, 1476, 1461, 1408, 1378, 1310, 1279, 1217, 1130, 1097, 1066, 924, 839 cm^{-1}.

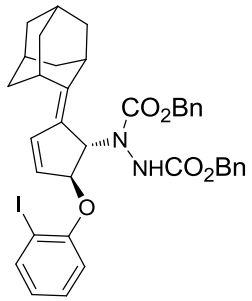
^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.9 (s, 1H), 7.49-7.19 (m, 16H), 7.05 (s,1H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.70 (d, *J* = 6.0 Hz, 1H), 5.97 (d, *J* = 5.5 Hz, 1H), 5.81 (d, *J* = 7.5 Hz, 1H), 5.50 (d, *J* = 7.5 Hz, 1H), 5.11-4.99 (m, 4H), 2.45-2.38 (m, 3H), 2.11-2.07 (m, 1H), 1.89-1.85 (m, 1H), 1.64-1.41(m, 5H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 155.9, 155.4, 155.2, 141.2, 139.1, 137.8, 136.5, 136.4, 136.0, 135.5, 129.0, 128.8 (2), 128.4, 128.3(2), 128.2 (2), 128.1, 128.0, 127.9, 127.7, 127.5, 127.3 (2), 126.7, 113.1, 80.9, 67.8, 66.7, 57.6, 31.9, 31.4, 29.7, 27.7, 27.2, 22.7, 14.2 ppm.

HRMS (ESI): Calcd for $C_{39}H_{37}IN_2O_5Na$ $[M+Na]^+$: 763.16448: Found: 763.16501.

Preparation of compound 54ga

Following the general procedure (Section 3.7.2), the reaction of pentafulvene derived diazanorbornene **32g** (336 mg, 0.68 mmol) and 2-iodophenol **53a** (50 mg, 0.23 mmol), in dry acetonirile (2 mL) in the presence of Ag(OTf) (1 mg, 0.005 mmol) and Na_2CO_3 (36 mg, 0.34 mmol) at room temperature for 4 h yielded **54ga** (46 mg, 28 %) as yellow viscous liquid upon purification by column chromatography (12 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3368, 3063, 3032, 2960, 2960, 2908, 2848, 1762, 91, 1467, 1716, 1609, 1578, 1491, 1467, 1444, 1407, 1359, 1300, 1262, 1238, 1211, 1100, 1050, 871, 801, 748, 697, 657, 602, 556 cm^{-1}

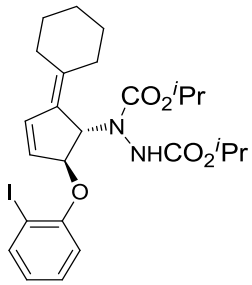
^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 7.69 (d, *J* = 7.5 Hz, 1H), 7.33-7.21 (m, 11H), 7.10 (s, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.71-6.67 (m, 2H), 5.92 (d, *J* = 6.0 Hz, 1H), 5.79 (d, *J* = 7.0 Hz, 1H), 5.49 (d, *J* = 7.0 Hz, 1H), 5.16-5.04 (m, 4H), 3.04-2.83 (m, 3H), 2.46-2.43 (m, 1H), 1.95-1.66 (m, 10H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ 156.0, 155.9, 155.1, 148.8, 139.3, 136.5, 136.1, 135.0, 128.4(3), 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 123.1, 113.1, 80.7, 68.1, 67.8, 67.7, 66.7, 57.4, 40.0, 38.0, 37.2, 37.1, 35.1, 35.0, 28.4, 27.9(2) ppm.

HRMS (ESI): Calcd for $C_{37}H_{37}IN_2O_5Na$ $[M+Na]^+$: 739.16448: Found: 739.16400.

Diisopropyl 1-(-2-cyclohexylidene-5-(2-iodophenoxy) cyclopent-3-enyl) hydrazine-1,2-dicarboxylate (54ca)

Following the general procedure (Section 3.7.2), the reaction of pentafulvene derived diazanorbornene **32c** (235 mg, 0.68 mmol) and 2-iodophenol **53a** (50 mg, 0.23 mmol), in dry acetonirile (2 mL) in the presence of Ag(OTf) (1 mg, 0.005 mmol) and Na_2CO_3 (36 mg, 0.34 mmol) at room temperature for 4 h yielded **54ca** (73 mg, 56 %) as white solid upon purification by column chromatography (12 % ethyl acetate-hexane)



Mp: 138 ^{o}C;

R_f = 0.73 (hexane/ethyl acetate = 7:3).

IR (Neat) ν_{max}: 3367, 3066, 2977, 2926, 2853, 1756, 1710, 1577, 1468, 1443, 1404, 1382, 1300, 1220, 1177, 1110, 1043, 961, 936, 874, 854, 806, 749 cm^{-1}.

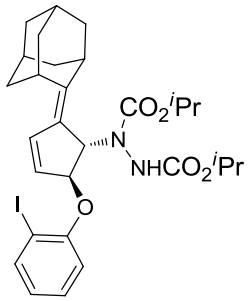
^{1}H NMR (300 MHz, $CDCl_3$, TMS)**:** 7.73 (d, *J* = 8.0 Hz, 1H), 7.30-7.26 (m, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.73-6.69 (m, 3H), 5.95 (d, *J* = 6.0 Hz, 1H), 5.77 (d, *J* = 7.0 Hz, 1H), 5.47 (d, *J* = 7.0 Hz, 1H), 4.85-4.71 (m, 2H), 2.64-2.59 (m, 1H), 2.45-2.34 (m, 2H), 2.15-2.10 (m, 1H), 1.87 (d, *J* = 6.0 Hz, 1H), 1.68-1.38 (m, 5H), 1.23-0.95 (m, 12H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$, TMS)**:** δ 155.4, 155.1, 140.7, 139.3, 135.2, 130.1, 129.6, 129.5, 128.4, 122.9, 113.0, 80.6, 69.9, 68.6, 57.0, 31.8, 31.4, 27.8, 27.3, 26.5, 22.2, 22.0 ppm.

HRMS (ESI): Calcd for $C_{25}H_{33}IN_2O_5Na$ $[M+Na]^+$: 591.13318: Found: 591.13366

Preparation of compound 54ea

Following the general procedure (Section 3.7.2), the reaction of pentafulvene derived diazanorbornene **32e** (270 mg, 0.68 mmol) and 2-iodophenol **53a** (50 mg, 0.23 mmol), in dry acetonirile (2 mL) in the presence of Ag(OTf) (1 mg, 0.005 mmol) and Na_2CO_3 (36 mg, 0.34 mmol) at room temperature for 4 h yielded **54ea** (70 mg, 49 %) as white solid upon purification by column chromatography (12 % ethyl acetate-hexane)



Mp: 154 ^{o}C;

R_f = 0.69 (hexane/ethyl acetate = 7:3).

IR (Neat) ν_{max}: 3366, 3065, 2979, 2908, 2850, 1757, 1709, 1661, 1577, 1468, 1404, 1381, 1301, 1217, 1178, 1110, 1046, 1025, 974, 942, 870, 806, 750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.73 (d, *J* = 7.5 Hz, 1H), 7.31-7.26 (m, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.75-6.69 (m, 3H), 5.93 (d, *J* = 6.5 Hz, 1H), 5.75 (d, *J* = 7.0 Hz, 1H), 5.48 (d, *J* = 7.0

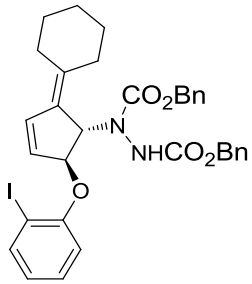
Hz, 1H), 4.86-4.69 (m, 2H), 2.93-2.87 (m, 2H), 2.42 (d, *J* = 12.0 Hz, 1H), 1.97-1.79 (m, 11H), 1.25-0.94 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 155.4, 154.8, 148.3, 139.3, 134.7, 129.6, 128.0, 126.3, 113.0, 80.9, 69.9, 68.5, 56.9, 40.0(2), 38.3, 37.3, 35.0(2), 28.4, 28.0, 22.1, 22.0 ppm.

HRMS (ESI): Calcd for $C_{29}H_{37}IN_2O_5Na$ $[M+Na]^+$: 643.16448; Found: 643.16521.

Dibenzyl 1-(-2-cyclohexylidene-5-(2-iodophenoxy) cyclopent-3-enyl) hydrazine-1,2-dicarboxylate (54fa)

Following the general procedure (Section 3.7.2), the reaction of pentafulvene derived diazanorbornene **32f** (300 mg, 0.68 mmol) and 2-iodophenol **53a** (50 mg, 0.23 mmol), in dry acetonirile (2 mL) in the presence of Ag(OTf) (1 mg, 0.005 mmol) and Na_2CO_3 (36 mg, 0.34 mmol) at room temperature for 4 h yielded **54fa** (79 mg, 52 %) as yellow viscous liquid upon purification by column chromatography (15 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3366, 3064, 3032, 2925, 2852, 1762, 1716, 1660, 1578, 1491, 1467, 1443, 1407, 1302, 1237, 1211, 1125, 1050, 1023, 974, 928, 875, 851, 806, 748, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS)**:** δ 7.67 (d, *J* = 7.5 Hz, 1H), 7.31-7.19 (m, 12H), 7.04 (s, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.70-6.67 (m, 2H), 5.94 (d, *J* = 5.5 Hz, 1H), 5.79 (d, *J* = 7.5 Hz, 1H), 5.47 (d, *J* = 7.5 Hz, 1H), 5.12-4.97 (m, 4H), 2.42-2.32 (m, 2H), 2.10-2.08 (m, 1H), 1.63-1.40 (m, 7H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS)**:** δ 155.9, 155.2, 141.1, 139.4, 136.5, 136.1, 135.4, 129.7, 129.6, 128.6, 128.4, 128.3 (2), 128.2, 127.9 (2), 127.7, 127.5, 127.4, 123.1, 113.1, 80.6, 67.8, 66.7, 57.6, 31.4, 29.7, 29.5, 29.4, 27.7, 27.2 ppm.

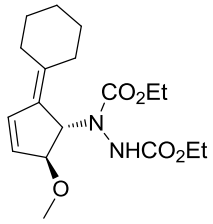
HRMS (ESI): Calcd for $C_{33}H_{33}IN_2O_5Na$ $[M+Na]^+$: 687.13318; Found: 687.13368.

3.6.3. General Procedure for the Lewis Acid Catalyzed Reaction of Pentafulvene Derived Bicyclic Hydrazines with Alcohols

A mixture of pentafulvene derived diazabicyclic olefin (3.0 equiv.), alcohol (1.0 equiv.) and $Cu(OTf)_2$ (5 mol%) was weighed in a Schlenk tube and degassed for 10 minutes. Dry toluene (2 ml) was added and the reaction mixture was purged with argon and allowed to stir at room temperature for 1 hour. The solvent was evaporated *in vacuo* and the residue on silica gel (100–200 mesh) column chromatography yielded trans-3,4- disubstituted alkylidenecyclopentene.

Diethyl-1-(2-cyclohexylidene-5-methoxycyclopent-3-enyl) hydrazine-1,2-dicarbo xylate (56da)

Following the general procedure (Section 3.7.3), the reaction of pentafulvene derived diazanorbornene **32d** (887 mg, 2.79 mmol) and alcohol **55a** (30 mg, 0.93 mmol) in dry toluene (2 mL) in the presence of $Cu(OTf)_2$ (17 mg, 0.046 mmol) at room temperature for 1 h yielded **56da** (96 mg, 29 %) as a pale yellow liquid upon purification by column chromatography (20 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}**:** 3297**,** 2927, 2852, 1715, 1416, 1383, 1227, 1061, 760 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$):δ 6.61 (s, 1H), 6.35-6.21 (m, 1H), 5.93 (s,1H), 5.13-4.98 (m,1H), 4.63-4.52 (m, 1H), 4.29-4.10 (m, 4H), 3.47 (s, 3H), 2.39- 2.36 (m, 1H), 2.16 -2.07 (m, 3H), 1.59-1.54 (m, 6H), 1.26-1.25 (m, 6H) ppm.

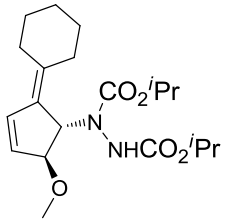
^{13}C NMR (125 MHz, $CDCl_3$): δ 156.7, 154.6, 137.8, 135.0, 134.3, 131.5, 88.5, 62.5, 62.3, 61.8, 56.8, 31.5, 31.1, 27.9, 26.4, 24.6, 14.4 ppm.

HRMS (ESI): calcd for $C_{18}H_{29}N_2O_5$ $[M+H]^+$**:** 353.20765; Found: 353.20721.

Diisopropyl-1-(2-cyclohexylidene-5-methoxycyclopent-3-enyl) hydrazine-1,2-dicarbo xylate (56ca)

Following the general procedure (Section 3.7.3), the reaction of pentafulvene derived diazanorbornene **32c** (965 mg, 2.79 mmol) and alcohol **55a** (30 mg, 0.93 mmol) in dry toluene (2

mL) in the presence of $Cu(OTf)_2$ (17 mg, 0.046 mmol) at room temperature for 1 h yielded **56ca** (110 mg, 31 %) as a colourless viscous liquid upon purification by column chromatography (18 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3441, 3301, 2935, 1719, 1468, 1376, 1297, 1238 cm^{-1}.

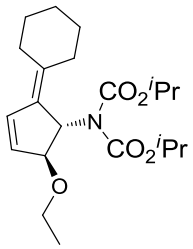
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.60 (d, *J*= 5.5 Hz, 1H), 6.07-6.00 (m, 1H), 5.92(s, 1H), 5.13-4.89 (m, 3H), 4.63-4.55 (m, 1H), 3.49 (s, 3H), 2.35-2.26 (m, 2H), 2.13- 2.08 (m, 2H), 1.58-1.54 (m, 6H), 1.26-1.22 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.8, 154.5, 137.8, 134.1, 132.0, 129.9, 88.5, 70.1, 69.5, 61.7, 57.0, 31.6, 31.0, 28.1, 27.9, 26.4, 22.1, 21.8 ppm.

HRMS (ESI): calcd for $C_{20}H_{32}N_2O_5$ $[M+Na]^+$: 403.22089; Found: 403.22098.

Diisopropyl-1-(2-cyclohexylidene-5-ethoxycyclopent-3-enyl) hydrazine-1, 2-dicarbo xylate (56cb)

Following the general procedure (Section 3.7.3), the reaction of pentafulvene derived diazanorbornene **32c** (674 mg, 1.95 mmol) and alcohol **55b** (30 mg, 0.65 mmol) in dry toluene (2 mL) in the presence of $Cu(OTf)_2$ (12 mg, 0.033 mmol) at room temperature for 1 h yielded **56cb** (76 mg, 31 %) as a yellow viscous liquid upon purification by column chromatography (15 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3303, 2935, 1715, 1411, 1232, 1101, 1061 cm^{-1}.

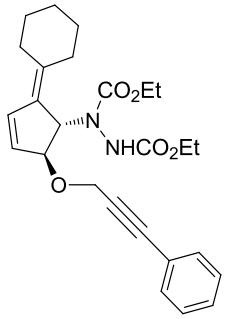
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.59 (d, *J*= 5.0 Hz, 1H), 6.06-5.98 (m, 1H), 5.92 (s,1H), 5.12-4.89 (m, 3H), 4.74-4.63 (m, 1H), 3.88-3.80 (m, 1H), 3.60 (brs, 1H), 2.35-2.26 (m, 2H), 2.12-2.04 (m, 2H), 1.76- 1.58 (m, 6H), 1.25-1.22 (m, 15H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6, 154.6, 137.4, 133.9, 132.8, 132.1, 86.8, 69.9, 69.5, 64.8, 62.1, 34.7, 31.6, 31.0, 28.1, 26.9, 26.6, 25.2, 22.2, 22.0, 15.5 ppm.

HRMS (ESI) calcd for $C_{21}H_{34}N_2O_5$ $[M]^+$: 395.24677; Found: 395.14380.

Diethyl-1-(-2-cyclohexylidene-5-(3-phenylprop-2-ynyloxy) cyclopent-3-enyl) hydra zine-1,2-dicarboxylate (56dc)

Following the general procedure (Section 3.7.3), the reaction of pentafulvene derived diazanorbornene **32d** (363 mg, 1.14 mmol) and alcohol **55c** (50 mg, 0.38 mmol) in dry toluene (2 mL) in the presence of $Cu(OTf)_2$ (7 mg, 0.019 mmol) at room temperature for 1 h yielded **56dc** (46 mg, 27 %) as a colourless liquid upon purification by column chromatography (20 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3316, 3059, 2935, 2861, 2223, 1712, 1603, 1413, 1380, 1232, 1173, 1062 cm^{-1}.

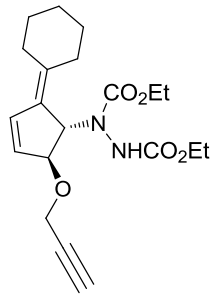
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44-7.28 (m, 5H), 6.63 (d, *J*= 4.5 Hz, 1H), 6.28-6.16 (m, 1H), 5.99 (d, *J*= 3.5 Hz, 1H), 5.15- 5.12 (m, 1H), 5.08- 5.05(m, 1H), 4.66- 4.49 (m, 2H), 4.23- 4.06 (m, 4H), 2.40-2.35 (m, 1H), 2.24- 2.03 (m, 3H), 1.61- 1.54 (m, 6H), 1.25- 1.23 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 155.1, 134.7, 131.8, 131.2, 129.0, 128.1, 122.9, 99.1, 87.0, 85.7, 62.5, 61.8, 57.5, 31.6, 31.2, 30.8, 28.0, 26.4, 14.6, 14.4 ppm.

HRMS (ESI): calcd for $C_{26}H_{32}N_2NaO_5$ $[M+Na]^+$: 475.22089; Found: 475.22125.

Diethyl-1-(-2-cyclohexylidene-5-(prop-2-ynyloxy) cyclopent-3-enyl) hydrazine-1,2-dicarboxylate (56cd)

Following the general procedure (Section 3.7.3), the reaction of pentafulvene derived diazanorbornene **32c** (512 mg, 1.61 mmol) and alcohol **55d** (30 mg, 0.53 mmol) in dry toluene (2 mL) in the presence of $Cu(OTf)_2$ (10 mg, 0.027 mmol) at room temperature for 1 h yielded **56cd** (42 mg, 21 %) as a colourless liquid upon purification by column chromatography (20 % ethyl acetate-hexane)



R_f: 0.53 (Hexane: Ethyl acetate = 7:3).

IR (Neat) ν_{max}: 3292, 2922, 2854, 1714, 1414, 1232, 1061 cm^{-1}.

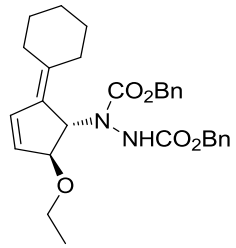
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.62 (d, *J*= 4.5 Hz, 1H), 6.07 (brs, 1H), 5.95 (s, 1H), 5.08 (brs, 1H), 4.88 (s, 1H), 4.42-4.10 (m, 6H), 2.40-2.35 (m, 2H), 2.24-2.06 (m, 3H), 1.66-1.55 (m, 6H), 1.28-1.24 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.1, 154.4, 136.8, 134.3, 132.0, 129.4, 87.8, 74.5, 65.2, 62.5, 57.3, 31.7, 31.3, 29.7, 26.8, 25.7, 20.8, 14.6, 14.1 ppm.

HRMS (ESI) calcd for $C_{20}H_{28}N_2NaO_5$ $[M+Na]^+$: 399.18959; Found: 399.19028

Dibenzyl-1-(2-cyclohexylidene-5-ethoxycyclopent-3-enyl) hydrazine-1,2-dicarbo xylate (56fb)

Following the general procedure (Section 3.7.3), the reaction of pentafulvene derived diazanorbornene **32f** (862 mg, 1.95 mmol) and alcohol **55b** (30 mg, 0.65 mmol) in dry toluene (2 mL) in the presence of $Cu(OTf)_2$ (12 mg, 0.033 mmol) at room temperature for 1 h yielded **56fb** (127 mg, 40 %) as a pale yellow liquid upon purification by column chromatography (18 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3287, 3033, 2933, 2860, 1718, 1498, 1454, 1408, 1220, 1127, 1084 cm^{-1}.

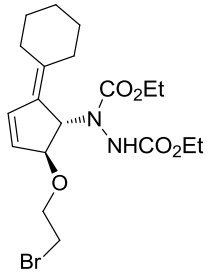
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30-7.24 (m, 10H), 6.55 (s, 1H), 6.29-6.21 (m,1H), 5.90 (s,1H), 5.26-4.72 (m,7H), 3.59- 3.48 (m,1H), 2.32- 2.18 (m, 1H), 2.11-1.96 (m, 3H), 1.70-1.40 (m, 6H), 1.25-1.10 (m, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.8, 154.7, 135.1, 134.0, 132.7, 131.5, 128.5, 128.1, 127.9, 127.8, 127.6, 87.2, 68.1, 67.6, 65.0, 62.5, 31.5, 31.1, 27.9, 26.4, 25.6, 15.3 ppm.

HRMS (EI): calcd for $C_{29}H_{34}N_2O_5Na$, $[M+Na]^+$: 513.23654; Found: 513.23627.

Diethyl-1-(-2-(2-bromoethoxy)-5-cyclohexylidenecyclopent-3-enyl) hydrazine-1, 2-dicarboxylate (56de)

Following the general procedure (Section 3.7.3), the reaction of pentafulvene derived diazanorbornene **32d** (382 mg, 1.20 mmol) and alcohol **55e** (50 mg, 0.40 mmol) in dry toluene (2 mL) in the presence of $Cu(OTf)_2$ (7 mg, 0.020 mmol) at room temperature for 1 h yielded **56de** (46 mg, 26 %) as a colourless liquid upon purification by column chromatography (18 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3320, 2931, 1711, 1414, 1379, 1234, 1061 cm^{-1}.

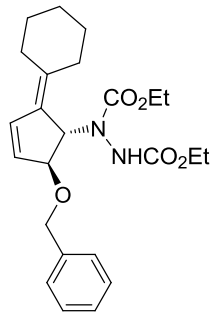
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (d, *J*= 5.5 Hz, 1H), 6.15-6.07 (m, 1H), 5.93 (s, 1H), 5.12-5.01 (m, 1H), 4.80-4.69 (m, 1H), 4.31-4.00 (m, 5H), 3.90-3.83 (m, 1H), 3.49 (brs, 2H), 2.39-2.36 (m, 1H), 2.26-2.05 (m, 3H), 1.67-1.50 (m, 6H), 1.39-1.22 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3, 155.1, 138.3, 134.5, 131.7, 128.3, 87.5, 69.9, 69.3, 62.7, 62.0, 32.0, 31.6, 29.7, 28.1, 27.9, 26.4, 14.4 ppm.

HRMS (ESI): calcd for $C_{19}H_{29}BrN_2O_5$, $[M+Na]^+$: 467.11575; Found: 467.11561.

Diethyl 1-((1S, 2S)-2-(benzyloxy)-5-cyclohexylidenecyclopent-3-enyl) hydrazine-1,2-dicarboxylate (56df)

Following the general procedure (Section 3.7.3), the reaction of pentafulvene derived diazanorbornene **32d** (439 mg, 1.38 mmol) and alcohol **55f** (50 mg, 0.46 mmol) in dry toluene (2 mL) in the presence of $Cu(OTf)_2$ (8 mg, 0.023 mmol) at room temperature for 1 h yielded **56df** (142 mg, 72 %) as a pale yellow liquid upon purification by column chromatography (18 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3296, 2923, 2855, 1711, 1414, 1376, 1267, 1225, 1063 cm^{-1}.

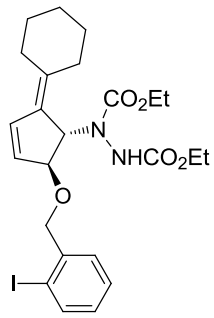
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.24 (m, 5H), 6.60 (d, *J*= 5.0 Hz, 1H), 6.05 -5.94 (m, 1H), 5.84 (s, 1H), 5.24-5.10 (m, 1H), 4.85-4.7 0 (m, 2H), 4.62-4.60 (m, 1H), 4.24-4.10 (m, 4H), 2.39- 2.36 (m, 1H), 2.26 -2.05 (m, 3H), 1.59 -1.53 (m, 6H), 1.28-1.24 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.7, 155.1, 138.6, 134.3, 132.5, 130.9, 129.9, 128.5, 128.2, 127.4, 126.9, 88.1, 71.8, 62.5, 62.0,, 53.3, 31.6, 30.6, 28.0, 27.8, 26.4, 14.6, 14.4 ppm.

HRMS (ESI): calcd for $C_{24}H_{32}N_2O_5$ $[M+Na]^+$: 451.22089; Found: 451.22040

Diethyl-1-(-2-cyclohexylidene-5-(2-iodobenzyloxy) cyclopent-3-enyl) hydrazine-1, 2-dicarboxylate (56dg)

Following the general procedure (Section 3.7.3), the reaction of pentafulvene derived diazanorbornene **32d** (200 mg, 0.63 mmol) and alcohol **55g** (50 mg, 0.21 mmol) in dry toluene (2 mL) in the presence of $Cu(OTf)_2$ (4 mg, 0.01 mmol) at room temperature for 1 h yielded **56dg** (64 mg, 55 %) as pale yellow liquid upon purification by column chromatography (20 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3296, 2923, 2855, 1711, 1414, 1376, 1267, 1225, 1063 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J= 7.5 Hz, 1H), 7.46 (d, J=7.5 Hz, 1H), 7.31 (s, 1H), 6.95 (s, 1H), 6.64 (d, J= 6.0 Hz, 1H,), 6.20-6.04 (m, 1H), 6.00-5.90 (m, 1H), 5.67- 5.56 (m, 2H), 5.31- 5.16 (m, 1H), 4.92-4.78 (m, 1H), 4.22- 4.11 (m, 4H), 2.40-2.26 (m, 1H), 2.16-2.05 (m, 3H), 1.77- 1.43 (m, 6H), 1.26- 1.25 (m, 6H) ppm.

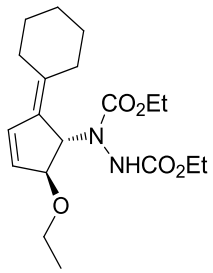
^{13}C NMR (125 MHz, $CDCl_3$): δ 156.0, 155.4, 140.6, 139.2, 137.4, 136.0, 135.0, 130.4, 129.4, 127.7, 125.2, 97.4, 79.8, 73.7

69.1, 62.6, 61.8, 32.2, 31.7, 28.4, 27.8, 24.9, 14.9, 13.7 ppm.

HRMS (ESI): calcd for $C_{24}H_{31}IN_2O_5$ $[M+Na]^+$: 577.11753; Found: 577.11853**.**

Diethyl-1-(2-cyclohexylidene-5-ethoxycyclopent-3-enyl) hydrazine-1,2-dicarboxylate (56db)

Following the general procedure (Section 3.7.3), he reaction of pentafulvene derived diazanorbornene **32d** (620 mg, 1.95 mmol) and alcohol **55b** (30 mg, 0.65 mmol) in dry toluene (2 mL) in the presence of $Cu(OTf)_2$ (12 mg, 0.033 mmol) at room temperature for 1 h yielded **56db** (57 mg, 24 %) as a pale yellow liquid upon purification by column chromatography (25 % ethyl acetate-hexane)



$R_{,f}$: 0.51 (hexane : ethyl acetate=7:3).

IR (Neat) ν_{max}: 2923, 2855, 2355, 1711, 1411, 1232, 1101, 1061 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.60 (d, *J*= 5.0 Hz, 1H), 6.06 (brs, 1H), 5.93- 5.89 (m, 1H), 5.13-4.98 (m, 1H), 4.72-4.61 (m, 1H), 4.29-4.10 (m, 4H), 3.87-3.78 (m, 1H), 3.59- 3.54 (m, 1H), 2.38-2.35 (m, 1H), 2.25- 2.05 (m, 3H), 1.63-1.53 (m, 6H), 1.27-1.22 (m, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.5, 155.5, 134.5, 133.0, 131.7, 130.5, 87.2, 70.1, 65.2, 62.9, 62.6, 32.0, 31.5, 30.1, 28.2, 26.8, 26.0, 15.8, 14.8 ppm.

HRMS (ESI): calcd for $C_{19}H_{30}N_2O_5$, $[M+Na]^+$: 389.20524, Found: 389.20565.

CHAPTER 4

Sequential Tandem Transformations of Pentafulvene Derived Diazabicyclic Olefins: Facile Strategy Towards the Synthesis of Pentacyclic Framework with Multiple Stereocenters

4.1. Introduction

During the last few decades, synthetic organic chemistry sustained enormous efforts to develop methodologies that proceed economically and efficiently in a simple fashion. The easiest way to accomplish such a synthetic sequence is to perform more than one independent reaction in a single step without the isolation of intermediates and a number of versatile synthetic tools have been developed for achieving this target. In this scenario, catalytic tandem transformations appear promising as they offer a broad range of options for the proficient construction of highly complex molecules in a single step with increased molecular diversity, lesser time and higher atom economy [Ho 1992, Tietze 1993, Tietze 1996, Tietze 2006].

Nitrogen and oxygen embedded heterocyclic frameworks remain one of the important constituents of many natural products, marketed drugs, functionalized materials and thus attracted the interest of researchers over the years [Berhr 1967, Donelly 1984, Lipshutz 1986, Keay 1996, Brzozowski 2000, Smythe 2003, Alonso 2004, Larock 2004, Sondhi 2007, Yamamoto 2008, Afonso 2009, Shi 2014, Shi 2015]. Usually, the most abundant and most essential heterocyclic systems are those with five and six membered rings and sequential tandem reactions play a vital role in the design and production of such systems. Among these heterocycles, nitrogen heterocycles such as indole [Hamann 2010], indoline [Boger 1997], 1,3-oxazinan-2-one [Macdonald 2002, Wang 2006, Tice 2011, Poirier 2014] and pyrazolidine [Poli 2004, Ahn 2005] motifs are biologically significant. Some of the important molecules are shown in figure 4.1.

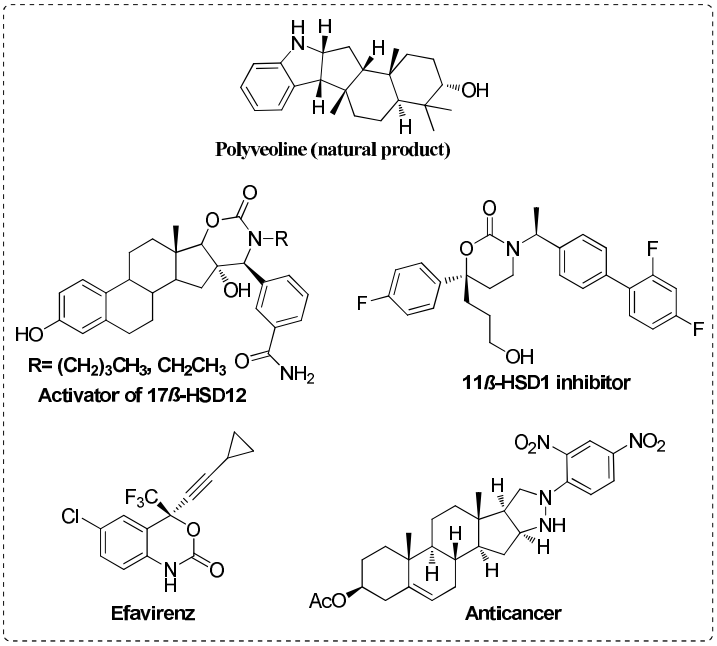


Figure 4.1: Important molecules with indoline, 1,3-oxazinan-2-one and pyrazolidine moiety

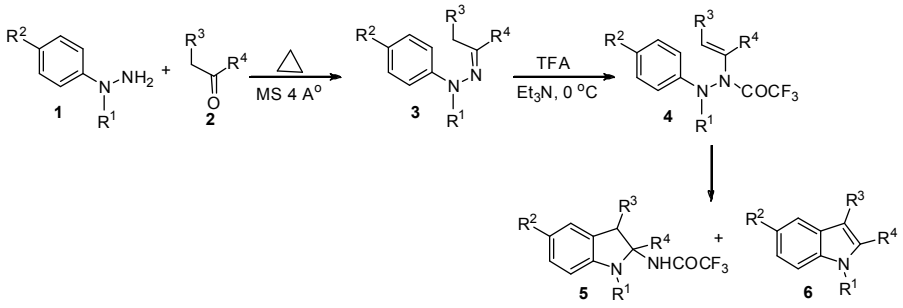
The *meso* diazanorbornenes are considered to be a promising scaffold due to their unique reactivity. The availability of suitable methods for the desymmetrization of these molecular species has enormously contributed to the progress of their chemistry. The effective utilization of the strain within the diazabicyclic olefins have been studied by Micouin [Micouin 2002, Micouin 2006, Micouin 2007, Micouin 2008, Micouin 2010], Kaufmann [Kaufmann 2001, Kaufmann 2002], Pineschi [Pineschi 2005, Pineschi 2008], Lautens [Lautens 2007, Lautens 2008a, Lautens 2008b] and also by our research group [Radhakrishnan 2005, Radhakrishnan 2006a, Radhakrishnan 2006b, Radhakrishnan 2007, Radhakrishnan 2008, Radhakrishnan 2013, Radhakrishnan 2014]. Still, there exists lots of opportunities for researchers to develop an appropriate synthetic protocol for the construction of polycyclic molecules from these scaffolds by modifying the latent functionality and thereby destroying the symmetry. However, the tandem cyclization of these olefins in this direction is less explored, as it is much more challenging and thus needs more attention. In light of our experience and persistent efforts to dig out novel chemistry of pentafulvene and their derivatives, we disclosed a sequential Lewis acid-palladium mediated transformation of hydroxyl group tethered diazanorbornene towards the synthesis of cyclopentene fused tetrahydropyran and novel pentacyclic frameworks with cyclopentene fused to indoline, pyrazolidine, and 1,3-oxazinan-2-one skeletons and the details are presented in this chapter.

Before going to the details of the work, a brief discussion on the synthesis of indoline appended systems is summarized below.

4.2. Synthesis of Indoline Derivatives

4.2.1. Fischer Indolization Reactions

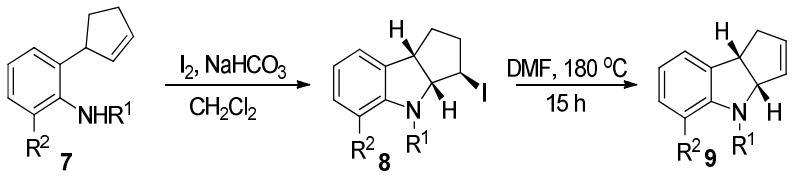
Fischer indolization reaction of arylhydrazones leading to the formation of indoline derivatives was reported by Laronze *et al.* in 1991 [Laronze 1991]. As an extension, later in 2001, Naito and coworkers developed a facile one-pot protocol for the synthesis of indoles *via* condensation of a ketone with hydrazine followed by acylation and rearrangement [Naito 2001] (Scheme 4.1).



Scheme 4.1: Fischer indolization reaction of arylhydrazone

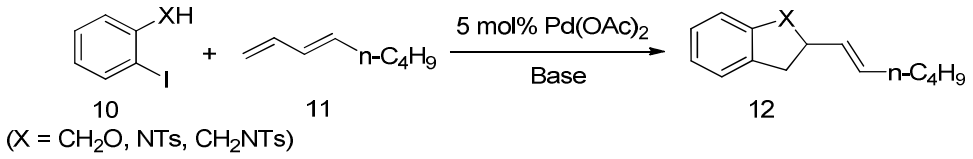
4.2.2. Indoline Derivatives from Substituted Anilines

One of the easiest ways to synthesize indoline derivatives is the derivatization of indoles. A novel method was developed for the preparation of 4,4a,9,9a-tetrahydrocarbazoles and 1,3a,4,8b-tetrahydrocyclopenta[b]indolines by the halocyclization of 2-(cyclopent-2-en-1-yl)anilines with I_2 in the presence of $NaHCO_3$ and subsequent dehydrohalogenation of the cyclization products [Gataullin 2006] (Scheme 4.2).



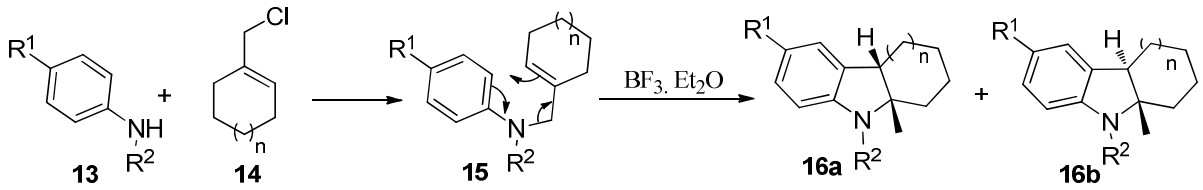
Scheme 4.2: Halocyclization of 2-(cyclopent-2-en-1-yl)anilines with I_2

1,3-dienes readily undergo heteroannulation with appropriately functionalized aryl iodides and a suitable Pd catalyst. For example the *ortho*- functionalized aryl halides afforded the corresponding indolines or dihydro benzofuran derivatives on reaction with 1,3-dienes [Larock 1990a, Larock 1990b] (Scheme 4.3).



Scheme 4.3: Heteroannulation of 1,3-diene

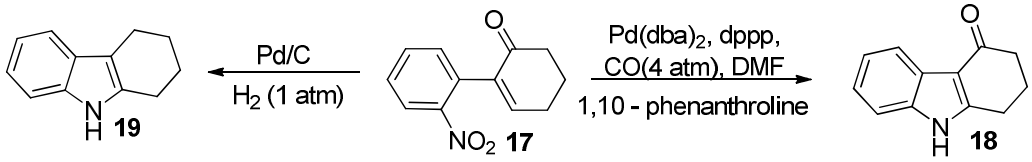
Later, a straightforward approach was developed for the synthesis of indoline appended systems from the easily available starting materials like aniline and 1-(chloromethyl)cyclohex-1-ene based on a tandem aza-Claisen rearrangement /intramolecular ring-closure reaction of the N-allylaniline derivatives [Novak 2008] (Scheme 4.4).



Scheme 4.4: Tandem aza-Claisen rearrangement /intramolecular ring-closure reaction

4.2.3. Reductive Annulation

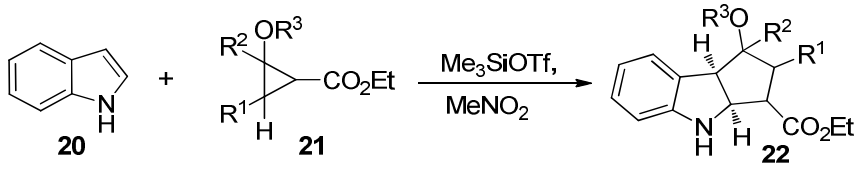
In 2007, Söderberg and co-workers reported a short synthetic sequence towards the synthesis of 1,2,3,4-tetrahydrocarbazoles and related tricyclic indoles, by employing a Stille type cross coupling and a palladium catalyzed reductive annulation as the key steps [Söderberg 2007] (Scheme 4.5).



Scheme 4.5: Reductive annulation

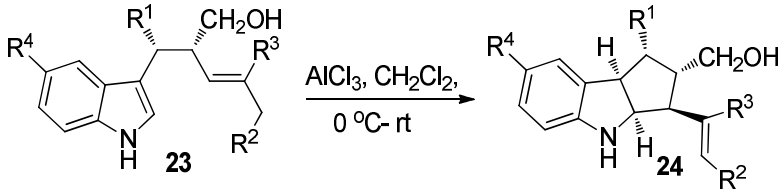
4.2.4. Indoline Derivatives from Indoles and Substituted Indoles

A series of indoline derivatives were synthesized through the annulation of indoles with 2-alkoxycyclopropanoate esters in nitromethane mediated by a silyl triflate catalyst. In this reaction, a single stereocenter on the cyclopropane controls the diastereoselective formation of four new stereocenters [Pagenkopf 2007] (Scheme 4.6).



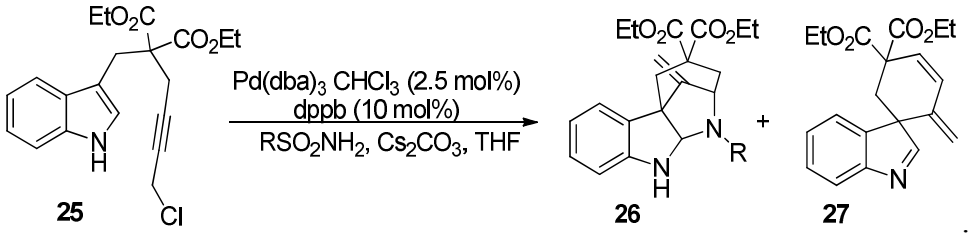
Scheme 4.6: Annulation of indoles

A highly efficient and diastereoselective intramolecular imino-ene reaction of indoles bearing a tethered olefinic functionality was reported. This results in the formation of indoline derivatives *via* a Lewis acid catalyzed enamine–imine isomerization, followed by ene cyclization [Chen 2010] (Scheme 4.7).



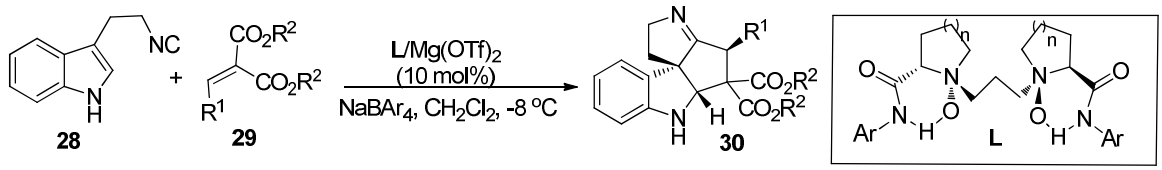
Scheme 4.7: Intramolecular imino-ene reaction of substituted indoles

Later, an efficient palladium-catalysed cascade cyclization of indoles having a propargyl chloride side chain at the 3-position with several external nucleophiles resulted in the formation of corresponding tetracyclic spiroindoles [Fujii 2014] (Scheme 4.8). The reaction was catalyzed by $Pd_2(dba)_3.CHCl_3$/dppb in the presence of Cs_2CO_3. The nucleophilic attack took place in succession with the initial reaction of the internal indole and the subsequent reaction with the external sulfonamide.



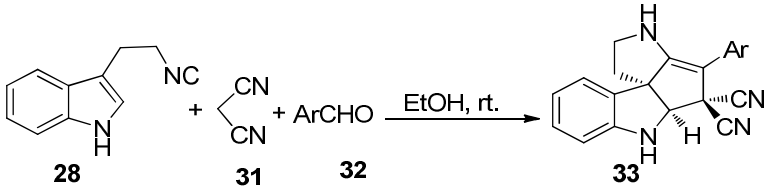
Scheme 4.8: Palladium-catalysed cascade cyclization of indoles

In 2015, Liu and co-workers developed a novel asymmetric dearomatization of 2-isocyanoethylindoles based on Michael/Friedel Crafts type reaction cascade with alkylidene malonates towards a variety of fused polycyclic indolines using chiral *N,N'*-dioxide/Mg (II) complex as the catalyst [Liu 2015] (Scheme 4.9).



Scheme 4.9: Asymmetric dearomatization of 2-isocyanoethylindoles

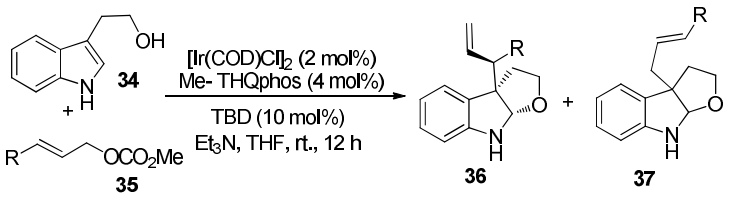
Interestingly, a catalyst-free multicomponent reaction of 2-isocyanoethylindole with different types of aromatic aldehydes and malononitrile was developed for the synthesis of polycyclic spiroindolines in ethanol at room temperature [Wang 2013] (Scheme 4.10). The reaction proceeded under mild conditions and afforded products with high diastereoselectivities and in good to excellent yields.



Scheme 4.10: Multicomponent reaction for the synthesis of polycyclic spiroindolines

Later on, an iridium-catalyzed intermolecular allylic alkylation reaction of 3-substituted indoles afforded indoline products containing multiple contiguous stereocenters with high site-, regio-, diastereo-, and enantioselectivities through *via* a tandem allylic

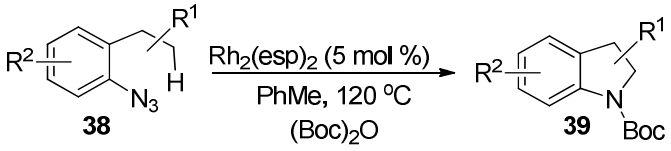
alkylation/cyclization sequence catalyzed by an iridacycle complex (Scheme 4.11) [You 2015].



Scheme 4.11: Iridium-catalyzed intermolecular allylic alkylation reaction of 3-substituted indoles

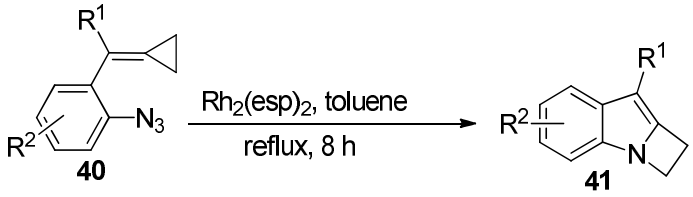
4.2.5. Indoline Derivatives from Substituted Aromatic Azides

`The indoline derivatives were also prepared by the intramolecular amination of unactivated primary, secondary, or tertiary aliphatic C –H bonds using aryl azides as the N-atom precursor using rhodium(II)dicarboxylate complexes as a catalyst [Driver 2012] (Scheme 4.12). In contrast to existing amination methodology, this one does not need an electron withdrawing group on the nitrogen.



Scheme 4.12: Intramolecular amination of unactivated aryl azides

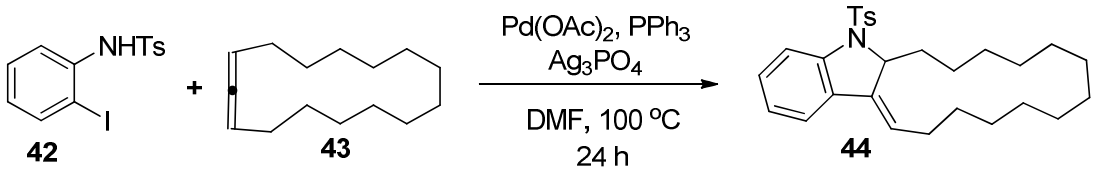
A single electron transfer (SET) controlled Rh(II)-catalyzed diversified ring expansion of styryl azides afforded a series of indole fused azetidines and 1H-carbazoles or related derivatives in moderate to good yields *via* $Rh_2^{III,II}$ nitrene radical intermediates [Shi 2016] (Scheme 4.13).



Scheme 4.13: Ring expansion of styryl azide

4.2.6. Annulation with Allenes

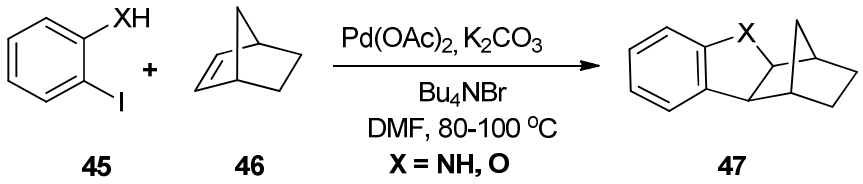
Normally, π-allylpalladium intermediates are generated when an organopalladium species adds to 1,2-dienes, and the latter readily undergo annulation with a variety of functionalized aryl halides. Following this strategy, variety of acyclic/cyclic allenes have been successfully annulated by functionalized aryl iodides as depicted in Scheme 4.14 [Larock 1999].



Scheme 4.14: Annulation with allene

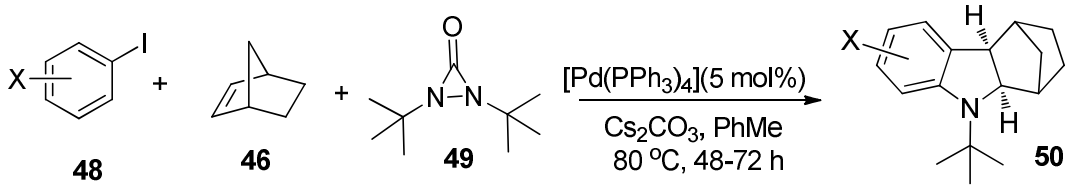
4.2.7. Annulation Reactions of Norbornene and Its Derivatives

In 1998, the direct trapping of the aryl alkyl Pd-intermediates by -OH and -NH_2 functional groups was reported by Catellani and Rio. Here the palladium mediated reaction of norbornadiene with *o*-iodophenol/*o*-iodoaniline resulted in the formation of fused dihydrofurans/pyrroles in moderate yields [Catellani 1998] (Scheme 4.15).



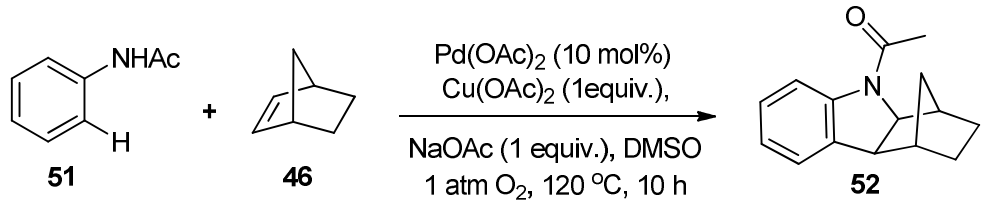
Scheme 4.15: Annulation reactions of norbornene

Later on, a Heck reaction/C-H activation/amination sequence towards indolines using aryl iodides, olefins and di-*tert*-butyldiaziridinone was developed in 2014, by Shi and co-workers [Shi 2014] (Scheme 4.16). The strategy can be extended to various *para*-, *meta*-, *ortho*-, disubstituted aryl iodides and the corresponding indoline products are obtained in good to excellent yields.



Scheme 4.16: Heck reaction/C-H activation/amination sequence towards indoline

An efficient and effective Pd-catalyzed oxidative cyclization reaction for the synthesis of indoline derivatives was developed *via* direct C–H bond activation of acetanilide [Jiang 2014] (Scheme 4.17). Unlike oxidative Heck reaction, this methodology suppresses the *β*-hydride elimination and prevents the formation of Heck type products.

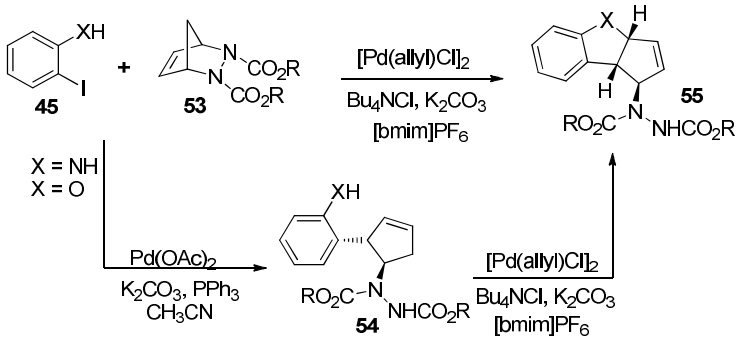


Scheme 4.17: Direct C–H bond activation of acetanilide

4.2.8. Annulation Reactions of Diazanorbornenes

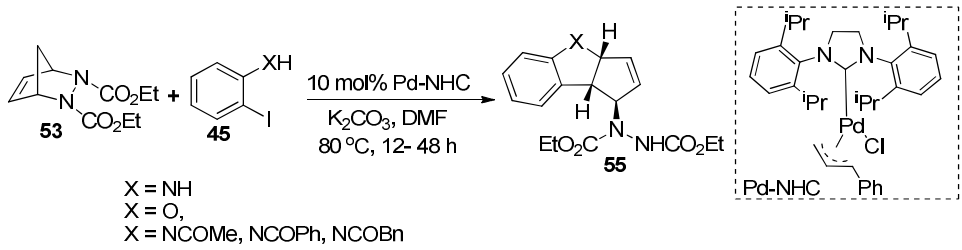
4.2.8.1. Domino Ring Annulation of Diazanorbornenes

As already mentioned, domino transformations are effective tools in organic synthesis for the creation of several new bonds through simple and elegant one-pot synthetic procedures. We have established a very promising route towards cyclopentene annulated benzofuran and indoline derivatives by the palladium catalyzed ring opening of diazabicyclic alkenes with *ortho*-substituted phenols and anilines followed by ring closure [Radhakrishnan 2009b] (Scheme 4.18).



Scheme 4.18: Domino ring annulation of diazanorbornenes

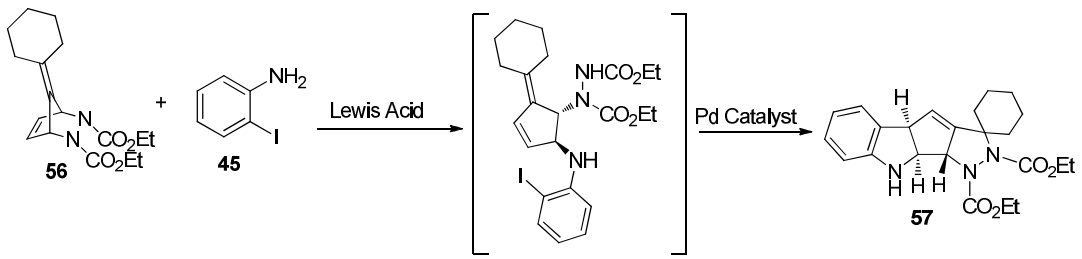
Later, a chiral version of the above cyclopentannulation reaction was developed using a palladium-NHC catalyst [Gilbertson 2010] (Scheme 4.19).



Scheme 4.19: Cyclopentannulation reaction using a palladium-NHC catalyst

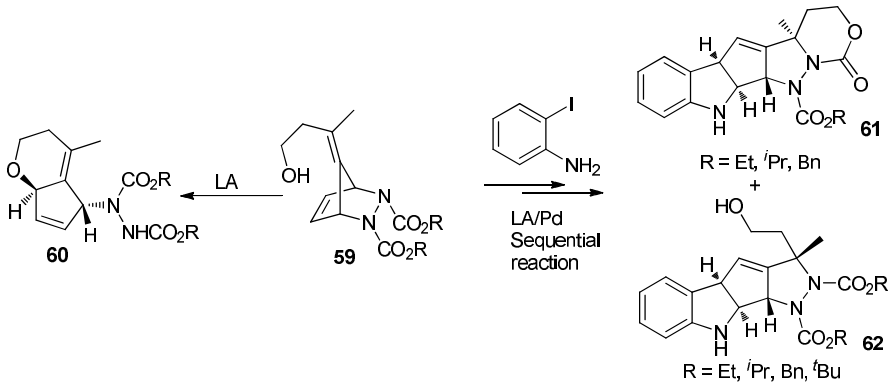
4.3. Background of the Present Work

Over the years, we have been exploring the potential and scope of the chemistry of diazabicyclic olefins with a variety of nucleophiles for the synthesis of useful carbocycles and heterocycles. In this direction, we have developed a Lewis acid/ Pd catalysed strategy for the synthesis of a new spiropentacyclic motif **58** having indoline and pyrazolidine fused to the cyclopentene core [Radhakrishnan 2013a] (Scheme 4.20).



Scheme 4.20: Lewis acid/ Pd catalysed strategy for the synthesis of a spiropentacyclic motif

Encouraged by the results, we examined the reactivity of hydroxyl group tethered diazanorbornenes. Through our systematic efforts, we have unravelled a sequential Lewis acid/palladium mediated transformation of hydroxy group tethered diazanorbornene towards the synthesis of tetrahydrocyclopenta[*b*]pyrans and novel pentacyclic frameworks having cyclopentene fused to indoline, pyrazolidine, and 1,3-oxazinan-2-one skeletons (Scheme 4.21), details are presented in the following sections.

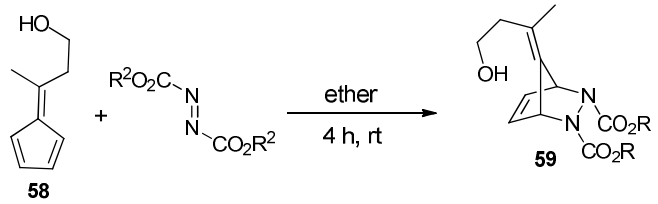


Scheme 4.21: Reactivity of hydroxyl group tethered diazanorbornene

4.4. Results and Discussion

4.4.1. Preparation of Hydroxyl Group Tethered Diazanorbornenes

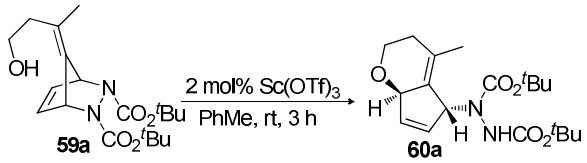
The Diels-Alder cycloaddition reaction [Diels 1925] of pentafulvene derived from 4-hydroxy-2-butanone with dialkylazodicarboxylates furnished the hydroxyl group tethered diazanorbornenes in excellent yields.



Scheme 4.22: Preparation of hydroxyl group tethered diazanorbornene

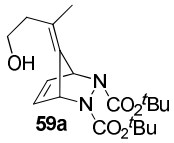
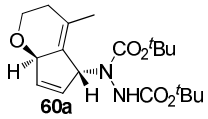
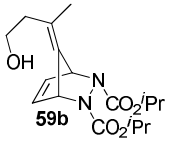
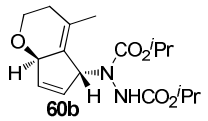
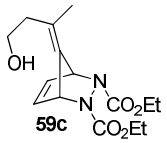
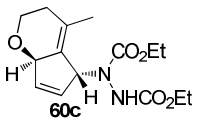
4.4.2. Preparation of Tetrahydrocyclopenta[*b*]pyran Derivatives

In order to study the reactivity of hydroxy group as an internal nucleophile, we attempted a Lewis acid catalyzed skeletal rearrangement of the bicyclic alkene **59a** (R = ^{t}Bu). The skeletal rearrangement of **59a,** synthesized from the corresponding 4-hydroxybutan-2-one-derived pentafulvene was carried out in the presence of 2 mol% of $Sc(OTf)_3$ as the catalyst and the reaction afforded the tetrahydrocyclopenta[*b*]pyran **60a** in 82 % yield. The reaction was then successfully extended to various isopropyl and ethyl ester derivatives of the hydrazine (Scheme 4.22 and Table 4.1).



Scheme 4.22: Synthesis of tetrahydrocyclopenta[*b*]pyran

Table 4.1: Intramolecular cyclisation of bicyclic olefins

Entry	Diazabicyclic olefins	Products	Yield
1			82 %
2			86 %
3			88 %

Reaction conditions: Diazabicyclic olefins (1 equiv.), $Sc(OTf)_3$ (2 mol%), toluene (2 mL), rt, 3 h

The structure of the compound **60a** was established by various spectroscopic studies. In the IR spectrum, the signals at 3321 and 1731 cm^{-1} were diagnostic of the -NH absorption

and carbethoxy groups respectively. In the ^{1}H NMR spectrum (Figure 4.2), the two olefinic protons were observed as a multiplet in the region δ 6.67- 6.66 ppm and a doublet at δ 5.96 ppm respectively. A broad singlet at δ 6.45 ppm represents the -NH proton of the hydrazine moiety. Two doublet at δ 5.51 and 5.09 ppm were assigned as the protons attached to the C-1 and C-4 carbon atom respectively. The proton at C-5 carbon atom resonated as a multiplet in the range δ 2.44- 2.39 ppm. The CH_2 protons attached to the oxygen atom resonated in the range δ 3.44- 3.40 ppm as a multiplet.

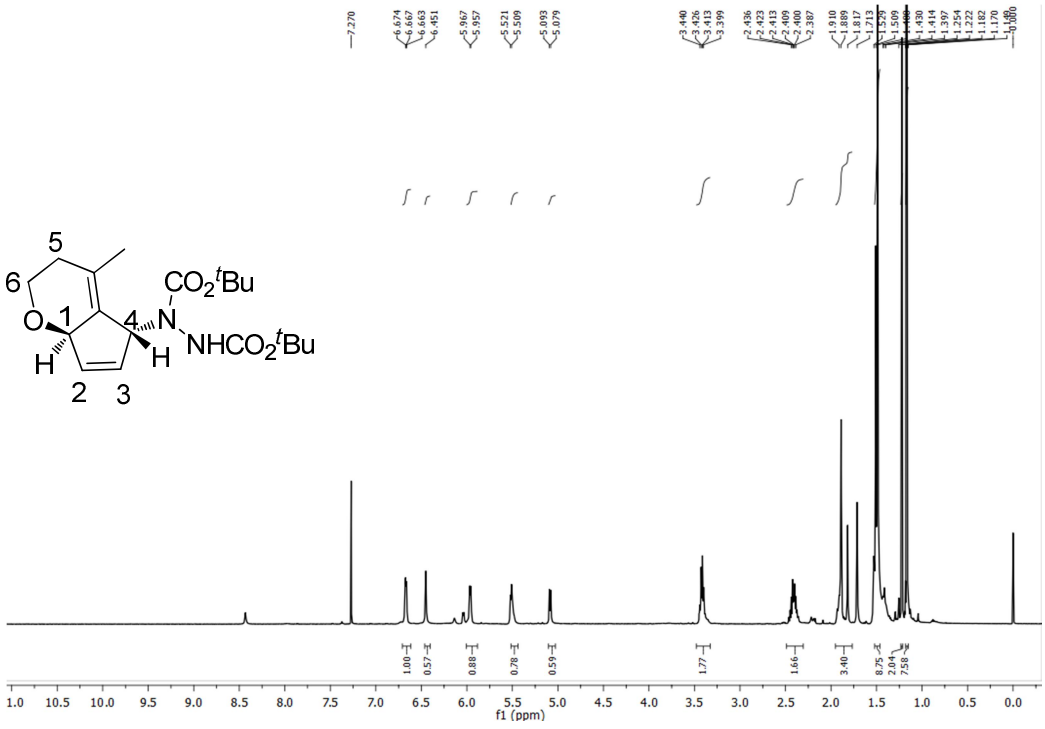


Figure 4.2: ^{1}H NMR spectrum of compound **60a**

The ^{13}C NMR spectrum (Figure 4.3) of **60a** showed peaks at δ 156.2 and 154.1 ppm matching to the ester carbonyl carbons. The two olefinic carbons were found to resonate at δ 135.6 and 130.1 ppm respectively. The peaks at δ 80.8 and 57.9 ppm were assigned to C-1 and C-4 respectively. The CH_2 carbon attached to the oxygen atom resonated at δ 60.0 ppm. The methyl carbons of the carbethoxy groups resonated as a sharp signal at δ 20.2 ppm.

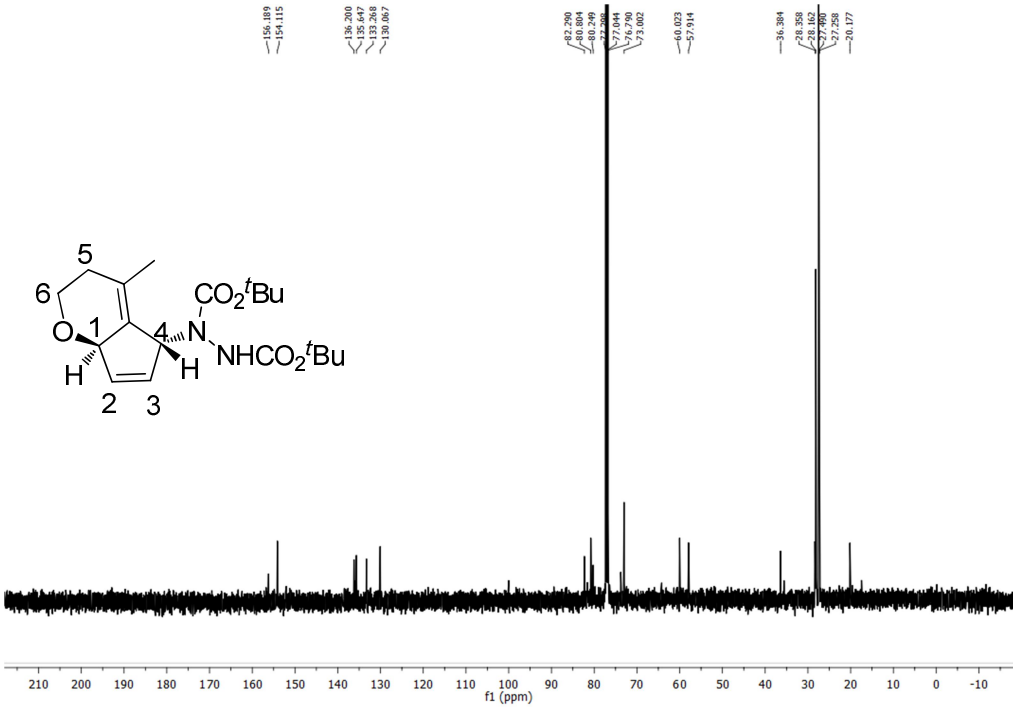


Figure 4.3: ^{13}C NMR spectrum of compound **60a**

The explanation of the relative stereochemistry of protons at the carbons C_1 and C_4 using coupling constant is difficult due to the presence of rotamers [Ley 2012]. So we took NOESY spectrum of the compound **60a,** which showed that there is no interaction between those two protons. So those protons are opposite in direction (Figure 4.4).

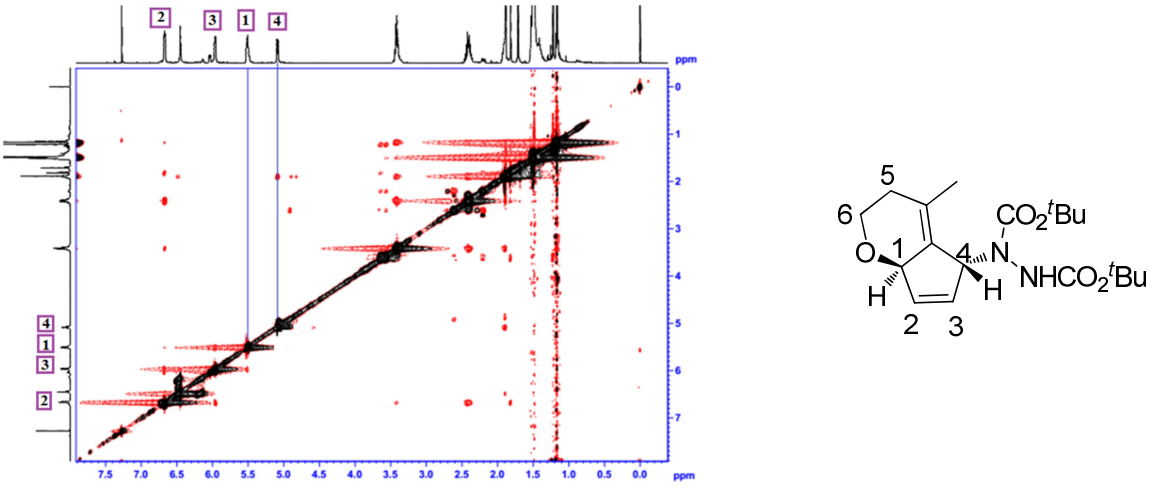


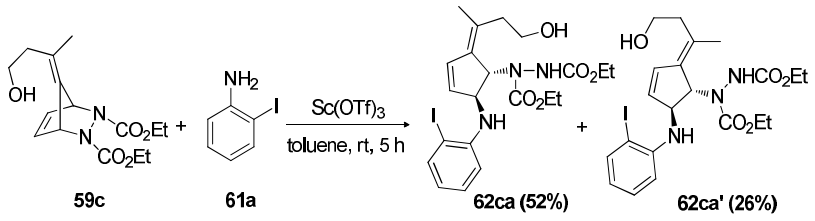
Figure 4.4: NOESY spectrum of the compound **60a**

Further evidence for the structure was obtained from the high resolution mass spectral analysis of **60a** which showed the molecular ion peak at *m/z* = 389.2036 [$C_{19}H_{30}N_2NaO_5$].

4.4.3. Preparation of Hydroxy Appended Alkylidene Cyclopentene Derivatives

After investigating the nucleophilicity of the internal hydroxyl group in these bicycles, we were interested in checking the reactivity of external nucleophiles. Our previous report on the Lewis acid catalyzed ring opening of fulvene derived bicyclics towards the construction of 3,4-alkylidene cyclopentene derivatives [Radhakrishnan 2013a] prompted us to expand the scope of this reaction to hydroxy appended diazabicyclic olefins.

With this idea in mind, we carried out the reaction of bicyclic alkene **59c** with 2-iodoaniline **61a** in the presence of $Sc(OTf)_3$ in toluene at room temperature. The reaction afforded two isomeric products **62ca** and **62ca′** in 52 % and 26 % yields, respectively (Scheme 4.23). The products were characterized by various spectroscopic methods.



Scheme 4.23: Formation of regioisomer

The formation of two regioisomers by the reaction of Lewis acid is explained on the basis of unsymmetrical nature of the diazanorbornene due to the presence of unsymmetrical substitutents on the exocyclic position of pentafulvene derived diazanorbornene (see Scheme 4.23). There are two possibilities for the attack of nucleophile in presence of Lewis acid just as shown in the Figure 4.5. It is difficult to distinguish the two regioisomers using NMR techniques.

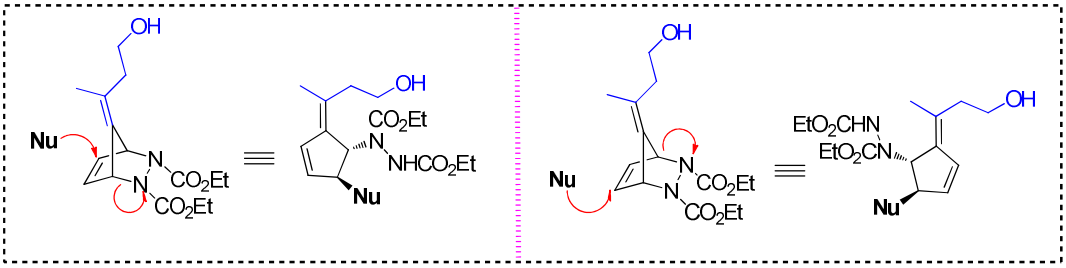


Figure 4.5: Formation of two regioisomers

The structure of the compound **62ca** was established by various spectroscopic studies.The IR spectrum showed characteristic carbonyl absorption at 1708 cm^{-1} and the absorptions indicative of the -NH and -OH stretching at 3383 and 3726 cm^{-1} respectively. In the ^{1}H NMR spectrum (Figure 4.6), the aromatic protons appeared in the region δ 7.76- 6.60 ppm. The -NH protons resonated as multiplet in the range δ 6.42-6.39 ppm. The olefinic protons were found to resonate as two distinct peaks; as doublet at δ 6.58 ppm and as a broad singlet at δ 5.96 ppm. The protons on ring, C-3 and C-4 appeared in the region δ 5.08- 4.71 ppm. The protons on the carbon adjacent to the hydroxyl group were spotted as broad singlets at δ 3.80 and 3.72 ppm. Methyl proton resonated as a singlet at δ 1.87 ppm. OCH_2 protons on the hydrazine moiety resonated as a multiplet in the region δ 4.18- 4.12 ppm Methyl proton on the hydrazine group resonated in the region δ 1.26- 1.21 ppm. All other signals were in agreement with the proposed structure.

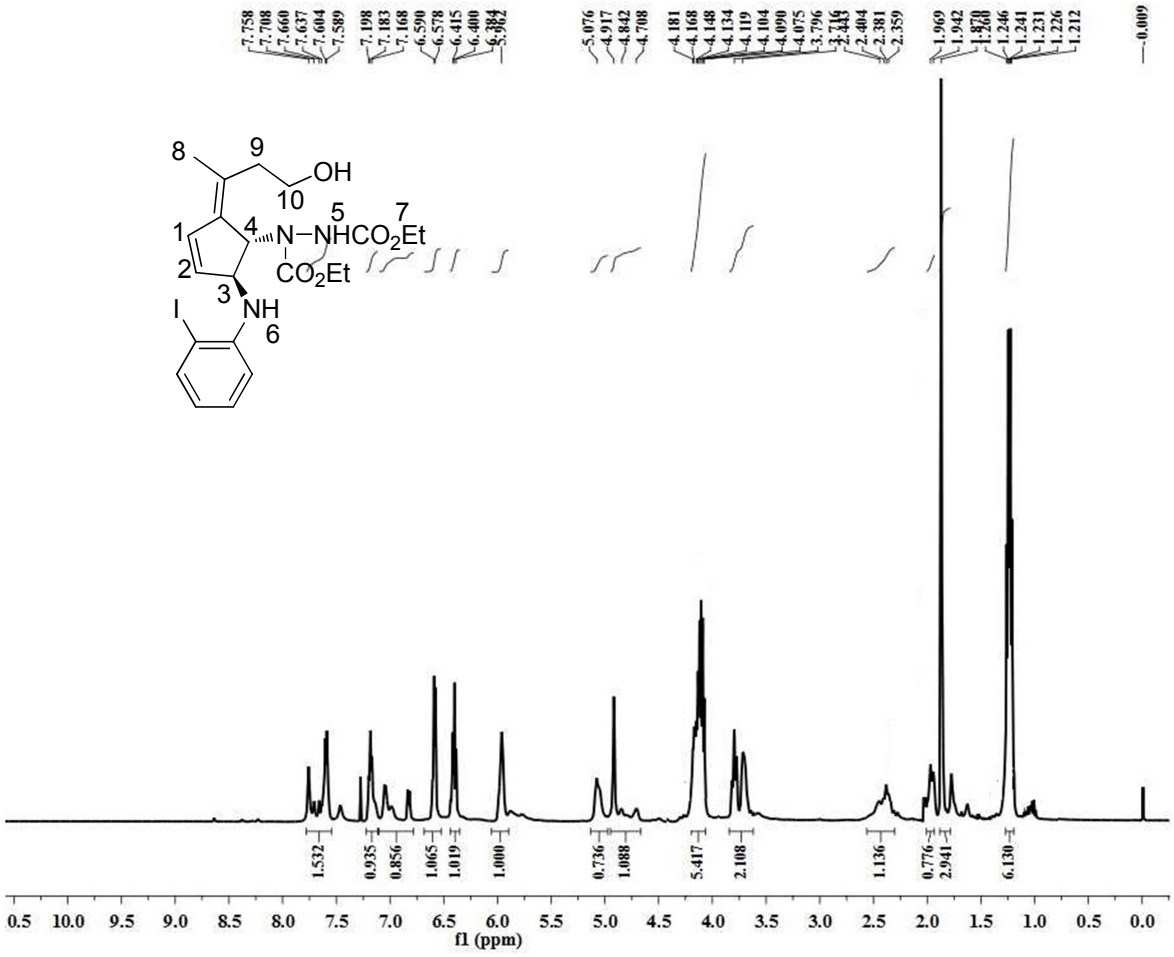


Figure 4.6: ^{1}H NMR spectrum of compound **62ca**

The ^{13}C NMR spectrum (Figure 4.7) of **62ca** showed peaks at δ 157.2 and 155.8 ppm which correspond to the ester carbonyl carbons. The two olefinic carbons were found to resonate at δ 134.1 and 133.1 ppm respectively. The aromatic carbon attached to iodine resonated at δ 85.4 ppm. The peaks at δ 64.1 and 62.3 ppm were assigned to the C-4 and C-3 respectively. The methyl carbons of the ester groups resonated at δ 14.4 ppm whereas the methyl carbon C-8 resonated at δ 17.7 ppm.

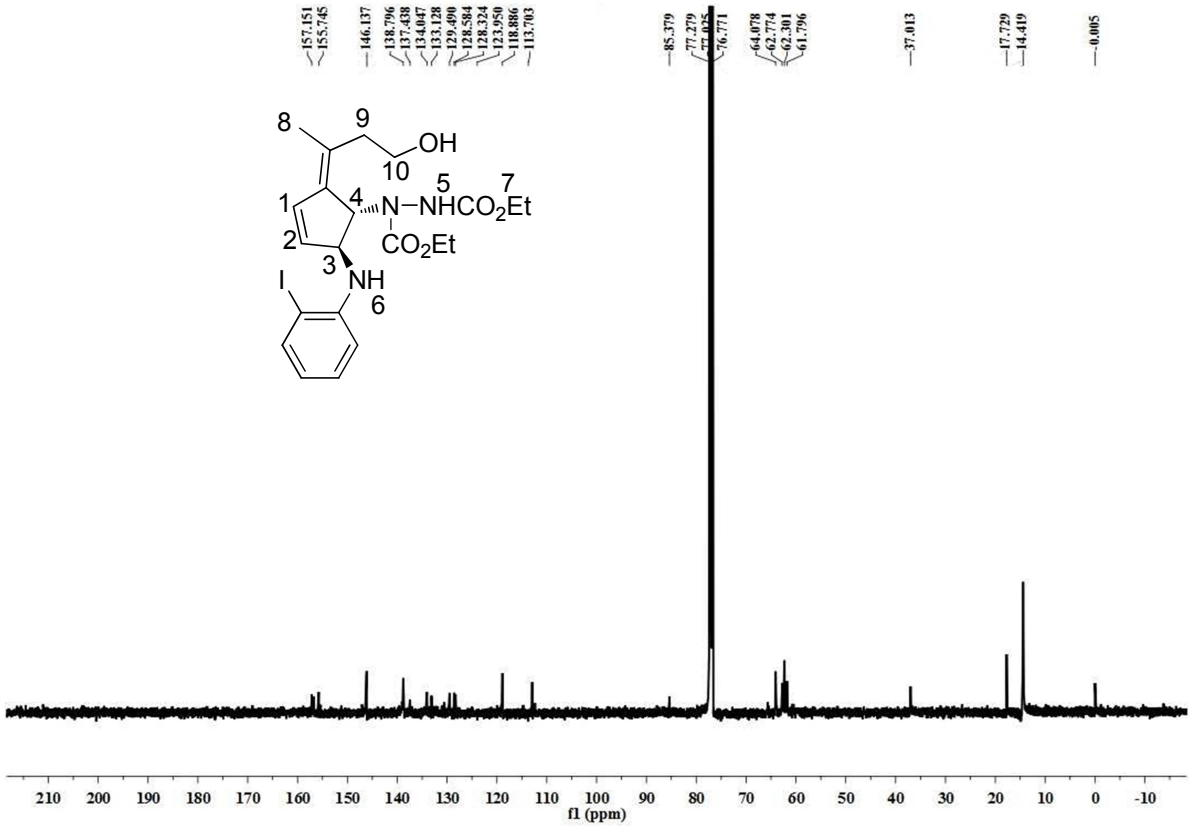


Figure 4.7: ^{13}C NMR spectrum of compound **60ca**

Further evidence for the structure was obtained from the high resolution mass spectral analysis of **62ca** which showed the molecular ion peak at *m/z* = 552.0976 [$C_{25}H_{31}N_3O_4Na$]. All the synthesized compounds bear hydrazine moiety and the proton NMR spectra of these compounds were found to be complex due to the presence of rotamers [Ley 2012]. The structure and relative stereochemistry of compound was unambiguously confirmed by single crystal X-ray analysis of one of the derivative **62ba** (Figure 4.8).

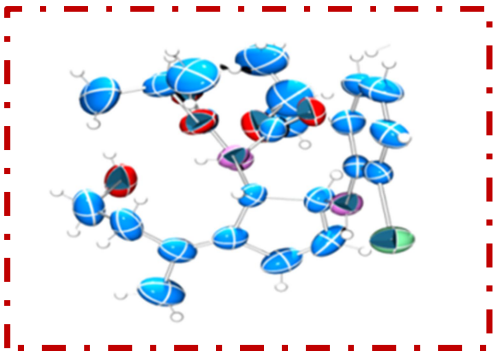


Figure 4.8: Single crystal X-ray structure of compound **62ba**

The structure of the other regioisomer **62ca'** was also established by various spectroscopic studies. The IR spectrum showed characteristic ester carbonyl absorption at 1707 cm^{-1} and the absorptions indicative of the -NH and -OH stretching at 3382 and 3724 cm^{-1} respectively. In the ^1H NMR spectrum (Figure 4.9), the two ring olefinic protons were observed as broad singlets at δ 6.83 and 5.96 ppm respectively. A broad peak in the range of δ 6.44- 6.42 ppm represents the -NH proton of the hydrazine moiety. The multiplet in the range δ 3.76- 3.71 ppm was assigned to the proton attached to the oxygen atom. The ring carbon atom at C-4 and C-3 resonated as a multiplet in the region δ 5.11- 4.76 ppm. The two CH_2 protons of the carbethoxy group along with the -NH proton (exchangeable with deuterium) resonated in the range δ 4.19-4.05 ppm as multiplet.

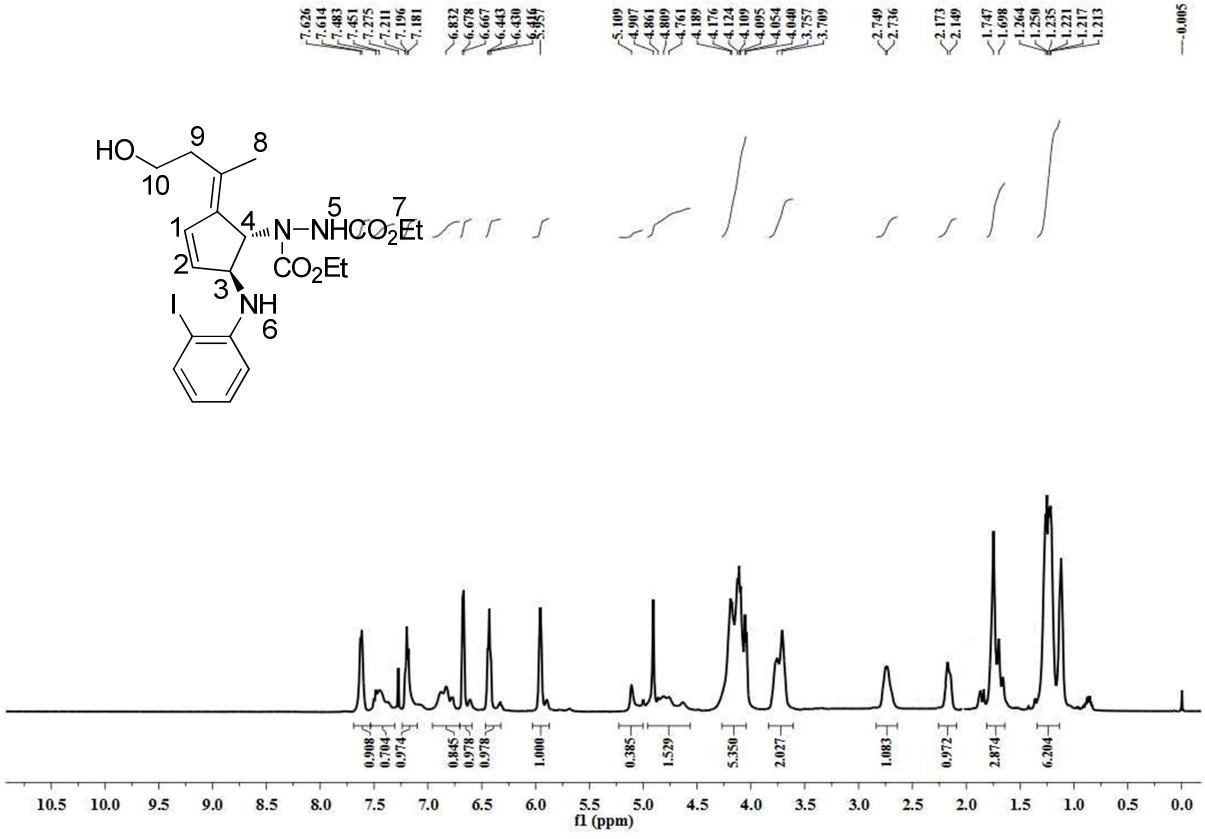


Figure 4.9: ^1H NMR spectrum of compound **62ca'**

The ^{13}C NMR spectrum (Figure 4.10) of **62ca'** showed peaks at δ 157.2 and 156.0 ppm which correspond to the carbonyl carbons. The two olefinic carbons were found to resonate at δ 134.5 and 132.0 ppm respectively. The aromatic carbon attached to iodine

resonated at δ 85.5 ppm. The peaks at δ 63.1 and 61.9 ppm were assigned to C-4 and C-3 respectively. The carbon attached to the oxygen atom resonated at δ 60.4 ppm and the carbon C-9 resonated at δ 38.6 ppm. The methyl carbons of the carbethoxy group showed sharp peak at δ 14.3 ppm whereas the methyl carbon resonated at δ 18.6 ppm. Further evidence for the structure was obtained from the high resolution mass spectral analysis of **62ca'** which showed the molecular ion peak at *m/z* = 552.0974 [$C_{21}H_{28}IN_3NaO_5$].

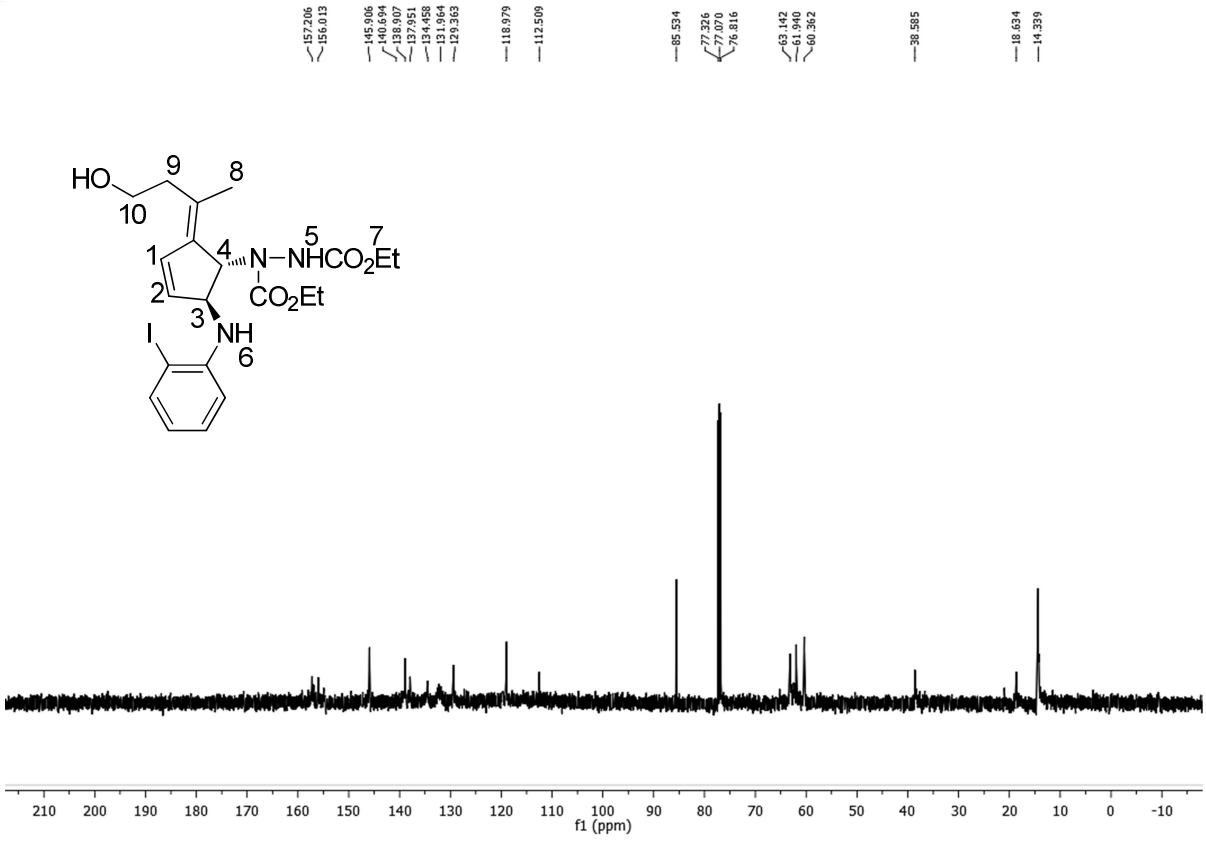
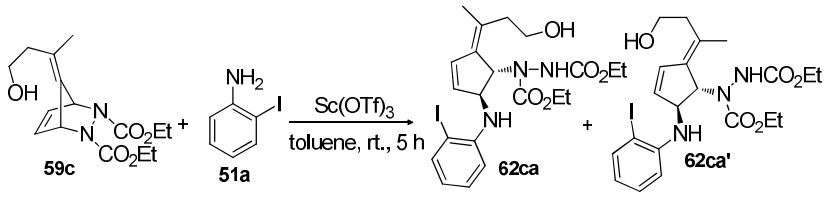


Figure 4.10: ^{13}C NMR spectrum of compound **62ca'**

We then carried out detailed optimization studies to find out the best reaction condition for this transformation (Table 4.2). With $Sc(OTf)_3$, products could be produced in better yields (Table 4.2, entries 1-5) compared to other Lewis acids. Evaluating a range of Lewis acids in various solvents revealed that the best yield was obtained with 1.2 equiv. of bicyclic olefin and 1.0 equiv. of 2-iodoaniline in the presence of 2 mol% of $Sc(OTf)_3$ in toluene. Under this condition, **62ca** and **62ca'** were obtained in 56% and 39% yields respectively.

Table 4.2: Optimization of the reaction condition

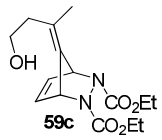
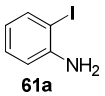
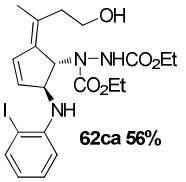
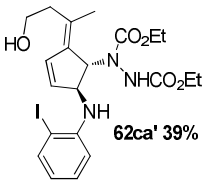
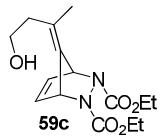
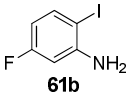
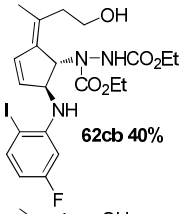
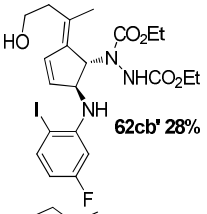
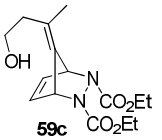
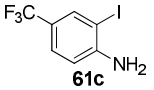
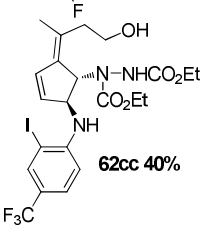
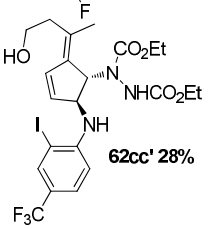
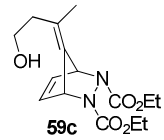
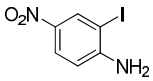
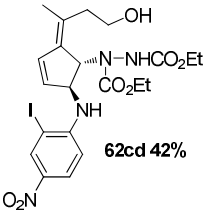
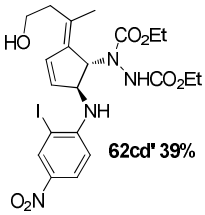
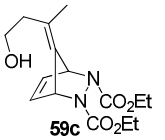
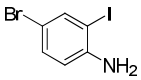
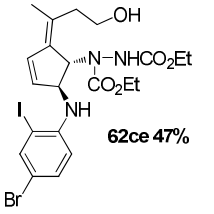
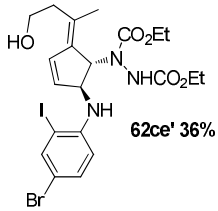
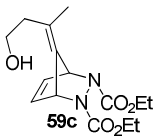
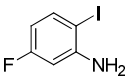
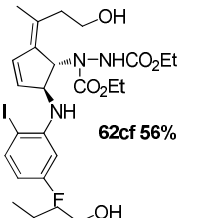
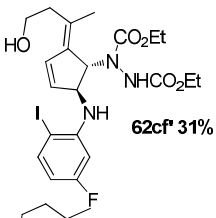
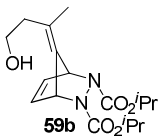
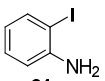
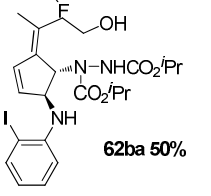
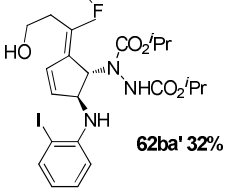


Entry	Lewis acid	Solvent	Time(h)	Yield (%)	
				62ca	62ca'
1	$Sc(OTf)_3$	toluene	5	52	26
2	$Sc(OTf)_3$	CH_3CN	5	26	19
3	$Sc(OTf)_3$	DMF	5	27	16
4	$Sc(OTf)_3$	THF	5	26	18
5	$Sc(OTf)_3$	toluene	6	56	39
6	$Yb(OTf)_3$	toluene	6	54	26
7	$Zn(OTf)_2$	toluene	6	48	24
8	$La(OTf)_3$	toluene	6	50	27
9	$Cu(OTf)_2$	toluene	6	12	10
10	$AlCl_3$	toluene	6	15	7

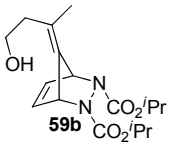
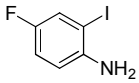
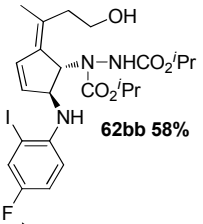
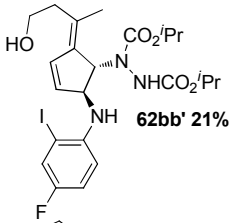
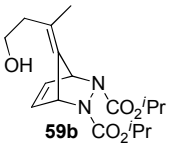
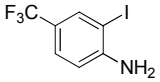
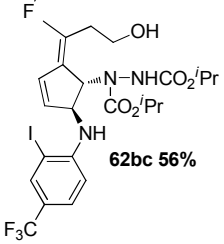
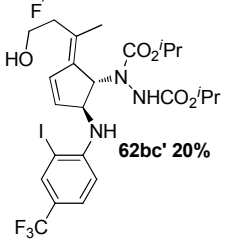
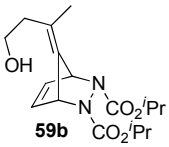
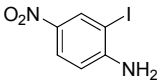
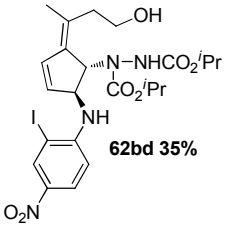
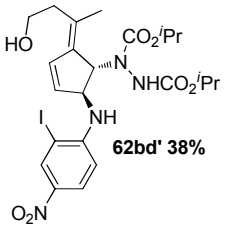
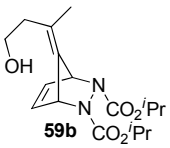
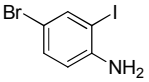
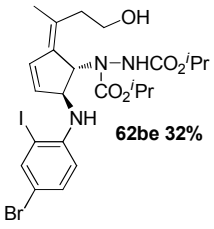
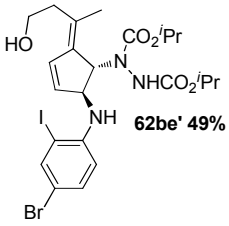
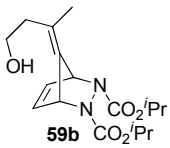
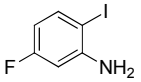
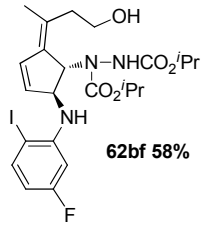
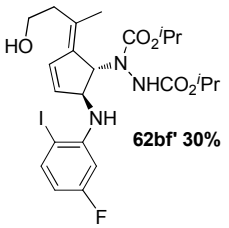
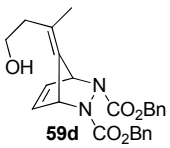
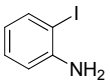
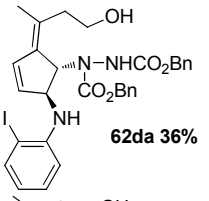
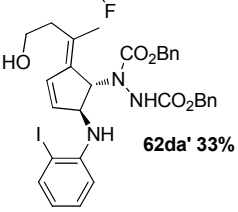
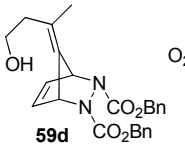
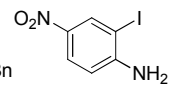
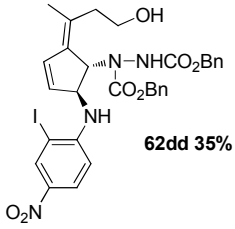
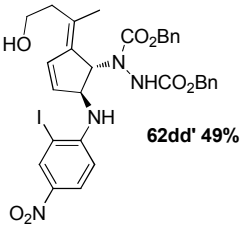
Reaction conditions: azabicyclic olefin (1.2 equiv.), iodoaniline (1.0 equiv.), $Sc(OTf)_3$ (2 mol%), toluene (2.5 mL), rt, 6 h

To investigate the scope and generality of this methodology, we carried out reactions with 2-iodoanilines bearing fluoro, bromo, nitro and trifluoromethyl groups (Table 4.3). All the substituted *o*-iodoanilines afforded the expected alkylidenecyclopentenes in moderate to good yields. In the case of adducts derived from di-*tert*-butyl azodicarboxylate (DTAD) and dibenzyl azodicarboxylate (DBAD), the yields were comparatively low. In most of the cases, the yield of product **62** was higher than that of **62′**.

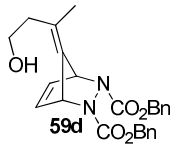
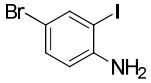
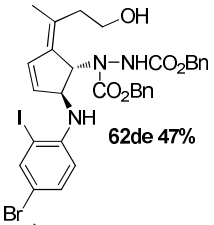
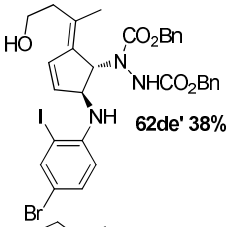
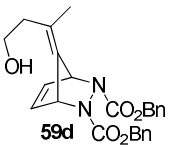
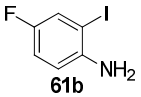
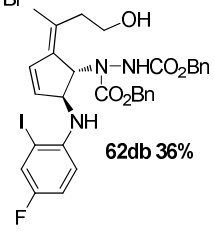
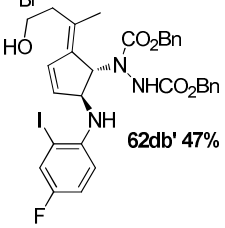
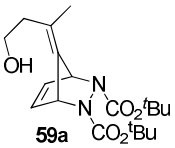
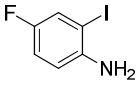
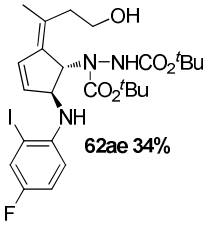
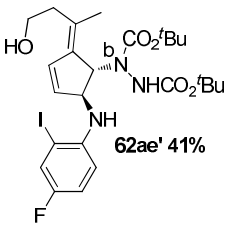
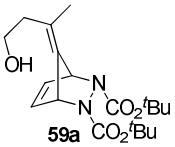
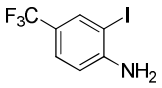
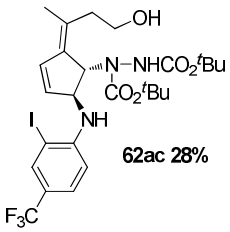
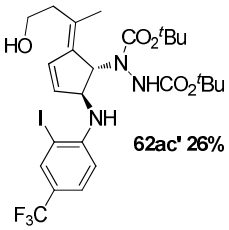
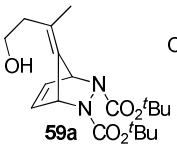
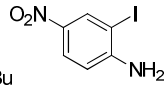
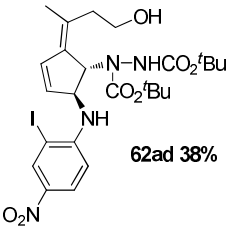
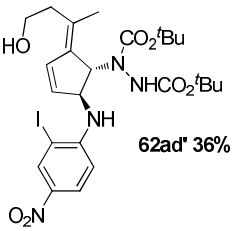
Table 4.3: Reaction of various hydroxyl derived diazanorbornenes with substituted 2-iodo aniline

Entry	Diazabicyclic olefins	2-iodoanilines	Products -Yield	
1	 **59c**	 **61a**	 **62ca 56%**	 **62ca' 39%**
2	 **59c**	 **61b**	 **62cb 40%**	 **62cb' 28%**
3	 **59c**	 **61c**	 **62cc 40%**	 **62cc' 28%**
4	 **59c**	 **61d**	 **62cd 42%**	 **62cd' 39%**
5	 **59c**	 **61e**	 **62ce 47%**	 **62ce' 36%**
6	 **59c**	 **61f**	 **62cf 56%**	 **62cf' 31%**
7	 **59b**	 **61a**	 **62ba 50%**	 **62ba' 32%**

Reaction conditions: diazabicyclic olefin (1.2 equiv.), iodoaniline (1.0 equiv.), $Sc(OTf)_3$ (2 mol%), toluene (2.5 mL), rt, 6 h

Entry	Diazabicyclic olefins	2-iodoanilines	Products -Yield	
8	 **59b**	 **61b**	 **62bb 58%**	 **62bb' 21%**
9	 **59b**	 **61c**	 **62bc 56%**	 **62bc' 20%**
10	 **59b**	 **61d**	 **62bd 35%**	 **62bd' 38%**
11	 **59b**	 **61e**	 **62be 32%**	 **62be' 49%**
12	 **59b**	 **61f**	 **62bf 58%**	 **62bf' 30%**
13	 **59d**	 **61a**	 **62da 36%**	 **62da' 33%**
14	 **59d**	 **61d**	 **62dd 35%**	 **62dd' 49%**

Reaction conditions:diazabicyclic olefin (1.2 equiv.), iodoaniline (1.0 equiv.), $Sc(OTf)_3$ (2 mol%), toluene (2.5 mL), rt, 6 h

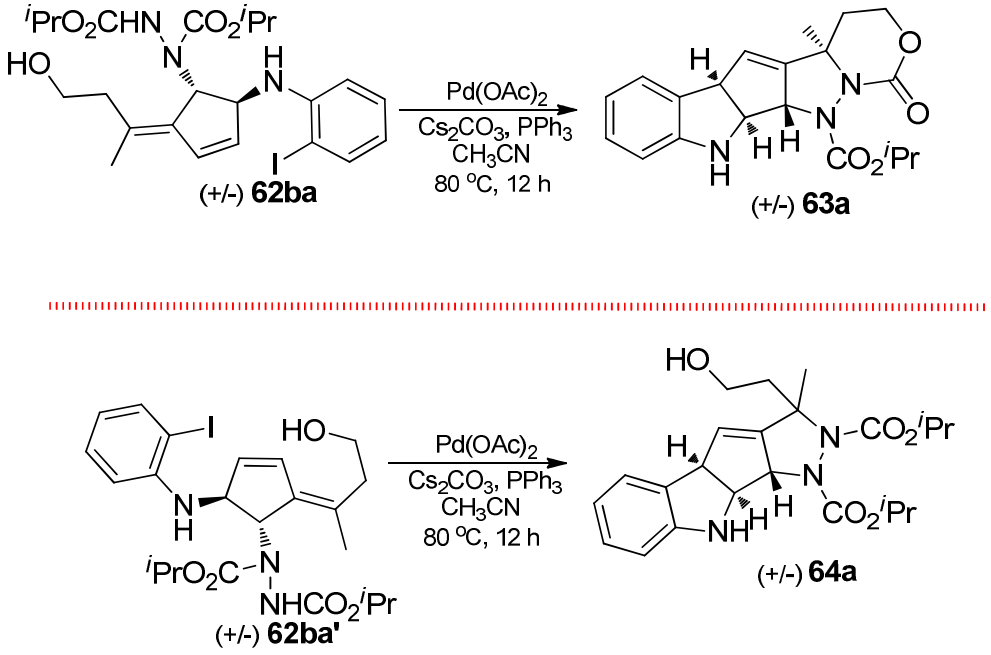
Entry	Diazabicyclic olefins	2-iodoanilines	Products -Yield	
15	 **59d**	 **61e**	 **62de 47%**	 **62de' 38%**
16	 **59d**	 **61b**	 **62db 36%**	 **62db' 47%**
17	 **59a**	 **61e**	 **62ae 34%**	 **62ae' 41%**
18	 **59a**	 **61c**	 **62ac 28%**	 **62ac' 26%**
19	 **59a**	 **61d**	 **62ad 38%**	 **62ad' 36%**

Reaction conditions: diazabicyclic olefin (1.2 equiv.), iodoaniline (1.0 equiv.), $Sc(OTf)_3$ (2 mol%), toluene (2.5 mL), rt, 6 h

4.4.4. Syntheses of Cyclopentene Fused to Indoline, Pyrazolidine and 1,3-Oxazinan- 2-one

To explore the synthetic utility of the hydroxyl appended alkylidene cyclopentene, the intramolecular Heck cyclization was conducted in the presence of $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%) and Cs_2CO_3 in acetonitrile at 80 ^oC for 12 hours. Gratifyingly, the expected novel pentacyclic framework (±)-**63a** was obtained from the isomer **62ba** in 51%

yield, and the regular indoline, pyrazolidine fused cyclopentene (±)-**64a** was obtained from **62ba′** in 68% yield (Scheme 4.24).



Scheme 4.24: The synthetic utility of the hydroxyl appended alkylidene cyclopentene

The structure of (±)-**63a** was established by IR, ^{1}H, ^{13}C and mass spectrometry. The IR spectrum showed characteristic -NH absorption at 3375 cm^{-1} whereas the carbethoxy groups showed a sharp signal at 1734 cm^{-1}. The ^{1}H NMR spectrum showed the aromatic protons as a multiplet in the region δ 7.06- 6.67 ppm. The olefin proton was observed as broad singlet at δ 5.99 ppm. The proton attached to the C-5 carbon atom resonated as a multiplet in the region δ 4.31- 4.28 ppm. The proton on the ring junction carbon (C-4) resonated as a multiplet in the region δ 4.13- 4.10 ppm. The proton attached to C-3 resonated as a singlet at δ 4.79 ppm. The multiplet in the region δ 4.38- 4.13 ppm was assigned to the proton on C-9 which is attached to oxygen. The proton on the carbon C-8 resonated as a multiplet in the region δ 2.24- 2.16 ppm. The multiplet in the region δ 5.02- 5.01 ppm was assigned to the -CH- protons of two isopropyl groups. The methyl protons of isopropyl group resonated as multiplets at δ 1.36- 1.27 ppm along with the methyl group. The ^{1}H NMR spectrum of the compound (±)-**63a** is shown in Figure 4.11.

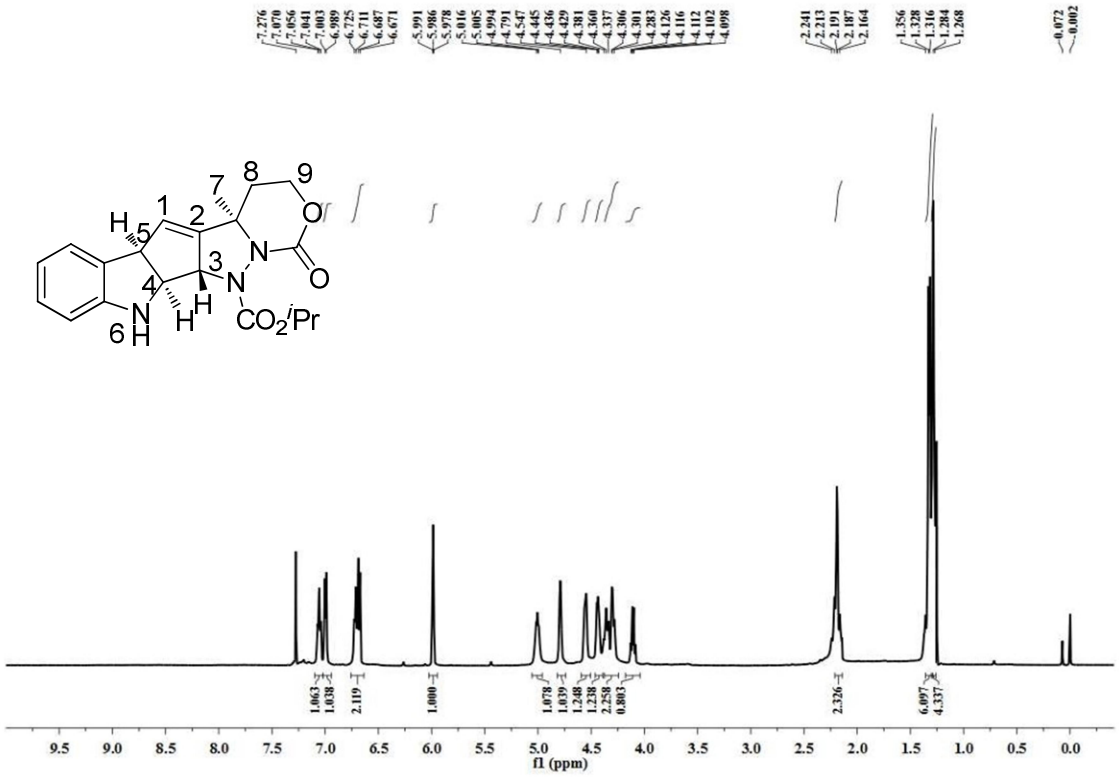


Figure 4.11: ^{1}H NMR spectrum of compound (±)-**63a**

The ^{13}CNMR spectrum (Figure 4.12) of (±)-**63a** showed peaks at δ 154.5 and 153.1 ppm corresponding to the carbonyl carbons. The signals of the olefinic carbons could be found along with the aromatic carbons in the region δ 135.1- 116.0 ppm. The peak at δ 57.8 ppm was assigned to the C-5 carbon atom. The signal of ring junction carbon (C-4) was observed at δ 72.1 ppm. The signal at δ 63.4 was attributed to the carbon C-9 which is attached to the oxygen atom. The methyl carbons of the hydrazine group showed a sharp signal at 21.8 ppm, whereas the secondary carbon of the isopropyl group resonated at δ 72.5 ppm. The assigned structure of (±)-**63a** was well supported by mass spectra, showing the molecular ion peak at *m/z* 392.1586. [$C_{20}H_{23}N_3NaO_4$].

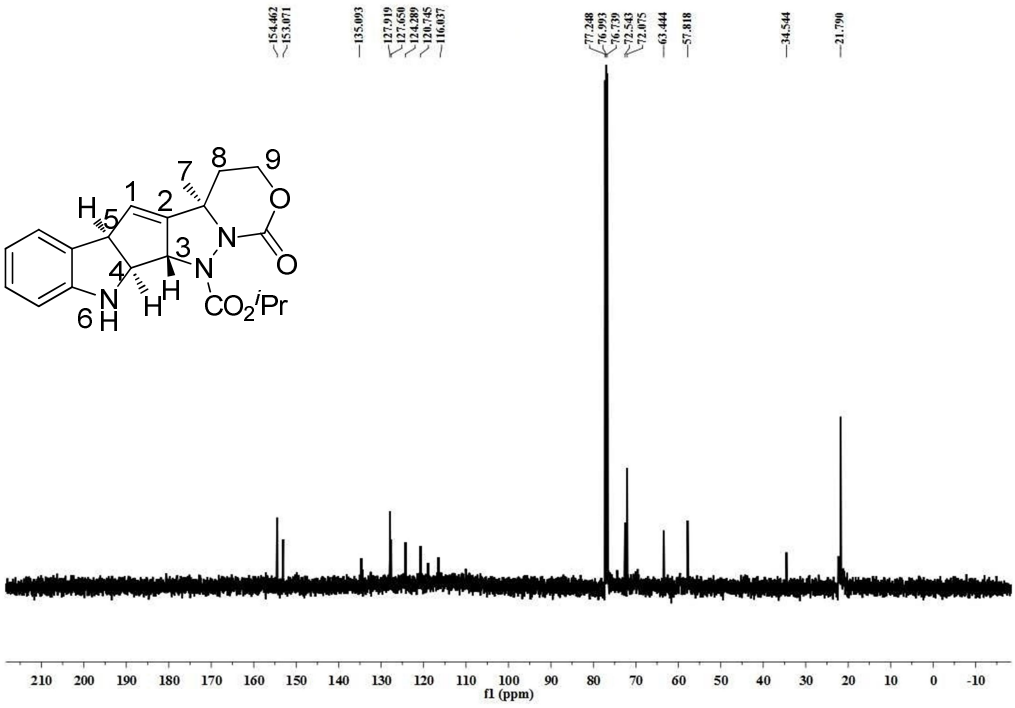


Figure 4.12: ^{13}C NMR spectrum of compound **(±)-63a**

The structure and relative stereochemistry of the pentacyclic molecules were supported by spectral analysis and unambiguously confirmed by single crystal X-ray analysis of the compound (±)-**63b** (Figure 4.13).

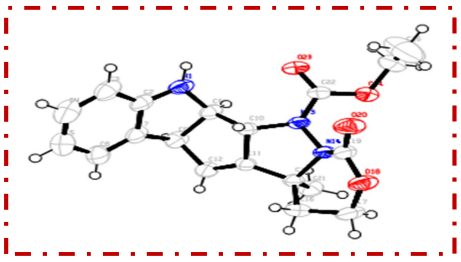
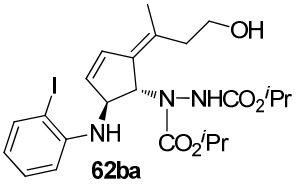
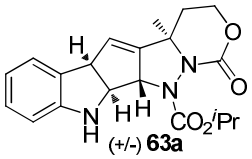
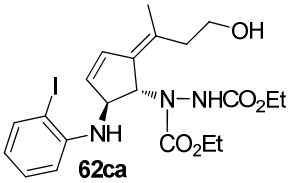
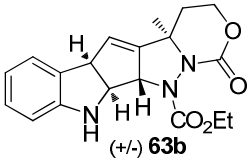
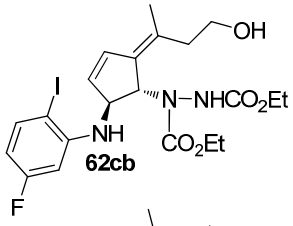
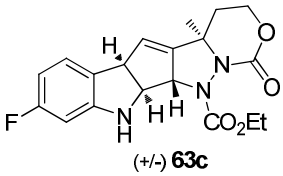
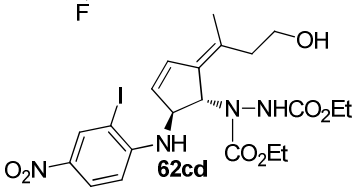
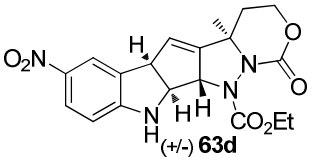
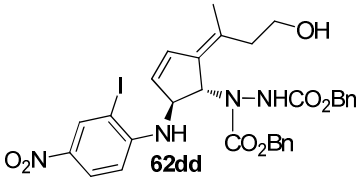
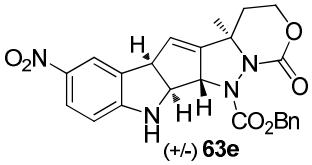
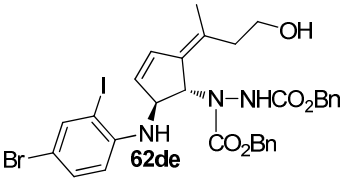
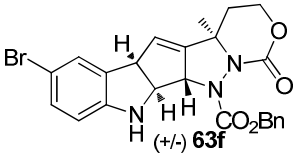
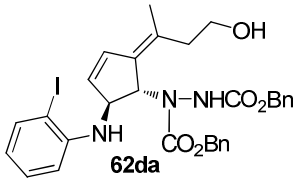
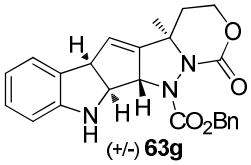


Figure 4.13: Single crystal X-ray structure of compound **(±)-63b**

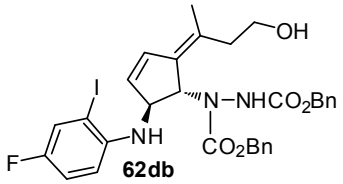
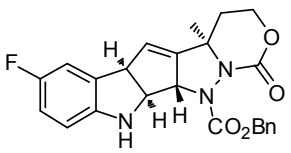
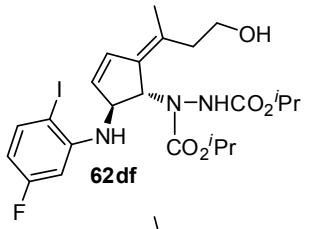
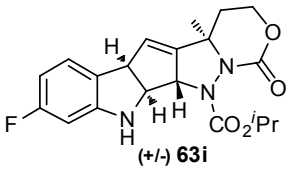
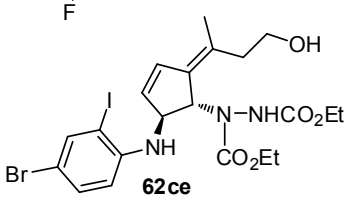
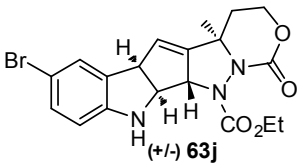
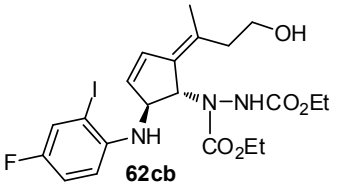
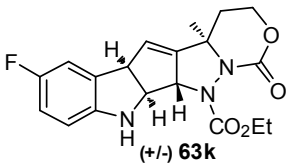
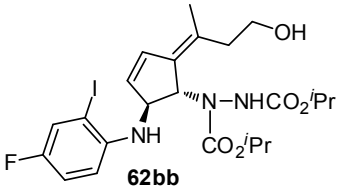
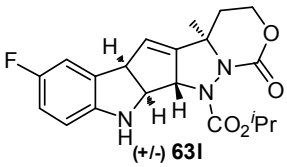
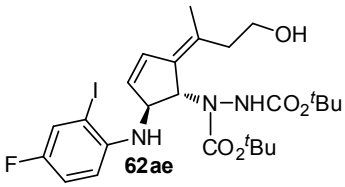
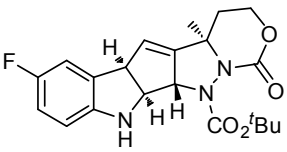
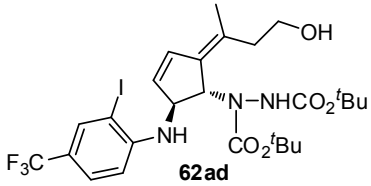
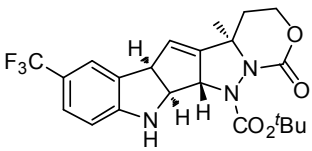
Surprised and pleased by these interesting results, the generality of the intramolecular Heck cyclization of different alkylidenecyclopentene isomers **62** were examined. The palladium catalyzed cyclization smoothly afforded the corresponding pentacyclic products in moderate to good yields (Table 4.4). Nitro-substituted alkylidenecyclopentenes gave lower yields than other substituted cyclopentenes. In the case of *tert*-butyl protected hydrazine containing alkylidenecyclopentene, the expected product was not observed, which might be

due to the steric hindrance involved in the final intramolecular nucleophilic attack of the hydroxy group.

Table 4.4: Intramolecular Heck cyclisation of alkylidenecyclopentenes **62**

Entry	Alkylidenecyclopentene	Products	Yield
1	 **62ba**	 (+/-) **63a**	51%
2	 **62ca**	 (+/-) **63b**	68%
3	 **62cb**	 (+/-) **63c**	72%
4	 **62cd**	 (+/-) **63d**	36%
5	 **62dd**	 (+/-) **63e**	42%
6	 **62de**	 (+/-) **63f**	48%
7	 **62da**	 (+/-) **63g**	52%

Reaction conditions: Alkylidenecyclopentene (1.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (2 equiv.), CH_3CN (2 mL), 80 °C, 12 h.

Entry	Alkylidenecyclopentene	Products	Yield
8	 **62db**	 **(+/-) 63h**	49%
9	 **62df**	 **(+/-) 63i**	70%
10	 **62ce**	 **(+/-) 63j**	69%
11	 **62cb**	 **(+/-) 63k**	62%
12	 **62bb**	 **(+/-) 63l**	52%
13	 **62ae**		(0%)
14	 **62ad**		(0%)

Reaction conditions: Alkylidenecyclopentene (1.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (2 equiv.), CH_3CN (2 mL), 80 °C, 12 h.

4.4.5. Syntheses of Regular Indoline Pyrazolidine Fused Cyclopentene

In the case of the second isomer **62ba**', the intramolecular Heck reaction affords the regular indoline, pyrazolidine fused cyclopentenes (±)-**64a**; which is in accordance of a previous report [Radhakrishnan 2013a]. The presence of a free hydroxyl group in the product makes it amenable to further modifications.

The structure of (±)-**64a** was established by IR, ^{1}H, ^{13}C and mass spectrometry. The IR spectrum showed characteristic -OH and -NH absorption at 3468 and 3386 cm^{-1} respectively whereas the carbethoxy groups showed a sharp signal at 1698 cm^{-1}. The ^{1}H NMR spectrum showed the aromatic protons as two multiplets in the region δ 7.08- 7.01 and 6.74- 6.68 ppm respectively. The olefinic proton was observed as a triplet at δ 5.98 ppm.The proton attached to the C-5 carbon atom resonated as a multiplet in the region δ 4.56- 4.52 ppm. The proton on the ring junction carbon (C-4) resonated as a broad singlet at δ 4.42 ppm. The proton attached to the neighboring carbon (C-3) shows a broad singlet at δ 4.69 ppm. The multiplet in the region δ 5.00- 4.92 ppm was assigned to the -CH- of the isopropyl group. The methyl protons resonated as a singlet at δ 1.70 ppm. The ^{1}H NMR spectrum of the compound (±)-**64a** is shown in Figure 4.14.

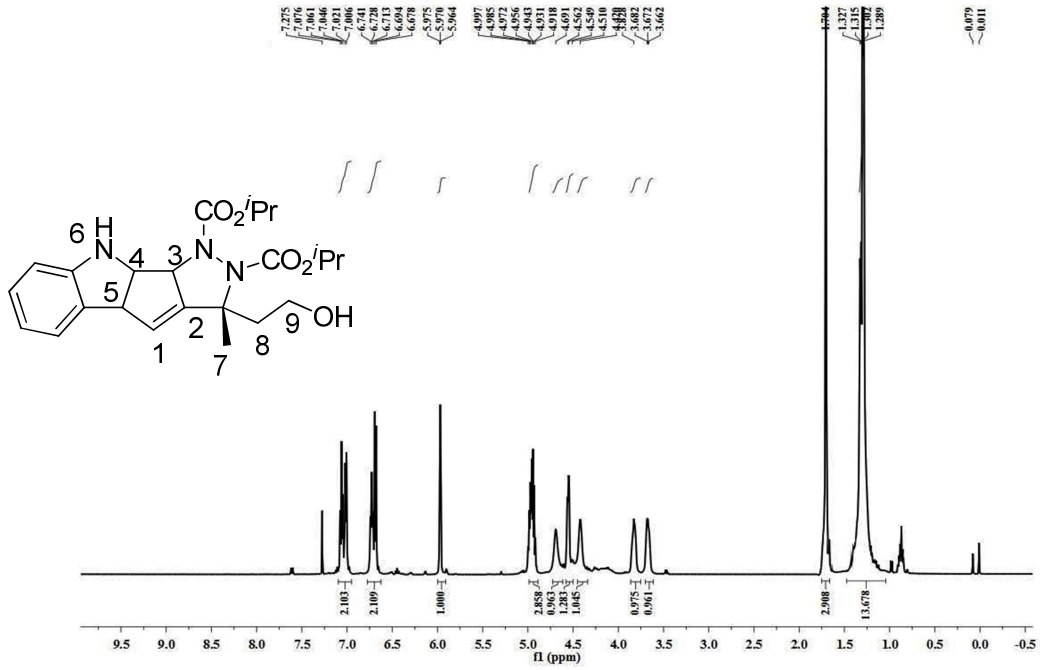


Figure 4.14: ^{1}H NMR spectrum of compound **(±)-64a**

The ^{13}C NMR spectrum (Figure 4.15) of (±)-**64a** showed peaks at δ 155.4 and 151.2 ppm which correspond to the carbonyl carbons. The signals of the olefinic carbons could be found along with the aromatic carbons in the region δ 149.4- 110.2 ppm, whereas the carbon attached to the oxygen atom resonated at 58.9 ppm. The signals of the ring junction carbons C-4 and C-5 were observed at δ 72.9 and 56.9 ppm respectively. The signal at δ 75.2 ppm was attributed to the carbon C-3 and the methylene carbons resonated at δ 22.2 ppm. The methyl carbons of the hydrazine group showed sharp peaks at δ 22.0 and 21.8 ppm. The assigned structure was well supported by mass spectra, showing the molecular ion peak at *m/z* 452.2165 [$C_{23}H_{31}N_3NaO_5$].

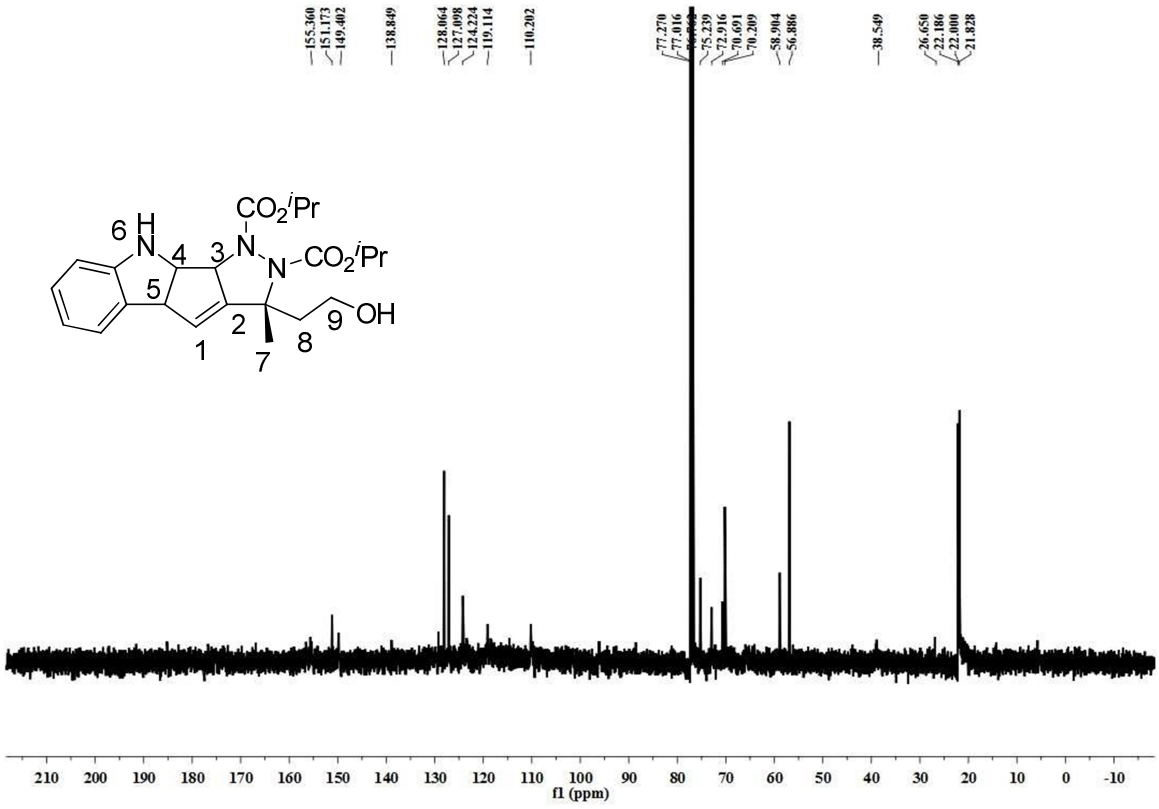
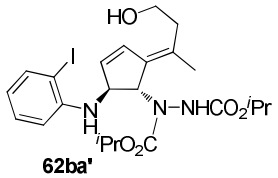
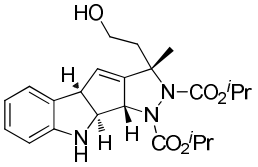
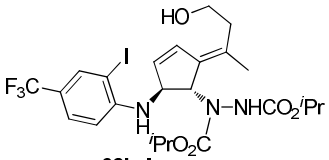
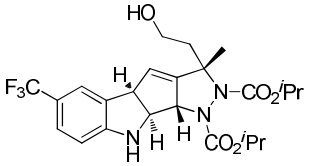
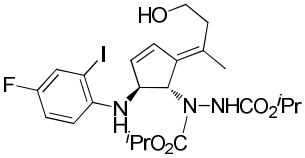
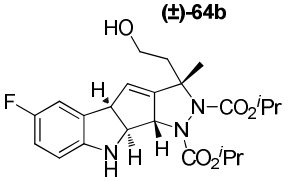
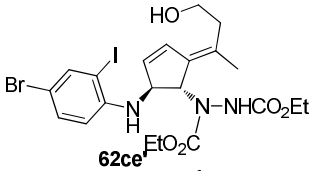
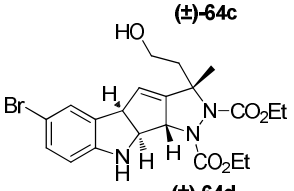
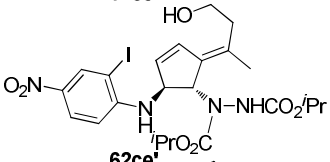
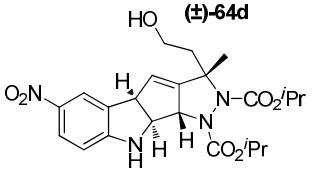
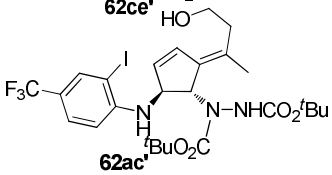
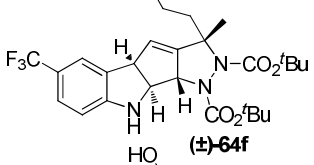
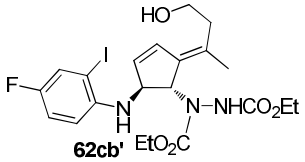
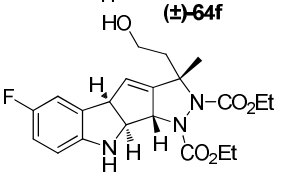
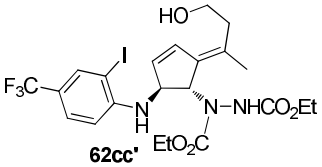
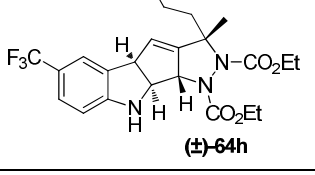


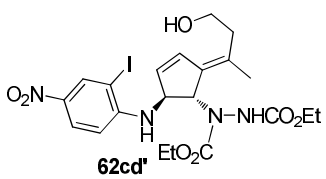
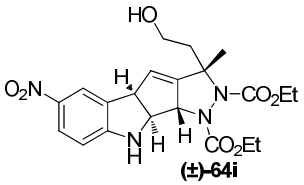
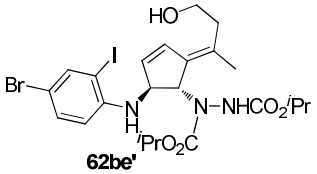
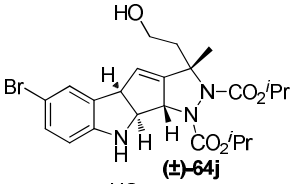
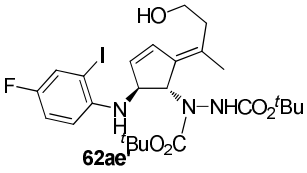
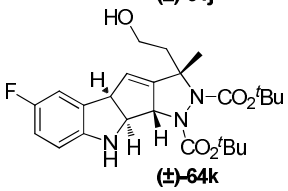
Figure 4.15: ^{13}C NMR spectrum of compound **(±)-64a**

To verify the scope of this reaction, we have extended this strategy to various 3,4-disubstituted alkylidene cyclopentenes **62'** and the results are summarized in Table 4.5.

Table 4.5: Intramolecular Heck cyclisation of alkylidenecyclopentenes **62'**

Entry	Alkylidenecyclopentene	Products	Yield
1	 **62ba'**	 **(±)-64a**	68%
2	 **62bc'**	 **(±)-64b**	48%
3	 **62bb'**	 **(±)-64c**	53%
4	 **62ce'**	 **(±)-64d**	66%
5	 **62ce'**	 **(±)-64e**	58%
6	 **62ac'**	 **(±)-64f**	31%
7	 **62cb'**	 **(±)-64g**	39%
8	 **62cc'**	 **(±)-64h**	74%

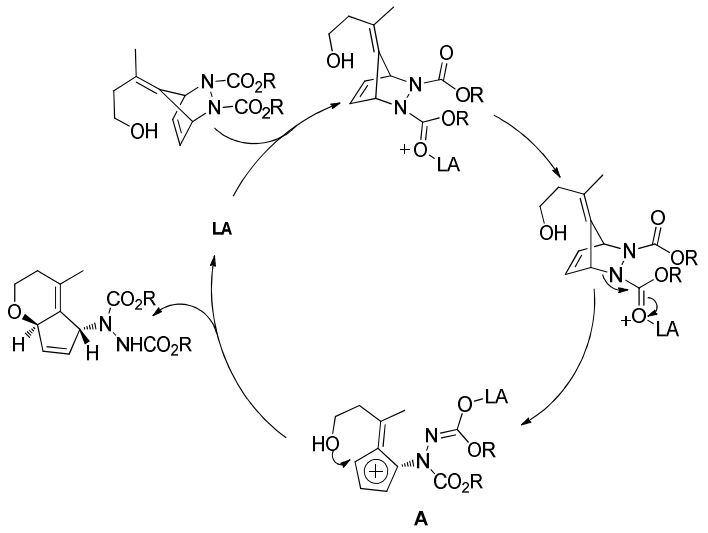
Reaction conditions: Alkylidenecyclopentene (1.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (2 equiv.), CH_3CN (2 mL), 80 °C, 12 h.

Entry	Alkylidenecyclopentene	Products	Yield
9	 **62cd'**	 **(±)-64i**	60%
10	 **62be'**	 **(±)-64j**	42%
11	 **62ae'**	 **(±)-64k**	49%

Reaction conditions: Alkylidenecyclopentene (1.0 equiv.), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (2 equiv.), CH_3CN (2 mL), 80 °C, 12 h.

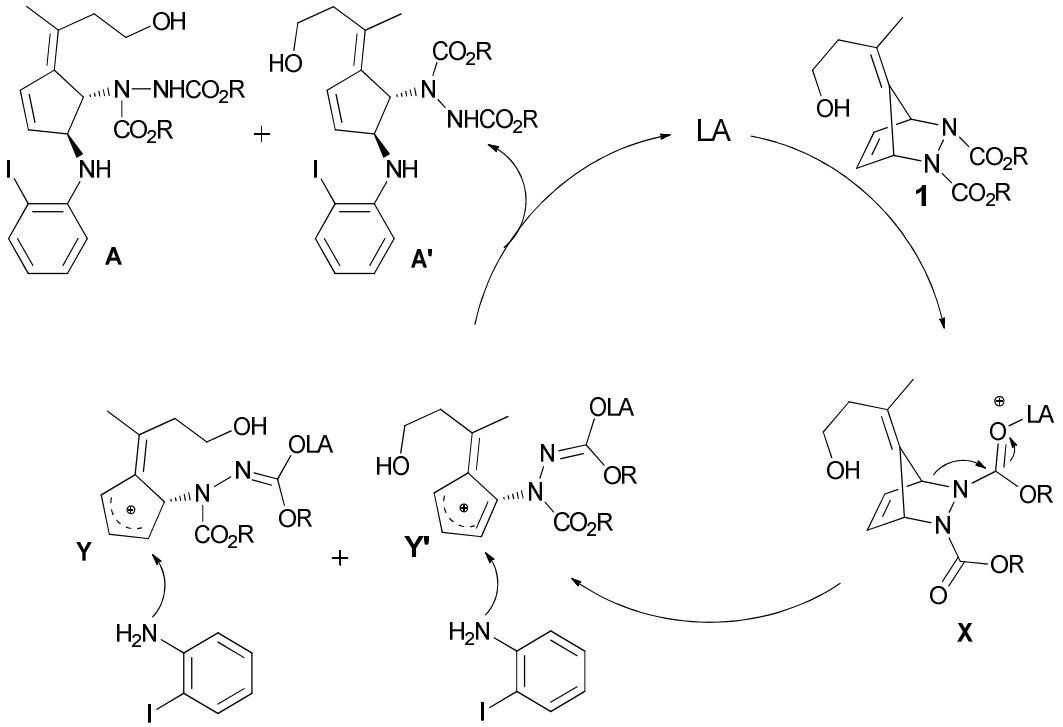
4.5. Mechanistic Pathway

A plausible mechanism for the formation of cyclopentene fused dihydro-2H-pyran core is shown in Scheme 4.25. In the first step, the Lewis acid coordinates to the ester carbonyl group of diazabicyclic olefin. Subsequent cleavage of the adjacent ring C–N bond leads to a transient allylic cationic species **A**, which on intramolecular nucleophilic attack by the hydroxyl group from the face opposite to that of the hydrazine moiety furnish the fused tetrahydrocyclopenta[b]pyran.



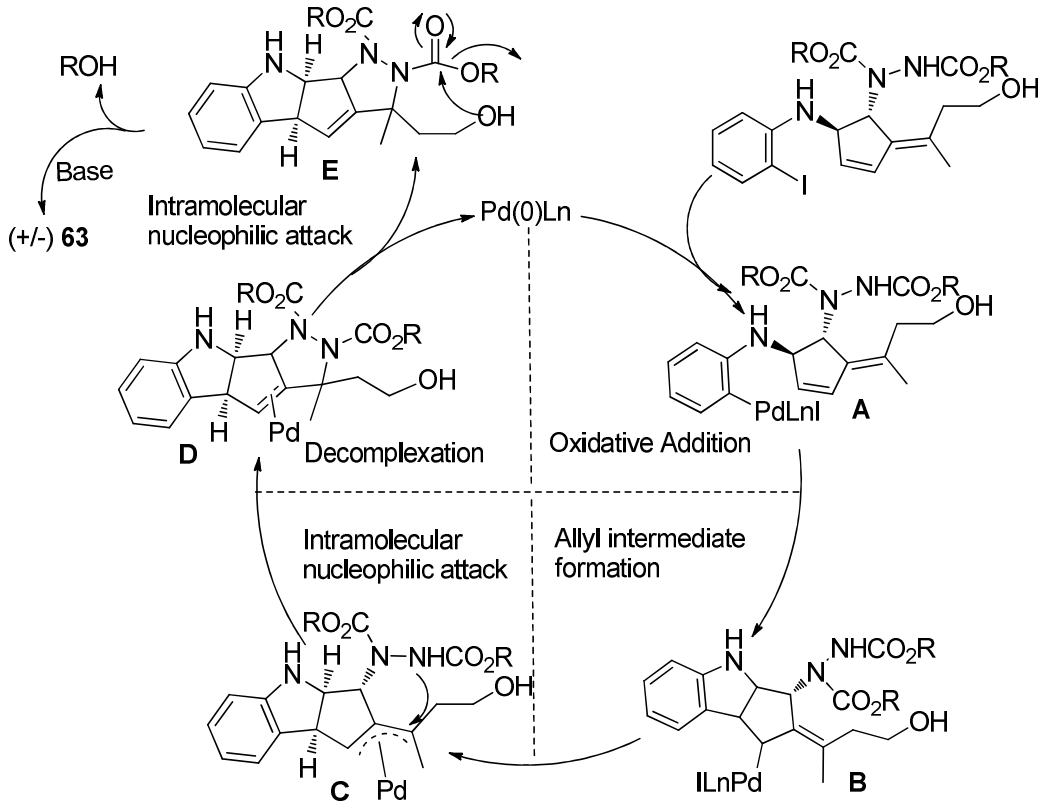
Scheme 4.25: Mechanistic Pathway

A plausible mechanism for the Lewis acid catalyzed ring-opening of diazabicyclic olefin with *o*-iodoaniline is illustrated in Scheme 4.26. In the first step, Lewis acid coordinates to the ester carbonyl group of the bicyclic alkene resulting in the cleavage of C-N bond furnishing allylic cationic species **Y** and **Y'**. The external nucleophile (*o*-iodoaniline) then attacks the allylic intermediate through the less hindered face affording *trans*-1,2-disubstituted alkylidene cyclopentene.



Scheme 4.26: Mechanistic Pathway

A plausible mechanism for the formation of a novel pentacyclic framework having cyclopentene fused to indoline, pyrazolidine and 1,3-oxazinan-2-one skeleton (±)-**64** is illustrated in Scheme 4.27**.** The first step in the catalytic cycle is the oxidative addition of Pd(0) to the aryl iodide, which leads to the formation of **A**. Coordination of palladium species to the double bond of intermediate **A** generates the key intermediate D through a π-allyl palladium complex **C**. The base assisted intramolecular nucleophilic attack furnishes the intermediate **E**. In the final step, the intramolecular nucleophilic attack of the hydroxy group onto the ester carbonyl of the hydrazine moiety followed by the elimination of an alcohol moiety give rise to the observed product (±)-**64a.**



Scheme 4.27: Mechanistic Pathway

4.6. Conclusion

In conclusion, we have unravelled a sequential Lewis acid-palladium mediated transformation of hydroxy group tethered diazanorbornene towards the synthesis of tetrahydrocyclopenta[b]pyrans and novel pentacyclic frameworks with cyclopentene fused to indoline, pyrazolidine, and 1,3-oxazinan-2-one skeletons. Through the present strategy, we have efficiently exploited the strain release in pentafulvene derived diazanorbornenes with internal/external nucleophiles furnishing products with multiple stereo centers.

4.7. Experimental Details

General information about the experiments is given in section 2.9.1 of Chapter 2a.

4.7.1. General procedure for the Preparation of Pentafulvene Derived Diazabicyclic Olefins

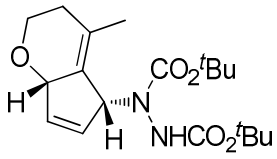
General procedure for the preparation of pentafulvene derived diazabicyclic olefins is given in section 3.6.1 of Chapter 3

4.7.2. General Procedure for the Lewis Acid Catalyzed Intramolecular Rearrangement of Strained Alkenes Towards Cyclopentannulated dihydro[*2H*]pyrans.

A mixture of pentafulvene derived bicyclic hydrazine (1.0 equiv.) and $Sc(OTf)_3$ (2 mol %) were weighed in a schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added, and the reaction mixture was purged with argon and allowed to stir at room temperature for 3 hours. The solvent was evaporated *in vacuo* and the residue on silica gel (100-200 mesh) column chromatography yielded cyclopentannulated dihydro[*2H*]pyrans**.**

Preparation of Compound 60a

Following the general procedure (Section 4.7.2), the treatment of pentafulvene derived diazanorbornene **59a** (60 mg, 0.16 mmol) and $Sc(OTf)_3$ (2 mg, 0.003 mmol) in dry toluene (2 mL) at room temperature for 3 h yielded **60a** (49 mg, 82 %) as a light yellow viscous liquid upon purification by column chromatography (25 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3321, 2975, 2933, 2875, 1783, 1731, 1481, 1459, 1393, 1367, 1277, 1248, 1162, 1078, 1044, 1015, 925, 783, 749 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 6.67- 6.66 (m, 1H), 6.45 (bs, 1H), 5.96 (d, *J*= 5.0 Hz, 1H), 5.51 (d, *J*= 6.0 Hz, 1H), 5.09 (d, *J*= 7.0 Hz, 1H), 3.44-3.40 (m, 2H), 2.44-2.39 (m, 2H), 1.93-1.82 (m, 3H), 1.53- 1.40 (m, 9H), 1.22-1.15 (m, 9H) ppm.

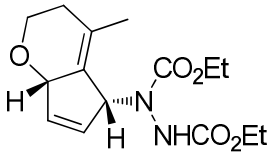
^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.2, 154.1, 136.2, 135.6, 133.3, 130.1, 82.3, 80.8, 73.0, 60.0, 57.9, 36.3, 28.4, 28.2, 27.3, 20.2 ppm.

HRMS (ESI): Calcd for $C_{19}H_{30}N_2NaO_5$: 389.2052; Found: 389. 2036.

Preparation of Compound 60c

Following the general procedure (Section 4.7.2), the treatment of pentafulvene derived diazanorbornene **59c** (60 mg, 0.19 mmol) and $Sc(OTf)_3$ (2 mg, 0.004 mmol) in dry toluene (2 mL) at room temperature for 3 h yielded **60c** (53 mg, 88 %) as a light yellow

viscous liquid upon purification by column chromatography (30 % ethyl acetate-hexane)



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

IR (Neat) ν_{max}: 3325, 2984, 2928, 1710, 1515, 1473, 1415, 1381, 1306, 1231, 1099, 1061, 863, 767 cm^{-1}.

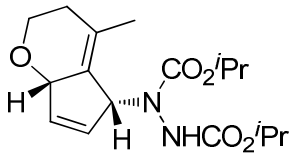
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 6.72 (bs,1H), 6.32-6.17 (m, 1H), 6.00-5.72 (m, 1H), 4.75 (s, 1H), 4.23- 4.13 (m, 6H), 3.76-3.71 (m, 1H), 2.31-2.28 (m, 1H), 2.01- 1.73 (m, 4H), 1.29- 1.21 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.8, 155.3, 137.2, 135.8, 132.0, 130.0, 80.4, 65.1, 64.1, 63.4, 59.2, 30.3, 29.6, 20.2, 18.8, 14.4, 14.1 ppm.

HRMS (ESI): Calcd for $C_{15}H_{22}N_2NaO_5$: 333.1426; Found: 333.1424.

Preparation of Compound 60b

Following the general procedure (Section 4.7.2), the treatment of pentafulvene derived diazanorbornene **59b** (57 mg, 0.17 mmol) and $Sc(OTf)_3$ (2 mg, 0.004 mmol) in dry toluene (2 mL) at room temperature for 3 h yielded **60b** (49 mg, 86 %) as a light yellow viscous liquid upon purification by column chromatography (25 % ethyl acetate-hexane)



R_f: 0.65 (hexane/ethyl acetate = 7:3).

IR (Neat) ν_{max}: 3320, 2983, 2932, 1716, 1514, 1464, 1382, 1306, 1232, 1179, 1110, 931, 769, 629 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 6.52 (bs,1H), 6.16-5.84 (m, 2H), 5.01-4.90 (m, 3H), 4.74 (s, 1H), 4.14- 4.10 (dd, J_1= 11.5Hz, J_2= 7.5 Hz, 1H), 2.31-2.26 (m, 1H), 1.98-1.78 (m, 4H), 1.26 (d, J= 6.0 Hz, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.6, 154.7, 136.9, 132.1, 129.8, 80.4, 69.7, 69.4, 65.0, 53.8, 30.2, 29.6, 29.1, 21.1, 18.6 ppm.

HRMS (ESI): Calcd for $C_{17}H_{26}N_2NaO_5$: 361.1739; Found: 361.1739.

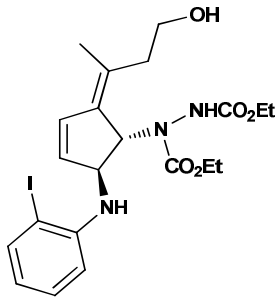
4.7.3. General Procedure for the Lewis Acid Catalyzed Reaction of Pentafulvene

Derived Bicyclic Hydrazines Towards the Synthesis of 62 and 62'.

A mixture of pentafulvene derived bicyclic hydrazine (1.4 equiv.), 2-iodo aniline (1.0 equiv.) and $Sc(OTf)_3$ (2 mol %) were weighed in a schlenk tube and degassed for 10 minutes. Dry toluene (2 mL) was added, and the reaction mixture was purged with argon and allowed to stir at room temperature for 6 hours. The solvent was evaporated *in vacuo* and the residue on silica gel (100-200 mesh) column chromatography yielded *trans*-3,4-disubstituted alkylidene cyclopentene (**62**) along with other isomer (**62').**

Preparation of Compounds 62ca and 62ca'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59c** (117 mg, 0.38 mmol) and 2-iodoanilines **61a** (60 mg, 0.27 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (3 mg, 0.005 mmol) at room temperature for 6 h yielded **62ca** (80 mg, 56 %) and **62ca'** (56 mg, 39 %) as yellow viscous liquids upon purification by column chromatography (25 % and 30 % ethyl acetate-hexane respectively).



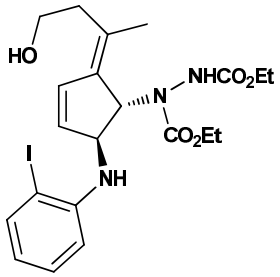
R_f: 0.48 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3726, 3383, 3285, 3066, 2977, 2920, 1708, 1594, 1414, 1386, 1302, 1267, 1226, 1128, 1158, 1022, 862, 808, 758 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.76-7.59 (m, 2H), 7.20-7.17 (m, 2H), 6.58(d, *J*= 6.0 Hz, 1H), 6.40 (t, *J*= 7.5 Hz, 1H), 5.96 (s, 1H), 5.08-4.71 (m, 2H), 4.18-4.0 8 (m, 5H), 3.80 (s, 1H), 3.72 (s, 1H), 2.44-2.36 (m, 1H), 1.97-1.94 (m, 1H), 1.87 (s, 3H), 1.26-1.21(m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.2, 155.8, 146.1, 138.8, 137.4, 134.1, 133.1, 129.5, 128.6, 128.3, 124.0, 119.0, 113.7, 85.4, 64.1, 62.8, 62.3, 61.8, 37.0, 17.7, 14.4 ppm.

HRMS (ESI): Calcd for $C_{21}H_{28}IN_3NaO_5$: 552.0971; Found: 552.0976.



R_f : 0.33 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3724, 3382, 3283, 3064, 2975, 2918, 1707, 1592, 1414, 1386, 1301, 1265, 1228, 1127, 1156, 1023, 861, 807, 756 cm^{-1}.

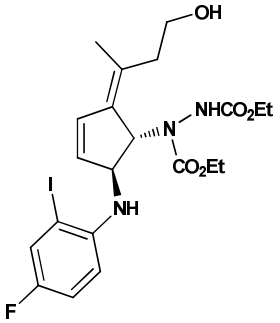
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.62 (d, *J*= 6.0 Hz, 1H), 7.48-7.45 (m,1H), 7.21-7.18 (m, 1H), 6.83 (bs, 1H), 6.67 (d, *J*= 5.5 Hz, 1H), 6.44-6.42 (m, 1H), 5.96 (s, 1H), 5.11-4.76 (m, 2H), 4.19-4.05 (m, 5H), 4.04-3.71 (m, 2H), 2.74 (bs, 1H), 2.17-2.14 (m, 1H), 1.75-1.70 (m, 3H), 1.26-1.21(m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.2, 156.0, 145.9, 140.7, 138.9, 138.0, 134.5, 132.0, 129.4, 119.0, 112.5, 85.5, 63.1, 61.9, 60.4, 38.6, 18.6, 14.3 ppm.

HRMS (ESI): Calcd for $C_{21}H_{28}IN_3NaO_5$: 552.0971; Found: 552.0974

Preparation of Compound 62cb and 62cb'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59c** (109 mg, 0.35 mmol) and 2-iodoanilines **61b** (60 mg, 0.25 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (3 mg, 0.005 mmol) at room temperature for 6 h yielded **62cb** (56 mg, 40 %) and **62cb'** (38 mg, 28 %) as yellow viscous liquids upon purification by column chromatography (25 % and 30 % ethyl acetate-hexane respectively)

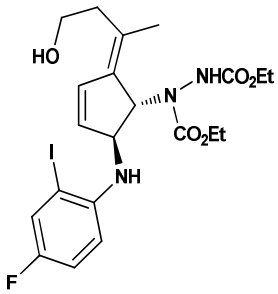


R_f: 0.53 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3728, 3386, 3289, 3066, 2977, 2920, 1708, 1594, 1504, 1412, 1386, 1303, 1266, 1226, 1125, 1060, 1023, 861, 808, 758 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.57-7.39 (m, 2H), 7.05-6.99 (m, 2H), 6.62 (d, *J*= 5.5 Hz, 1H), 5.98 (s, 1H), 5.10-4.76 (m, 2H), 4.27-4.20 (m, 5H), 3.95 (bs, 1H), 3.85 (bs, 1H), 3.78 (bs, 1H), 2.48-2.30 (m, 1H), 2.05-1.99 (m, 1H), 1.90 (s, 3H), 1.32-1.24 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.9, 155.7, 143.1, 136.7, 134.1, 130.7, 125.2, 116.0, 112.8, 83.2,



64.6, 62.8, 61.8, 59.4, 36.9, 30.4, 17.7, 14.4 ppm.

HRMS (ESI): Calcd for $C_{21}H_{27}FIN_3NaO_5$: 570.0877; Found: 570.0885.

R_f: 0.38 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3731, 3368, 3289, 3288, 2977, 2980, 2924, 1710, 1595, 1504, 1411, 1385, 1302, 1262, 1228, 1193, 1124, 1059, 1025, 861, 809, 759 cm^{-1}.

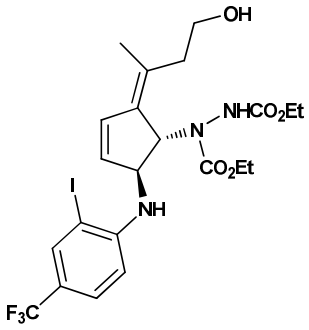
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.41 (bs, 1H), 6.99-6.84 (m, 2H), 6.61 (m, 1H), 5.98 (s,1H), 5.12-4.93 (m,1H), 4.73 (m,1H), 4.27-4.13 (m, 5H), 3.92 (bs, 1H), 3.77 (m, 2H), 2.72-2.71 (m, 1H), 2.27-2.24 (m, 1H), 1.72 (s, 3H), 1.33-1.26 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.3, 155.8, 153.9, 142.9, 137.9, 134.5, 132.6, 125.4, 115.9, 112.4, 84.0, 63.9, 63.2, 62.1, 60.4, 38.5, 29.7, 18.6, 14.4, 14.1 ppm.

HRMS (ESI): Calcd for $C_{21}H_{27}FIN_3NaO_5$: 570.0877; Found: 570.0886.

Preparation of Compound 62cc and 62cc'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59c** (91 mg, 0.29 mmol) and 2-iodoanilines **61c** (60 mg, 0.21 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (2 mg, 0.004 mmol) at room temperature for 6 h yielded **62cc** (50 mg, 40 %) and **62cc'** (36 mg, 28 %) as yellow viscous liquids upon purification by column chromatography (25 % and 30 % ethyl acetate-hexane respectively)



R_f: 0.58 (hexane/ethyl acetate = 3:2).

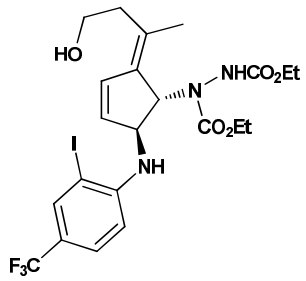
IR (Neat) ν_{max}: 3732, 3307, 2984, 2925, 1717, 1604, 1522, 1412, 1382, 1321, 1273, 1229, 1169, 1115, 1066, 894, 766, 672 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.87-7.85 (m, 1H), 7.49-7.47 (m, 1H), 6.67-6.66 (m,1H), 6.50 (bs, 2H), 5.98 (s, 1H), 5.13-4.95 (m, 2H), 4.49-4.43 (m, 1H), 4.24-4.13 (m, 4H), 3.89-3.81 (m, 2H), 2.52-2.39 (m, 1H), 2.06-2.01

(m, 1H), 1.91(s, 3H), 1.29-1.28 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.3, 156.9, 155.6, 148.7, 136.8, 135.8, 134.6, 131.9, 126.6, 119.8, 111.7, 83.6, 63.9, 62.9, 62.2, 61.8, 59.2, 36.8, 29.7, 17.7, 14.1 ppm.

HRMS (ESI): Calcd for $C_{22}H_{27}F_3IN_3NaO_5$: 620.0845; Found: 620.0847.



R_f: 0.30 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3732, 3459, 3384, 3294, 2980, 2925, 1711, 1604, 1522, 1451, 1409, 1382, 1321, 1279, 1228, 1116, 1070, 893, 859, 816, 759, 733, 676, 632 cm^{-1}.

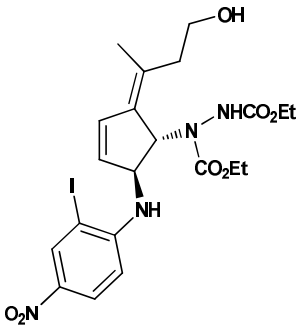
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.89-7.87 (m, 1H), 7.48-7.47 (m, 1H), 7.01-6.90 (m, 2H), 6.73 (d, *J*= 6.0 Hz, 1H), 5.98 (s, 1H), 5.14-4.79 (m, 2H), 4.45 (bs, 1H), 4.28-4.19 (m, 4H), 3.78 (bs, 2H), 2.74-2.70 (m ,1H), 2.29 (bs, 1H), 1.77 (s, 3H), 1.32-1.12 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.3, 155.7, 148.5, 135.9, 127.0, 124.8, 122.9, 120.5, 119.8, 111.3, 83.8, 63.1, 62.2, 60.4, 38.4, 29.7, 22.7, 18.6, 14.3, 14.1 ppm.

HRMS (ESI): Calcd for $C_{22}H_{27}F_3IN_3NaO_5$: 620.0845; Found: 620.0854.

Preparation of Compound 62cd and 62cd'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59c** (100 mg, 0.32 mmol) and 2-iodoanilines **61d** (60 mg, 0.23 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (3 mg, 0.005 mmol) at room temperature for 6 h yielded **62cd** (54 mg, 42 %) and **62cd'** (52 mg, 39 %) as pale yellow viscous liquids upon purification by column chromatography (30 % and 35 % ethyl acetate-hexane respectively)



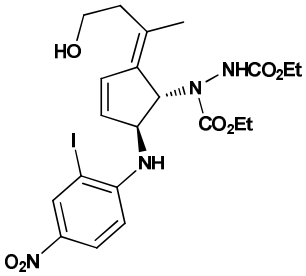
R_f: 0.43 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3730, 3471, 3374, 3075, 2980, 2920, 1736, 1708, 1582, 1501, 1412, 1381, 1322, 1227, 1118, 1060, 1022, 906, 818, 737, 695, 645, 606, 553 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.58 (d, *J*= 12.0 Hz, 1H), 8.17 (d, *J*= 9.0 Hz, 1H),7.64-7.44 (m, 1H), 7.15-7.06 (m, 1H), 6.72 (d, *J*= 6.0 Hz, 1H), 5.97 (s, 1H), 5.14-5.12 (m, 1H), 4.99-4.88 (m, 2H), 4.26-4.15 (m, 5H), 3.91-3.81 (m, 2H), 2.46-2.37 (m, 1H), 2.06-2.02 (m, 1H), 1.93 (s, 3H), 1.33-1.24 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.9, 155.4, 151.1, 138.4, 136.8, 135.3, 131.0, 126.0, 110.2, 82.4, 64.4, 64.1, 63.0, 61.9, 59.7, 36.6, 29.2, 17.8, 14.7, 14.4 ppm.

HRMS (ESI): Calcd for $C_{21}H_{27}IN_4NaO_7$: 597.0822; Found: 597.0828.



R_f: 0.31 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3732, 3468, 3374, 3076, 2980, 2925, 1709, 1582, 1502, 1411, 1381, 1323, 1228, 1117, 1058, 1023, 908, 817, 736, 695, 646, 609, 557 cm^{-1}.

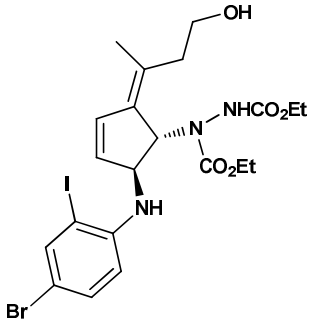
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.56 (d, *J*= 12.0 Hz, 1H), 8.16 (d, *J*= 9.0 Hz, 1H), 7.06-6.68 (m, 2H), 6.76 (d, *J*= 5.5Hz, 1H), 5.97 (s, 1H), 5.14 (s, 1H), 4.97-4.86 (m, 2H), 4.25-4.12 (m, 4H), 3.80 (bs, 2H), 2.75-2.70 (m, 1H), 2.36-2.31 (m, 1H), 1.76 (s, 3H), 1.30-1.25 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.9, 155.1, 150, 9, 138.5, 135.4, 135.1, 125.7, 110.0, 82.5, 63.2, 62.9, 62.0, 60.5, 37.6, 29.7, 14.4 ppm.

HRMS (ESI): Calcd for $C_{21}H_{27}IN_4NaO_7$: 597.0822; Found: 597.0827.

Preparation of Compound 62ce and 62ce'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59c** (87 mg, 0.28 mmol) and 2-iodoanilines **61e** (60 mg, 0.20 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (2 mg, 0.004 mmol) at room temperature for 6 h yielded **62ce** (58 mg, 47 %) and **62ce'** (44 mg, 36 %) as yellow viscous liquids upon purification by column chromatography (20 % and 25 % ethyl acetate-hexane respectively)



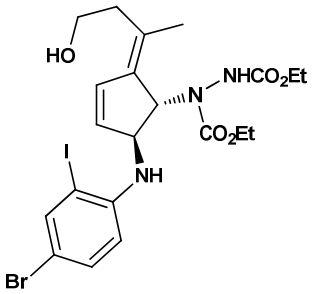
R_f: 0.45 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3371, 3383, 3288, 2979, 2918, 1708, 1579, 1494, 1414, 1382, 1307, 1267, 1227, 1165, 1123, 1060, 1021 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.76-7.64 (m, 1H), 7.45-7.26 (m, 1H), 699-6.88 (m, 2H), 6.73-6.59 (m, 1H), 5.94 (s, 1H), 5.06-4.72 (m, 2H), 4.20-4.15 (m, 5H), 3.83 3.72 (m, 2H), 2.43-2.34 (m, 1H), 2.17-1.95 (m, 1H), 1.88 (s, 3H), 1,32-1,22 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.2, 155.1, 145.4, 139.8, 136.3, 133.8, 132.0, 114.1, 108.5, 85.2, 64.1, 62.9, 62.1, 61.8, 58.9, 53.2, 36.3, 30.1, 17.7, 14.4 ppm.

HRMS (ESI): Calcd for $C_{21}H_{27}BrIN_3NaO_5$: 630.0076; Found: 630.0082.



R_f: 0.23 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3372, 3378, 3282, 2920, 2871, 1706, 1579, 1495, 1413, 1309, 1217, 1170, 1123, 1059, 1021 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.73-7.60 (m, 1H), 7.34-7.23 (m, 2H), 6.99-6.59 (m, 2H), 5.94 (s, 1H), 5.08-4.72 (m, 2H), 4.13-4.10 (m, 5H), 3.75-3.69 (m, 2H), 2.73-2.62(m, 1H), 2.35-2.17 (m, 1H), 1.74-1.66 (m, 3H), 1.37-1.22 (m, 6H) ppm.

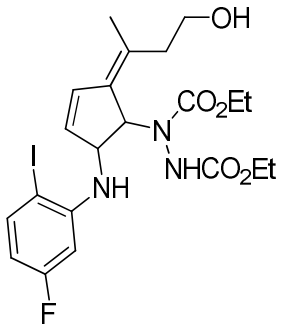
^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.3, 155.8, 145.2, 140.3, 137.9, 134.5, 132.0, 113.4, 109.0, 85.4,

63.4, 63.3, 62.7, 62.1, 60.4, 38.5, 29.7, 18.6, 14.4 ppm.

HRMS (ESI): Calcd for $C_{21}H_{27}BrIN_3NaO_5$: 630.0076; Found: 630.0085.

Preparation of Compound 62cf and 62cf'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59c** (109 mg, 0.35 mmol) and 2-iodoanilines **61f** (60 mg, 0.25 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (3 mg, 0.005 mmol) at room temperature for 6 h yielded **62cf** (78 mg, 56 %) and **62cf'** (44 mg, 31 %) as yellow viscous liquids upon purification by column chromatography (25 % and 35 % ethyl acetate-hexane respectively)



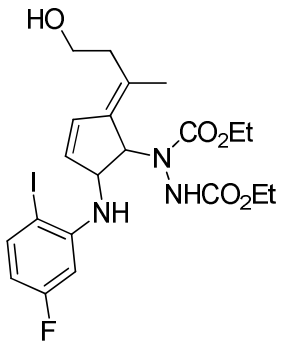
R_f: 0.50 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3728, 3383, 3287, 3061, 2975, 2921, 1708, 1593, 1504, 1411, 1385, 1300, 1268, 1229, 1128, 1064, 1022, 863, 809, 758 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.75-7.49 (m, 2H), 7.01 (bs, 1H), 6.80-6.78 (m, 1H), 6.60 (t, *J*= 6.0 Hz, 1H), 6.20-6.12 (m, 1H), 5.93 (d, *J*= 12.5 Hz, 1H), 5.07-4.70 (m, 2H), 4.22-4.08 (m, 5H), 3.79-3.70 (m, 2H), 2.37-2.33 (m, 1H), 1.95-1.92 (m, 1H), 1.87 (s, 3H), 1.23 (t, *J*= 7.0 Hz, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.0, 155.6, 147.5, 147.4, 137.2, 136.8, 134.5, 131.5, 105.4, 80.4, 65.0, 64.0, 62.9, 62.0, 61.8, 37.0, 30.4, 21.0, 14.4 ppm.

HRMS (ESI): Calcd for $C_{21}H_{27}FIN_3NaO_5$: 570.0877; Found: 570.0885.



R_f : 0.33 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3726, 3381, 3286, 3063, 2972, 2925, 1710, 1597, 1506, 1417, 1387, 1302, 1269, 1231, 1127, 1065, 1023, 861, 810, 761 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.55 (bs, 1H), 7.17-6.89 (m, 1H), 6.71-6.62 (m, 2H), 6.23 (s, 1H), 5.96 (s, 1H), 5.11-4.64 (m, 2H), 4.15-4.10 (m, 5H), 3.79-3.55 (m, 2H), 2.73-2.68 (m, 1H), 2.20-2.19 (m, 1H), 1.78-1.64

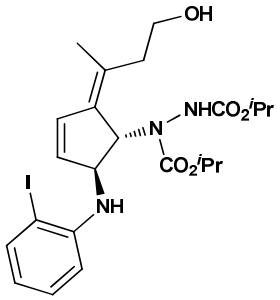
(m, 3H), 1.30-1.25 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.3, 154.4, 146.7, 137.6, 134.5, 131.6, 128.8, 120.7, 80.7, 65.7, 65.1, 63.8, 62.6, 38.8, 30.4, 22.1, 21.9, 17.8, 14.5 ppm.

HRMS (ESI): Calcd for $C_{21}H_{27}FIN_3NaO_5$: 570.0877; Found: 570.0886.

Preparation of Compound 62ba and 62ba'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59b** (128 mg, 0.38 mmol) and 2-iodoanilines **61a** (60 mg, 0.27 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (3 mg, 0.005 mmol) at room temperature for 6 h yielded **62ba** (76 mg, 50 %) and **62ba'** (48 mg, 32 %) as yellow viscous liquid upon purification by column chromatography (25 % and 30 % ethyl acetate-hexane respectively)



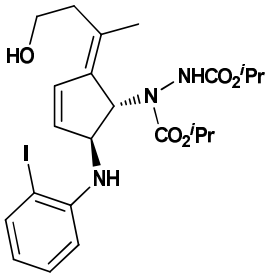
R_f : 0.55 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3730, 3461, 3390, 3294, 3066, 2981, 2924, 1706, 1595, 1502, 1461, 1396, 1301, 1265, 1184, 1108, 1038, 955, 915, 856, 806, 758, 660, 609 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.63-7.59 (m, 1H), 7.28-6.84 (m, 4H), 6.63-6.60 (m, 1H), 6.45-6.39 (m, 1H), 5.98 (bs, 1H), 5.08-4.77 (m, 4H), 4.08 (d, *J*= 7.5 Hz, 1H), 3.04-3.74 (m, 2H), 2.45-2.42 (m, 1H), 1.89 (bs, 1H), 1.87 (s, 3H), 1.30-1.04 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.6, 155.3, 146.0, 138.6, 137.7, 134.5, 134.0, 132.9, 129.6, 110.7, 112.3, 85.2, 70.6, 69.8, 69.5, 69.2, 65.4, 63.8, 59.8, 37.0, 36.6, 21.9, 17.7 ppm.

HRMS (ESI): Calcd for $C_{23}H_{32}IN_3NaO_5$: 580.1284; Found: 580.1286.



R_f : 0.40 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3732, 3459, 3391, 3295, 3066, 2980, 2924, 1707, 1595, 1501, 1460, 1395, 1302, 1264, 1185, 1107, 1038, 954, 914, 856, 807, 759, 659, 609 cm^{-1}.

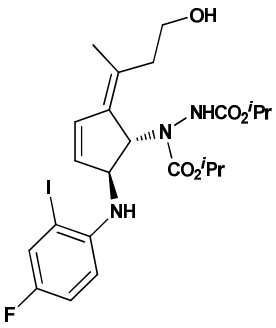
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.63-7.34 (m, 1H), 7.23-7.12 (m, 1H), 6.78-6.42 (m, 4H), 5.98 (bs, 1H), 5.01-4.94 (m, 3H), 4.61 (bs, 1H), 4.27-4.09 (m, 1H), 3.79-3.74 (m, 2H), 2.72 (bs, 1H), 2.36-2.31 (m, 1H), 1.61 (s, 3H), 1.43-1.14 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.0, 155.0, 145.9, 138.9, 138.3, 134.6, 132.1, 129.6, 127.3, 119.0, 112.3, 85.5, 71.0, 69.8, 64.7, 63.4, 60.6, 60.4, 38.6, 22.0, 19.0 ppm.

HRMS (ESI): Calcd for $C_{23}H_{32}IN_3NaO_5$: 580.1284; Found: 580.1284.

Preparation of Compound 62bb and 62bb'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59b** (118 mg, 0.35 mmol) and 2-iodoanilines **61b** (60 mg, 0.25 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (3 mg, 0.005 mmol) at room temperature for 6 h yielded **62bb** (84 mg, 58 %) and **62bb'** (30 mg, 21 %) as yellow viscous liquid upon purification by column chromatography (25 % and 30 % ethyl acetate-hexane respectively)



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

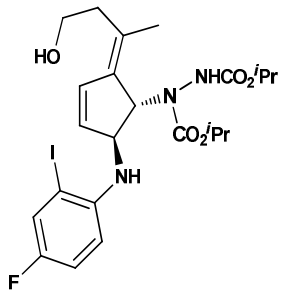
IR (Neat) ν_{max}: 3731, 3460, 3391, 3295, 3067, 2980, 2925, 1706, 1594, 1504, 1462, 1397, 1302, 1266, 1185, 1109, 1038, 955, 915, 857, 807, 759, 663, 611 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.40-7.31 (m, 2H), 7.08-6.96 (m, 2H), 6.64-6.61 (m, 1H), 5.97(s, 1H), 5.08 (s, 1H), 4.98-4.93 (m, 3H), 3.96-3.94 (m, 1H), 3.85-3.76 (m, 2H), 2.45-2.43 (m, 1H), 2.02 (bs, 1H), 1.89 (s, 3H), 1.30-1.20 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.9, 153.5, 143.1, 137.2, 136.7, 134.1, 131.0, 124.8, 116.0, 112.3,

83.5, 70.8, 70.1, 69.5, 69.1, 64.4, 37.0, 30.1, 29.7, 22.1 ppm.

HRMS (ESI): Calcd for $C_{23}H_{31}FIN_3NaO_5$: 598.1190; Found: 598.1205.



R_f : 0.44 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3733, 3455, 3390, 3291, 3067, 2981, 2929, 1709, 1594, 1504, 1460, 1396, 1300, 1264, 1186, 1108, 1045, 954, 913, 859, 808, 757, 662, 610 cm^{-1}.

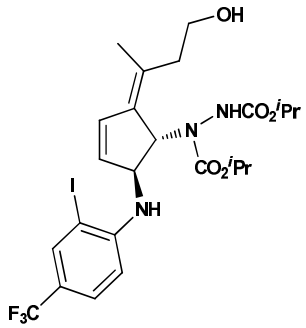
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.41 (bs, 1H), 6.98-6.97 (m, 1H), 6.84 (bs, 1H), 6.69-6.53 (m, 2H), 5.97 (s, 1H), 5.09 (s, 1H), 4.98-4.93 (m, 2H), 4.65 (bs, 1H), 3.93-3.91 (m, 1H), 3.77-3.72 (m, 2H), 2.69 (bs, 1H), 2.37-2.30 (m, 1H), 1.78-1.73 (m, 3H), 1.28-1.23 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 155.8, 155.0, 143.0, 138.2, 134.7, 132.3, 125.4, 116.2, 111.9, 83.8, 71.1, 70.3, 70.0, 63.9, 60.5, 38.3, 29.7, 22.0, 18.8 ppm.

HRMS (ESI): Calcd for $C_{23}H_{31}FIN_3NaO_5$: 598.1190; Found: 598.1212.

Preparation of Compound 62bc and 62bc'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59b** (99 mg, 0.29 mmol) and 2-iodoanilines **61c** (60 mg, 0.21 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (2 mg, 0.004 mmol) at room temperature for 6 h yielded **62bc** (74 mg, 56 %) and **62bc'** (26 mg, 20 %) as yellow viscous liquids upon purification by column chromatography (20 % and 25 % ethyl acetate-hexane respectively)



R_f : 0.68 (hexane/ethyl acetate = 3:2).

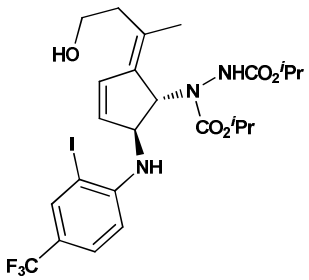
IR (Neat) ν_{max}: 3735, 3453, 3388, 3312, 3070, 2982, 2932, 1719, 1604, 1524, 1467, 1455, 1404, 1387, 1321, 1279, 1175, 1143, 1111, 1076, 1041, 956, 893, 817, 760, 676 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.91-7.84 (m, 1H), 7.50-7.47 (m, 2H), 6.69-6.66 (m, 1H), 5.97 (s, 1H), 5.12

(bs, 1H), 5.01-4.83 (m, 4H), 4.49-4.47 (m, 1H), 3.85-3.78 (m, 2H), 2.48-2.40 (m, 1H), 2.03-1.91 (m, 1H), 1.89 (s, 3H), 1.30-1.23 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.6, 154.7, 148.5, 135.7, 134.7, 131.3, 126.7, 119.5, 111.7, 83.2, 70.9, 70.4, 69.8, 69.1, 63.7, 49.4, 37.0, 29.5, 22.1, 21.9, 21.5 ppm.

HRMS (ESI): $C_{24}H_{31}F_3IN_3NaO_5$: 648.1158; Found: 648.1151.



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

IR (Neat) ν_{max}: 3732, 3379, 3292, 2982, 2928, 1710, 1604, 1525, 1461, 1400, 1321, 1281, 1173, 1112, 1076, 1030, 959, 897, 819 cm^{-1}.

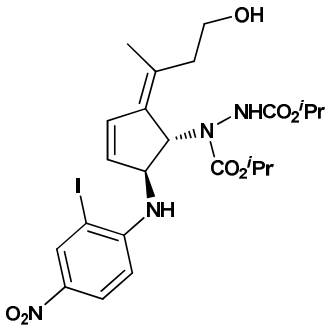
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.89-7.84 (m, 2H), 7.48-7.43 (m, 2H), 6.73-6.50 (m, 1H), 5.98 (s, 1H), 5.13 (bs, 1H), 4.99-4.84 (m, 3H), 4.46-4.44 (m, 1H), 3.78 (bs, 2H), 2.69 (bs, 1H), 2.36-2.32 (bs, 1H), 1.78-1.69 (m, 3H), 1.30-1.26 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.1, 154.7, 148.5, 135.9, 132.0, 126.9, 124.8, 122.5, 120.4, 111.3, 83.8, 71.4, 70.5, 69.8, 64.8, 63.1, 60.6, 38.3, 29.7, 22.0, 21.9 ppm.

HRMS (ESI): $C_{24}H_{31}F_3IN_3NaO_5$: 648.1158; Found: 648.1168.

Preparation of Compound 62bd and 62bd'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59b** (109 mg, 0.32 mmol) and 2-iodoanilines **61d** (60 mg, 0.23 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (3 mg, 0.005 mmol) at room temperature for 6 h yielded **62bd** (48 mg, 35 %) and **62bd'** (52 mg, 38 %) as yellow viscous liquid upon purification by column chromatography (30 % and 35 % ethyl acetate-hexane respectively)



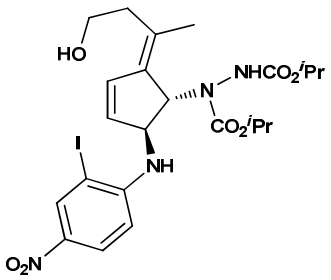
R_f : 0.43 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3731, 3373, 3284, 2978, 2922, 1706, 1583, 1503, 1405, 1322, 1180, 1113, 1027, 911, 749 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.55 (d, *J*= 12.0 Hz, 1H), 8.18-8.14 (m, 1H), 7.52-7.47 (m, 1H), 7.29-7.12 (m, 1H), 6.71-6.68 (m, 1H), 5.97-5.93 (m, 1H), 5.11-4.83 (m, 5H), 3.87-3.77 (m, 2H), 2.46-2.41 (m, 1H), 2.01-1.91 (m, 1H), 1.90 (s, 3H), 1.31-1.20 (m,12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.9, 155.0, 151.3, 138.7, 135.6, 135.4, 131.6, 126.5, 110.8, 82.5, 71.3, 70.3, 69.4, 66.1, 64.1, 59.5, 37.0, 30.0, 22.2, 18.1 ppm.

HRMS (ESI): Calcd for $C_{23}H_{31}IN_4NaO_7$: 625.1135; Found: 625.1144.



R_f : 0.30 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3731, 3374, 3283, 2979, 2927, 1710, 1583, 1503, 1459, 1387, 1323, 1179, 1112, 1042, 954, 908, 820, 747 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.55 (d, *J*= 12.0 Hz, 1H), 8.15-8.13 (m, 1H), 7.23-6.68 (m, 2H), 5.96 (s, 1H), 5.11-4.79 (m, 6H), 3.77-3.69 (m, 2H), 2.70-2.67 (m, 1H), 2.35-2.17 (m, 1H),1.77-1.75 (m, 3H), 1.30-1.24 (m,12H) ppm.

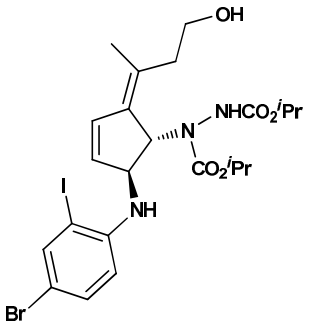
^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 154.8, 152.8, 149.2, 136.7, 133.6, 133.0, 130.5, 128.6, 124.3, 81.1, 72.7, 69.1, 68.6, 62.4, 59.4, 52.4, 36.1, 30.2, 27.1, 22.2, 17.2 ppm.

HRMS (ESI): Calcd for $C_{23}H_{31}IN_4NaO_7$: 625.1135; Found: 625.1141.

Preparation of Compound 62be and 62be'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived

diazanorbornene **59b** (95 mg, 0.28 mmol) and 2-iodoanilines **61e** (60 mg, 0.20 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (2 mg, 0.004 mmol) at room temperature for 6 h yielded **62be** (42 mg, 32 %) and **62be'** (62 mg, 49 %) as yellow viscous liquids upon purification by column chromatography (25 % and 30 % ethyl acetate-hexane)



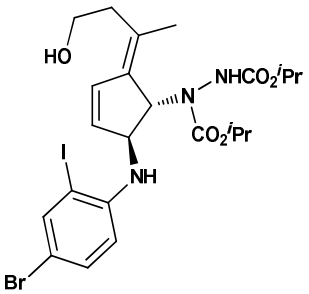
R_f : 0.53 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3732, 3581, 3283, 2980, 2923, 1707, 1580, 1494, 1384, 1306, 1268, 1233, 1179, 1109, 1033, 955, 914, 806, 760, 735 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.76-7.70 (m, 1H), 7.38-7.34 (m, 1H), 7.16-6.74 (m, 1H), 6.64-6.61 (m, 1H), 6.16-5.95 (m, 1H), 5.07-4.74 (m, 5H),4.14-4.11 (m, 1H), 3.84-3.74 (m, 2H), 2.46-2.41 (m, 1H), 2.05-1.98 (m, 1H), 1.87 (s, 3H), 1.25-1.19 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.9, 155.2, 145.4, 145.3, 140.0, 134.3, 132.3, 113.8, 108.8, 85.1, 70.8, 70.0, 69.4, 64.0, 59.4, 36.7, 29.8, 22.3, 17.8 ppm.

HRMS (ESI): Calcd for $C_{23}H_{31}BrIN_3NaO_5$: 658.0389; Found: 658.0394.



R_f : 0.40 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3728, 3387, 3293, 2980, 2931, 2879, 1710, 1559, 1493, 1383, 1307, 1266, 1237, 1179, 1143, 1108, 1044,955, 913, 887, 805, 733, 682 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.71 (d, *J*= 12.5 Hz, 1H), 7.28-7.22 (m, 1H), 6.75-6.57 (m, 2H), 5.93 (s, 1H), 5.06-4.64 (m, 5H), 4.11-4.08 (m, 1H), 3.72-3.71 (m, 2H), 2.67-2.66 (m, 1H), 2.26 (bs, 1H), 1.75-1.67 (m, 3H), 1.25-1.22 (m, 12H) ppm.

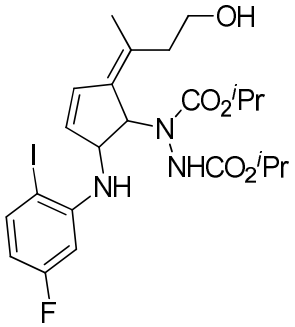
^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.9, 155.0, 145.3, 145.1, 140.3, 137.6, 134.1, 132.3, 113.4, 109.1, 85.3, 70.3, 70.0, 63.5, 60.5, 53.5, 38.4, 29.7, 22.0, 18.8 ppm.

HRMS (ESI): Calcd for $C_{23}H_{31}BrIN_3NaO_5$: 658.0389;

Found: 658.0398.

Preparation of Compound 62bf and 62bf'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59b** (118 mg, 0.35 mmol) and 2-iodoanilines **61f** (60 mg, 0.25 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (3 mg, 0.005 mmol) at room temperature for 6 h yielded **62bf** (84 mg, 58 %) and **62bf'** (44 mg, 30 %) as yellow viscous liquids upon purification by column chromatography (25 % and 30 % ethyl acetate-hexane respectively)



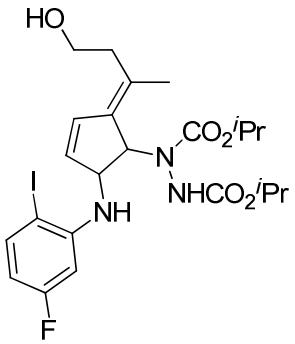
R_f : 0.58 (hexane/ethyl acetate = 3:2).

IR (Neat) $\nu_{max:}$ 3732, 3461, 3389, 3291, 3063, 2978, 2928, 1703, 1597, 1502, 1465, 1396, 1303, 1265, 1187, 1112, 1039, 956, 914, 859, 802, 761 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.53-7.41 (m, 1H), 6.63-6.58 (m, 1H), 6.17-6.11 (m, 2H), 5.93-5.79 (m, 2H), 4.95-4.89 (m, 5H), 4.17-4.04 (m, 2H), 2.16-1.93 (m, 2H), 1.86-1.60 (m, 3H), 1.28-1.20 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.3, 155.1, 147.3, 137.6, 134.5, 132.3, 131.0, 120.4, 105.7, 80.1, 70.4, 70.1, 65.1, 63.9, 30.4, 22.1, 21.9 ppm.

HRMS (ESI): Calcd for $C_{23}H_{31}FIN_3NaO_5$: 598.1190; Found: 598.1194.



R_f : 0.43 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3728, 3369, 3287, 2978, 2926, 1709, 1593, 1502, 1410, 1386, 1305, 1263, 1230, 1189, 1120, 1056, 1027, 863, 812, 756 cm^{-1}.

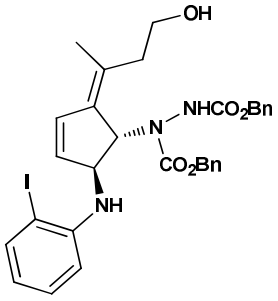
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.51-7.50 (m, 1H), 7.20-7.13 (m, 1H), 6.68-6.60 (m, 2H), 6.18 (bs, 1H), 5.90 (bs, 1H), 5.05-4.65 (m, 5H), 4.19-4.14 (m, 1H), 3.72-3.68 (m, 2H), 2.68 (bs, 1H), 2.31-2.13 (m, 1H), 1.76-1.65 (m, 3H), 1.25-1.20 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.3, 155.1, 147.4, 139.2, 138.1, 135.1, 128.5, 127.6, 105.7, 71.6, 70.3, 69.8, 63.2, 38.8, 21.9 ppm.

HRMS (ESI): Calcd for $C_{23}H_{31}FIN_3NaO_5$: 598.1190; Found: 598.1196.

Preparation of Compound 61da and 61da'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59d** (165 mg, 0.38 mmol) and 2-iodoanilines **61a** (60 mg, 0.27 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (3 mg, 0.005 mmol) at room temperature for 6 h yielded **61da** (64 mg, 36 %) and **61da'** (58 mg, 33 %) as yellow viscous liquids upon purification by column chromatography (20 % and 25 % ethyl acetate-hexane respectively)



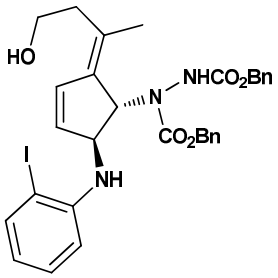
R_f : 0.70 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3732, 3457, 3371, 3287, 3063, 3032, 2956, 2894, 1711, 1586, 1498, 1452, 1408, 1272, 1218, 1123, 1052, 1006, 912, 848, 744, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.77-7.09 (m, 13H), 6.55-6.38 (m, 2H), 5.99-5.97 (m, 1H), 5.18-4.96 (m, 6H), 4.12-4.06 (m, 1H), 3.66-3.41 (m, 2H), 2.36-2.18 (m, 2H), 1.87-1.81 (m, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.6, 155.3, 146.0, 139.1, 135.6, 128.6, 128.6, 128.5, 128.2, 119.8, 118.5, 112.9, 85.5, 67.6, 67.0, 63.8, 59.4, 37.0, 17.7 ppm.

HRMS (ESI): Calcd for $C_{31}H_{32}IN_3NaO_5$: 676.1284; Found: 676.1290.



R_f : 0.58 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3731, 3456, 3364, 3286, 3061, 3031, 2954, 1710, 1627, 1587, 1499, 1450, 1407, 1312, 1255, 1220, 1123, 1051, 911, 850, 743, 698 cm^{-1}.

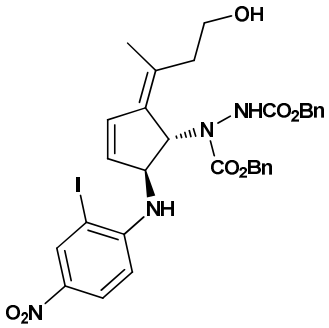
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.30-7.09 (m, 13H), 6.77 (d, *J*= 6.0 Hz, 1H), 6.59 (s, 1H), 6.35-6.32 (m, 1H), 5.89 (s, 1H), 5.24-4.86 (m, 6H), 3.66 (bs, 2H), 2.59 (bs, 1H), 2.18-2.15 (m, 1H),1.56 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.6, 155.3, 145.7, 144.7, 137.5, 135.0, 128.6, 128.5, 128.1, 128.0, 110.2, 85.4, 68.5, 67.6, 53.6, 38.2, 17.9 ppm.

HRMS (ESI): Calcd for $C_{31}H_{32}IN_3NaO_5$: 676.1284; Found: 676.1287.

Preparation of Compound 62dd and 62dd'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59d** (140 mg, 0.32 mmol) and 2-iodoanilines **61d** (60 mg, 0.23 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (3 mg, 0.005 mmol) at room temperature for 6 h yielded **62dd** (56 mg, 35 %) and **62dd'** (78 mg, 49 %) as yellow viscous liquids upon purification by column chromatography (25 % and 35 % ethyl acetate-hexane)



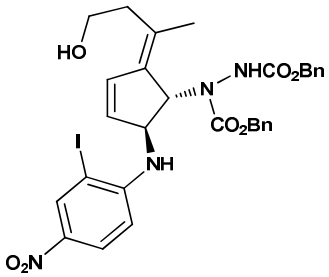
R_f : 0.53 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3732, 3477, 3374, 3295, 3067, 3032, 2957, 2921, 1711, 1582, 1499, 1450, 1408, 1322, 1287, 1218, 1117, 1052, 989, 906, 819, 745, 697, 647, 602 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.49-8.34 (m, 1H), 8.03-7.79 (m, 2H), 7.34-7.28 (m, 12H), 6.64-6.61 (m, 1H), 5.91-5.87 (m, 1H), 5.19-4.99 (m, 6H), 3.71 (bs, 1H), 3.54-3.48 (m, 1H), 2.38-2.07 (m, 2H),1.83 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.3, 155.1, 151.0, 138.2, 136.9, 136.3, 135.4, 134.7, 128.2, 127.6, 126.0, 110.4, 110.1, 82.4, 68.2, 67.9, 67.3, 64.2, 63.6, 59.2, 36.7, 29.7, 17.7 ppm.

HRMS (ESI): Calcd for $C_{31}H_{31}IN_4NaO_7$: 721.1135; Found: 721.1140.



R_f : 0.30 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3734, 3488, 3375, 3298, 3067, 3032, 2955, 2923, 1712, 1582, 1500, 1449, 1407, 1322, 1285, 1219, 1117, 1078, 1051, 985, 905, 818, 746, 697, 645, 600 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.48-8.43 (m, 1H), 7.93-7.33 (m, 2H), 7.28-7.09 (m, 12H), 6.68 (s, 1H), 5.88-5.74 (m, 1H), 5.21-4.78 (m, 6H), 3.70 (bs, 2H), 2.67-2.65 (bs, 1H), 2.18-2.12 (m, 1H), 1.68-1.61 (m,3H)

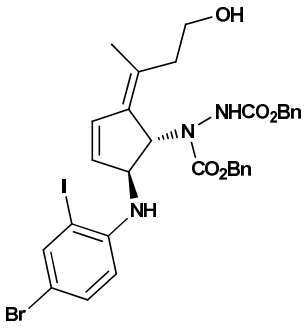
ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.9, 155.3, 154.7, 150.7, 138.6, 135.9, 135.0, 134.8, 128.5(2), 128.3, 128.2, 127.9, 126.3, 109.7, 82.4, 69.0, 68.4, 67.6, 63.1, 60.3, 53.4, 38.3, 29.7, 18.9 ppm.

HRMS (ESI): Calcd for $C_{31}H_{31}IN_4NaO_7$: 721.1135; Found: 721.1136.

Preparation of Compound 62de and 62de'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59d** (122 mg, 0.28 mmol) and 2-iodoanilines **61e** (60 mg, 0.20 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (2 mg, 0.004 mmol) at room temperature for 6 h yielded **62de** (70 mg, 47 %) and **62de'** (56 mg, 38 %) as yellow viscous liquids upon purification by column chromatography (20 % and 30 % ethyl acetate-hexane)



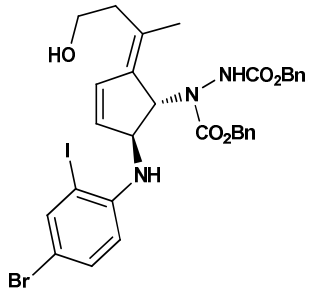
R_f : 0.63 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3734, 3465, 3383, 3291, 3063, 3033, 2957, 2896, 1711, 1579, 1494, 1450, 1407, 1302, 1264, 1217, 1124, 1081, 1052, 991, 911, 809, 747, 697, 598 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.67-7.60 (m, 1H), 7.32-7.14 (m, 13H), 6.56-6.34 (m, 1H), 5.93-5.76 (m, 1H), 5.14-5.03 (m, 6H), 4.11-3.99 (m, 2H), 3.68-3.41 (m, 1H), 2.20-1.91 (m, 1H), 1.88-1.81 (m, 1H), 1.77 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.0, 156.6, 155.5, 140.1, 136.0, 135.9, 135.4, 132.3, 128.5, 128.4, 128.3, 128.2, 128.1, 113.2, 109.0, 85.2, 68.5, 67.4, 67.2, 65.0, 64.0,58.9, 36.7, 30.3, 17.7 ppm.

HRMS (ESI): Calcd for $C_{31}H_{31}BrIN_3NaO_5$: 754.0389; Found: 754.0385.



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

IR (Neat) ν_{max}: 3732, 3384, 3285, 3063, 3031, 2953, 2922, 1712, 1579, 1494, 1452, 1406, 1304, 1265, 1219, 1121, 1052, 745, 696 cm^{-1}.

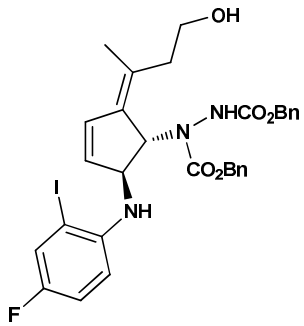
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.67-7.58 (m, 1H), 7.34-7.10 (m, 13H), 6.59-6.55 (m, 1H), 5.12-4.91 (m, 6H), 4.04-3.94 (m, 2H), 3.64 (bs, 1H), 2.62-2.61 (m, 1H), 2.34-2.10 (m, 1H), 1.70-1.57 (m, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.8, 155.6, 154.7, 145.0, 140.3, 136.1, 135.0, 132.2, 128.5, 128.3, 128.2, 128.0, 127.9, 113.3, 109.3, 109.2, 85.3,68.9, 68.2, 67.6, 63.2, 60.4, 60.1, 34.7, 34.6, 31.6, 22.8, 22.7, 14.3 ppm.

HRMS (ESI): Calcd for $C_{31}H_{31}BrIN_3NaO_5$: 754.0389; Found: 754.0399.

Preparation of Compound 62db and 62db'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59d** (152 mg, 0.35 mmol) and 2-iodoanilines **61b** (60 mg, 0.25 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (3 mg, 0.005 mmol) at room temperature for 6 h yielded **62db** (62 mg, 36 %) and **62db'** (80 mg, 47 %) as yellow viscous liquids upon purification by column chromatography (20 % and 30 % ethyl acetate-hexane respectively)

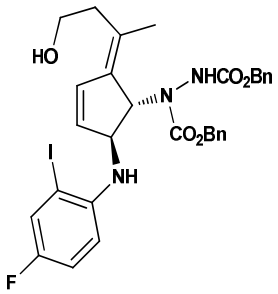


R_f : 0.65 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3730, 3386, 3299, 3068, 3035, 2957, 2920, 1701, 1503, 1456, 1408, 1302, 1263, 1220, 1123, 1052, 812, 748, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.28-7.10 (m, 13H), 6.54-6.51 (m, 1H), 5.94-5.76 (m, 2H), 5.12-5.00 (m, 6H), 4.01-3.43 (m, 3H), 2.10-1.97 (m, 1H), 1.89-1.84 (m, 1H), 1.79 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.0, 156.6, 155, 5, 143.0, 136.6, 136.1, 136.0, 135.5, 128.5, 128.4, 128.3, 128.1, 127.0, 116.05, 112.6, 83.8, 80.4, 67.8, 67.7, 67.4,



67.3, 65.0, 64.8, 60.4, 59.1, 34.5, 31.4, 22.6, 13.9 ppm.

HRMS (ESI): Calcd for $C_{31}H_{31}FIN_3NaO_5$: 694.1190; Found: 694.1198

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

IR (Neat) ν_{max}: 3729, 3387, 3295, 3067, 3034, 2954, 1708, 1594, 1502, 1454, 1406, 1295, 1263, 1220, 1125, 1052, 912, 859, 810, 746, 697, 663, 608 cm^{-1}.

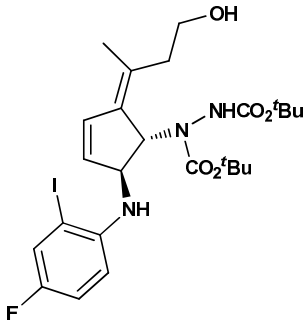
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.42-7.12 (m, 12H), 6.84-6.56 (m, 2H), 5.91-5.89 (m, 2H), 5.20-4.93 (m, 6H), 3.85-3.67 (m, 3H), 2.64 (bs, 1H), 2.15-2.00 (m, 1H), 1.75-1.58 (m, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.0, 155.5, 142.7, 136.1, 135.7, 135.1, 128.5(2), 128.4, 128.2, 128.0, 127.8, 125.1, 116.1, 111.9, 83.9, 68.8, 68.2, 67.5, 63.7, 60.4, 34.5, 31.0, 22.6, 14.2 ppm.

HRMS (ESI): Calcd for $C_{31}H_{31}FIN_3NaO_5$: 694.1190; Found: 694.1202.

Preparation of Compound 62ae and 62ae'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59a** (128 mg, 0.35 mmol) and 2-iodoanilines **61e** (60 mg, 0.25 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (3 mg, 0.005 mmol) at room temperature for 6 h yielded **62ae** (52 mg, 34 %) and **62ae'** (62 mg, 41 %) as yellow viscous liquids upon purification by column chromatography (18 % and 30 % ethyl acetate-hexane respectively)



R_f : 0.70 (hexane/ethyl acetate = 3:2).

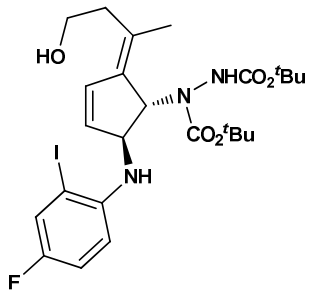
IR (Neat) ν_{max}: 3732, 3390, 3294, 2975, 2924, 1704, 1599, 1504, 1393, 1308, 1253, 1163, 1053, 1022, 953, 860, 812, 758, 666, 611 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.42-7.36 (m, 1H), 7.08-6.88 (m, 3H), 6.62 (d, J= 5.5 Hz, 1H), 6.12- 5.80 (m, 2H), 4.14-4.10 (m, 1H), 3.80-3.74 (m, 2H), 2.44-2.28 (m, 2H), 1.91-1.87 (m, 3H), 1.56-1.41 (m, 18H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.4, 155.0,

143.7, 138.2, 138.0, 134.9, 132.7, 125.8, 116.7, 115.0, 82.4, 81.1, 66.0, 65.0, 56.2, 31.0, 30.3, 29.0, 28.9, 28.8, 23.3 ppm.

HRMS (ESI): Calcd for $C_{25}H_{35}FIN_3NaO_5$: 626.1503; Found: 626.1510.



R_f: 0.55 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3730, 3391, 3301, 2976, 2929, 1707, 1595, 1503, 1392, 1304, 1253, 1162, 1051, 942, 914, 858, 810, 736 cm^{-1}.

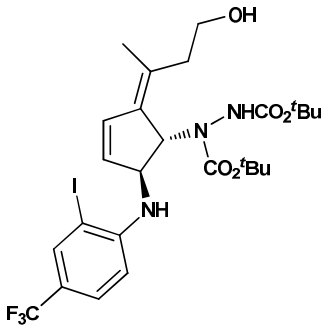
^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.41-7.37 (m, 1H), 7.01-6.80 (m, 2H), 6.68 (d, *J*= 4.0 Hz, 1H), 6.42 (d, *J*= 17.0 Hz, 1H), 5.97 (s, 1H), 5.03-4.86 (m, 1H), 4.64-4.62 (m, 1H), 3.91 (bs, 1 H), 3.75-3.74 (m, 2H), 2.67-2.45 (m, 1H), 2.42-2.29 (m, 1H), 1.89-1.72 (m, 3H), 1.49-1.44 (m, 18H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 155.9, 154.0, 143.0, 138.5, 134.1, 131.6, 125.3, 116.0, 112.6, 83.9, 81.7, 81.5, 60.6, 53.4, 38.5, 29.7, 28.2, 28.1, 27.5, 18.8 ppm.

HRMS (ESI): Calcd for $C_{25}H_{35}FIN_3NaO_5$: 626.1503; Found: 626.1513.

Preparation of Compound 62ac and 62ac'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived diazanorbornene **59a** (108 mg, 0.29 mmol) and 2-iodoanilines **61c** (60 mg, 0.21 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (2 mg, 0.004 mmol) at room temperature for 6 h yielded **62ac** (38 mg, 28 %) and **62ac'** (36 mg, 26 %) as yellow viscous liquids upon purification by column chromatography (20 % and 30 % ethyl acetate-hexane respectively)



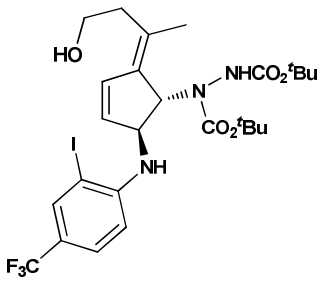
R_f : 0.70 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3731, 3388, 3316, 2977, 2928, 1703, 1605, 1524, 1479, 1397, 1371, 1321, 1280, 1252, 1162, 1119, 1073, 1022, 857, 759, 675 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.88-7.82 (m, 1H), 7.54-7.34 (m, 1H), 7.14-6.65 (m, 3H), 5.96 (s, 1H), 5.13-4.75 (m, 2H), 4.44-4.40 (m, 1H), 3.83-3.75 (m, 2H), 2.45-2.35 (m, 1H), 2.01-1.98 (m, 1H), 1.90(s, 3H), 1.51-1.43 (m, 18H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 154.8, 153.3, 147.3, 136.3, 134.8, 133.9, 130.1, 125.4, 110.9, 111.1, 81.9, 80.1, 68.7, 62.6, 59.6, 58.9, 35.8, 29.0, 27.0, 16.8 ppm.

HRMS (ESI): Calcd for $C_{26}H_{35}F_3IN_3NaO_5$: 676.1471; Found: 676.1470.



R_f : 0.58 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3732, 3389, 3310, 2997, 2932, 1709, 1604, 1521, 1479, 1454, 1395, 1370, 1321, 1281, 1251, 1164, 1118, 1075, 942, 914, 854, 818, 784, 760, 676 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 7.87-7.84 (m, 1H), 7.49-7.40 (m, 1H), 7.00-6.37 (m, 3H), 5.96 (s, 1H), 5.08-5.04 (m, 1H), 4.84-4.68 (m, 1H), 4.42 (d, *J*= 7.5 Hz, 1H), 3.75 (bs, 2H), 2.69-2.67 (bs, 1H), 2.42-2.30 (m, 1H), 1.82-1.69 (m, 3H), 1.62-1.43 (m, 18H) ppm.

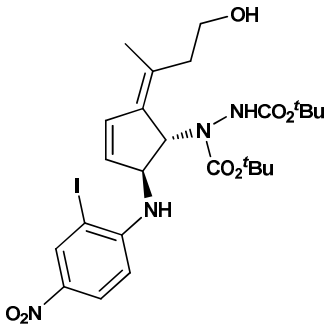
^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 155.1, 154.2, 148.6, 135.9, 131.0, 126.3, 119.8, 114.3, 111.0, 83.8, 81.7, 81.3, 63.2, 60.1, 38.4, 27.9, 27.0, 18.8 ppm.

HRMS (ESI): Calcd for $C_{26}H_{35}F_3IN_3NaO_5$: 676.1471; Found: 676.1477.

Preparation of Compound 62ad and 62ad'

Following the general procedure (Section 4.7.3), the reaction of pentafulvene derived

diazanorbornene **59a** (118 mg, 0.32 mmol) and 2-iodoanilines **61d** (60 mg, 0.23 mmol) in dry toluene (2 mL) in the presence of $Sc(OTf)_3$ (3 mg, 0.005 mmol) at room temperature for 6 h yielded **62ad** (54 mg, 38 %) and **62ad'** (52 mg, 36 %) as yellow viscous liquids upon purification by column chromatography (25 % and 35 % ethyl acetate-hexane)



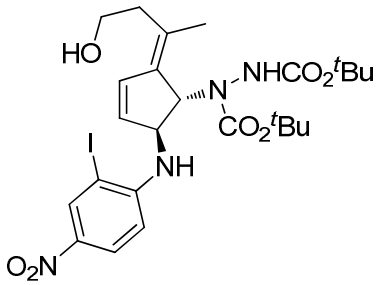
R_f : 0.63 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3731, 3376, 3322, 3073, 2973, 2926, 1775, 1728, 1583, 1503, 1457, 1393, 1370, 1322, 1282, 1250, 1162, 1180, 1075, 1050, 1018, 943, 898, 856, 783, 755, 693, 648 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.55(d, *J*= 14.0 Hz, 1H), 8.22-8.10 (m, 1H), 7.19-7.16 (m, 1H), 6.70-6.58 (m, 2H), 5.95 (s, 1H), 5.51 (s, 1H), 5.08-5.05 (m, 1H), 4.88-4.85 (m, 1H), 3.83- 3.56 (m, 2H), 3.423.39 (m, 1H), 2.42-2.35 (m, 1H), 1.91 (s, 3H), 1.50-1.49 (m, 18H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 155.7, 154.1, 138.5, 136.0, 135.6, 134.5, 129.8, 126.0, 81.5, 80.7, 60.0, 57.9, 53.3, 36.4, 28.2, 27.3, 22.6 ppm.

HRMS (ESI): Calcd for $C_{25}H_{35}IN_4NaO_7$: 653.1448; Found: 653.1455.



R_f : 0.48 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3730, 3377, 3321, 2966, 2924, 1707, 1583, 1503, 1455, 1393, 1323, 1284, 1161, 1118, 1078, 1051, 1022, 860, 752, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.57-8.54 (m, 1H), 8.20-8.09 (m, 1H), 7.01-6.47 (m, 3H), 5.96 (s, 1H), 5.05-4.75 (m, 3H), 3.76 (s, 2H), 2.73-3.65 (m, 1H), 2.30-2.17 (m, 1H), 1.82-1.70 (m, 3H), 1.50-1.43 (m, 18H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.9, 156.3, 154.1, 151.3, 139.1, 136.1, 135.5, 126.5, 82.9, 82.2, 81.8, 63.9, 61.0, 38.9, 30.3, 28.4, 19.3 ppm.

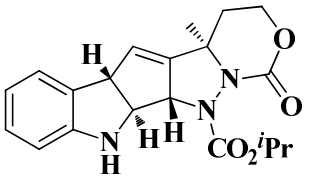
HRMS (ESI): Calcd for $C_{25}H_{35}IN_4NaO_7$: 653.1448; Found: 653.1451.

4.7.4. General Procedure for the Intramolecular Heck Reaction

A mixture of *trans*-3,4-disubstituted alkylidenecyclopentene (1.0 equiv.), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %) and Cs_2CO_3 (2.0 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 solvent was evaporated *in vacuo* and the residue on silica gel (100-200 mesh) column chromatography yielded indoline-pyrazolidine fused cyclopentene

Preparation of Compound (±)-**63a**

Following the general procedure (Section 4.7.4), the reaction of compound **62ba** (50 mg, 0.089 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.009 mmol), PPh_3 (5 mg, 0.018 mmol) and Cs_2CO_3 (58 mg, 0.18 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**63a** (17 mg, 51 %) as a pale yellow viscous liquid upon purification by column chromatography (30 % ethyl acetate-hexane).



R_f : 0.20 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3375, 3053, 2956, 2927, 2870, 2854, 1734, 1615, 1491, 1468, 1439, 1395, 1381, 1324, 1287, 1181, 1138, 1119, 1028, 997, 954, 839, 750, 722,696, 541 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.06 (t, *J*= 7.0 Hz, 1H), 7.0 (d, *J*= 7.0 Hz, 1H), 6.73-6.67 (m, 2H), 5.99 (s, 1H), 5.02-4.99 (m, 1H), 4.79 (s, 1H), 4.55-4.13 (m, 4H), 4.13-4.10 (m, 1H), 2.24-2.16 (m, 2H), 1.36-1.27 (m, 9H) ppm.

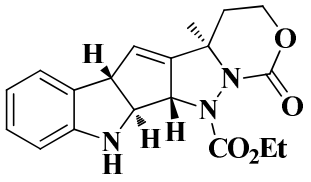
^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 154.5, 153.1, 135.1, 127.9, 127.6, 124.3, 120.7, 116.0, 72.5, 72.1, 63.4, 57.8, 34.5, 21.8 ppm.

HRMS (ESI): Calcd for $C_{20}H_{23}N_3NaO_4$: 392.1586; Found: 392.1586.

Preparation of Compound (±)-**63b**

Following the general procedure (Section 4.7.4), the reaction of compound **62ca** (50 mg, 0.095 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.009 mmol), PPh_3 (5 mg, 0.018 mmol) and Cs_2CO_3 (62 mg, 0.19 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**63b**

(23 mg, 68 %) as colourless solid upon purification by column chromatography (35 % ethyl acetate-hexane).



Mp: 243-248 ^{o}C ,

R_f : 0.14 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3336, 3078, 2970, 2921, 2859, 1724, 1609, 1462, 1426, 1392, 1350, 1318, 1272, 1217, 1164, 1134, 1088, 1037, 950, 913, 871,837 cm^{-1}.

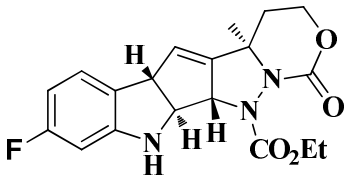
^{1}H NMR (500MHz, $CDCl_3$): δ 7.07-6.97 (m, 1H), 6.98 (d, *J*=7.5 Hz, 1H), 6.73-6.66 (m, 2H), 5.09 (s, 1H), 4.62-4.52 (M, 3H), 4.34-4.11 (m, 5H), 2.05-2.00 (m, 2H), 1.60 (s, 3H), 1.34(t, *J*= 7.0 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 154.7, 149.7, 132.1, 132.1, 128.5, 126.7, 124.0, 122.3, 119.1, 110.2, 70.2, 69.7, 65.1, 64.0, 63.6, 63.3, 62.3, 58.4, 31.9, 29.5, 22.3, 14.2 ppm.

HRMS (ESI): Calcd for $C_{19}H_{21}N_3O_4$: 355.1532; Found (M+1): 356.1620.

Preparation of Compound (±)-63c

Following the general procedure (Section 4.7.4), the reaction of compound **62cb** (50 mg, 0.091 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.009 mmol), PPh_3 (5 mg, 0.018 mmol) and Cs_2CO_3 (59 mg, 0.18 mmol) in dry CH_3CN (2 mL) at 80 ^{o}C for 12 h yielded (±)-**63c** (25 mg, 72 %) as colourless solid upon purification by column chromatography (35 % ethyl acetate-hexane).



mp: 244-247 ^{o}C

R_f : 0.16 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3334, 2969, 2921, 2859, 1724, 1609, 1462, 1426, 1392, 1350, 1318, 1272, 1217, 1164, 1134, 1088, 1037, 950, 913, 871, 837, 796, 728, 673, 635 cm^{-1}.

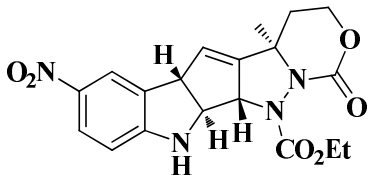
^{1}HNMR (500MHz, $CDCl_3$): δ 6.90-6.88 (m, 1H), 6.38-6.35 (m, 2H), 5.88 (s, 1H), 4.67-4.64 (m, 2H), 4.53-4.52 (m, 2H), 4.51-4.24 (m, 4H), 2.09-2.01 (m, 2H),1.60 (s, 3H), 1.34(t, *J*= 8.0 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 164.1, 162.6, 155.1, 151.2, 124.8, 121.9, 115.4, 105.4, 97.5, 70.4, 63.8, 62.3, 57.9, 32.6, 27.9, 15.1 ppm.

HRMS (ESI): Calcd for $C_{19}H_{20}FN_3O_4$: 373.1437; Found (M+1): 374.1517.

Preparation of Compound (±)-63d

Following the general procedure (Section 4.7.4), the reaction of compound **62cd** (50 mg, 0.087 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.009 mmol), PPh_3 (5 mg, 0.017 mmol) and Cs_2CO_3 (59 mg, 0.182 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**63d** (13 mg, 36 %) as pale yellow viscous liquid upon purification by column chromatography (40 % ethyl acetate-hexane).



R_f : 0.08 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3732, 3293, 2955, 2919, 2857, 2356, 1713, 1648, 1608, 1504, 1454, 1408, 1381, 1318, 1250, 1157, 1121, 1068, 1029 cm^{-1}.

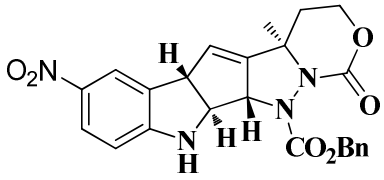
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08-8.06 (m, 1H), 7.94 (s, 1H), 6.61 (d, *J* = 9.0 Hz, 1H), 6.02 (s, 1H), 4.84 (s, 1H), 4.83 (bs, 2H), 4.37-4.12 (m, 5H), 2.25-2.24 (m, 2H), 1.68 (s, 3H), 1.33 (t, *J*= 8.5 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 155.0, 154.2, 150.7, 146.4, 139.8, 131.6, 127.9, 126.7, 126.0, 122.6, 120.7, 107.6, 72.6, 66.0, 62.6, 60.4, 56.3, 31.6, 23.0, 15.1 ppm.

HRMS (ESI): Calcd for $C_{19}H_{20}N_4NaO_6$: 423.1281; Found: 423.1280.

Preparation of Compound (±)-63e

Following the general procedure (Section 4.7.4), the reaction of compound **62dd** (50 mg, 0.072 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.007 mmol), PPh_3 (4 mg, 0.014 mmol) and Cs_2CO_3 (47 mg, 0.14 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**63e** (14 mg, 42 %) as yellow viscous liquid upon purification by column chromatography (20 % ethyl acetate-hexane).



R_f : 0.38 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3731, 3325, 2920, 2854, 2392, 2035, 1641, 1539, 1371, 1271, 1156, 1107, 1030 cm^{-1}.

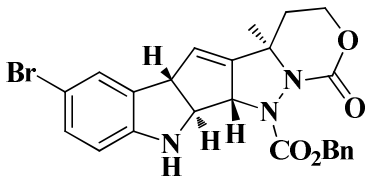
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.5 Hz, 1H), 7.91 (s, 1H), 7.41-7.30 (m, 6H), 6.52 (d, *J*= 8.5 Hz, 1H), 5.92 (s, 1H), 5.24-5.20 (m, 2H), 4.80 (bs, 1H), 4.62-4.53 (m, 2H), 4.39-4.29 (m, 2H), 2,13-2.00 (m, 2H), 1.63 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 155.3, 155.1, 139.9, 135.5, 128.7, 128.6, 128.4, 128.2, 127.0, 126.4, 121.3, 120.9, 107.8, 69.5, 68.4, 64.9, 63.9, 58.9, 57.6, 56.1, 32.8, 29.7, 27.7 ppm.

HRMS (ESI): Calcd for $C_{24}H_{22}N_4NaO_6$: 485.1437; Found: 485.1448.

Preparation of Compound (±)-63f

Following the general procedure (Section 4.7.4), the reaction of compound **62de** (50 mg, 0.068 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.007 mmol), PPh_3 (4 mg, 0.014 mmol) and Cs_2CO_3 (44 mg, 0.14 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**63f** (16 mg, 48 %) as yellow viscous liquid upon purification by column chromatography (25 % ethyl acetate-hexane).



R_f : 0.28 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3734, 3417, 2957, 2924, 2858, 2357, 1705, 1652, 1466, 1417, 1356, 1274, 1126, 1042, 744, 699 cm^{-1}.

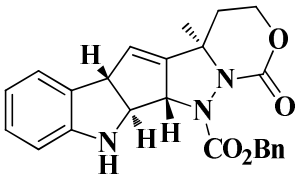
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.06 (m, 8H), 6.46 (d, *J*= 8.5 Hz, 1H), 5.85 (s, 1H), 5.22 (s, 2H), 4.58 (d, *J*= 6.5Hz, 1H), 4.51-4.50 (m, 2H), 4.34-4.28 (m, 2H), 2.64-2.00 (m, 2H), 1.56 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 155.1, 154.6, 148.7, 138.9, 135.7, 131.0, 129.1, 128.5, 126.7, 121.7, 119.4, 111.3, 110.6, 69.5, 68.2, 64.2, 63.2, 57.9, 32.9, 27.7 ppm.

HRMS (ESI): Calcd for $C_{24}H_{22}BrN_3NaO_4$: 518.0691; Found: 518.0696.

Preparation of Compound (±)-63g

Following the general procedure (Section 4.7.4), he reaction of compound **62da** (50 mg, 0.077 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.008 mmol), PPh_3 (4 mg, 0.016 mmol) and Cs_2CO_3 (50 mg, 0.17 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**63g** (17 mg, 52 %) as yellow viscous liquid upon purification by column chromatography (25 % ethyl acetate-hexane).



R_f : 0.30 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3734, 3416, 2955, 2923, 2857, 2356, 1705, 1651, 1466, 1417, 1356, 1274, 1126, 1042, 744, 699 cm^{-1}.

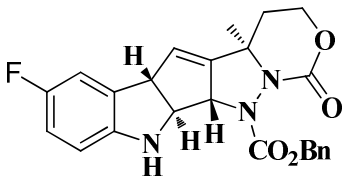
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.31 (m, 6H), 7.05-6.96 (m, 2H), 6.70 (t, *J* = 7.5 Hz, 1H), 6.59 (d, *J* = 7.5 Hz, 1H), 5.91-5.89 (m, 1H), 5.23 (s, 2H), 4.60-4.54 (m, 3H), 4.34-4.25 (m, 2H), 2.04-2.02 (m, 2H), 1.57 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 154.5, 149.7, 135.8, 128.6, 128.4, 128.1, 126.6, 124.0, 122.4, 119.0, 69.7, 68.1, 64.1, 63.7, 58.4, 32.9, 27.8 ppm.

HRMS (ESI): Calcd for $C_{24}H_{23}N_3NaO_4$: 440.1586; Found: 440.1594.

Preparation of Compound (±)-63h

Following the general procedure (Section 4.7.4), the reaction of compound **62db** (50 mg, 0.075 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.008 mmol), PPh_3 (4 mg, 0.016 mmol) and Cs_2CO_3 (49 mg, 0.15 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**63h** (16 mg, 49 %) as pale yellow viscous liquid upon purification by column chromatography (25 % ethyl acetate-hexane).



R_f : 0.30 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3732, 3278, 2915, 2849, 2347, 1640, 1540, 1475, 1374, 1315, 1156, 1108, 1023 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.34 (m, 5H), 6.74-

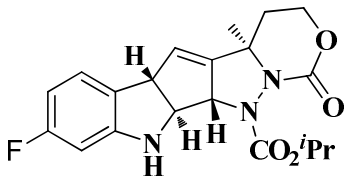
6.68 (m, 2H), 6.50 (bs, 1H), 5.86 (s, 1H), 5.27 (s, 2H), 4.60-4.51 (m, 3H), 4.35-4.26 (m, 3H), 2.05-2.01 (m, 2H), 1.57 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.6, 154.1, 135.7, 133.9, 128.6, 128.5, 125.0, 121.7, 118.3, 114.5, 68.2, 65.8, 64.1, 63.7, 60.2, 52.2, 32.8, 29.9 ppm.

HRMS (ESI): Calcd for $C_{24}H_{22}FN_3O_4$: 435.1594; Found (M+1): 436.1676.

Preparation of Compound (±)-63i

Following the general procedure (Section 4.7.4), the reaction of compound **62df** (50 mg, 0.087 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.009 mmol), PPh_3 (5 mg, 0.018 mmol) and Cs_2CO_3 (57 mg, 0.17 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**63i** (24 mg, 70 %) as pale yellow viscous liquid upon purification by column chromatography (30 % ethyl acetate-hexane).



R_f : 0.20 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3464, 3385, 3053, 2982, 2932, 1699, 1608, 1483, 1466, 1377, 1319, 1223, 1180, 1143, 1106, 1071, 918, 788, 751, 705, 625, 552 cm^{-1}.

^{1}H NMR (500MHz, $CDCl_3$): δ 6.90-6.88 (m, 1H), 6.40-6.36 (m, 2H), 5.96 (s, 1H), 5.02-5.00 (m, 1H), 4.79 (s, 1H), 4.37-4.12 (m, 5H), 2.2-2.16 (m, 2H), 1.34-1.31 (m, 9H) ppm.

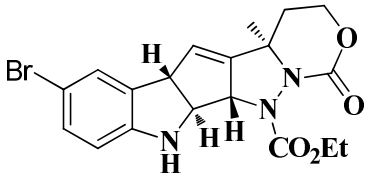
^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 164.4, 162.6, 154.1, 149.8, 124.7, 123.2, 121.9, 73.3, 70.1, 64.8, 63.2, 62.3, 59.4, 56.0, 32.3, 29.5, 22.0 ppm.

HRMS (ESI): Calcd for $C_{20}H_{22}FN_3O_4$: 387.1594; Found (M+1): 388.4047.

Preparation of Compound (±)-63j

Following the general procedure (Section 4.7.4), the reaction of compound **62ce** (50 mg, 0.082 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.008 mmol), PPh_3 (5 mg, 0.016 mmol) and Cs_2CO_3 (52 mg, 0.16 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**63j** (25 mg, 69 %) as pale yellow semi solid upon purification by column chromatography (35 %

ethyl acetate-hexane).



R_f : 0.13 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3730, 3365, 3056, 2954, 2923, 1731, 1615, 1491, 1463, 1440, 1401, 1329, 1289, 1183, 1121, 1033, 950, 839 cm^{-1}.

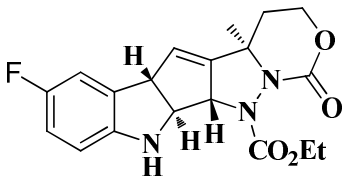
^{1}H NMR (500MHz, $CDCl_3$): δ 7.16-7.14 (m, 1H), 7.10 (s, 1H), 6.56 (d, *J*= 8.0 Hz, 1H), 5.96-5.94 (m, 1H), 4.79-4.77 (m, 1H), 4.56-4.24 (m, 7H), 2.22-2.19 (M, 2H), 1.34-1.32 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 153.5, 150.5, 148.8, 132.9, 130.8, 129.1, 127.3, 122.0, 111.3, 73.1, 63.0, 62.8, 60.3, 57.1, 32.1, 22.7, 14.6 ppm.

HRMS (ESI): Calcd for $C_{19}H_{20}BrN_3O_4$: 433.0637; Found (M+1): 434.0715.

Preparation of Compound (±)-63k

Following the general procedure (Section 4.7.4), the reaction of compound **62cb** (50 mg, 0.091 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.009 mmol), PPh_3 (5 mg, 0.018 mmol) and Cs_2CO_3 (59 mg, 0.18 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**63k** (21 mg, 62 %) as yellow viscous liquid upon purification by column chromatography (35 % ethyl acetate-hexane).



R_f : 0.13 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3731, 3365, 3058, 2958, 2924, 1734, 1613, 1490, 1463, 1438, 1402, 1329, 1289, 1181, 1122, 1032, 952, 838, 754, 723, 695,542 cm^{-1}.

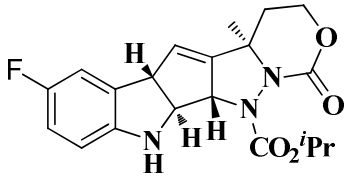
^{1}H NMR (500MHz, CDCl3): δ 6.76-6.71 (m, 2H), 6.61-6.58 (m, 1H), 5.96 (s, 1H), 4.79 (S, 1H), 4.52-4.25 (m, 7H), 2.20-2.19 (m, 2H), 1.31 (bs, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 158.1, 156.2, 154.0, 145.9, 122.9, 114.5, 114.3, 111.6, 111.4, 110.4, 73.5, 62.9, 62.8, 57.3, 32.1, 22.7, 14.6 ppm.

HRMS (ESI): Calcd for $C_{19}H_{20}FN_3O_4$: 373.1437; Found (M+1): 374.1522.

Preparation of Compound (±)-63l

Following the general procedure (Section 4.7.4), he reaction of compound **62bb** (50 mg, 0.087 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.009 mmol), PPh_3 (5 mg, 0.018 mmol) and Cs_2CO_3 (57 mg, 0.17 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**63l** (17 mg, 52 %) as pale yellow viscous liquid upon purification by column chromatography (35 % ethyl acetate-hexane).



R_f : 0.15 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3729, 3362, 3060, 2955, 2922, 1731, 1616, 1494, 1460, 1436, 1405, 1327, 1286, 1178, 1125, 1030, 949, 837 cm^{-1}.

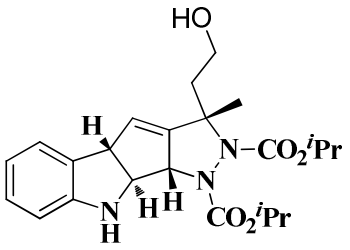
^{1}H NMR (500MHz, CDCl3): δ 6.77-6.72 (m, 2H), 6.61-6.58 (m, 1H), 5.95 (s, 1H), 5.01 (m, 1H), 4.79 (s, 1H), 4.53-4.31 (m, 5H), 2.22-2.17 (m, 2H), 1.33-1.19 (m, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.9, 153.5, 150.7, 132.9, 132.1, 132.0, 131.9, 128.5, 128.4, 114.1, 111.3, 73.5, 70.7, 62.8, 57.3, 32.1, 22.7, 22.1 ppm.

HRMS (ESI): Calcd for $C_{20}H_{22}FN_3O_4$: 387.1594; Found (M+1): 388.1675.

Preparation of Compound (±)-64a

Following the general procedure (Section 4.7.4), the reaction of compound **62ba'** (50 mg, 0.09 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.009 mmol), PPh_3 (5 mg, 0.018 mmol) and Cs_2CO_3 (59 mg, 0.18 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**64a** (26 mg, 68 %) as pale yellow viscous liquid upon purification by column chromatography (20 % ethyl acetate-hexane).



R_f : 0.30 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3468, 3386, 3051, 2980, 2930, 1698, 1606, 1481, 1465, 1379, 1316, 1225, 1182, 1144, 1108, 1071, 919, 789, 750, 703, 623, 551 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 – 7.01 (m, 2H), 6.74 – 6.68 (m, 2H), 5.98 (t, *J* = 2.9 Hz, 1H), 5.00-4.92 (m, 3H), 4.69 (bs, 1H), 4.56-4.52 (m, 1H), 4.42 (bs, 1H), 3.82

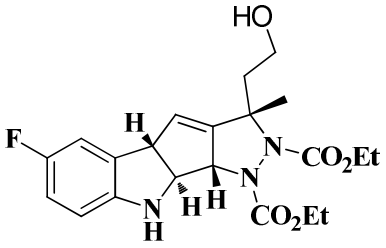
(bs, 1H), 3.68 – 3.66 (m, 1H), 1.70 (s, 3H), 1.32-1.29 (m, 14H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 155.4, 151.2, 149.4, 138.8, 120.1, 127.1, 124.2, 119.1, 110.2, 75.2, 72.9, 70.7, 70.2, 58.9, 56.9, 38.5, 26.6, 22.2, 22.0, 21.8 ppm.

HRMS (ESI): Calcd for $C_{23}H_{31}N_3NaO_5$: 452.2161; Found: 452.2165.

Preparation of Compound (±)-64g

Following the general procedure (Section 4.7.4), the reaction of compound **62cb'** (50 mg, 0.091 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.009 mmol), PPh_3 (5 mg, 0.018 mmol) and Cs_2CO_3 (60 mg, 0.18 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**64g** (15 mg, 39 %) as pale yellow viscous liquid upon purification by column chromatography (25 % ethyl acetate-hexane).



R_f : 0.25 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3733, 3269, 2918, 2851, 2375, 1687, 1541, 1481, 1380, 1331, 1171, 1122, 1047, 543 cm^{-1}.

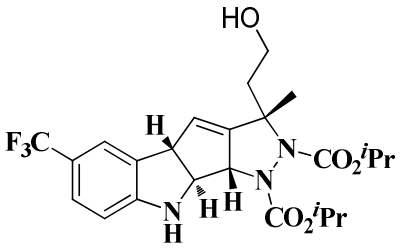
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 – 6.73 (m, 2H), 6.61 – 6.59 (m, 1H), 5.94 (s, 1H), 4.70 (s, 1H), 4.53-4.43 (m, 2H), 4.25-4.19 (m, 5H), 3.84-3.69 (m, 2H), 1.71-1.64 (m, 5H), 1.29 (t, J = 7.0 Hz, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 157.9, 156.8, 151.5, 145.5, 138.9, 132.1, 132.0, 131.8, 128.5, 127.4, 67.5, 62.7, 61.5, 59.1, 57.7, 41.8, 29.2, 15.5 ppm.

HRMS (ESI): Calcd for $C_{21}H_{26}FN_3O_5$: 419.1856; Found (M+1): 420.1941.

Preparation of Compound (±)-64b

Following the general procedure (Section 4.7.4), the reaction of compound **62bc'** (50 mg, 0.08 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.008 mmol), PPh_3 (4 mg, 0.016 mmol) and Cs_2CO_3 (52 mg, 0.16 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**64b** (19 mg, 48 %) as pale yellow viscous liquid upon purification by column chromatography (18 % ethyl acetate-hexane).



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

IR (Neat) ν_{max}: 3734, 3359, 2954, 2921, 2854, 2301, 1695, 1619, 1501, 1462, 1380, 1323, 1152, 1107, 1054, 915, 823, 770 cm^{-1}.

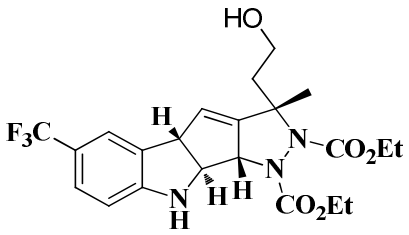
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 6.68 (d, *J*= 8.0 Hz, 1H), 5.96 (s, 1H), 4.97-4.92 (m, 3H), 4.68 (bs, 1H), 4.58 (m, 1H), 4.51 (bs, 1H), 3.86 (bs, 1H), 3.70 (bs, 1H), 1.75 (s, 3H),1.71-1.62 (m, 2H), 1.28 (d, *J* = 20.0 Hz, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 152.0, 151.6, 145.5, 126.8, 125.5, 123.2, 122.2, 114.1, 110.9, 109.2, 75.4, 73.7, 71.5, 70.6, 60.0, 58.3, 55.0, 38.8, 29.5, 22.1, 21.8 ppm.

HRMS (ESI): Calcd for $C_{24}H_{30}F_3N_3NaO_5$: 520.2035; Found: 520.2036.

Preparation of Compound (±)-64h

Following the general procedure (Section 4.7.4), the reaction of compound **62cc'** (50 mg, 0.084 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.008 mmol), PPh_3 (5 mg, 0.017 mmol) and Cs_2CO_3 (55 mg, 0.17 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**64h** (29 mg, 74 %) as pale yellow viscous liquid upon purification by column chromatography (20 % ethyl acetate-hexane).



R_f : 0.33 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3732, 3282, 2918, 2852, 2355, 1648, 1539, 1510, 1461, 1415, 1378, 1324, 1272, 1152, 1108, 1050, 824, 766 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 14 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 5.98 (s, 1H), 4.83 (bs, 1H), 4.69- 4.50 (m, 2H), 4.25-4.22 (m, 5H), 3.83-3.82 (bs, 1H), 3.69 (bs, 1H), 1.83-1.71 (m, 5H), 1.29 (t, *J* = 7.0 Hz, 6H) ppm.

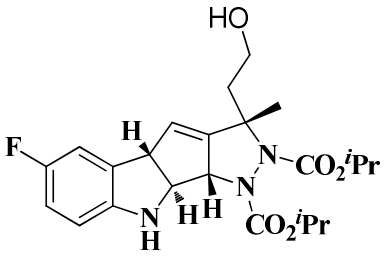
^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 152.3, 151.3, 131.6, 128.2, 127.0, 126.0, 124.1, 122.9, 121.4, 108.5,

75.4, 72.3, 62.9, 62.3, 60.1, 58.5, 56.3, 38.5, 20.4, 13.9 ppm.

HRMS (ESI): Calcd for $C_{22}H_{26}F_3N_3NaO_5$: 492.1722; Found: 492.1732.

Preparation of Compound (±)-64c

Following the general procedure (Section 4.7.4), the reaction of compound **62bb'** (50 mg, 0.087 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.009 mmol), PPh_3 (5 mg, 0.018 mmol) and Cs_2CO_3 (57 mg, 0.17 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**64c** (21 mg, 53 %) as pale yellow viscous liquid upon purification by column chromatography (20 % ethyl acetate-hexane).



R_f : 0.43 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3732, 3275, 2917, 2851, 2352, 1646, 1540, 1375, 1316, 1157, 1107, 1024, 668 cm^{-1}.

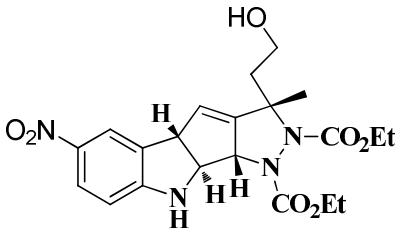
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78-6.73 (m 2H), 6.61-6.59 (m, 1H), 5.93 (s, 1H), 4.98-4.90 (m, 3H), 4.69 (bs, 2H), 4.52-4.50 (m, 1H), 4.42 (bs, 1H), 3.85-3.79 (m, 1H), 3.69-3.68 (m, 1H), 1.70 (m, 5H), 1.29 (d, J = 6.0 Hz, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 160.1, 156.1, 152.3, 146.0, 134.6, 129.9, 126.5, 124.4, 123.4, 116.4,115.1, 113.3, 113.1, 76.5, 75.3, 72.1, 71.6, 70.6, 60.9, 58.7, 40.9, 30.9, 24.4, 23.8 ppm.

HRMS (ESI): Calcd for $C_{23}H_{30}FN_3O_5$: 447.2169; Found (M+1): 448.2249.

Preparation of Compound (±)-64i

Following the general procedure (Section 4.7.4), the reaction of compound **62cd'** (50 mg, 0.087 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.009 mmol), PPh_3 (5 mg, 0.018 mmol) and Cs_2CO_3 (57 mg, 0.17 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**64i** (23 mg, 60 %) as pale yellow viscous liquid upon purification by column chromatography (35 % ethyl acetate-hexane).



R_f : 0.15 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3731, 3276, 2918, 2852, 2354, 1646, 1540, 1464, 1158, 1110, 1023 cm^{-1}.

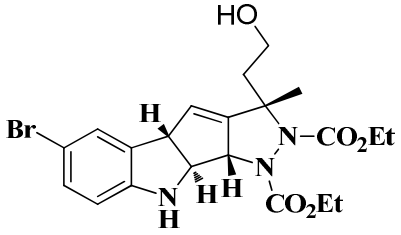
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1H), 7.91 (bs, 1H), 6.59 (d, J = 9.0 Hz, 1H), 5.99 (s, 1H), 4.72-4.71 (m, 1H), 4.63 (bs, 2H), 4.24-4.21 (m, 5H), 3.79-3.78 (m, 1H), 3.67-3.66 (m, 1H), 1.79-1.76 (m, 1H), 1.71 (s, 3H), 1.61 (bs, 1H), 1.29 (t, J = 7.0 Hz, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 155.2, 153.3, 139.7, 136.0, 127.2, 126.3, 125.3, 120.9, 114.6, 107.5, 62.6, 62.3, 60.1, 58.2, 56.3, 38.8, 21.0, 14.2 ppm.

HRMS (ESI): Calcd for $C_{21}H_{26}N_4NaO_7$: 469.1699; Found: 469.1706.

Preparation of Compound (±)-64d

Following the general procedure (Section 4.7.4), the reaction of compound **62ce'** (50 mg, 0.082 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.008 mmol), PPh_3 (5 mg, 0.017 mmol) and Cs_2CO_3 (54 mg, 0.17 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**64d** (26 mg, 66 %) as pale yellow viscous liquid upon purification by column chromatography (25 % ethyl acetate-hexane).



R_f : 0.30 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3733,3347, 2921, 2854, 2303, 1697, 1601, 1472, 1412, 1378, 1330, 1234, 1174, 1131, 1045, 882, 811, 762 cm^{-1}.

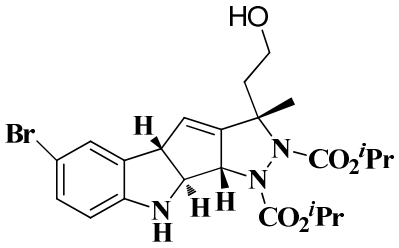
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 8.0 Hz, 1H), 7.12 (s, 1H), 6.57(d, J = 8.5 Hz, 1H), 5.94 (s, 1H), 4.68 (bs, 1H), 4.55-4.54 (m, 1H), 4.44 (bs, 1H), 4.25-4.20 (m, 6H), 3.83-3.82 (m, 1H), 3.69-3.68 (m, 1H), 1.83-1.76 (m, 1H), 1.71 (s, 3H), 1.29 (t, J = 7.0 Hz, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 151.5, 148.8, 130.8, 129.3, 127.4, 111.4, 110.7, 75.2, 73.1, 62.9, 62.4, 58.9, 56.7, 38.9, 21.0, 14.5, 14.4 ppm.

HRMS (ESI): Calcd for $C_{21}H_{26}BrN_3O_5$: 479.1055; Found (M+1): 480.1141.

Preparation of Compound (±)-64j

Following the general procedure (Section 4.7.4), the reaction of compound **62be'** (50 mg, 0.079 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.008 mmol), PPh_3 (4 mg, 0.016 mmol) and Cs_2CO_3 (52 mg, 0.16 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**64j** (17 mg, 42%) as pale yellow viscous liquid upon purification by column chromatography (18 % ethyl acetate-hexane).



R_f : 0.50 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3733, 3383, 2924, 2856, 2361, 2333,1697, 1601, 1539, 1470, 1379, 1312, 1243, 1180, 1147, 1107, 1053, 915, 813 cm^{-1}.

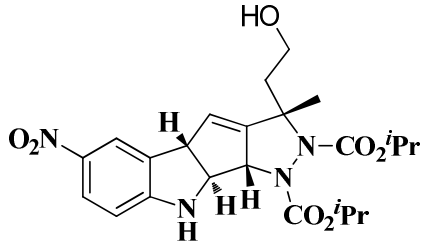
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 8.5 Hz, 1H), 7.11 (s, 1H), 6.56 (d, J = 8.0 Hz, 1H), 5.92 (s, 1H), 4.98-4.91 (m, 3H), 4.67 (bs, 1H), 4.55-4.57 (m, 1H), 4.42 (bs, 1H), 3.86-3.82 (m, 1H), 3.70-3.68 (m, 1H), 1.75 (s, 3H), 1.70-1.55 (m, 2H), 1.29 (d, J = 6.5 Hz, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 151.8, 148.7, 131.0, 129.5, 127.6, 111.7, 100.2, 75.0, 73.1, 66.2, 61.8, 58.7, 56.5, 38.8, 29.9, 22.4, 22.2, 22.0 ppm.

HRMS (ESI): Calcd for $C_{23}H_{30}BrN_3O_5$: 507.1368; Found (M+1): 508.1455.

Preparation of Compound (±)-64e

Following the general procedure (Section 4.7.4), the reaction of compound **62ce'** (50 mg, 0.083 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.008 mmol), PPh_3 (5 mg, 0.017 mmol) and Cs_2CO_3 (54 mg, 0.17 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**64e** (23 mg, 58 %) as pale yellow viscous liquid upon purification by column chromatography (25 % ethyl acetate-hexane).



R_f : 0.30 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3732, 3403, 2920, 2853, 1644, 1464, 1424, 1375, 1318, 1158, 1115, 1043 cm^{-1}.

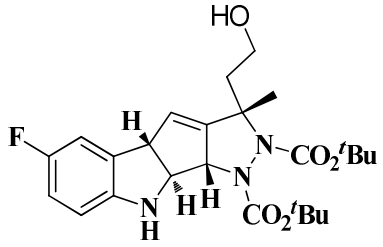
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.0 Hz, 1H), 7.93 (s,1H), 6.61 (d, *J* = 8.5 Hz, 1H), 5.99 (s, 1H), 4.97-4.94 (m, 3H), 4.71 (bs, 1H), 4.64 (bs, 2H), 3.86 (bs, 1H), 3.69 (bs, 1H), 1.78 (s, 2H), 1.74 (s, 3H), 1.30 (d, *J* = 6.5 Hz, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 155.1, 151.9, 139.9, 132.1, 128.5, 127.2, 126.3, 122.5, 120.9, 107.6, 75.2, 72.9, 71.1, 70.6, 60.3, 58.9, 56.1, 36.6, 29.7, 22.1, 22.0, 21.8 ppm.

HRMS (ESI): Calcd for $C_{23}H_{30}N_4NaO_7$: 497.2012; Found: 497.2024.

Preparation of Compound (±)-64k

Following the general procedure (Section 4.7.4), the reaction of compound **62ae'** (50 mg, 0.083 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.008 mmol), PPh_3 (5 mg, 0.017 mmol) and Cs_2CO_3 (54 mg, 0.17 mmol) in dry CH_3CN (2 mL) at 80 °C for 12 h yielded (±)-**64k** (19 mg, 49 %) as pale yellow viscous liquid upon purification by column chromatography (15-18 % ethyl acetate-hexane).



R_f : 0.60 (hexane/ethyl acetate = 3:2).

IR (Neat) ν_{max}: 3731, 3378, 2976, 2366, 2288, 1697, 1608, 1483, 1452, 1390, 1293, 1252, 1159, 1055, 873, 855, 817, 755 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78-6.72 (m, 2H), 6.59 (bs, 1H), 5.90 (s, 1H), 4.67 (bs, 1H), 4.53 (d, *J*= 7.5 Hz, 1H), 4.41 (bs, 1H), 3.89 (bs, 1H), 3.68 (bs, 1H), 1.67-1.49 (m, 23H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 156.3, 155.7, 152.6, 146.0, 130.1, 128.5, 128.2, 125.7, 113.8, 81.3, 74.6, 73.8, 65.8, 60.3, 59.0, 57.0, 38.8, 34.5, 28.6, 26.6, 15.5 ppm.

HRMS (ESI): Calcd for $C_{25}H_{34}FN_3O_5$: 475.2482; Found (M+1): 476.2566.

Preparation of Compound (±)-64f

Following the general procedure (Section 4.7.4), the reaction of compound **62ac'** (50 mg, 0.077 mmol) in presence of $Pd(OAc)_2$ (2 mg, 0.008 mmol), PPh_3 (4 mg, 0.015 mmol) and Cs_2CO_3 (50 mg, 0.15 mmol) in dry CH_3CN (2 mL) at 80 ^oC for 12 h yielded (±)-**64f** (12 mg, 31 %) as pale yellow viscous liquid upon purification by column chromatography (15 % ethyl acetate-hexane).

R_f: 0.65 (hexane/ethyl acetate = 3:2).

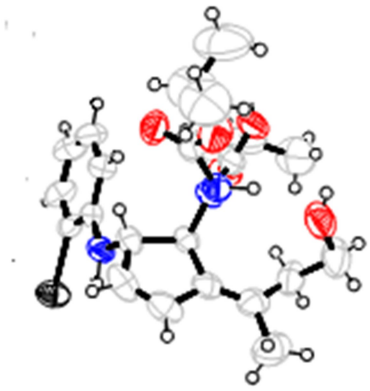
IR (Neat) ν_{max}: 3732, 3385, 2973, 2925, 2860, 1663, 1620, 1369, 1326, 1263, 1153, 1112, 1055, 756 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.0 Hz, 1H), 7.24 (s, 1H), 6.67 (d, J = 8.0 Hz, 1H), 5.94 (s, 1H), 4.83 (bs, 1H), 4.66-4.49 (m, 2H), 3.91 (bs, 1H), 3.68 (bs, 1H), 1.67 (s, 2H), 1.57 (s, 3H), 1.49 (s, 18H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ 155.3, 152.0, 129.6, 127.3, 125.9, 122.3, 121.4, 112.9, 108.9, 81.9, 73.1, 658, 60.3, 59.0, 56.4, 38.8, 29.7, 28.2, 21.0 ppm.

HRMS (ESI): Calcd for $C_{26}H_{34}F_3N_3NaO_5$: 548.2348; Found: 548.2357.

Ortep diagram of 62ba



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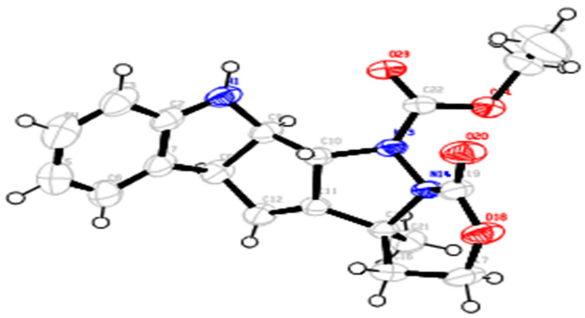
Ortep diagram of (±)-63b



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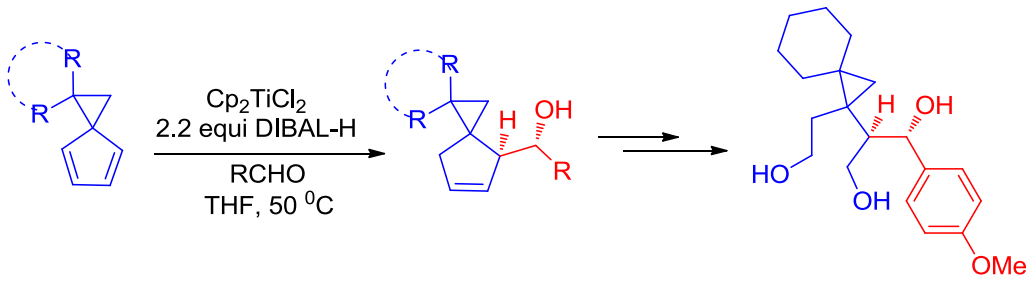
SUMMARY

The thesis entitled "**Transition Metal Catalyzed Transformations of Pentafulvenes and Its Derivatives: Facile Strategies Toward Carbocycles and Heterocycles**" symbolizes the outcomes of the investigations carried out in the zone of the development of efficient protocols for the effective utilization of pentafulvene and its derivatives for the synthesis of carbocycles and heterocycles. The thesis is divided into four chapters, which comprises of comprehensive discussion on the syntheses of carbocycles and heterocycles, *via* transition metal catalyzed transformations of pentafulvene and its derivatives.

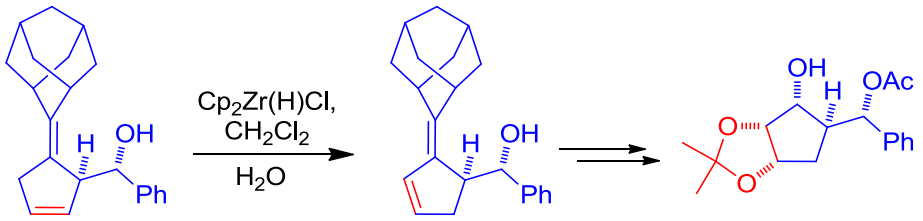
The literature surveys included in introductory chapter mostly cover the available synthetic routes to pentafulvenes and a selected portion of the reactivity of pentafulvene and pentafulvene derived systems. In line with this, the thesis is entirely focused on methodology development based on the transition metal mediated transformations of pentafulvene derived systems. Design and definition of the research problem have also been unified in this chapter.

The second chapter, titanium and zirconium catalyzed regioselective synthesis of five membered carbocycles, has been divided into two parts. Part A describes the approach towards the methodology for the generation of the functionalized spiro appended cyclopentenyl homoallylic alcohols *via*, a titanium catalyzed hydroalumination of various spirocyclopentadienes with different aromatic aldehydes. The generality and scope of the methodology were established by the reactions of simple spirocyclopentadienes as well as many fulvene derived spirocyclopentadienes (Scheme 1).



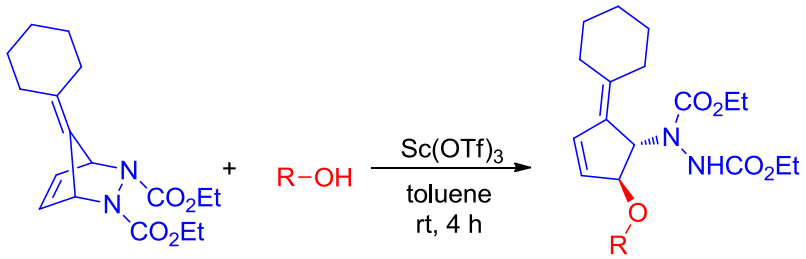
Scheme 1

As a part of our ongoing interest in the endocyclic activation of pentafulvene and its derivatives, a detailed investigation on selective functionalization of the endocyclic C-C double bond by hydrozirconation, which was then developed into a simple method towards the synthesis of a new class of substituted 1,2-dihydrofulvenes was carried out in the part B of second chapter. The successful extension of the new methodology towards complex cyclopentanols with multiple stereocenters, is also presented towards the end of this chapter (Scheme 2).



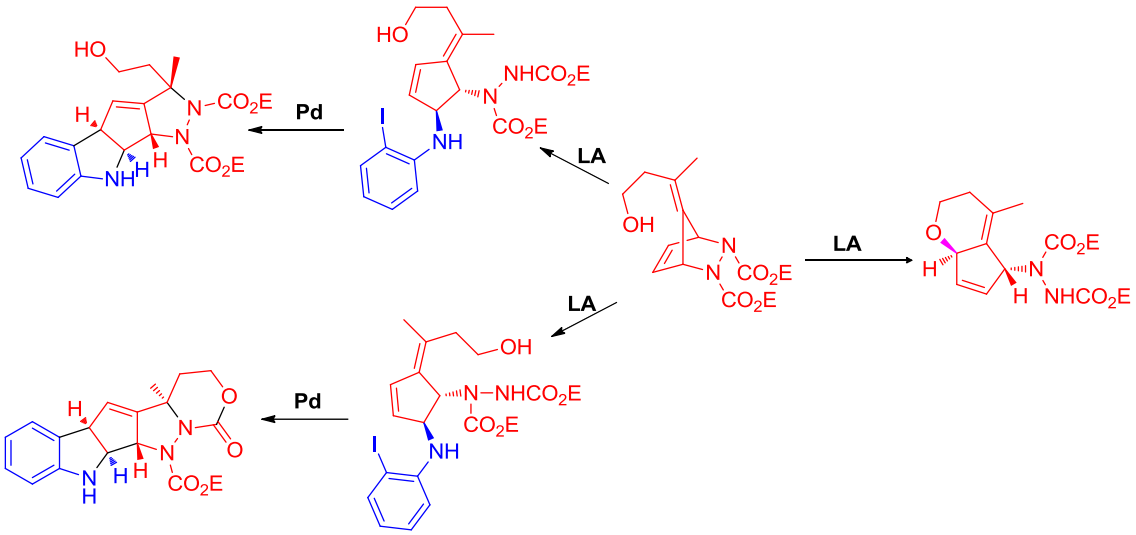
Scheme 2

The third chapter, deals with the Lewis acid catalyzed desymmetrization of pentafulvene derived diazanorbornenes with aromatic and aliphatic alcohols towards the synthesis of various aryl and alkyl cyclopentenyl ethers. An efficient procedure for the direct creation of carbon-oxygen bonds in pentafulvene derivatives for the synthesis of carbocycles is presented (Scheme 3).



Scheme 3

A general and efficient methodology for the synthesis of indoline derivatives from diazabicyclic olefins through a one-pot ring opening/ring closing mechanism is described in the last chapter. Due to our continuing interest in the chemistry of pentafulvene and its derivatives, we developed a sequential transition metal mediated transformation of hydroxy tethered diazanorbornene towards tetrahydrocyclopenta[*b*]pyrans and novel cyclopentene fused indoline, pyrazolidine and 1,3-oxazinan-2-one skeletons (Scheme 4).



Scheme 4

In conclusion, we have established proficient protocols for the synthesis of carbocycles and heterocycles from pentafulvene and its derivatives *via* transition metal catalysis. These products possess biologically significant cores and hold multiple points for functionalization as well as stereocenters, which making them useful moieties for the synthesis of many complex molecules with biologically relevant scaffolds.

LIST OF PUBLICATIONS

1. "Recent Advances in the Chemistry of Pentafulvenes". **Preethanuj P**., Syam Krishnan.; Sreeja Thulasi.; Sarath Chand S.; Vijay Nair.; Florian Jaroschik.; Jomy Joseph.; Radhakrishnan K. V. *Chem. Rev.* **2017,** *117*, 3930.
2. **"**Titanium and Zirconium Hydride-Catalyzed Regioselective Isomerization of 1,4-Dihydrofulvenes: Access to 1-Substituted 1,2-Dihydrofulvenes". Jomy Joseph.; **Preethanuj Preethalayam**.; K. V. Radhakrishnan.; Florian Jaroschik.; Jean-Luc Vasse, *Org. Lett.***, 2015**, *17*, 6202.
3. "Sequential Tandem Transformations of Functionalized Diazanorbornenes: Facile Strategy towards Pentacyclic Framework with Multiple Stereocenters". **P. Preethanuj**., V. Jijitha., Ajesh Vijayan., Jubi John., K. V. Radhakrishnan, *Synthesis.* **2016**, *49*, 1816.
4. "Palladium-Catalyzed Skeletal Rearrangement of Spirotricyclic Olefins: A Facile One-Pot Strategy for the Synthesis of a Novel Motif with Cyclopentene Fused to Benzofuran and Pyrazolidine". Praveen Prakash.; Eliyan Jijy.; **Preethalayam Preethanuj.;** Petri M. Pihko.; Sarngadharan Sarath Chand.; K. V. Radhakrishnan. *Chem. Eur. J.* **2013**, *19*, 10473.
5. **"**Trapping the Lewis Acid Generated Transient Species from Pentafulvene Derived Diazanorbornenes with *ortho*-Functionalized Aryl Iodides and Aliphatic Alcohols" S. Sarath Chand.; S. Saranya.; **P. Preethanuj**.; B. P. Dhanya.; E. Jijy.; Praveen Prakash.; B. S. Sasidhar.; Jan Szymoniak.; P. V. Santhini.; K. V. Radhakrishnan. *Org. Biomol. Chem.* **2014,** *12*, 3045.
6. **"**Lewis Acid Catalyzed Regioselective Hydroheteroarylation of Pentafulvenes". S. Sarath Chand.; Greeshma Gopalan.; P. V. Santhini.; **P. Preethanuj** .; Jubi John.; Dominique Harakat.; Florian Jaroschik.; K. V. Radhakrishnan. *Org. Lett.*, **2016**, *18*, 964.
7. "Palladium/Lewis Acid Mediated Domino Reaction of Pentafulvene Derived Diazabicyclic Olefins: Efficient Access to Spiropentacyclic Motif with an Indoline and Pyrazolidine Fused to Cyclopentene". S. Sarath Chand.; E. Jijy.; Praveen Prakash.; Jan Szymoniak.; **P. Preethanuj**.; B. P. Dhanya .; K. V. Radhakrishnan, *Org. Lett*., **2013** , *15*, 3338.

8. **"**Lewis Acid Catalyzed C-3 Alkylidenecyclopentenylation of Indoles: An Easy Access to Functionalized Indoles and Bisindoles". S. Sarath Chand.; B. S. Sasidhar.; Praveen Prakash.; P. Sasikumar.; **P. Preethanuj**.; Florian Jaroschik.; Dominique Harakat.; Jean-Luc Vasse .; K. V. Radhakrishnan, *RSC Adv.*, **2015**, *5*, 38075.
9. "Rhodium (III)-catalyzed ring-opening of strained olefins through C–H activation of O-acetyl ketoximes: an efficient synthesis of trans-functionalized cyclopentenes and spiro[2.4]heptenes". E. Jijy.; Praveen Prakash.; M. Shimi.; S. Saranya**.; P. preethanuj**.; Petri M. Pihko.; Sunil Varughese.; K.V. Radhakrishnan. *Tett.Let* **2013**, *54*, 7127.
10. "Bis-Functionalization of 1,3-Dienes through 1,4-Conjugate Addition of Amphiphilic Bis-π-Allyl and Related Palladium Intermediates . Bis-Functionalization of 1,3-Dienes". T. V. Baiju.; Ajesh Vijayan.; Nayana Joseph.; **Preethanuj Preethalayam**.; K. V. Radhakrishnan.; E. Suresh.; Yoshinori Yamamoto.; *Synlett.* **2014**, *25*, 359.
11. "Diazabicyclic Olefin: A Valuable Diels–Alder Adduct for the One-pot Access of Functionalized Carbocyclic and Heterocyclic Scaffolds". Jijy E.; Praveen Prakash.; Nayana Joseph.; Sarath Chand S.; **Preethanuj Preethalayam**.; Jubi John.; K. V. Radhakrishnan [To be communicated to *Chemical Society Reviews*].
12. "Stereoselective functionalization of spirocyclopentadienes: Facile synthesis of highly substituted Cyclopropane "**P. Preethanuj**.; Jomy Joseph.; P. Sasikumar.; Florian Jaroschik.; Dominique Harakat.; Jean-Luc Vasse .; K. V. Radhakrishnan. [To be communicated].
13. "pH Responsive fluorescent organogelators derived from pyrene-carbohydrate orthoesters". Shimi M**.**; **Preethanuj, P.;** Nitha, P. R.; Santhini, P. V.; Suresh Das.; Radhakrishnan, K. V. [To be communicated]
14. "Lewis acid promoted Regioselective Double Hydro (hetero) arylation of 6,6'-dialkyl Substituted Pentafulvene : A Facile Approach to Bisindole Derivatives". P. Sasikumar.; B. Prabha.; S. Sarath Chand.; M. Aswathy.; **P. Preethanuj**.; E. Suresh.; Florian Jaroschik.; K. V. Radhakrishnan. [Accepted in *European journal of organic chemistry*]
15. "Generation of ε,ε-difluorinated metal-pentadienyl species through lanthanide-mediated C-F activation". Tarun Kumar, Fabien Massicot, Dominique Harakat, Sylviane Chevreux, Agathe Martinez, **Preethanuj Preethalayam**, Radhakrishnan Kokkuvayil Vasu, Jean-Bernard Behr, Jean-Luc Vasse, and Florian Jaroschik. [To be communicated]

PAPERS PRESENTED AT CONFERENCES

1. "Palladium catalyzed skeletal rearrangement of spirotricyclic olefins toward the synthesis of a novel tetracyclic scaffold" **Preethanuj P.**, K.V. Radhakrishnan ; National symposium on Transcending Frontiers in Organic Chemistry, CSIR-NIIST, October 9-11, 2014 (**Poster Presentation**).
2. "Lewis acid catalyzed C-3alkylidenecyclopentenylation of indoles: An easy access to functionalized indoles and bisindoles" **Preethanuj P.** and K.V. Radhakrishnan ; International Conference on Nascent Developments in Chemical Sciences; Opportunities for Academia-Industry Collaboration, NDCS-2015, October 16-18, 2015, Pilani (**Poster Presentation**).
3. "Ortho-functionalized Aryl Iodides and Aliphatic Alcohols for Trapping the Transient Species generated from Pentafulvene derived Diazanorbornenes via Lewis Acid Catalysis" **Preethanuj P**. and K.V. Radhakrishnan ; CRSI NSC-19, 2016(**Poster Presentation**).
4. "Gain from Strain: Exciting Journey from Synthetic Organic Chemistry to Natural Products" **Preethanuj P.** and K.V. Radhakrishnan; Emerging Trends In Agroscience-Chemistry and Technology, Syngenta Biosciences Pvt. Ltd., November 22-23, 2016 (**Poster Presentation**).
5. "Sequential Tandem Transformations of Functionalized Diazanorbornenes: Facile Strategy towards Heterocycles with Multiple Stereocenters" **P. Preethanuj** and K. V. Radhakrishnan, International conference on tropical plants and molecular design-TKMCC-2017 Feb 14-15, 2017 (**Oral Presentation**).

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