PALLADIUM CATALYZED CARBON-CARBON/CARBON-HETEROATOM BOND FORMATION REACTIONS UTILIZING PENTAFULVENE DERIVED BICYCLIC HYDRAZINES

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BY
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DECLARATION

I hereby declare that the Ph.D. thesis entitled **"PALLADIUM CATALYZED CARBON-CARBON/CARBON-HETEROATOM BOND FORMATION REACTIONS UTILIZING PENTAFULVENE DERIVED BICYCLIC HYDRAZINES"** is an independent work carried out by me in the Organic Chemistry Section, Chemical Sciences and Technology Division of National Institute for Interdisciplinary Science and Technology (*formerly*, Regional Research Laboratory), Thiruvananthapuram, under the supervision of Dr. K. V. Radhakrishnan and it has not been submitted anywhere else for any other degree, diploma or title.

Rani Rajan

Thiruvananthapuram
April, 2013

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CERTIFICATE

This is to certify that the work embodied in the thesis entitled ***"PALLADIUM CATALYZED CARBON-CARBON/CARBON-HETEROATOM BOND FORMATION REACTIONS UTILIZING PENTAFULVENE DERIVED BICYCLIC HYDRAZINES"*** *is an authentic record of the bonafide research work carried out by* ***Ms. Rani Rajan*** *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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Rani Rajan

ABBREVIATIONS

Ac	: acetyl	MS	: mass spectroscopy
Bn	: benzyl	m	: multiplet
^{t}Bu	: tertiary butyl	Me	: methyl
br s	: broad singlet	mg	: milligram
calcd	Calculated	mL	:millilitre
cod	: cyclooctadiene	NMR	: nuclear magnetic resonance
d	: doublet	Nu	: nucleophile
dba	: dibenzylidene acetone	*o*	: ortho
dd	: doublet of a doublet	*p*	: para
DMF	: dimethylformamide	Ph	: phenyl
DIEA	: diisopropylethylamine	^{i}Pr	: isopropyl
DIPA	: diisopropylamine	q	: quartet
DBU	: 1,8-diazabicyclo[5.4.0]undec-7-ene	R_f	: retention factor
dppe	: bis(diphenylphosphino)ethane	RT	: room temperature
dppf	: bis(diphenylphosphino)ferrocene	s	:singlet
Et	: ethyl	t	: triplet
FAB	: fast atom bombardment	THF	: tetrahydrofuran
h	: hour	TLC	: thin layer chromatography
HRMS	: high resolution mass spectra	TMS	: trimethyl silyl
Hz	: hertz	TPPTS	: 3,3′,3″-Phosphinidynetris(benzenesulfonic
IR	: infrared		acid) trisodium salt
J	: coupling constant	TPPMS	: (3-diphenylphosphanyl)benzenesulfonic
LA	: lewis acid		acid
Mp	: melting point	*tert*	: tertiary

CONTENTS

PREFACE

The reactions involving fulvenes and its derivatives have received a great deal of attention over the years in synthetic organic chemistry. Functionalizations of fulvenes provide versatile and powerful approaches to various polycyclic systems and natural products. They serve as versatile intermediates in the construction of various ring systems through inter- as well as intramolecular cycloadditions. Compared to the rich literature on the cycloaddition reactions of pentafulvenes, much less attention has been paid to the synthetic utilization of their cycloadducts. Tactical manipulations on the chosen adduct offer the prospects for designing a variety of useful molecular skeletons.

Addition of heterodienophiles to fulvenes offers an efficient strategy towards the synthesis of azabicyclic olefins. However, there have been no serious attempts to study the synthetic utility of these substrates. In this context and with the intention of utilizing pentafulvenes towards synthetically important molecules, we decided to explore the reactivity of pentafulvene derived azabicyclic olefins. Our attention was focused on the synthetic potential associated with the ring opening of fulvene derived bicyclic hydrazines under palladium catalysis. We envisioned that the desymmetrization of these adducts using various soft nucleophiles will provide a novel access to synthetically and biologically important alkylidene cyclopentenes. The investigations along this line form the focal theme of this thesis entitled **"PALLADIUM CATALYZED CARBON-CARBON/CARBON-HETEROATOM BOND FORMATION REACTIONS UTILIZING PENTAFULVENE DERIVED BICYCLIC HYDRAZINES".**

The thesis is divided into four chapters. Relevant references are given at the end of each chapter. An overview of the synthetic applications of pentafulvene derived cycloadducts is presented in the first chapter of the thesis. The definition of the present research problem is also incorporated in this chapter.

Second chapter presents the results of our investigations on the palladium mediated ring opening of pentafulvene derived bicyclic hydrazine with phenols and active methylene compounds leading to the novel synthesis of *cis*-1,2-disubstituted alkylidene cyclopentenes. It is noteworthy that alkylidene cyclopentenes are key intermediates in the synthesis of a number of biologically active molecules.

Substituted cyclopentenes are particularly important synthetic targets because further derivatization of the functional groups provides access to highly functionalized, stereochemically complex molecules. Third chapter presents the results of our investigations on the development of a novel palladium catalyzed methodology for the ring opening of different fulvene derived bicyclic hydrazines with aryl halides. The reaction at room temperature afforded substituted alkylidene cyclopentenes. The products of the developed methodology can be used as potential intermediates towards a number of biologically relevant molecules.

Annulation is one of the most efficient and economical ways of creating cyclic molecules. The advantage of these transformations is the formation of several bonds and the creation of two or more contiguous stereogenic centers by using a single catalyst in one pot, without the need for isolation of the intermediates. The last chapter describes the palladium catalyzed cyclopentannulation of pentafulvene derived bicyclic hydrazines with 2-iodophenols towards the synthesis of benzofuran fused bicyclic hydrazines. The generality of the methodology was established by carrying out the reactions of fulvene derived bicyclic hydrazines with various substituted 2-iodophenols.

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

Chapter 1

Pentafulvenes: An Overview

1.1. Introduction

Fulvenes and their derivatives have been extensively investigated in synthetic organic chemistry for more than a century. They are cyclic cross conjugated olefins with unique electronic, spectroscopic and chemical properties. Fulvenes, belong to the category of non-functionalized carbon-carbon double bonds.[1] Based on their ring skeleton, they are named as triafulvenes, pentafulvenes, heptafulvenes etc (Figure 1.1).

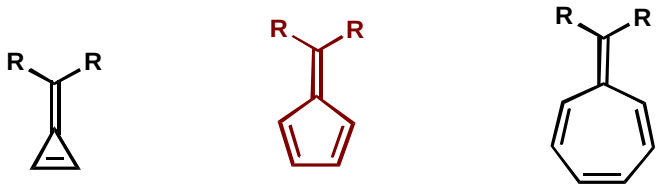


Figure 1.1. Types of fulvene

Pentafulvenes stands out among the various type of fulvenes and serve as versatile intermediates in the construction of a variety of ring systems, through inter as well as intramolecular cycloaddition reactions. They are mainly utilized as synthons to access new carbocyclic and heterocyclic systems, containing one or more five membered rings. They have found extensive use as valuable building block in the synthesis of natural products such as hirsutene,[2] capnellene,[3] β-vetivone,[4] hinesol,[5] silphinene,[6] viburtinal,[7] longifolene[8] etc (Figure 1.2). Fulvenes have also been utilized for the synthesis of titanocene anticancer drugs[9] and various aminocyclopentitols with glycosidase inhibitory activity.[10] Fulvenes and benzofulvenes have been patented as anti-inflammatory agents having antipyretic and analgesic activity.[11]

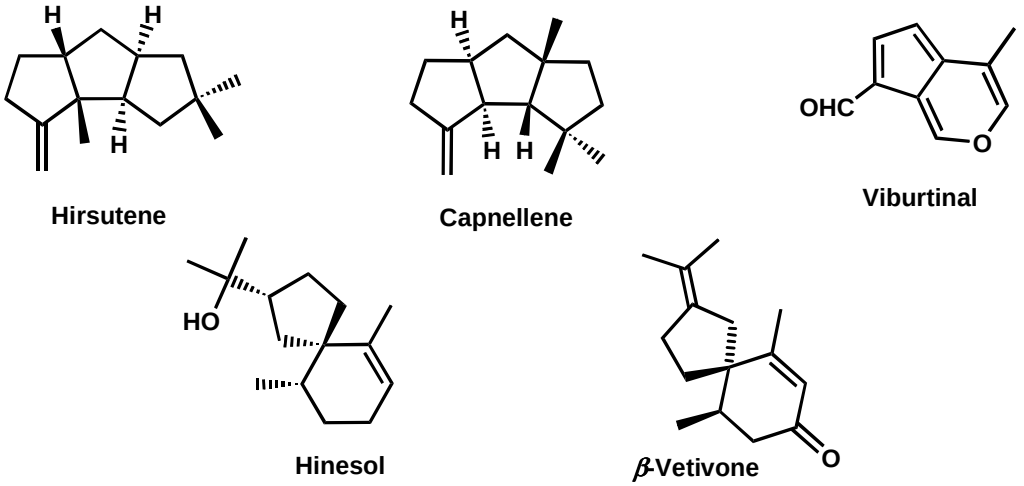
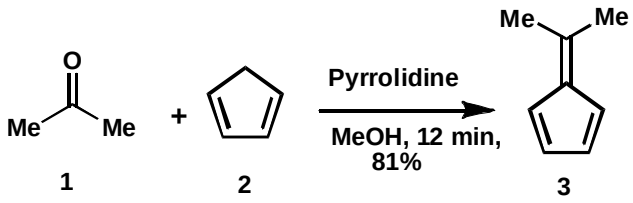


Figure 1.2 .Some natural products synthesized from pentafulvenes

1.2. Pentafulvenes: Synthesis and properties

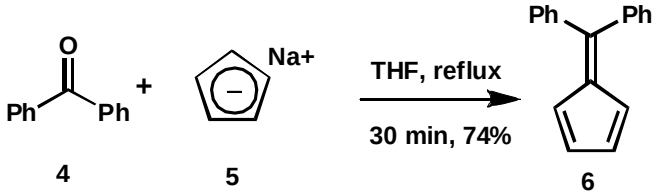
Pentafulvenes, colored dipolar hydrocarbon, were the first fulvenes prepared and named (Latin, *fulvus,* meaning yellow) by Thiele in 1900.[12] This method consists of condensation of cyclopentadiene with aldehydes or ketones in presence of alkali metal base in an alcohol, providing the product in modest to good yields. The scope and limitation of this method depends on the reactivity of the carbonyl compound and on the stability of the fulvene formed. It gives low yields with considerable amounts of resinous byproducts, presumably due to competing aldol condensations. Freiesleben modified this procedure by replacing the strong bases *via* primary or secondary amines.[13]

In 1983, Stone and Little developed a more versatile and convenient route towards a range of structurally diverse pentafulvenes.[14] They showed that pyrrolidine efficiently promotes fulvene formation from cyclopentadiene and a range of carbonyl compounds such as ketones, aldehydes with acidic α-hydrogen, and sterically encumbered aldehydes (Scheme 1.1**)**. Even though, this is the most widely accepted method for the synthesis of fulvenes in terms of generality and high yields; the reaction was unsuccessful with bulky ketones such as diaryl ketones.



Scheme 1.1

Oda and co-workers provided an alternate procedure towards 6,6-disubstituted pentafulvenes using N,N-dialkylamides, instead of ketones, with organolithium compounds and cyclopentadiene.[15] Recently, Ottoson described an improved synthesis of fulvenes through reaction of sodium cyclopentadienide with the appropriate ketones in refluxing THF and they showed that alkyl or aryl substituted fulvenes are formed rapidly in high yields (Scheme 1.2).[16]



Scheme 1.2

Pentafulvene is a cyclic isomer of benzene with non-benzenoid aromaticity and high polarizability. Based on their dipole moments as well as on their reactivity patterns, they would occupy an intermediate position between the open chain olefinic and aromatic targets in a number of synthetic studies. Due to chemical instability they have been considered for a long time as non-aromatic.[17] The aromatic character of pentafulvenes depends on the electronic nature of substituents at the exocyclic position.[18] Electron-donating groups in the case of pentafulvenes and electron-accepting ones in the case of heptafulvenes strongly stabilize the respective rings, leading to a substantial increase in aromatic character. This is evidently due to the electron-accepting power of the five membered ring and electron-repelling nature of the seven membered ring, inorder to satisfy the Huckel 4n+2 rule.

Pentafulvenes exhibits a wide range of reactions with nucleophiles, electrophiles and various cycloaddition partners.[19] The terminal exocyclic carbon of pentafulvenes is electrophilic and can be attacked directly by suitable nucleophiles. In addition, the protons in the α-position of this electrophilic carbon are sufficiently acidic to be removed by a suitable base.[20] Selective reduction of exocyclic double bond of pentafulvenes is facile with lithium aluminum hydride or with dissolving metal conditions. On the other hand, fulvenes with N- or O-functions at the exocyclic carbon show a pronounced tendency for electrophilic and nucleophilic substitution reactions like the isomeric anilines or phenols.[21] However, the synthetic potential of pentafulvenes were mainly exploited in periselective cycloaddition reactions.

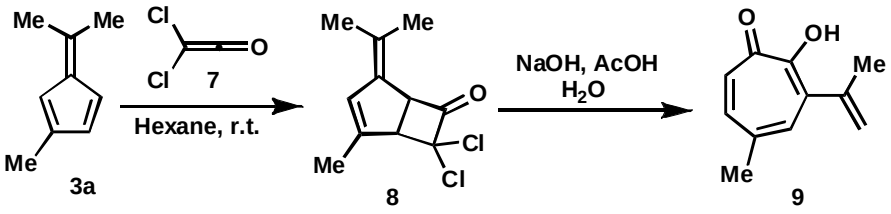
1.3. Cycloaddition chemistry of pentafulvenes

Cycloaddition reactions hold a prominent place in the arsenal of synthetic methods and are among the most trusted of chemical transformations available to date.[22] The rich and fascinating chemistry presented through these reactions has attracted synthetic chemists and propelled them to undertake challenging goals, consequently building a good headway in synthesis. The advent of pentafulvenes as convincing scaffolds expanded the credibility and scope of cycloaddition reactions. This was credited to its diverse cycloaddition profiles and the versatility of the reaction products. They perform flexibly as a 2π, 4π or 6π candidate and have been identified as the well known construction unit of many fused ring systems through intra- and inter-molecular cycloaddition reactions. The periselectivity of these reactions is controlled by the substituents on the fulvene and the other substrate. The following section discusses in brief the cycloaddition chemistry of pentafulvenes.

1.3.1. Pentafulvene as 2π-component

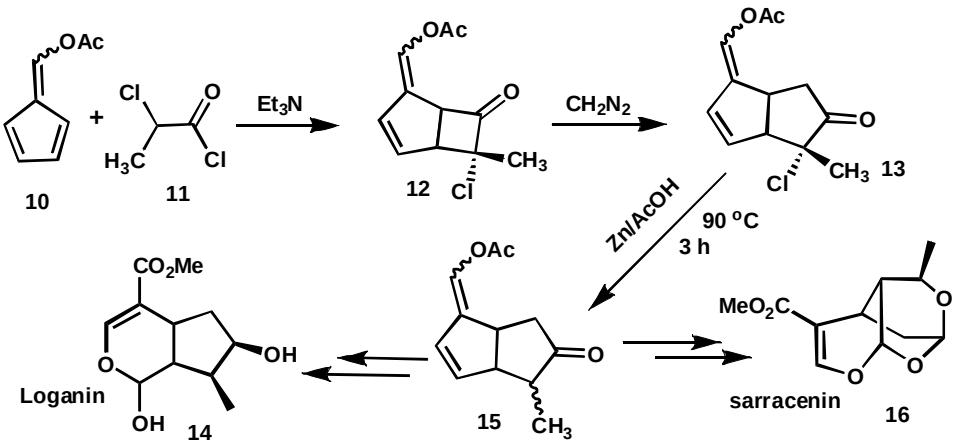
Pentafulvenes behave as 2π components with electron-deficient dienes. A noteworthy example of this type of cycloaddition was reported from the research

group of Imafuku. They have established an efficient route towards substituted tropolone derivatives through a [2+2] cycloaddition between 2-alkyl-6,6-dimethyl fulvene **3a** and dichloroketene **7** which is generated *in situ* from dichloroacetyl chloride (Scheme 1.3).[23]



Scheme 1.3

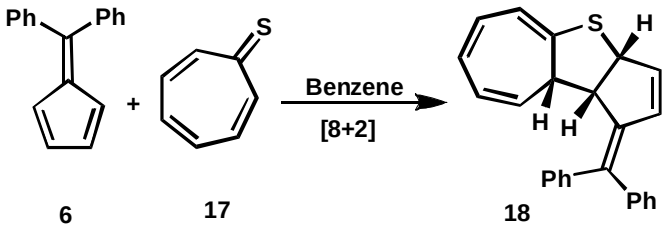
By adoption of the similar cycloaddition approach, Chang and coworkers introduced a new route for the total synthesis of Iridoid natural products Loganin and Sarracenin by utilizing the versatile diquinane **13**, which was obtained by the reaction of 6-acetoxy fulvene **10** with methyl chloroketene **11** generated *in situ* (Scheme 1.4).[24]



Scheme 1.4

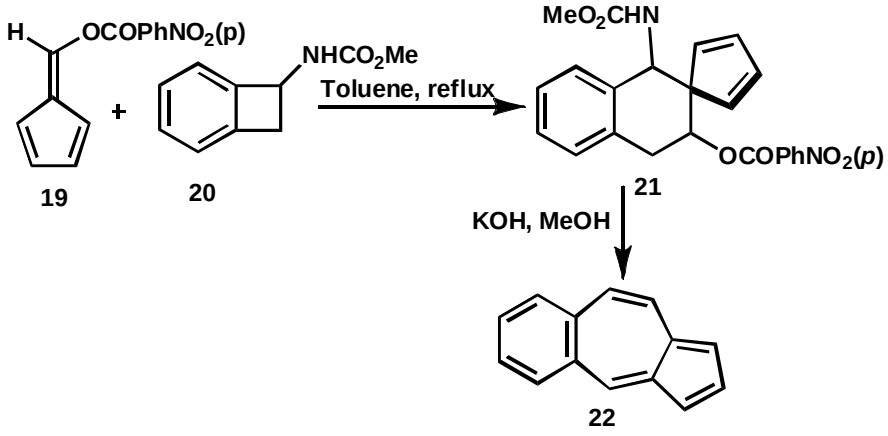
Fulvene shows different reactivity patterns with tropone and its sulphur analogue, tropothione. As early as 1970 Houk established that fulvene acts as a 4π component with tropone and gave a double [6+4] type adduct.[25] In contrast to this observation, Machiguchi *et al.* have reported that fulvene acts as a 2π component

in its reaction with tropothione **17**, with the latter serving as the 8π component (Scheme 1.5).[26]



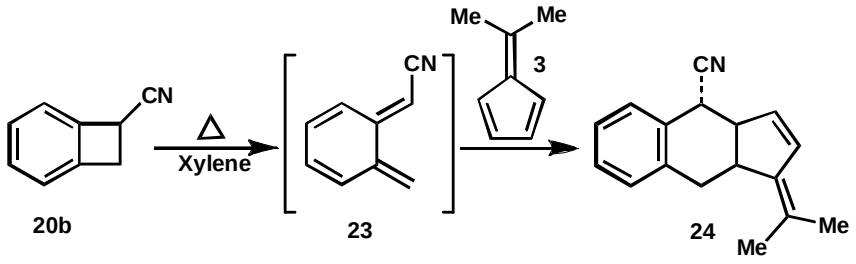
Scheme 1.5

In most of the cycloadditions involving pentafulvenes, exocyclic double bond does not engage as a 2π component, though rare examples of its involvement can be found in the literature. An impressive report on the cycloadditions of *o*-xylylenes to pentafulvenes were reported from Houk *et al*. Electron-deficient *o*-xylylenes react in a Diels-Alder manner to endocyclic double bonds of fulvenes whereas electron-rich ones add primarily in the same fashion to the exocyclic double bond of fulvenes. The presence of electron withdrawing substituents on the C-6 of fulvene further activates the exocyclic double bond in cycloaddition reactions. For example, the reaction of the fulvene **19** with [(methoxycarbonyl)amino]benzocyclobutene **20** afforded the spiro adduct **21** which can be converted to the benzoazulene **22** (Scheme 1.6).[27]



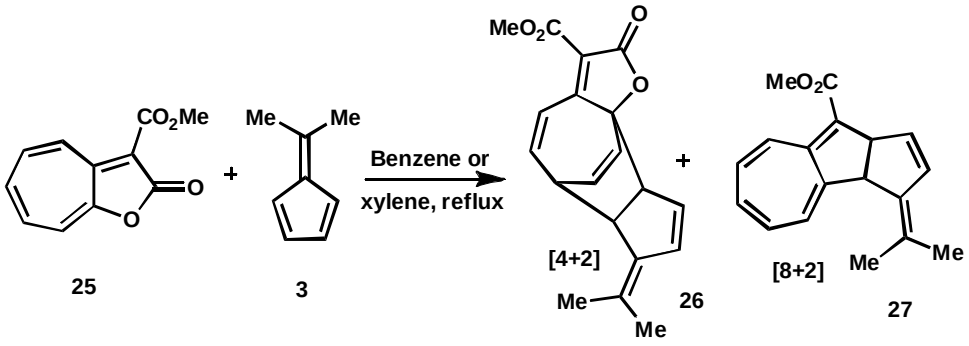
Scheme 1.6

On the other hand, the reaction of cyanobenzocyclobutene **20b** with excess dimethyl fulvene **3** afforded a single [4+2] adduct **24** (Scheme 1.7).



Scheme 1.7

Yasunami *et al.* reported an isolated example of the cycloaddition of 6,6-dimethylfulvene **3** with 3-methoxycarbonyl-2H-cyclohepta[b]furan-2-one **25** and described the unusual solvent effects observed in the reaction.[28] Depending on the solvent, the reaction proceeds either through a [4+2] or [8+2] cycloaddition pathway. The [4+2] cycloadduct **26** was formed as a major product in ethanol or benzene together with minor [8+2] adduct **27**, while the latter was formed exclusively in xylene (Scheme 1.8).

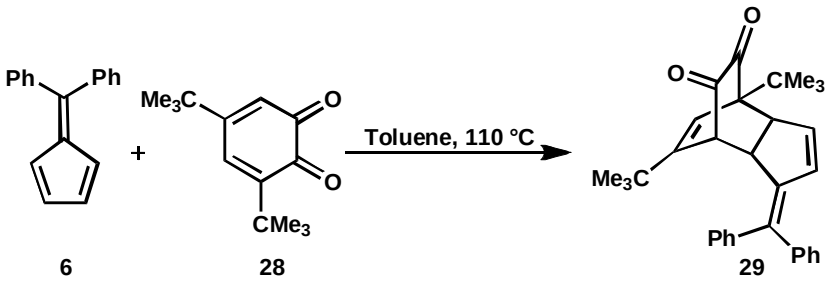


Scheme 1.8

Subsequent work from our laboratory have elaborated and generalized the above cycloaddition strategy for a number of 6,6-dialkyl, diaryl and cycloalkyl pentafulvenes.[29]

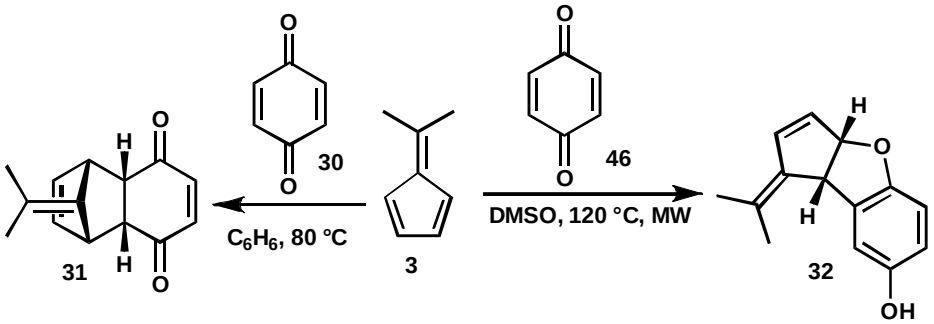
o-Quinones can function as carbodienes, heterodienes and dienophiles in cycloaddition reactions.[30] The investigations from our laboratory have revealed that pentafulvenes act as efficient 2π components with 1,2-bezoquinones affording

bicyclo[2.2.2]octen-7,8-dione adduct **29** in excellent yield from the reaction of 6,6-diphenyl fulvene **6** with the substituted *o*-quinone **28** (Scheme 1.9).[31]



Scheme 1.9

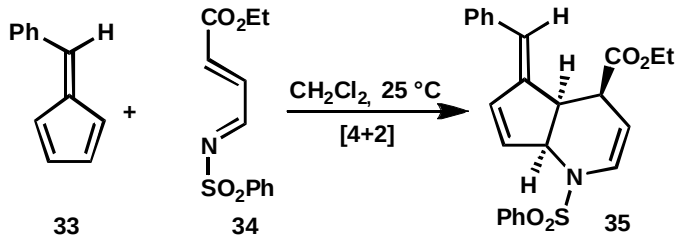
Normally, microwave–assisted organic reactions are faster than their conventional counterparts, high yielding and retain the backbone structure of the thermal products.[32] In an interesting observation, B. C. Hong *et al.* have reported that microwave irradiation can alter the reaction pathway for certain cycloadditions of fulvenes. For example, the reaction of 6,6-dimethyl fulvene **3** and benzoquinone **30**, under microwave conditions afforded the hetero [2+3] adduct **32,** which is a structural analogue of the natural products apylysin and pannellin;[33] it differs completely from the well-known thermal Diels-Alder cycloaddition products of fulvenes and benzoquinone (Scheme 1.10).[34]



Scheme 1.10

The chemistry of azadienes, especially their inverse electron demand profile in Diels-Alder reactions has attracted much attention in natural product synthesis.[35] In 2002, Hong and co-workers have demonstrated a highly regio- and stereoselective inverse electron demand Diels-Alder cycloaddition of

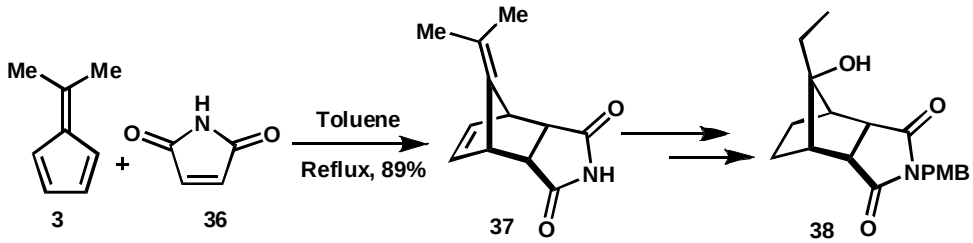
pentafulvenes with azadienes. The methodology provided an efficient route towards [1]-pyrindine system **35** (Scheme 1.11).[36] Similar trends in reactivity were found for a related series of pentafulvenes and azadienes.



Scheme 1.11

1.3.2. Fulvene as 4π-component

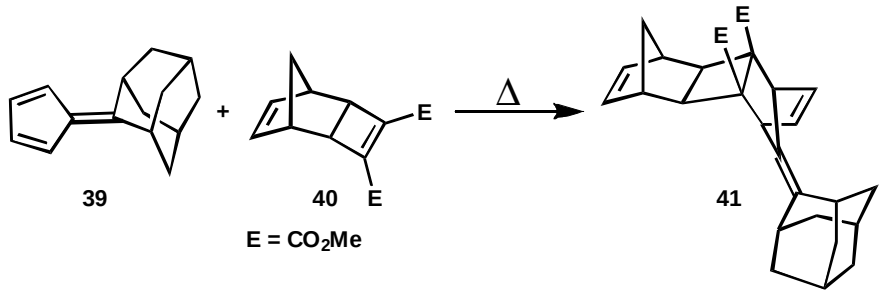
In addition to the reaction with various hetero and homodienes, pentafulvenes can function as highly reactive dienes and this is evident from the existing literature on the cycloaddition reactions involving fulvenes and various dienophiles. Deslongchamps *et al.* reported the design and synthesis of a novel scaffold for molecular recognition, employing simple Diels-Alder cycloaddition reaction between dimethyl fulvene and maleimide.[37] The reaction of 6,6-dimethylfulvene **3** and maleimide **36** in refluxing toluene produced [4+2] cycloadducts as an 8:1 mixture of *exo* and *endo* isomers. The major *exo* isomer **37** was easily converted into the module **38**, for the rapid assembly of abiotic receptors toward neutral organic guest molecules (Scheme 1.12).



Scheme 1.12

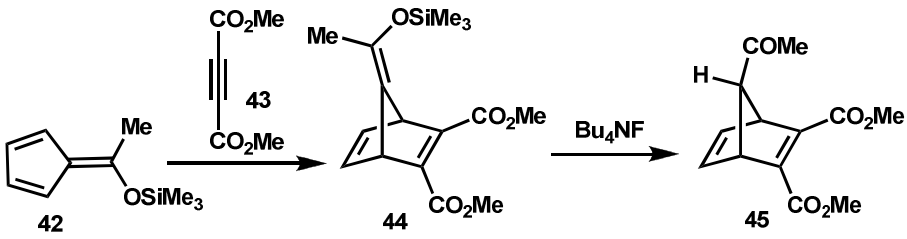
In comparison to simple dialkyl or diaryl fulvenes, 6,6-adamantylidene fulvene has received only limited attention in cycloaddition reactions. Warrener and co-workers have reported the reaction between 6,6-adamantylidene fulvene **39** and

Smith's diene **40,** which is a reactive dienophile. The reaction afforded the [4+2] cycloadduct **41** where the adamantyl group is positioned rigidly on to the molecular framework by virtue of the olefinic linkage originating from the fulvene (Scheme 1.13).[38] They have also demonstrated that under high pressure conditions the reaction can be utilized for the formation of bisadducts by using a modified Smith's diene.



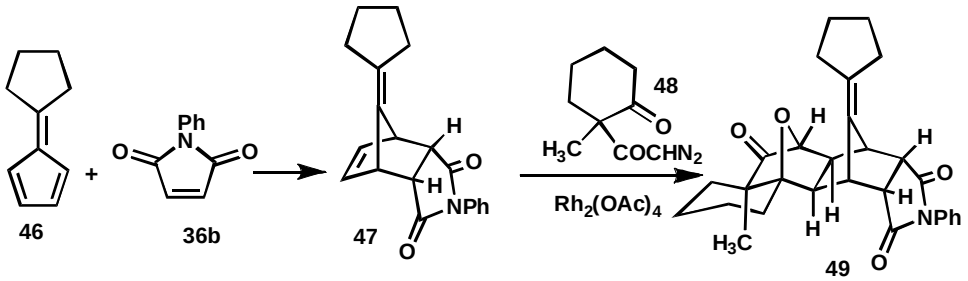
Scheme 1.13

Jousseaume *et al.* have reported the Diels-Alder reactions of 6-silyloxyfulvenes **42** with various dienophiles leading to 7-substituted bicyclo[2.2.1]hepta-2,5-diene derivatives. Treatment of these adducts with Bu_4NF produced 7-norborno-2,5-dienyl aldehydes and ketones in good yields (Scheme 1.14).[39]



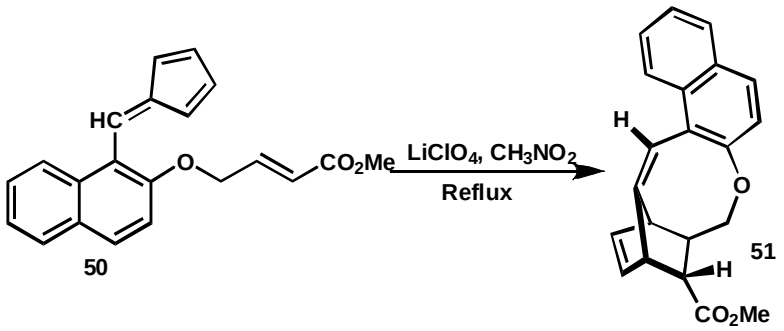
Scheme 1.14

Muthusamy *et al.* developed an efficient and stereoselective protocol for the construction of *syn*-facially bridged norbornane frameworks from pentafulvenes derivatives *via* reactions with rhodium carbenoids generated from diazo ketones (Scheme 1.15).[40]



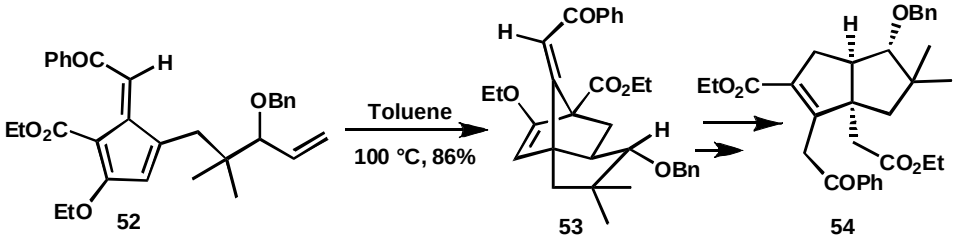
Scheme 1.15

Raghunathan and co-workers have reported an intramolecular [4+2] cycloaddition of fulvenes leading to 6-oxatricyclo[6.4.0.0]dodeca-2,11-diene ring system such as **51** (Scheme 1.16).[41]



Scheme 1.16

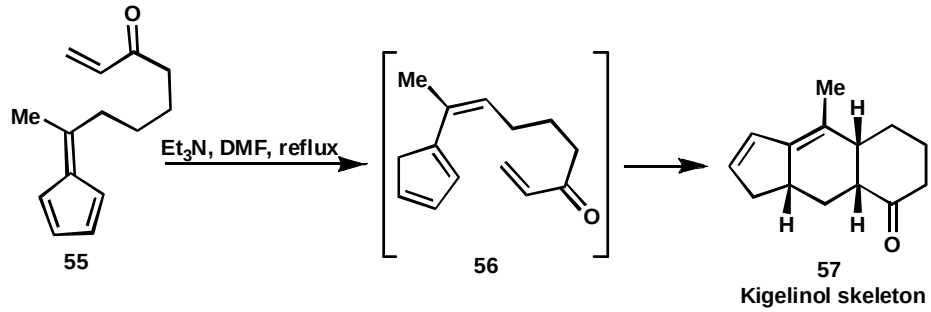
Hatanaka and co-workers have demonstrated the efficient synthesis as well a highly regio and stereoselective [4+2] cycloaddition reaction of 4-[(R)-3-benzyloxy-pent-4-en-1-yl)fulvene **52** and its transformation into bicyclo[3.3.0]octene **53** by mild acid treatment (Scheme 1.17).[42]



Scheme 1.17

Recently, Hong and co-workers have described an elegant Intramolecular Diels-Alder (IMDA) involving simple acyclic fulvene molecules toward the construction of a variety of polycyclic ring skeletons present in pharmaceutical agents such as

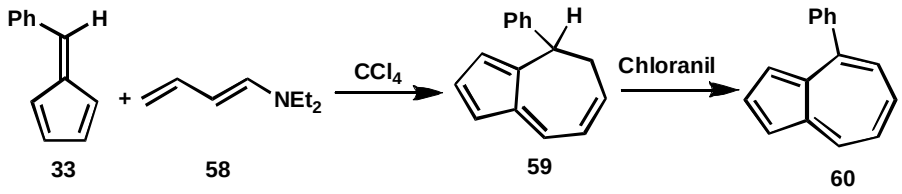
SP 18904, treprostinil, kigelinol etc. An example for the synthesis of kigelinol skeleton **57** from the fulvene **55** is depicted in scheme 1.18.[43]



Scheme 1.18

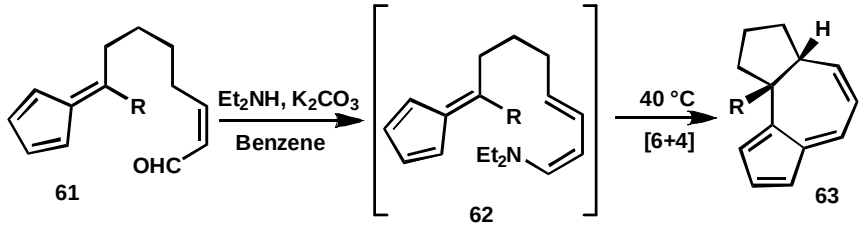
1.3.3. Pentafulvene as 6π-component

As already mentioned, pentafulvenes prefer to act as 6π component with electron-rich dienes. Pioneering work in this area was revealed by Houk and co-workers with the report of an efficient procedure for azulene synthesis *via* the [6+4] cycloaddition of pentafulvenes and electron rich amino butadienes.[44] For example the cycloaddition of 6-phenyl fulvene **33** with 1-diethylamino butadiene **58** followed by the loss of diethylamine afforded the hydrazulene derivative **59** which on treatment with chloranil produced the phenyl substituted azulene (Scheme 1.19).



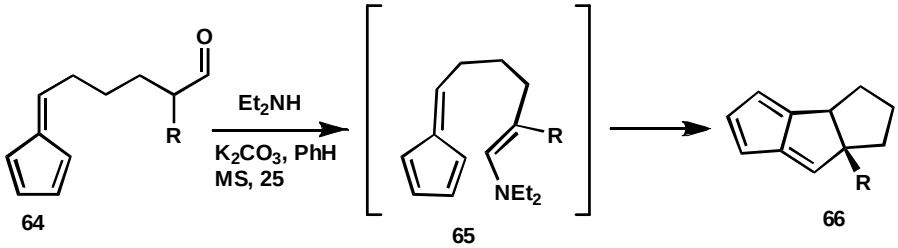
Scheme 1.19

Subsequently the same research group developed a successful intramolecular version of the reaction by resorting to a highly selective intramolecular [6+4] cycloaddition of aminodienylfulvenes leading to tricyclic systems (Scheme 1.20).[45]



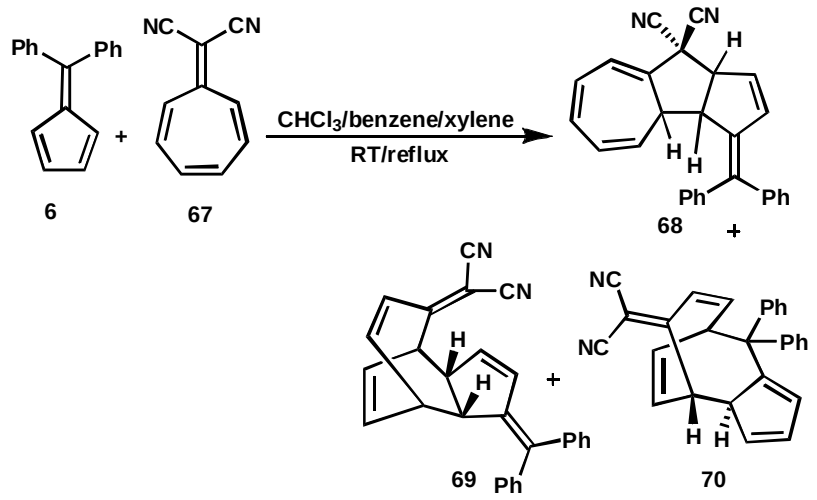
Scheme1.20

In 1985, yet another intramolecular variant of the reaction was attempted successfully by Houk *et al.* They have demonstrated a fascinating tricyclopentanoid synthesis with the report of an intramolecular [6+2] cycloaddition reaction of fulvenes with the pendant enamine (Scheme 1.21).[46]



Scheme 1.21

In comparison to intramolecular cycloaddition reactions involving higher-order π systems (*vide supra*) intermolecular versions suffer from the loss of regioselectivity, endo/exo selectivity, and diastereofacial selectivity. Liu and Ding provided a fine proof of this concept by attempting the cycloadditions of pentafulvenes with the higher homologue of the fulvenoid family, heptafulvene.[47] Multiple cycloaddition profiles are observed and the reactions suffer from low yields and lack of periselectivity and afforded a mixture of [6+4], [8+2] and/or [4+2] adducts depending on the reaction conditions (Scheme 1.22).[48]

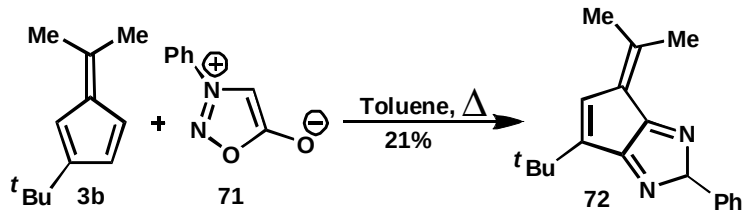


Scheme 1.22

1.3.4. Pentafulvenes in Dipolar cycloaddition reactions

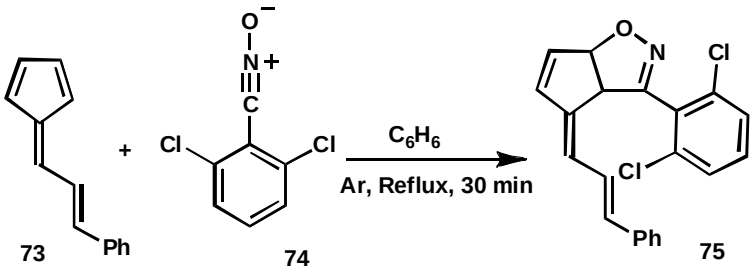
1,3-Dipolar cycloaddition reaction has found extensive use as a high-yielding and efficient, regio- and stereocontrolled protocol for the synthesis of many different heterocyclic compounds.[49] The dipolar family always motivated the search and combination of versatile dipolarophiles for performing superior chemistry. In view of the potential features attainable through the chemistry of pentafulvenes there was general acceptance of the latter in the arena of dipolar cycloaddition reactions. This section provides an overview of the available literature on this topic of organic chemistry with some emphasis on the recent accomplishments in our own laboratory.

Mesoionic ring systems are widely accepted 1,3-dipolar species and are utilized as starting compounds for rendering variety of heterocycles.[50] Kato and co-workers were the first to develop the successful dipolar chemistry of pentafulvenes with mesoionic compounds. The reaction of 3-phenylsydnone **71** with 2-*tert*-butyl-6,6-dimethyl fulvene **3b** gave the condensed pyrazole **72** by extrusion of carbon dioxide from the initially formed [4+2] cycloadduct followed by spontaneous dehydrogenation (Scheme 1.23).[51]



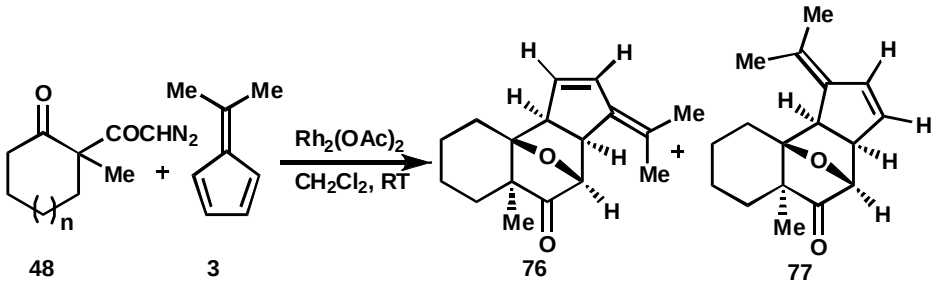
Scheme 1.23

Nair and co-workers reported the first dipolar cycloaddition reaction of conjugated pentafulvenes. They found that 6-(2-phenyl ethenyl)fulvene **73** underwent facile reaction with various aryl nitrile oxides leading to isooxazoline derivatives (Scheme 1.24).[52] Here the fulvene participate as a 2π addend.



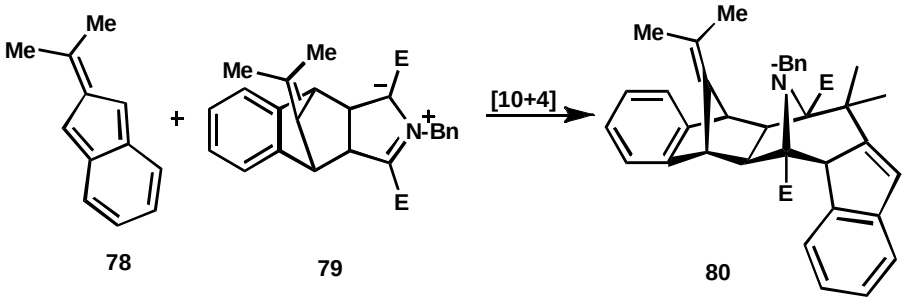
Scheme 1.24

As a novel route towards oxatetracyclo[6.5.1.0.0]tetradecanes, Muthusamy and co-workers have described a facile [3+2] dipolar cycloaddition of rhodium generated carbonyl ylides with pentafulvenes. The 1,3-dipole generated from the π-diazo carbonyl compound **48** on reaction with 6,6-dimethyl fulvene **3** furnished the cycloadducts **76** and **77** as a separable mixture of regioisomers (Scheme 1.25).[53]



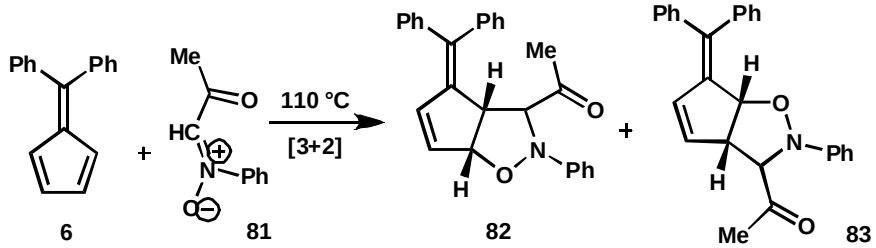
Scheme 1.25

Warrener and co-workers have revealed the solitary report on the reactivity of a conjugated pentafulvene performing as the 10π component in a symmetry allowed [10+4] dipolar cycloaddition reaction.[54] The reaction involved the trapping of 6,6-dimethylisobenzofulvene **78** by its 1,3-dipolar precursor **79** leading to a complex framework **80** (Scheme 1.26).



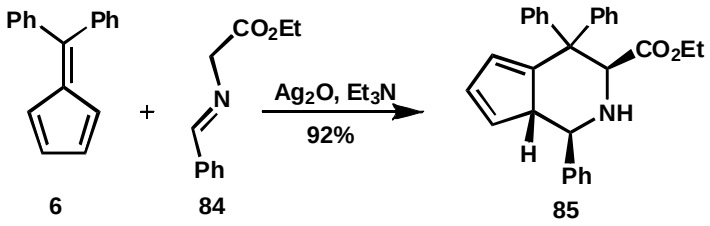
Scheme 1.26

In an isolated report, Chandrasekhar and co-workers outlined the cycloaddition reaction of a single pentafulvene with diphenylnitrone.[55] Nearly after a decade, Ciamala *et al*. have presented a more extensive description of the cycloaddition between the two substrates. They utilized a series of mono and di substituted pentafulvenes with various aroylnitrones and obtained the corresponding fused bicyclic adducts as a mixture of regioisomers in good yields (Scheme 1.27).[56]



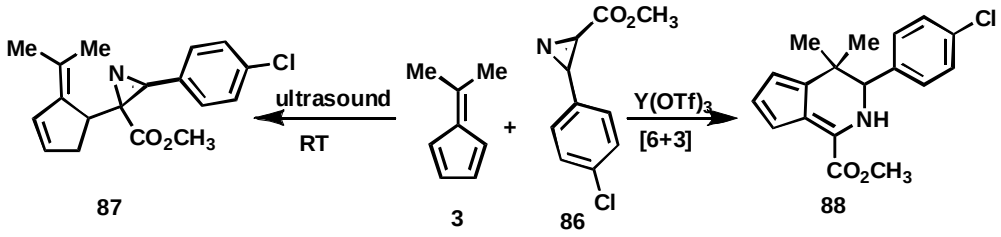
Scheme 1.27

In 2003, Hong and co-workers reported the [6+3] cycloaddition reaction of azomethine ylides generated from glycine-N-benzylidene ethyl ester **84** with a series of pentafulvenes leading to biologically important [2]-pyrindine systems (Scheme 1.28).[57]



Scheme 1.28

One year later, the same group has exposed the dual reactivity of pentafulvenes with 2H-azirine under varying conditions. In the presence of a Lewis acid, 2H-azirine **86** reacted with fulvenes through a formal regioselective [6+3] cycloaddition reaction and provided an alternative, efficient synthesis of [2]pyrindine derivatives. Conversely, under ultrasound conditions the reaction produced alkylated fulvene azirines **87** through an unexpected rearrangement of the initial Diels-Alder cycloadduct (Scheme 1.29).[58]

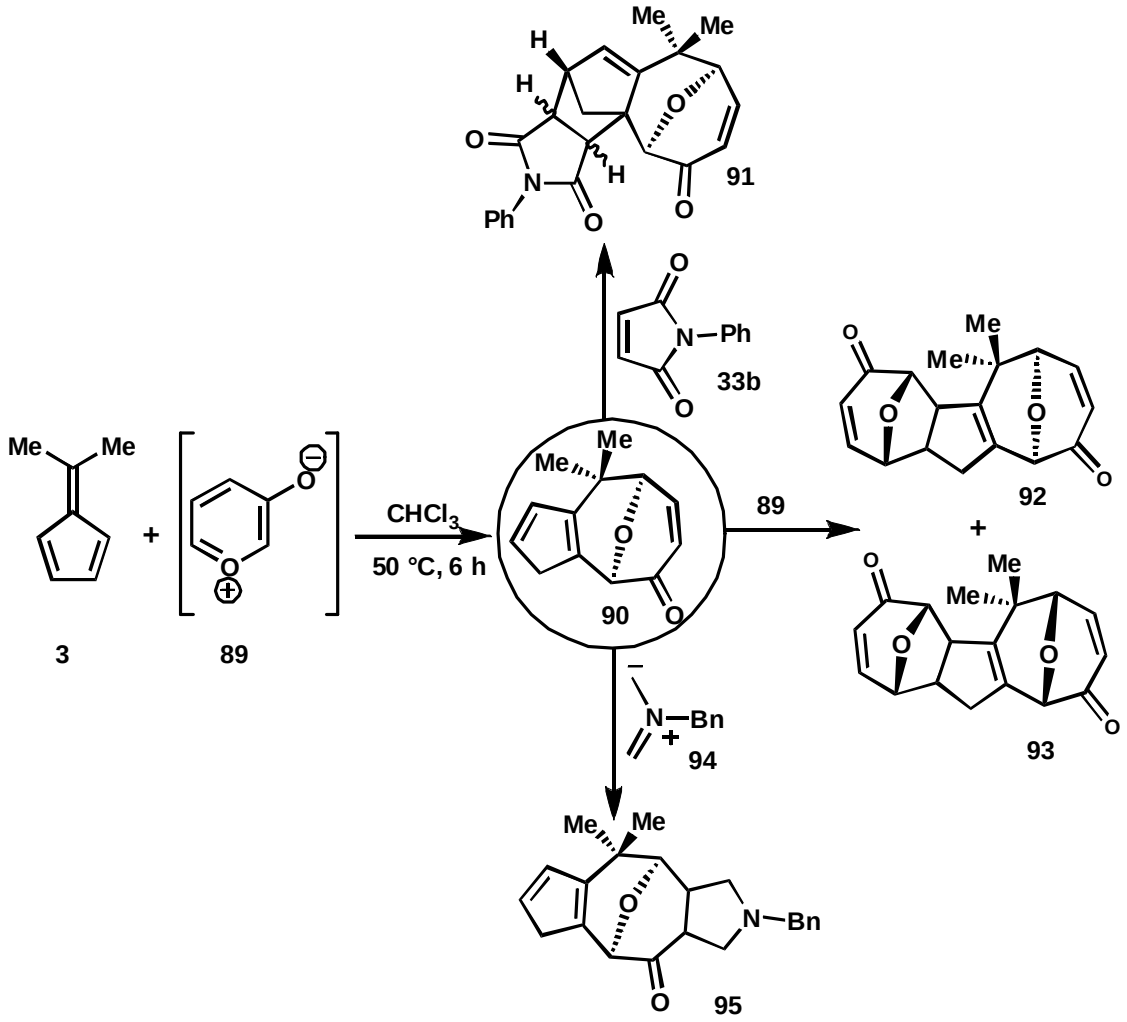


Scheme 1.29

As a result of the steady efforts in this scenario, recently our group have made significant hand-outs to the cycloaddition chemistry of pentafulvenes. We have unravelled a simple but efficient [6+3] cycloaddition reaction of pentafulvenes with 3-oxidopyrylium betaines and the approach offered a useful methodology for the construction of 5-8 fused cyclooctanoids **90**.[59]

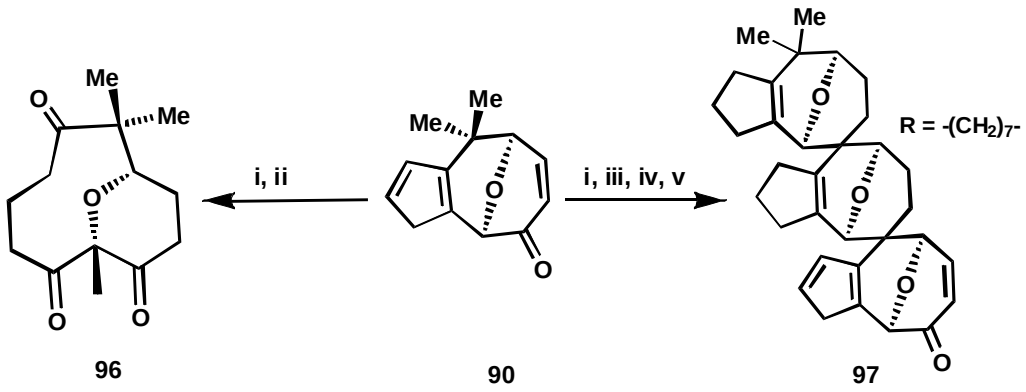
Inspired by the promising structural features offered by these cycloadducts, we explored their synthetic utility in the construction of more complex but useful polycyclic molecules. The carbon framework of the molecules was successfully expanded through Diels-Alder reaction, dipolar cycloaddition, Luche reduction, selective hydrogenation etc. All these alterations led to oxa-bridged cyclooctanoids having excellent synthetic value as these can act as key

intermediates in the synthesis of various biologically important molecular frame works (Scheme 1.30).[60]



Scheme 1.30

Our studies have further elaborated the synthetic utility of the adduct **90**, by converting it into synthetically and biologically useful molecular frameworks such as 11-membered carbocycles and spirocyclic cyclooctanoids (Scheme 1.31).[61]



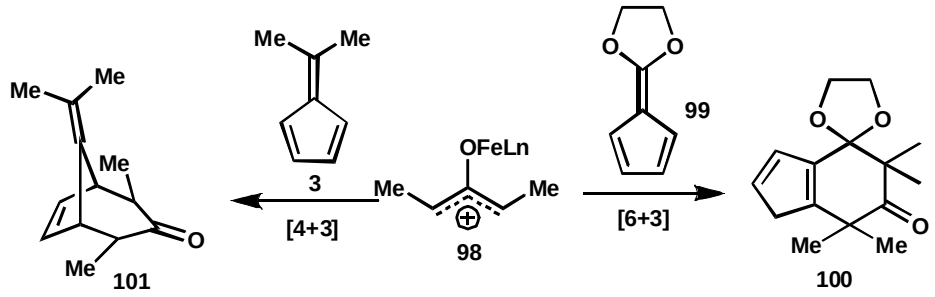
i) H_2, Pd/C, RT, EtOAc, 6 h; ii) $RuCl_3.3H_2O$, $NaIO_4$, RT, 5 h; iii) Cpd, Pyrrolidine, MeOH, RT, 6 h; iv) Oxidopyrylium betaine, $CHCl_3$, 50 °C, 4 h; v) Repeat i, iii, iv

Scheme 1.31

1.3.5. Cycloadditions of 6,6-dimethylamino fulvenes and fulveneketene acetals

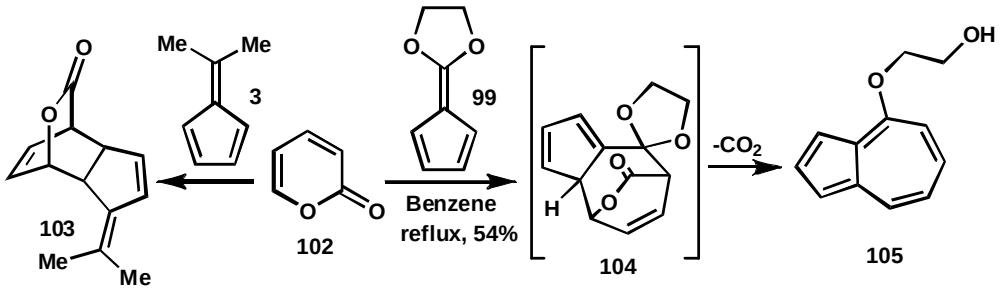
Increase in the electron density at the exocyclic position of pentafulvenes has a pronounced effect on their reactivity. According to FMO theory, electron donating substituents with large coefficients at the exocyclic position of fulvenes, sufficiently elevate the energy of the HOMO and activate their performance as 6π components. This statement was illustrated by the cycloaddition reactions of 6-(N,N-dimethylamino)fulvene and fulvene ketene acetal. Though the synthesis of these pentafulvenes was reported as early as 1973,[62] their chemistry was explored to a significant level only recently.

In 1996, Hong *et al.* introduced fulvene ketene acetal **99** endowd with more electron density compared to amino fulvene, into cycloaddition reactions. In this case the reaction afforded the [6+3] adducts in excellent yields and allowed an efficient synthesis of highly substituted indan systems (Scheme 1.32).[63] Later on, the same research group extended the scope of the above strategy and reported the synthetic transformations of the cycloadducts.[64]



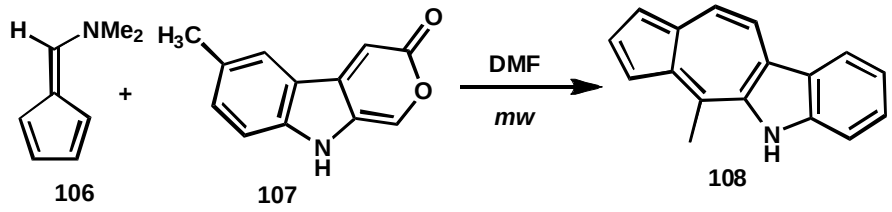
Scheme 1.32

Houk and co-workers were among the first to report the Diels-Alder cycloaddition between alkyl fulvenes and α-pyrone **102**, which is an electron deficient diene to afford **105**.[65] In contrast to this observation, Hong *et al.* have devised a highly efficient [6+4] cycloaddition of fulveneketene acetal with the same substrate (Scheme 1.33).[66] This method established the experimental framework for a conceptually new approach to the synthesis of azulenols.



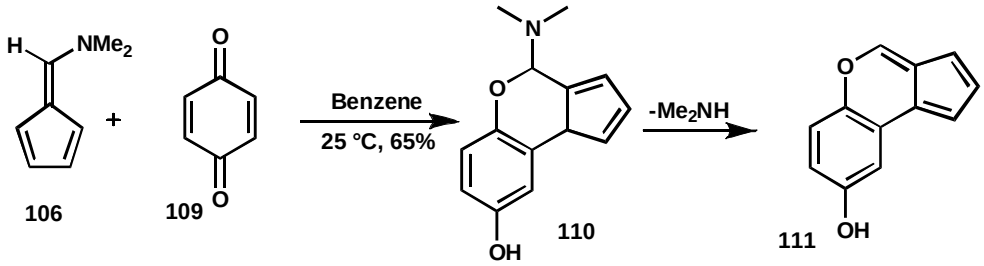
Scheme 1.33

6-(N,N-dimethylamino)fulvene also adds to α-pyrones in an analogous manner affording azulenes albeit in low yields.[67] Subsequently a higher yielding procedure utilizing microwave conditions was reported. The microwave assisted [6+4] cycloaddition reaction between 6-(N,N-dimethylamino)fulvene and indole annulated pyrones provided a facile and efficient entry into azulene-indoles with interesting antineoplastic activity (Scheme 1.34).[68]



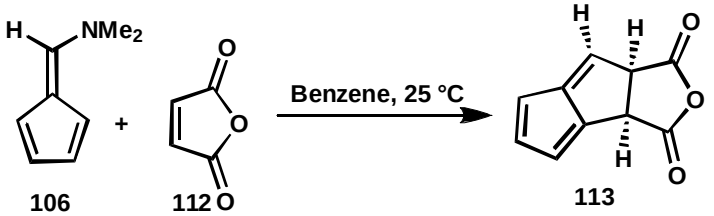
Scheme 1.34

Another exciting reactivity profile of activated fulvenes was uncovered in 1999. Pentafulvenes usually respond as a 2π component to benzoquinones affording [4+2] cycloadducts.[69] In conctrast, Hong *et al.* reported a novel [6+3] cycloaddition reaction of 6-(N,N-dimethylamino)fulvene to benzoquinones and the reaction provided a series of cyclopenta[c]chromene derivatives which form the basic skeleton of biologically active 11-oxasteroids (Scheme 1.35).[70]



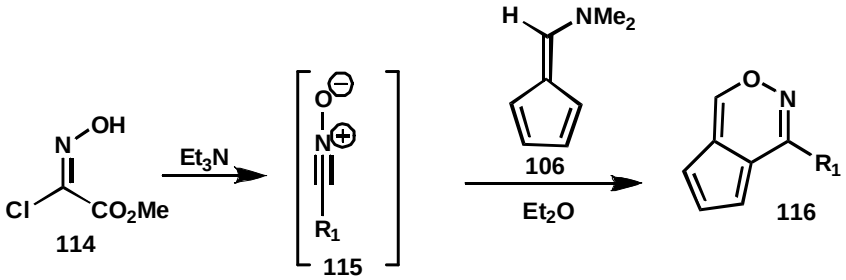
Scheme 1.35

On the basis of another interesting observation, the same research group has established the unusual but efficient [6+2] cycloaddition[71] reaction of 6-(N,N-dimethylamino)fulvene. For example, the reaction of aminofulvene with maleic anhydride **112** afforded pentaleno[1,2-c]furan skeleton **113** which constitutes the basic framework of many natural products such as anislactone A, merrilactone A etc (Scheme 1.36).[72]



Scheme 1.36

The latest information on the cycloaddition chemistry of activated pentafulvenes came from Cho and co-workers. They have established a convenient synthesis of biologically relevant cyclopenta[d][1,2]oxazines through a [6+4] cycloaddition between aminofulvenes and nitrile oxides **115** (Scheme 1.37).[73]

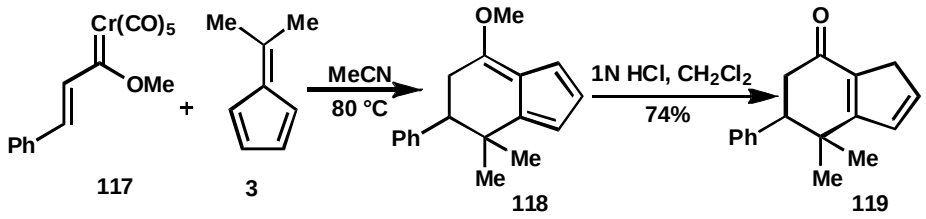


Scheme 1.37

1.3.6. Fischer-carbene complexes: An unusual cycloaddition partner of pentafulvenes

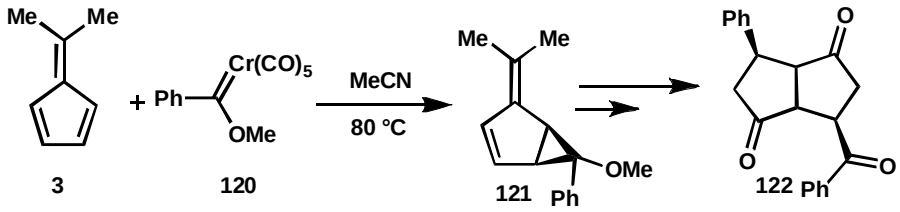
The early part of the present decade witnessed the introduction of a novel reactivity pattern of pentafulvenes and its quick acceptance as a general procedure for the synthesis of substituted indenes and annulated cyclopentanones. This has been credited to the efforts of Barluenga who unified the interesting chemistry of pentafulvenes with Fischer carbene complexes. Heteroatom stabilized carbene complexes have been demonstrated to be useful organometallic reagents for carbo and heterocyclization reactions.[74] Depending on the type of carbene complex used, it is possible to generate versatile carbon synthons for organic synthesis.

In their initial study they have reported the reactivity of alkenyl Fischer carbene complexes with pentafulvenes. The reaction of the alkenyl carbene complex **117** with dimethyl fulvene **3** afforded substituted indene **118** *via* a [6+3] cycloaddition. The reaction was found to be general for various alkyl and alkenyl fulvenes and produced a number of substituted indanones and indenes in a regioselective way (Scheme 1.38).[75]



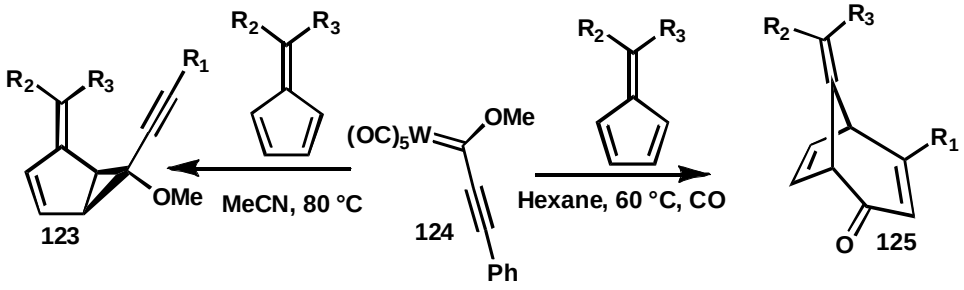
Scheme 1.38

In a systematic carry-over of the strategy, the same authors have demonstrated the most primitive cyclopropanation and cycloheptannulation reactions of pentafulvenes with Fischer carbene complexes. The cyclopropanation of pentafulvenes was achieved through a [2+1] cyclization with alkyl or aryl(methoxy) carbene complex **120**. Apart from this observation they successfully extended the cyclization of pentafulvenes toward more elaborated cyclopentane frameworks (Scheme 1.39).[76]



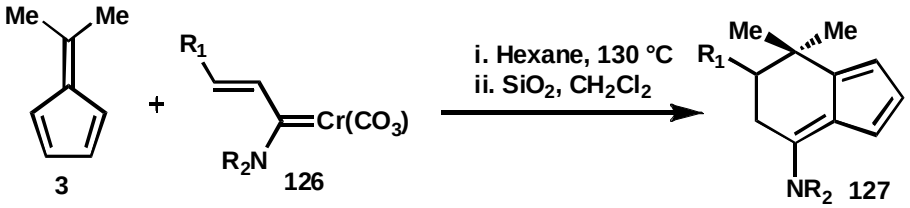
Scheme 1.39

With pentafulvenes, the alkynylcarbene complexes **124** also go through the similar cyclization under the normal conditions, however in the presence of CO, [4+3] cyclization leading to a cycloheptane skeleton **125** was observed (Scheme 1.40).[76]



Scheme 1.40

A closely related study was subsequently described by the same group with the report of a regioselective [6+3] cycloaddition reaction of alkenylaminocarbene complex **126** with pentafulvenes thus establishing an efficient entry to amino indenes **127** (Scheme 1.41).[77]



Scheme 1.41

Evidently, the pentafulvene-Fischer carbene combination offers a unique methodology to access substituted indenes and various annulated cyclopentanoids. It is noteworthy that the indenes obtained through this strategy maintain a reactive fulvene unit and is potential candidates for the synthesis of fascinating polycyclic systems.

1.4. Conclusion and present work

From the above discussions it is clear that fulvenes are fabulous collection of synthetically challenging molecules which form the structural motif of numerous biologically important natural products.

Addition of heterodienophiles to fulvenes offers an efficient strategy towards the synthesis of azabicyclic olefins.[78] However, there have been no serious attempts to study the synthetic utility of these substrates. In this context and with the intention of utilizing pentafulvenes towards synthetically important molecules, we investigated the reactivity of pentafulvene derived bicyclic hydrazine through Pd/Lewis acid catalyzed ring-opening with hard nucleophiles like organostannanes,[79] silanes, boronic acids,[80] and allylindium reagents which yielded alkylidene cyclopentenes.[81] As part of our continuing interest in the chemistry of these bicyclic hydrazines, we decided to investigate its reactivity with soft nucleophiles. The investigations along this line form the focal theme of the second thesis.

Substituted cyclopentenes are particularly important synthetic targets because further derivatizations of the functional groups provide access to highly functionalized, stereochemically complex molecules. Efficient synthesis of functionalized cyclopentane ring has been the objective of a large number of methodological studies. The third chapter of the thesis discusses the synthesis of 3,4-disubstituted alkylidene cyclopentene from pentafulvene derived bicyclic hydrazine and various aryl halides.

Annulation is one of the most efficient and economical ways of creating cyclic molecules. The advantage of these transformations is the formation of several bonds and the creation of two or more contiguous stereogenic centers by using a single catalyst in one pot, without the need for isolation of the intermediates. The last part of the thesis describes the palladium catalyzed cyclopentannulation of pentafulvene derived bicyclic hydrazines with 2-iodophenols, affording benzofuran fused bicyclic hydrazine.

1.5. References

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Chapter 2

Facile Route towards Alkylidene Cyclopentenes *via* Palladium Catalyzed Ring-Opening of Pentafulvene Derived Bicyclic Hydrazines with Soft Nucleophiles

2.1. Introduction

The development of environmentally benign and efficient synthetic methods continues to be the central goal of research in organic chemistry. Catalysis and organometallic chemistry are key techniques for achieving these objectives as it contributes to the development of environmentally benign methodologies.[1] Among the different catalytic reactions, palladium-catalyzed cross-coupling reactions have revolutionized the synthesis of diverse targets and intermediates[2] and have been applied in the industrial synthesis of fine chemicals, pharmaceutically active compounds, and agricultural chemicals,[3] as well as in natural product synthesis.[4] The formation of carbon-carbon or carbon-hetero atom bonds in this fashion has undergone significant development in recent years. One of the recent interest in this area is the generation of multiple stereocenters through the addition of nucleophiles to heterobicyclic alkenes, with concomitant ring opening.[5] The present chapter describes the palladium catalyzed ring-opening of pentafulvene derived bicyclic hydrazines with soft nucleophiles leading to the stereoselective synthesis of alkylidene cyclopentenes. Before going into the details of our investigations, a brief introduction about alkylidene cyclopentanes is presented in the following section.

2.2. Alkylidene cyclopentanes

Substituted cyclopentanes are important synthetic intermediates and key structural elements in various natural products, such as terpenes, steroids, and prostaglandins. Among various cyclopentane derivatives, alkylidene cyclopentanes hold special attention as intermediates in the construction of biologically interesting molecules including (+) and (-)-nigellamine A_2,[6] guanacastepene A[7] etc. Trost's synthesis of (+)-allocyathin B_2 which has interesting biological activities, involves an alkylidene cyclopentenone as the key intermediate.[8] Alkylidene cyclopentanes can easily be converted to piperidine alkaloids like streptazolins,[9] odoriferous compounds like β-vetivone,[10] α-vetispirene,[11] hirsutene,[12] liseaverticillols[13] etc. Some of the structurally related compounds are shown in figure 2.1.

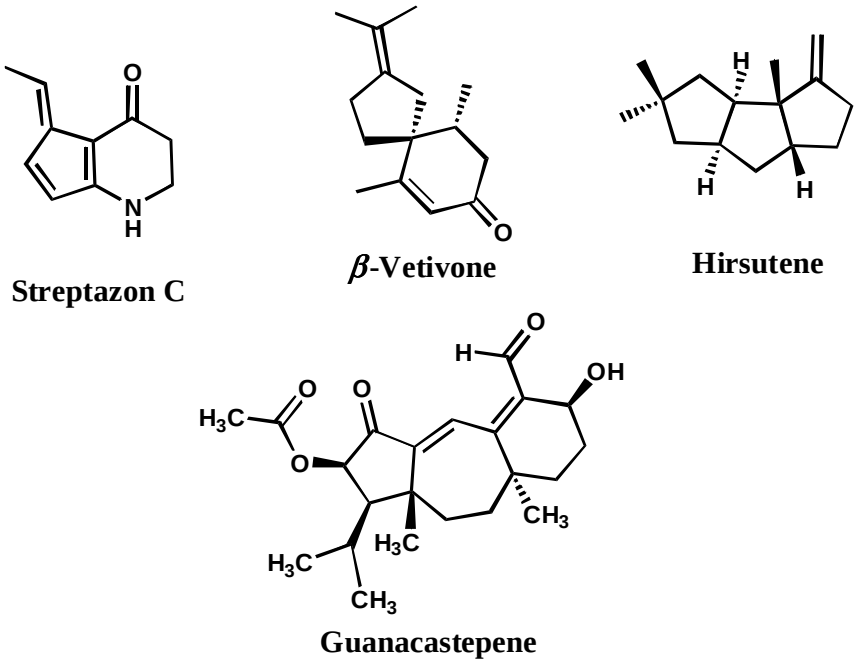
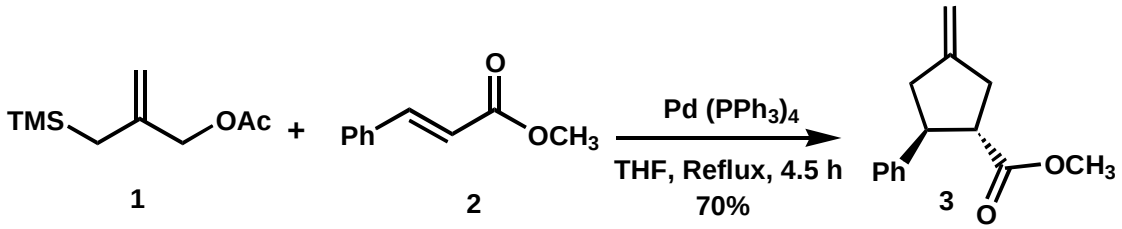


Figure 2.1. Natural products containing alkylidene cyclopentane skeleton

2.2.1. Synthesis of alkylidene cyclopentanes

A number of reports are known[14] in the literature toward the synthesis of alkylidene cyclopentenes and its derivatives. Trost and co-workers have elegantly

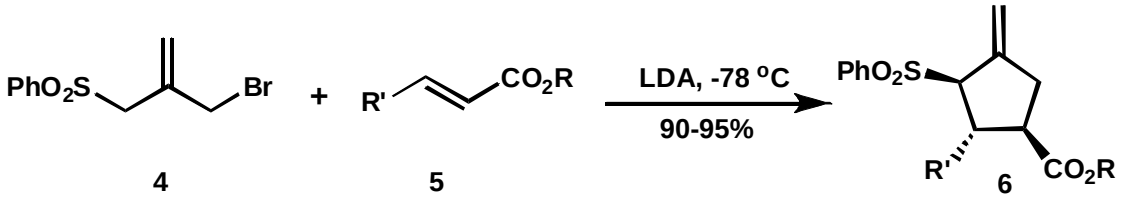
utilized the trimethylenemethane (TMM) chemistry for the introduction of various substituents to the cyclopentane core.[15] In 1979 they have reported a facile synthesis of disubstituted methylidene cyclopentane **3** by the palladium catalyzed cyclization of acetoxymethyl allyltrimethylsilane **1** with electron deficient olefins **2** (Scheme 2.1).



1 2 3

Scheme 2.1

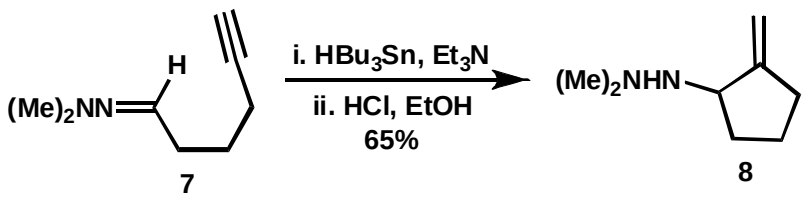
Hassner and co-workers have elaborated this methodology by using 2-bromomethyl-3-phenylsulfonyl-l-propene **4** as the TMM precursor and synthesized the trisubstituted methylidene cyclopentane **6** in good yields.[16] The reaction is outlined in scheme 2.2.



4 5 6

Scheme 2.2

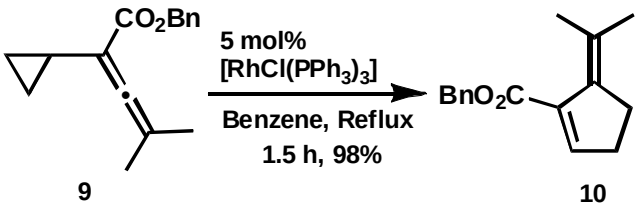
Jose Marco-Contelles described an interesting synthesis of methylidene cyclopentenes *via* 5-exo-trig free radical cyclization of alkyne tethered N,N-disubstituted hydrazones and imines **7** in presence of tributyltinhydride and triethylamine. The reaction sequence is shown in scheme 2.3.[17]



7 8

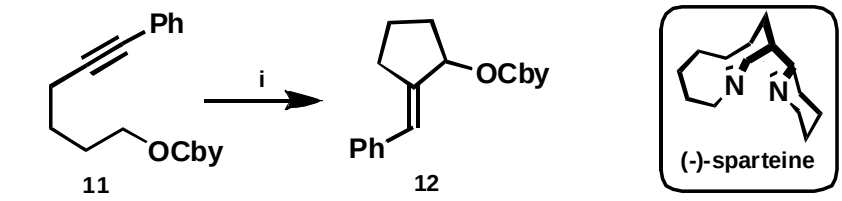
Scheme 2.3

A more efficient and interesting synthesis of methylidene cyclopentene was reported by Saigo *et al.* through a rhodium(I)-catalyzed regioselective ring-expanding rearrangement of allenylcyclopropanes.[18] For example, heating allenylcyclopropane **9** in refluxing benzene for 1.5 h in the presence of $[RhCl(PPh_3)_3]$ gave the corresponding methylene cyclopentene **10** in 88% yield (Scheme 2.4).



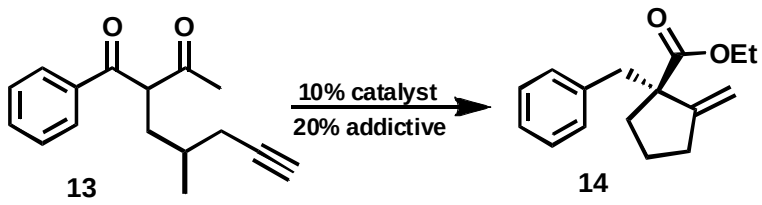
Scheme 2.4

D. Hoppe adopted a (-)-sparteine mediated stereoselective intramolecular carbolithiation strategy for the enantiopure synthesis of functionalized alkylidene cyclopentane **12** from substituted hexynyl carbamate **11** (Scheme 2.5).[19]



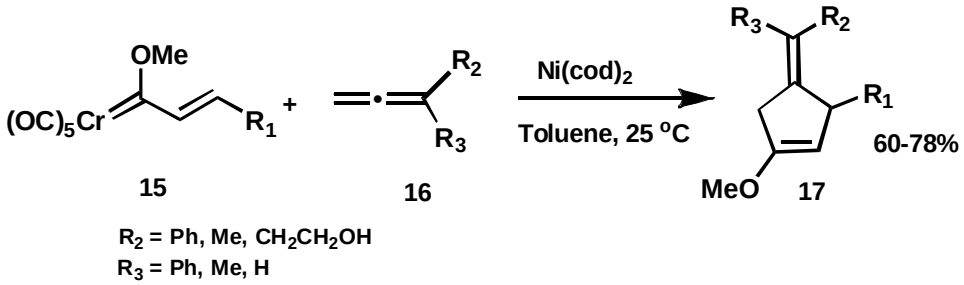
Scheme 2.5

Toste and co-workers reported the synthesis of highly functionalized methylidene cyclopentene through Conia-Ene reactions. A wide range of β-dicarbonyl compounds undergo Pd(II)/Yb(III)- catalyzed enantioselective intramolecular Conia-Ene reaction to produce methylidene cyclopentene in 90% yield (Scheme 2.6).[20]



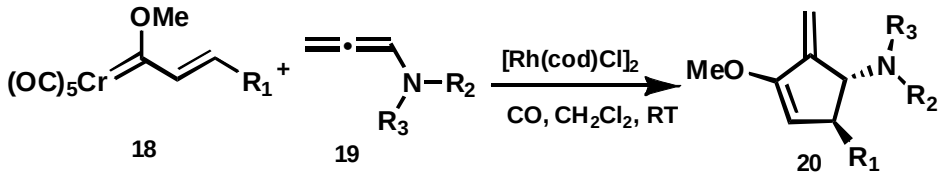
Scheme 2.6

In 2004, Barluenga and co-workers have unraveled a novel synthesis of alkylidene cyclopentenes by a nickel (0) mediated [3+2] cyclization of chromium alkenyl carbene complex **15** with 1,1-disubstituted allenes **16** (Scheme 2.7).[21]



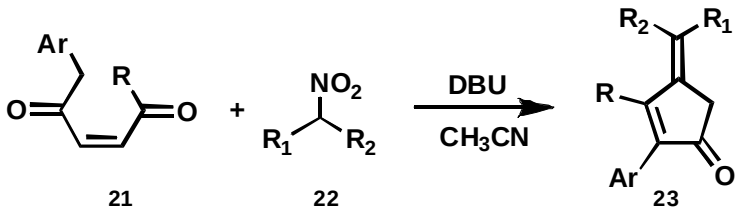
Scheme 2.7

Later, the same group have modified this methodology by using activated allenes in presence of Rh(I) catalyst.[22] The treatment of the chromium alkenyl carbene complex **18** with aminoallene **19** in the presence of 10 mol% of $[Rh(cod)Cl]_2$ resulted in the formation 5-methylidene cyclopentene derivatives **20**, in good yields (60-99%). The reaction is presented in scheme 2.8.



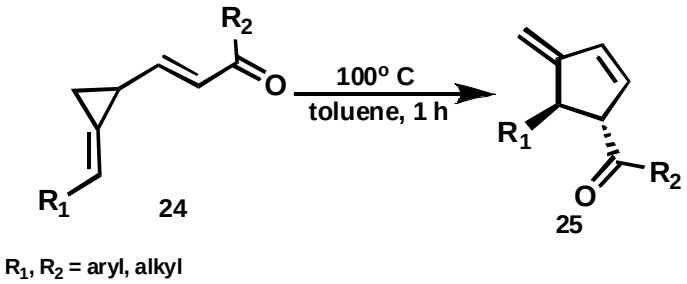
Scheme 2.8

Stereoselective synthesis of 4-alkylidene cyclopentenones **23** was reported by Petrini *et al.* by the reaction of 1,4-diketone **21** with various functionalized nitro alkenes **22** in presence of DBU (Scheme 2.9).[23]



Scheme 2.9

Recently, Shi *et al* reported an efficient method to stereo specifically synthesize *trans*-substituted cyclopentene derivatives *via* the ring-opening rearrangement of readily available MCP alkenyl derivatives (Scheme 2.10).[24]



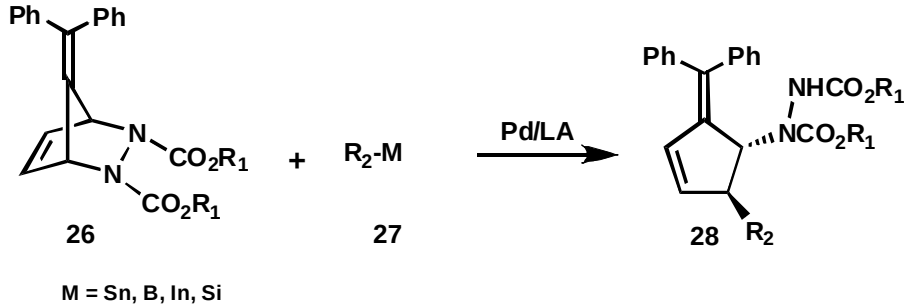
Scheme 2.10

It is evident from the literature that, alkylidene cyclopentenes are important intermediates for the construction of many synthetically and biologically important molecular skeletons. However, only limited attention has been paid to the synthesis of these molecules from simple and easily available starting materials. Therefore, search for a more efficient and novel method towards the synthesis of functionalized alkylidene cyclopentenes remains as an exciting challenge in synthetic organic chemistry.

2.3. Background to the Present Work

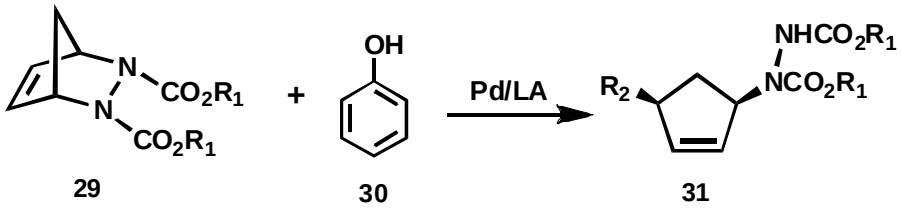
The discovery and development of new routes for the construction of functionalized carbocycles continues to be of importance in synthetic organic chemistry. In fact, such processes often play key roles in the total synthesis of natural products. In this context, the transition metal-catalyzed transformations of heterobicyclic alkenes have great potential to achieve these targets.[25] Recent

investigations from our laboratory have unraveled a facile method for the construction of alkylidene cyclopentenes through Pd/Lewis acid catalyzed ring-opening of fulvene derived azabicyclic olefins with hard nucleophiles like organostannanes,[26] silanes, boronic acids,[27] and allylindium reagents.[28] All these reactions furnished *trans*-3,4- disubstituted alkylidene cyclopentene good yields (Scheme 2.11).



Scheme 2.11

In 2003, Micouin and coworkers have reported the palladium catalyzed ring opening of cyclopentadiene derived bicyclic olefins with soft nucleophiles towards the synthesis of *cis*-3,5-disubstituted cyclopentenes (Scheme 2.12).[29]

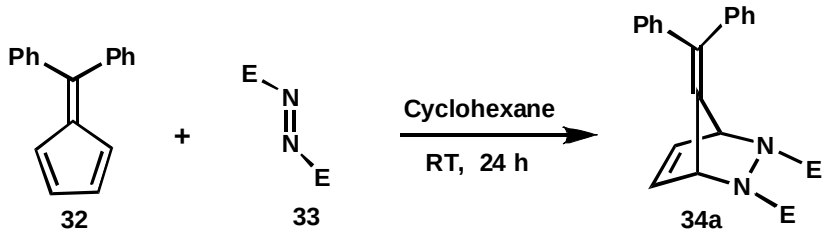


Scheme 2.12

Intrigued by these results, we decided to explore the desymmetrization reactions using pentafulvene derived bicyclic hydrazines with soft nucleophiles, envisioning that these reactions would provide a novel access to alkylidene cyclopentenes. A detailed investigation on the palladium mediated reactions of various pentafulvene derived bicyclic hydrazines with a variety of soft nucleophiles was carried out and the results of these studies are presented in the following sections.

2.4. Results and discussion

The azabicyclic olefins required for our investigations were prepared as per the literature procedures.[30] For example, the 2,3-diazabicyclo[2.2.1]hept-5-ene **34a** was synthesized by the Diels-Alder cycloaddition of pentafulvene **32** with dialkyl azodicarboxylate **33** (Scheme 2.13).

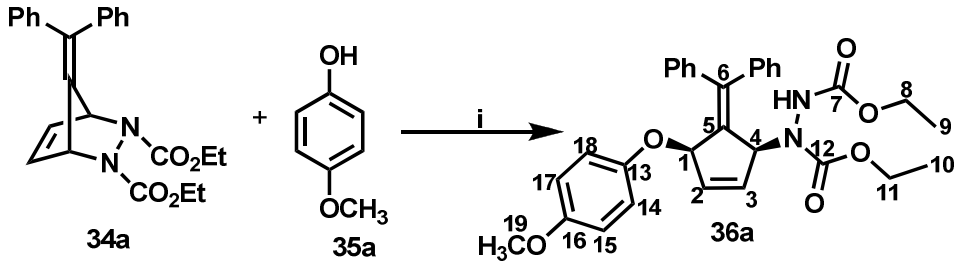


34a = E = CO_2Et
34b = E = $CO_2{}^iPr$
34c = E = $CO_2{}^tBu$

Scheme 2.13

2.4.1. Desymmetrization reactions using phenol

Our experiments started with the reaction of 2,3-carbethoxy-7-diphenylmethylene-2,3-diazabicyclo[2.2.1]hept-5-ene **34a**, with 4-methoxy phenol **35a.** In a pilot experiment, the bicyclic adduct **34a** was treated with 4-methoxyphenol **35a** in presence of catalyst $[Pd(allyl)Cl]_2$, ligand dppf, and base NaH in tetrahydrofuran at 60 ^oC. The reaction afforded the *cis*-1,4-disubstituted alkylidene cyclopentene **36a** in 43% yield (Scheme 2.14).



i = $[Pd(allyl)Cl]_2$ (5 mol%), dppf (10 mol%), NaH (1.0 equiv.), THF (2 mL), 60 ^oC, 16 h

Scheme 2.14

The structure of the compound **36a** was established by spectroscopic analysis. In the IR spectrum, the signals at 1748 and 1727 cm^{-1} were diagnostic of

the carboethoxy group, whereas NH absorption was discernible at 3368 cm^{-1}. In the ^1H NMR spectrum (Figure 2.2), the multiplet in the region δ 7.35-6.62 ppm was assigned to aromatic protons. The endocyclic olefinic protons resonated as multiplet in the region δ 6.13-6.09 ppm. The proton on C-1 and C-4 were observed as multiplet at δ 5.88-5.82 and δ 5.11 ppm respectively The $–CH_2$ protons of carboethoxy group appeared at δ 4.10-4.03 and δ 3.84-3.83 as multiplet. The singlet resonated at δ 3.69 ppm was indicative of protons on the methoxy group. The multiplet in the regions δ 1.19-1.16 and δ 1.05-0.98 ppm were assigned to the methyl protons of carboethoxy group respectively.

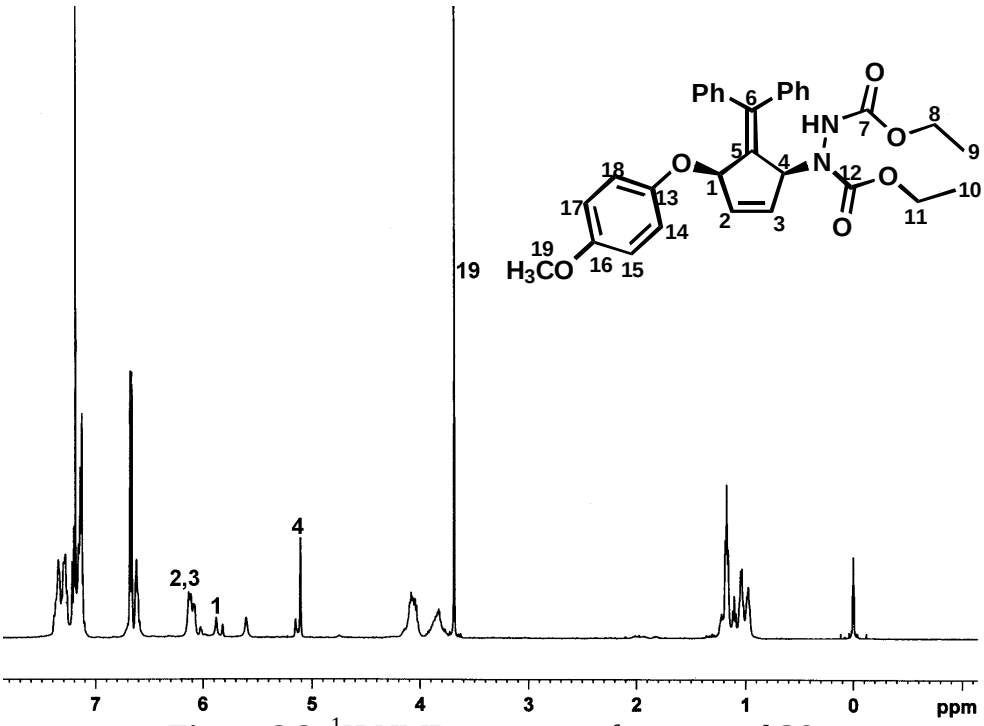


Figure 2.2. ^1H NMR spectrum of compound **36a**

^{13}C NMR spectrum of **36a** (Figure 2.3) positioned the two carbonyl peaks at δ 156.0 ppm and δ 155.1 ppm, while the signal due to methylene carbons of the carboethoxy groups appeared at δ 62.1 and 61.8 ppm. The C-1 and C-4 carbons were observed at δ 78.3 and 62.5 ppm respectively. The signal at δ 55.6 ppm was

characteristic of the methoxy carbon. The spectrum showed methyl carbons of carboethoxy group at δ 14.7 and δ 14.4 ppm respectively. All other signals were in good agreement with the proposed structure. The mass spectral analysis showed a peak at *m/z* 528.90 (M^+), which also supported the proposed structure.

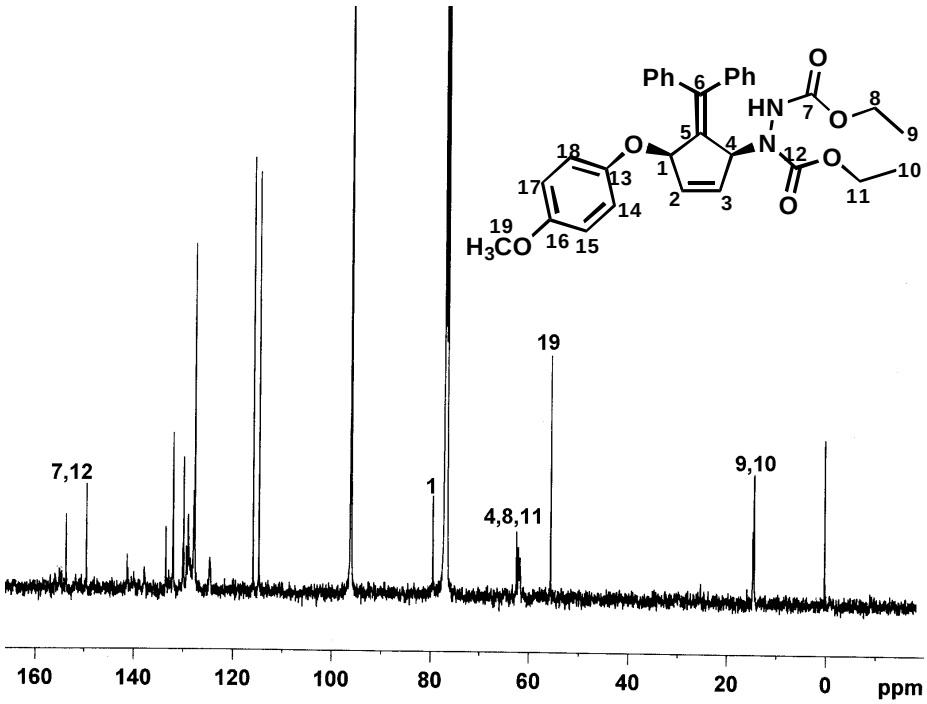


Figure 2.3. ^{13}C NMR spectrum of compound **36a**

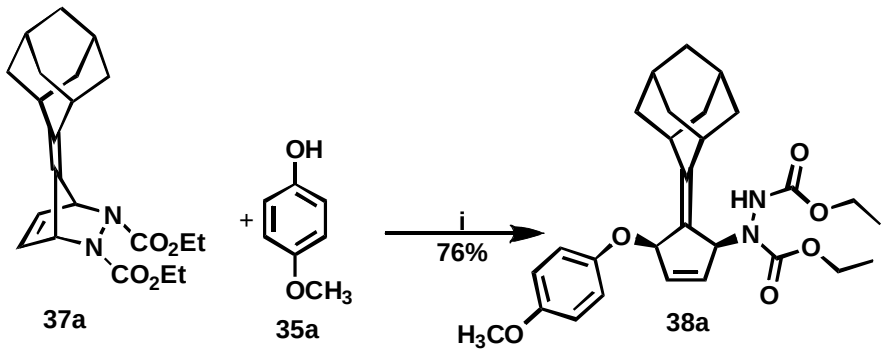
Detailed optimization studies were carried out to find the best condition for this transformation and the data are given in table 2.1. After the optimization studies, the best condition for the reaction was found to be a 1:1.5 mixture of phenol and bicyclic hydrazine with 5 mol% $Pd(PPh_3)_4$, 10 mol% dppf and 1.0 equiv. K_2CO_3 in dry THF as solvent at room temperature. Under the optimized condition the above reaction afforded the product **36a** 96% yield.

Table 2.1: Optimization studies

Entry	Catalyst	Ligand	Base	Solvent	Yield (%)[a]
1	$[Pd(allyl)Cl]_2$	dppf	NaH	THF	43
2	$[Pd(allyl)Cl]_2$	"	K_2CO_3	"	73
3	$[Pd(allyl)Cl]_2$	"	KO^tBu	"	38
4	$Pd(OAc)_2$	"	K_2CO_3	"	trace
5	$PdCl_2(PPh_3)_2$	"	"	"	21
6	$Pd_2(dba)_3.CHCl_3$	"	"	"	38
7	$PdCl_2$	"	"	"	trace
8	$Pd(PPh_3)_4$	"	"	"	80
9	$Pd(PPh_3)_4$	dppe	"	"	35
10	$Pd(PPh_3)_4$	PPh_3	"	"	42
11	$Pd(PPh_3)_4$	dppf	"	CH_3CN	34
12	$Pd(PPh_3)_4$	"	"	DMF	50
13	$Pd(PPh_3)_4$	"	"	THF	96[b]

Reaction Conditions: alkene (1.5 equiv.), phenol (1.0 equiv.), catalyst (5 mol%), ligand (10 mol%) base (1.0 equiv.), solvent (2 mL), 60 °C, 16 h.[a] isolated yield [b] r.t., solvent (4 mL), 1.5 h.

To explore the scope and generality of the method, the above reaction was repeated using different bicyclic hydrazines derived from various pentafulvenes and azodicarboxylates. For example the reaction of 6,6-adamantylidene fulvene derived bicyclic hydrazine **37a** and 4-methoxy phenol **35a** under the optimized conditions, afforded the corresponding cycloalkylidene cyclopentene **38a** in 76% yield. The reaction is shown in scheme 2.15.

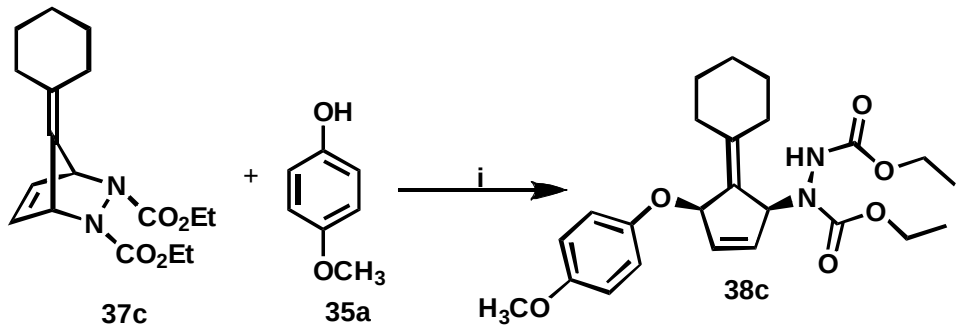


i = $Pd(PPh_3)_4$ (5 mol%), dppf (10 mol%), K_2CO_3 (1.0 equiv.), THF (4 mL), r.t., 1.5 h

Scheme 2.15

As in the previous cases, the characterization of the product **38a** was accomplished by spectroscopic analysis. The IR spectrum displayed absorption at 3306 cm^{-1} corresponding to the NH functionality; the carbonyls absorbed at 1753 and 1707 $cm.^{-1}$ In the ^1H NMR spectrum, the signal due to the NH proton was discernible as a broad singlet at δ 6.57 ppm (exchangeable with D_2O). The multiplets in the region δ 2.81-2.77 (2H) and δ 1.95-1.92 (12H) ppm were indicative of the adamantyl protons. ^{13}C NMR spectrum located the carbonyl signals at δ 156.4 and δ 155.8 ppm. The adamantyl carbons were visible in the region δ 39.5-28.0 ppm. The molecular ion peak at *m/z* 496.32, observed in the mass spectrum provided supporting evidence for the proposed structure.

The scope of this reaction was further tested by carrying out the reaction with the bicyclic hydrazine **37b** prepared from 6,6-cyclohexylidene fulvene and diethyl azodicarboxylate. This substrate also underwent smooth ring opening reaction with 4-methoxy phenol **35a** under similar conditions and furnished the product **38c** in 78% yield (Scheme 2.16).



i = $Pd(PPh_3)_4$ (5 mol%), dppf (10 mol%), K_2CO_3 (1.0 equiv.), THF (4 mL), r.t., 1.5 h

Scheme 2.16

The product **38c** was characterized on the basis of spectral data. IR spectrum confirmed the carbonyl absorptions in the region 1758-1714 cm^{-1} and the signal due to NH absorption was seen at 3308 cm^{-1}. ^1H NMR spectrum located characteristic cycloalkyl protons as two independent multiplets in the region δ 2.16 and 1.56-1.53 ppm. The multiplets at δ 4.17-4.15, 4.02 and 1.21-1.09 ppm were indicative of the presence of carboethoxy group. The carbonyl groups resonated at δ 156.0 and 155.7 ppm in the ^{13}C NMR spectrum. The cycloalkyl carbons were located in the region δ 26.0-21.0 ppm. A well defined molecular ion peak at *m/z* 445.03 (M+1) provided supporting evidence for the assigned structure.

The generality of the new ring-opening reaction was tested by repeating the reaction under the optimized condition with various phenols. Different fulvene-derived bicyclic adducts **34a**–**c** were subjected to the desymmetrization with substituted phenols **35a**–**e**. The results are summarized in table 2.2.

Table 2.2: Palladium catalyzed reaction of azabicyclic olefins with phenol

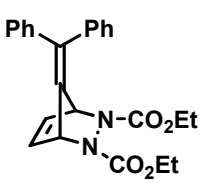
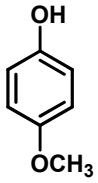
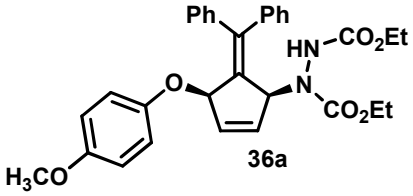
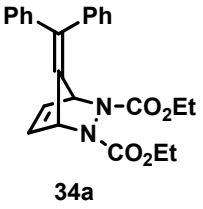
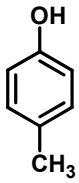
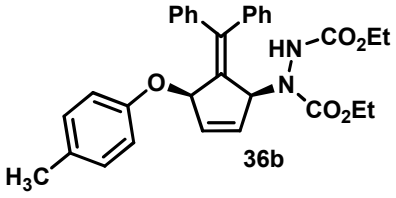
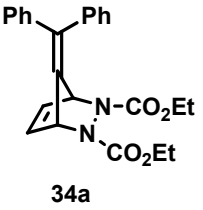
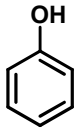
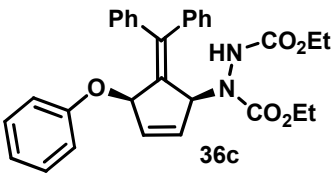
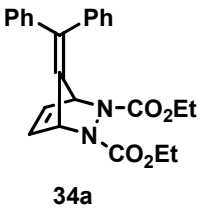
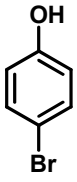
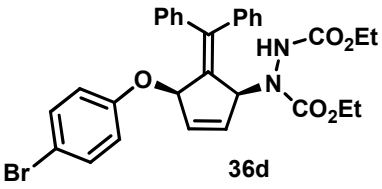
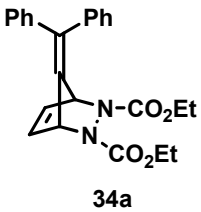
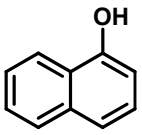
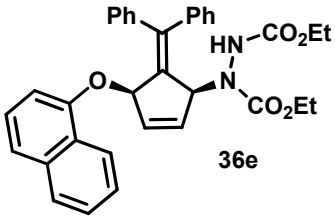
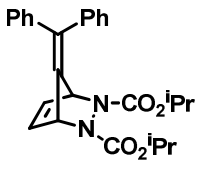
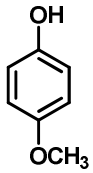
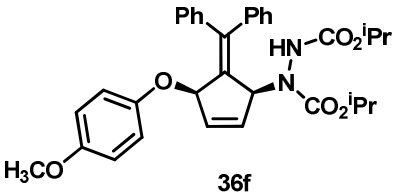
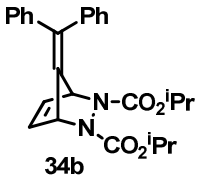
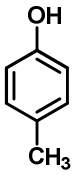
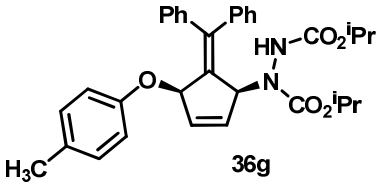
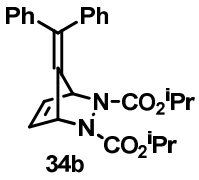
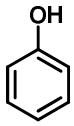
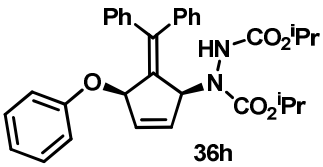
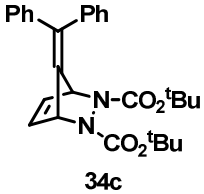
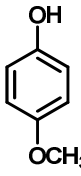
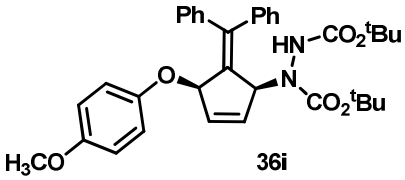
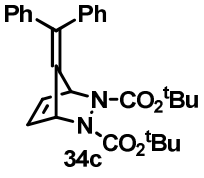
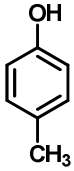
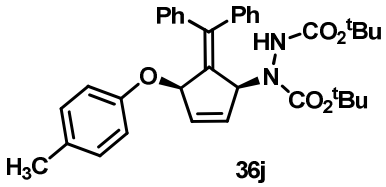
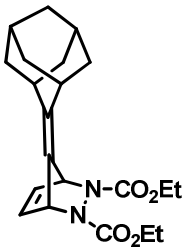
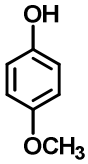
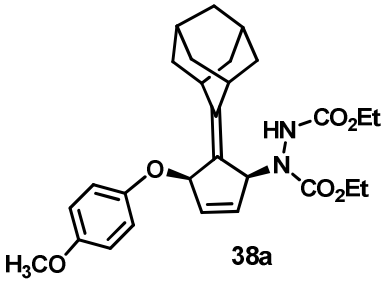
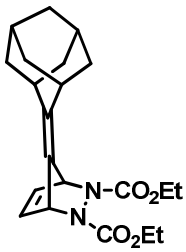
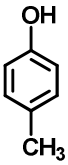
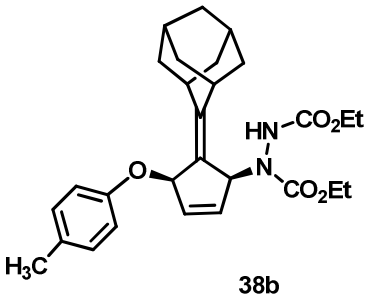
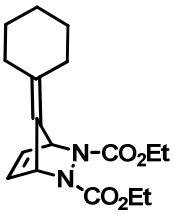
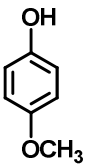
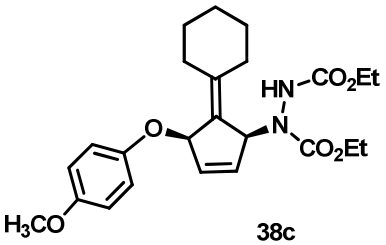
Entry	Alkene	Nucleophile	Product	Yield (%)
1	 34a	 35a	 36a	96
2	 34a	 35b	 36b	88
3	 34a	 35c	 36c	86
4	 34a	 35d	 36d	87
5	 34a	 35e	 36e	78

Table 2.2: Continued.....

Entry	Alkene	Nucleophile	Product	Yield (%)
6	 34b	 35a	 36f	81
7	 34b	 35b	 36g	80
8	 34b	 35c	 36h	75
9	 34c	 35a	 36i	60
10	 34c	 35b	 36j	55

This was further generalized with 6,6-dialkylfulvene derived bicyclic hydrazines (Table 2.3). The adduct **37a** was prepared from adamantanone-derived fulvene and **37b** from cyclohexanone-derived fulvene, respectively.

Table 2.3: Palladium catalyzed reaction of 6,6-dialkylidene fulvene derived alkene with phenol

Entry	Alkene	Nucleophile	Product	Yield (%)
1	 **37a**	 **35a**	 **38a**	76
2	 **37a**	 **35b**	 **38b**	73
3	 **37b**	 **35a**	 **38c**	78

Reaction conditions: alkene (1.5 equiv.), phenol (1.0 equiv.), $Pd(PPh_3)_4$ (5 mol%), dppf (10 mol%), K_2CO_3 (1.0 equiv.), THF (4.0 mL), r.t., 1.5 h.

The products shown in table 2.2 and table 2.3 were characterized by spectroscopic methods. In all the cases carbonyl absorptions were confirmed by IR and ^{13}C NMR spectra. In the proton NMR spectrum of **36b**, the methyl protons of *p*-cresol moiety appeared as singlet at δ 2.21 ppm. In the ^{13}C NMR spectrum, the

methyl carbon of *p*-cresol appeared at δ 21.0 ppm and the carbon bearing hydrazine moiety was spotted at δ 61.9 ppm. In **36c**, ^{1}H NMR spectrum located the aromatic protons as multiplets in the regions δ 7.38-7.16, 6.95-6.90 and δ 6.82-6.80 ppm. The olefinic protons resonated at δ 6.25-6.21 ppm as multiplets. In the ^{13}C spectrum, the carboethoxy carbon appeared at δ 156.9 and δ 156.2 ppm. In **36d** the aromatic protons were resonated as multiplet at δ 7.37-7.16 (m, 12H), 6.72–6.66 (m, 2H) ppm. The ^{1}H NMR spectrum of **36e** located the olefinic protons as multiplets at δ 6.26 and δ 6.07 ppm. The proton bearing the hydrazine moiety resonated at δ 5.81 ppm as singlet. In the ^{13}C spectrum, the carboethoxy carbon appeared at δ 156.5 and δ 156.1 ppm. The aromatic carbon near to oxygen at δ 152.9 ppm.

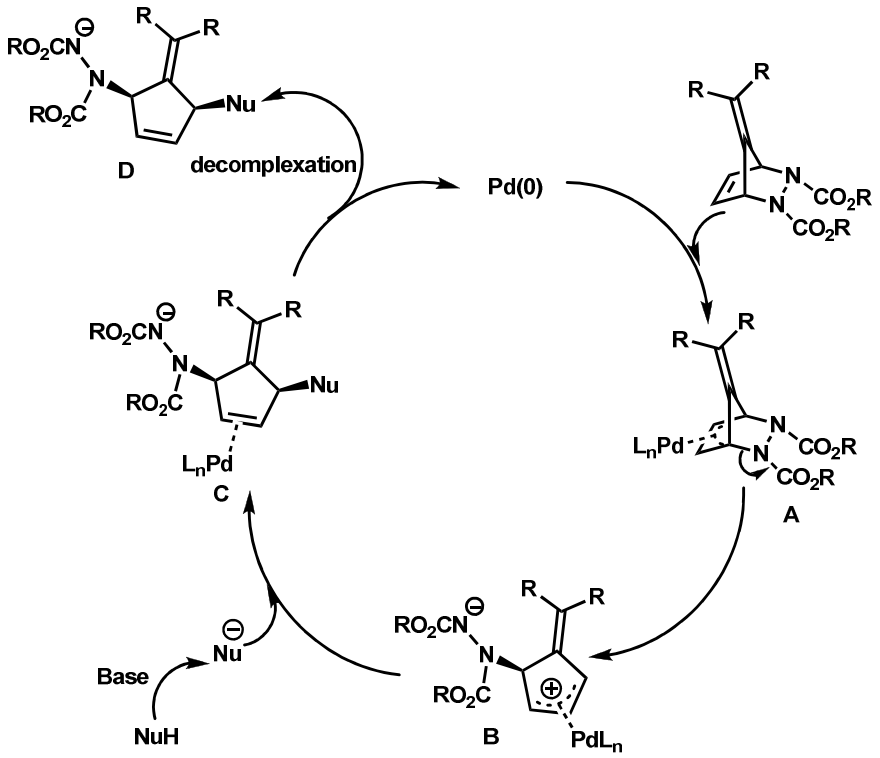
The ^{1}H NMR spectrum of **36f**, the methine protons of the isopropyl moiety appeared as two distinct multiplets in the regions δ 5.14-5.10 ppm and δ 4.86-4.82 ppm. In the ^{13}C NMR spectrum, these methine carbons were observed at δ 70.2 and 69.5 ppm and the carbon bearing the hydrazine group was spotted at δ 62.2 ppm. In **36g**, the methyl protons of *p*-cresol moiety appeared as singlet at δ 2.21 ppm and the methine protons of the isopropyl moiety resonated as two distinct multiplets in the regions δ 5.23–5.16 ppm and δ 4.83–4.82 ppm. In the ^{13}C NMR spectrum, these methine carbons were observed at δ 69.7 and 69.4 ppm and the carbon bearing the hydrazine group was spotted at δ 62.2 ppm. The proton NMR spectrum of **36h** showed the olefinic protons at δ 6.24–6.12 ppm as multiplet. The signal at δ 5.98–5.92 ppm was assigned to proton on the carbon bearing hydrazine moiety and at δ 5.34–5.28 ppm was allocated to proton on the cyclopentene ring adjacent to oxygen. The ^{13}C NMR spectrum showed the carbonyl carbon at δ 156.9 and δ 155.7 ppm. In **36i**, ^{1}H NMR spectrum located the methyl protons of the *tert*-butyl group as two distinct singlet at δ 1.34 ppm and δ 1.21 ppm. In the ^{13}C NMR spectrum, the two less intense peaks at δ 80.8 and 80.0 ppm corresponds

to the quaternary carbons of the *tert*-butyl group and the carbon bearing hydrazine substituent was discernible at δ 61.6 ppm. In **36j**, ^{1}H NMR spectrum located the methyl protons of the *tert*-butyl group as two distinct singlet at δ 1.40 ppm and δ 1.28 ppm. The methyl protons of *p*-cresol moiety appeared as singlet at δ 2.28 ppm In the ^{13}C NMR spectrum, the two less intense peaks at δ 80.4 and 79.1 ppm corresponds to the quaternary carbons of the *tert*-butyl group and the carbon bearing hydrazine substituent was discernible at δ 61.6 ppm.

In the ^{1}H NMR spectrum of **38b**, the signal corresponding to the N-H proton was discernible as a singlet at δ 6.54 ppm (exchangeable with D_2O). The adamantyl protons gave the signal as multiplets at δ 2.80–2.74 (2H) and δ 1.97–1.82 (12H) ppm. In the ^{13}C NMR spectrum, the adamantyl carbons were observed between δ 39.5 and 28.0 ppm. Further evidences for the structures were obtained from mass spectral analysis which showed the molecular ion peaks within the allowable limits.

2.4.1.1. Proposed mechanism of the reaction

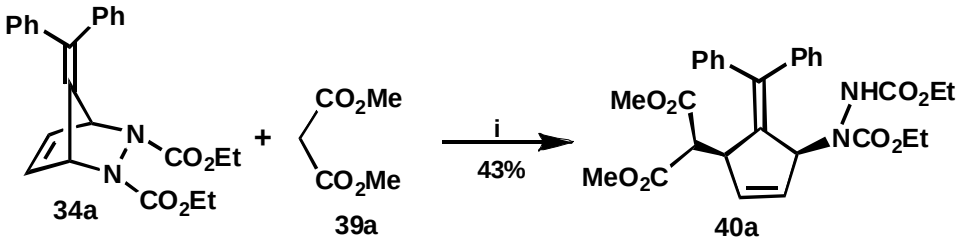
The mechanism outlined in scheme 2.17 has been suggested to rationalize the formation of the product **36**[31]. It involves two stages, the initial one being the ring opening of the bicyclic alkene. The first step of the catalytic cycle involves the formation of π-allylpalladium intermediate **B** by the attack of Pd(0) on the double bond (allylic species), and subsequent oxidative addition to C–N bond leading to the ring opening. In the second stage, the nucleophile regio- and stereospecifically attacks the π-allylpalladium species **B** thereby forming the intermediate **C**. The reason for the *cis* stereochemistry can be attributed to a classical mechanistic pathway involving a double inversion.



Scheme 2.17. Proposed mechanism of the reaction

2.4.2. Desymmetrization reactions using active methylene compound

Encouraged by the results obtained with phenol, we decided to extend the scope of the reaction using another class of soft nucleophile *viz* active methylene compounds. Diphenyl fulvene derived bicyclic hydrazine **34a** with dimethyl malonate **39a** under the optimized conditions for phenol showed similar reactivity and gave the corresponding substituted alkylidene cyclopentene **40a** in 43% yield (Scheme 2.18).



i = $Pd(PPh_3)_4$ (5 mol %), dppf (10 mol %), K_2CO_3 (1.0 equiv), THF (4 mL), r.t. , 1.5 h

Scheme 2.18

The structure of the product **40a** was established by spectroscopic analysis. The IR spectrum of **40a** confirmed the N-H absorption at 3317 cm^{-1}, while the stretching vibrations due to the carbonyls were observed at 1730 and 1720 cm^{-1}. In the ^{1}H NMR spectrum, (Figure 2.4) the signal due to proton on the carbon bearing hydrazine moiety was observed as multiplet in the region δ 5.78 ppm. The methyl proton on the active methylene group was discernable at δ 3.67 ppm.

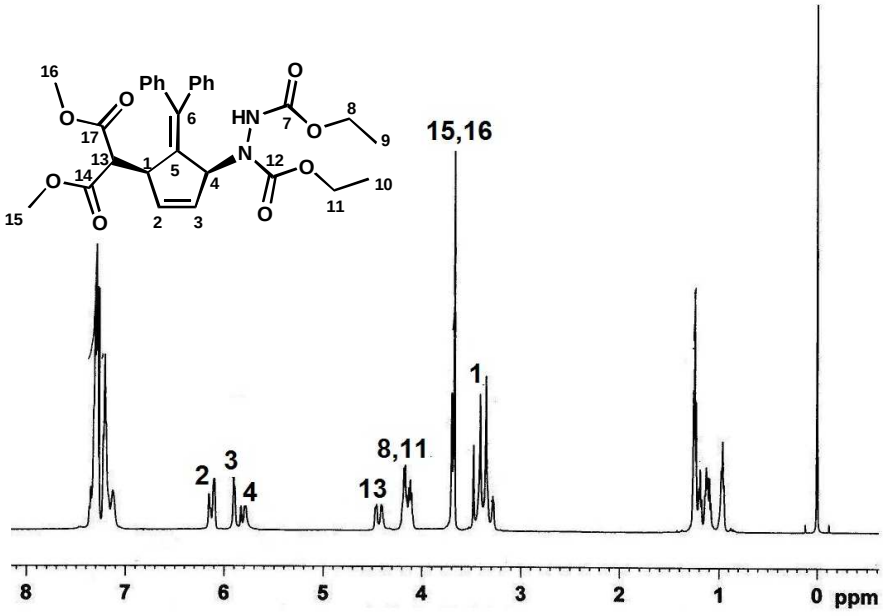


Figure 2.4. ^{1}H NMR spectrum of compound **40a**

In the ^{13}C NMR spectrum (Figure 2.5), the ester and amide carbonyls were positioned at δ 168.7, 168.4, 156.5 and 156.0 ppm. All other signals in the ^{1}H NMR spectrum and ^{13}C NMR spectrum were in agreement with the proposed structure. The molecular ion peak observed at *m/z* 536.30 $(M+Na)^{+}$, in the mass spectrum provided further evidence for the assigned structure.

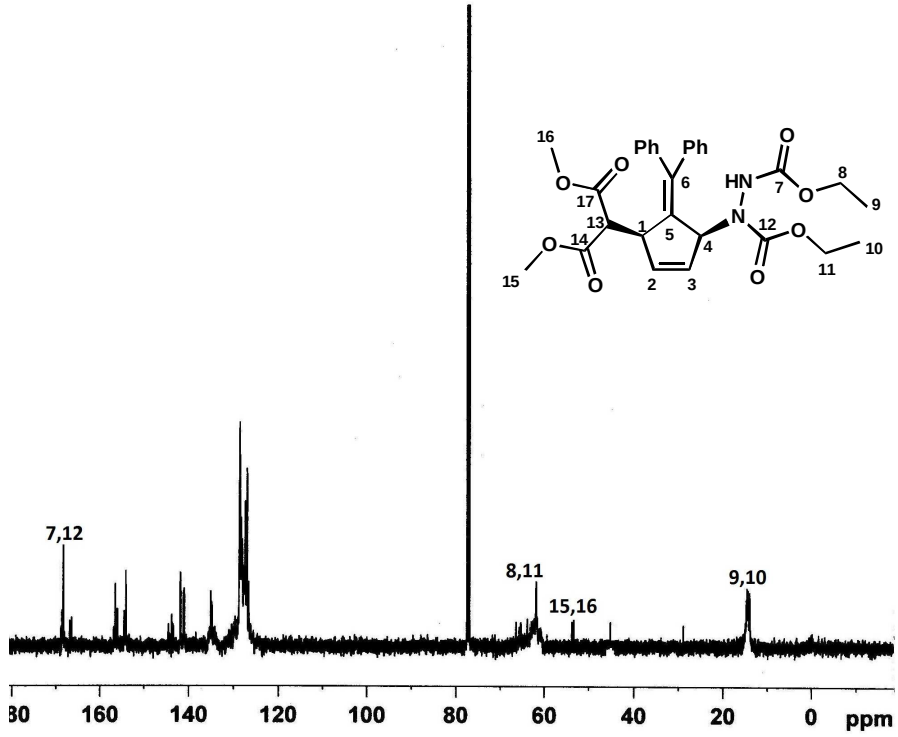


Figure 2.5. ^{13}C NMR spectrum of compound **40a**

The low yield of the reaction shown in scheme 2.18 prompted us to conduct further optimization studies and the results are given in table 2.3.

Table 2.3: Screening of parameters

Entry	Nucleophile	Condition	Yield (%)[a]
1	$CH_2(CO_2Me)_2$	$Pd(PPh_3)_4$, dppf, K_2CO_3	43
2	$CH_2(CO_2Me)_2$	$Pd(PPh_3)_4$, dppf, NaH	73
3	$CH_2(CO_2Me)_2$	$[Pd(allyl)Cl]_2$, dppf, NaH	93

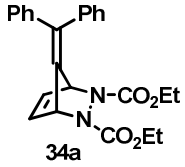
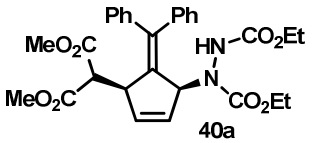
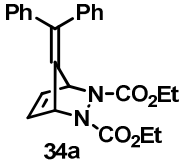
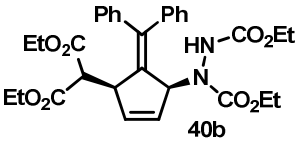
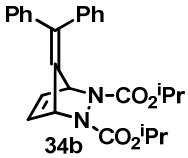
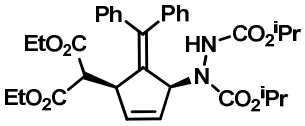
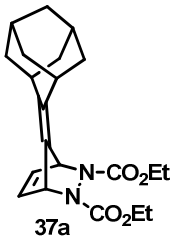
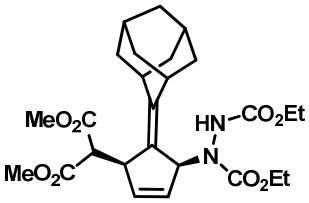
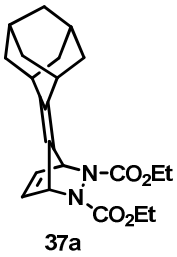
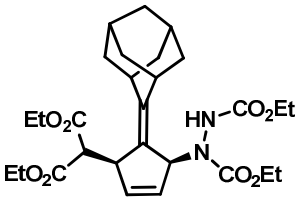
Reaction Conditions: alkene (1.5 equiv.), active methylene (1.0 equiv.), catalyst (5 mol%), dppf (10 mol%) base (1.0 equiv.), THF (4 mL), r.t., 1.5 h.[a] isolated yield

After the optimization studies, a combination of 5 mol% $[Pd(allyl)Cl]_2$, 10 mol% dppf, and 1 equiv. NaH in THF at room temperature was found to be the best condition for this transformation. Under this condition, the reaction was

repeated using different active methylene compounds, and the reactions afforded *cis*-1,4-substituted alkylidene cyclopentene in good yields.

The bicyclic hydrazines selected were from the cycloaddition of 6,6-diphenyl and adamantylidene fulvenes with different azodicarboxylates. The results of these investigations are summarized in table 2.4.

Table 2.4. Palladium-Catalyzed Reaction of Azabicyclic Olefins with Active Methylene Compounds

Entry	Alkene	Nucleophile	Product	Yield (%)
1	 34a	 39a	 40a	93
2	 34a	 39b	 40b	86[a]
3	 34b	 39b	 40c	76[a]
4	 37a	 39a	 40d	79
5	 37a	 39b	 40e	70[a]

Reaction conditions: alkene (1.5 equiv.), active methylene (1.0 equiv.), $[Pd(allyl)Cl]_2$ (5 mol %), dppf (10 mol %), NaH (1.0 equiv.), THF (4.0 mL), r.t., 1.5 h. [a] 60 °C.

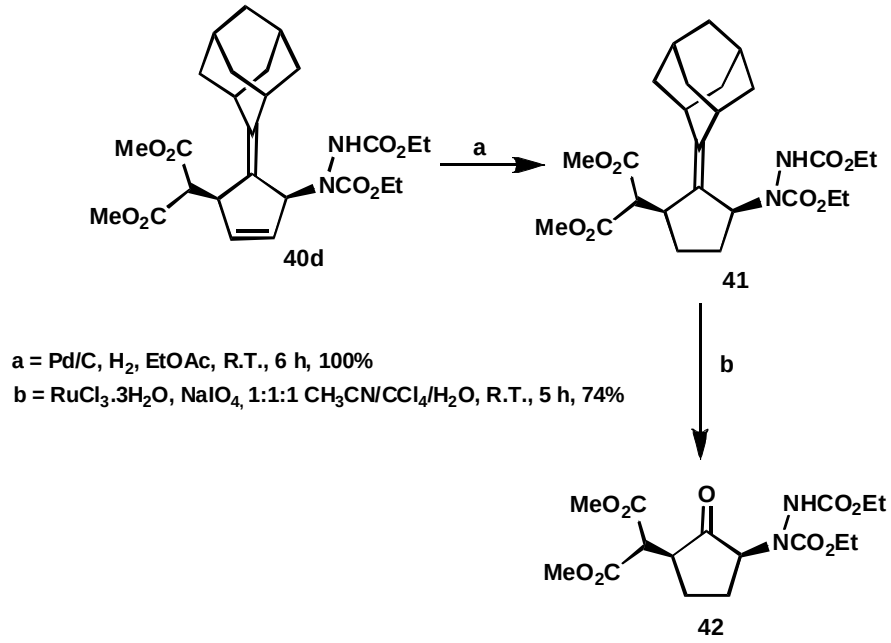
Usual spectral analyses were employed to establish the structures of the products. In ^{1}H NMR spectrum of **40b**, the signal due to proton on the carbon bearing hydrazine moiety was observed as multiplet in the region δ 5.77 ppm. The methylene proton on the active methylene group was discernable at δ 3.28-3.22

ppm as multiplet. In the ^{13}C NMR spectrum the ester and amide carbonyls were positioned at δ 168.4, 168.1, 156.4 and 154.2 ppm.

In **40c**, the methine protons of isopropyl moiety resonated at δ 4.89–4.88 and δ 4.54–4.40 ppm along with the methylene protons on the carboethoxy group. The ^{13}C NMR spectrum positioned the ester and amide carbonyls at δ 168.1, 167.7, 155.5 and 153.6 ppm. In **40d**, the adamantyl protons resonated as multiplets in the regions δ 2.79–2.75 (1H), 2.54–2.50 (1H) and 1.92–1.80 (12H) ppm. The adamantyl carbons were discernable at δ 39.2-27.7 ppm. In **40e**, the endocyclic olefinic protons appeared as multiplet at δ 6.07–6.04 ppm and as singlet at δ 5.91 ppm. The proton on the carbon bearing the hydrazine moiety resonated at δ 5.79–5.76 ppm. In the ^{13}C NMR spectrum the ester and amide carbonyls were positioned at δ 168.7, 168.4, 155.9 and 155.2 ppm.

2.4.3. Synthetic transformations of the product

To explore the synthetic utility of the synthesized alkylidene cyclopentenes and also to get further confirmation on the assigned structure, we carried out the hydrogenation of **40d** over Pd/C. The reaction afforded the reduced product **41** in quantitative yield. When **41** was treated with a system consisting of $RuCl_3$. $3H_2O$ and $NaIO_4$ in a 1:1:1 mixture of CH_3CN, CCl_4 and H_2O; oxidative cleavage of the tetra substituted double bond occurred furnishing the substituted cyclopentanone **42** in 74% yield (Scheme 2.19). This reaction can be viewed as an alternative route to *cis*-α,α'-disubstituted cyclopentanones.



Scheme 2.19

The characterization of the product **41** and **42** was accomplished by means of usual spectroscopic analysis. In the IR spectrum of **41**, the carbonyl and N-H absorptions were observed in the region 1732 and 3312 cm^{-1} respectively. The reduction of the ring double bond moiety in **40d** was confirmed by the absence of signals at δ 6.05-6.01 and δ 5.92 ppm in the ^{1}H spectrum of **41**. ^{13}C NMR spectrum supported the assigned structure of **41**, by providing four carbonyl signals in the region δ 169.2, 168.4, 156.3 and 155.2 ppm. The molecular ion peak observed at *m/z* 506.06 (M^{+}) in the mass spectrum, gave additional evidence to the proposed structure.

Unambiguous evidence for the structure and stereochemistry of the product **41** was obtained by single crystal X-ray analysis (Figure 2.6).

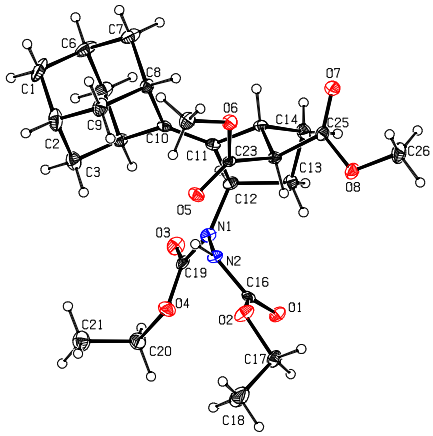
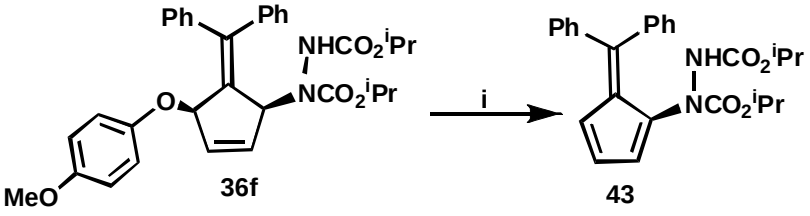


Figure 2.6. Single crystal X-ray structure of compound **41**

In the IR spectrum of **42**, the carbonyl and N-H absorptions were observed in the region 1744, 1713 and 3308 cm^{-1} respectively. The absence of signal at δ 1.81–1.56 (14H) was indicative of the removal of adamantylidene group. ^{13}C NMR spectrum supported the assigned structure of **42**, by providing five carbonyl signals in the region δ 211.7, 168.5, 168.0, 156.3 and 155.4 ppm and the signal at 211.7 ppm was due to the ketonic carbon. The molecular ion peak observed at *m/z* 388.17 (M^+) in the mass spectrum, gave additional evidence to the proposed structure.

(ii) The molecule **36f** can be converted to 2-hydrazino fulvene **43** by simple synthetic modifications. When **36f** was refluxed with 3 equiv. of chloranil in xylene, the reaction afforded the 2-hydrazino substituted fulvene **43** in 74 % yield (Scheme 2.20).



i = Chloranil, Xylene, 110 ºC, 74%

Scheme 2.20

The product was characterized on the basis of spectroscopic data**.** In the IR spectrum, the carbonyl carbon and –NH absorption were observed in the region 1726-1715 cm^{-1} and 3312 cm^{-1} respectively. ^{1}H NMR spectrum (Figure 2.7) showed the double bond protons as multiplets in the regions δ 6.80-6.66, 6.40-6.39 and 6.14-6.12 ppm. The two isopropyl methine protons were observed as multiplet in the region δ 4.90-4.83 ppm. ^{13}C spectrum (Figure 2.8) positioned isopropyl carbons at δ 70.0 and 69.7 ppm. All other signals in ^{1}H and ^{13}C NMR spectrums were in agreement with the proposed structure. The molecular ion peak observed at *m/z* 432.86 in the mass spectrum provided further support for the assigned structure.

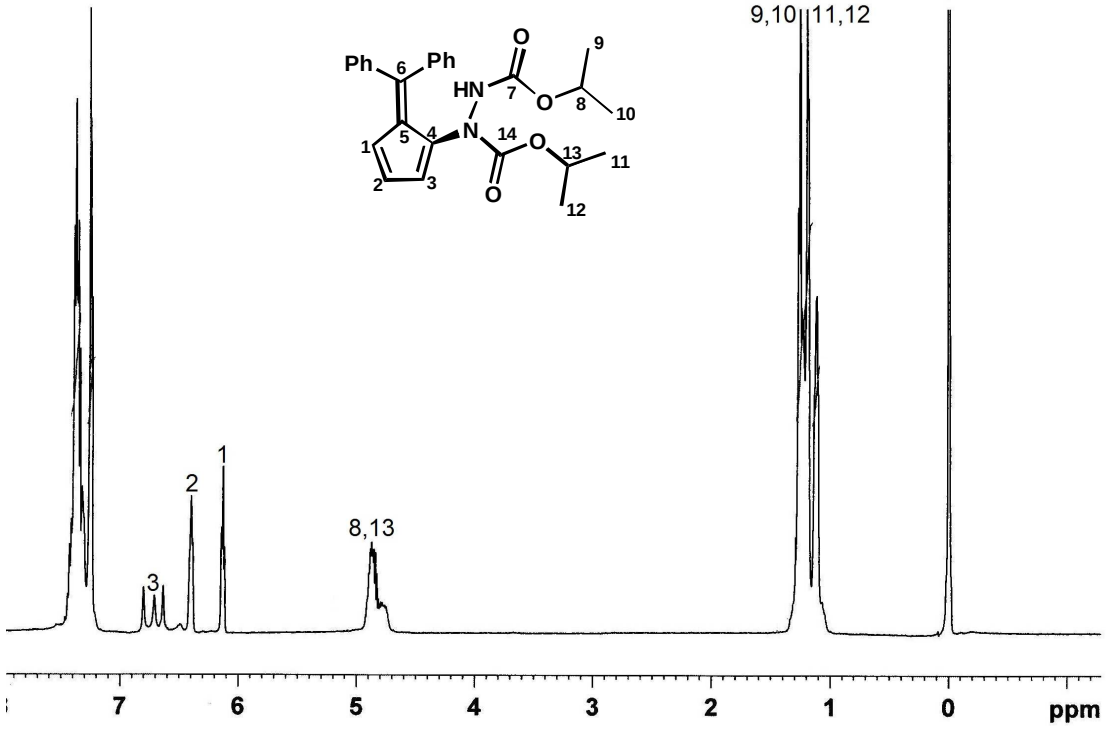


Figure 2.7. ^{1}H NMR spectrum of compound **43**

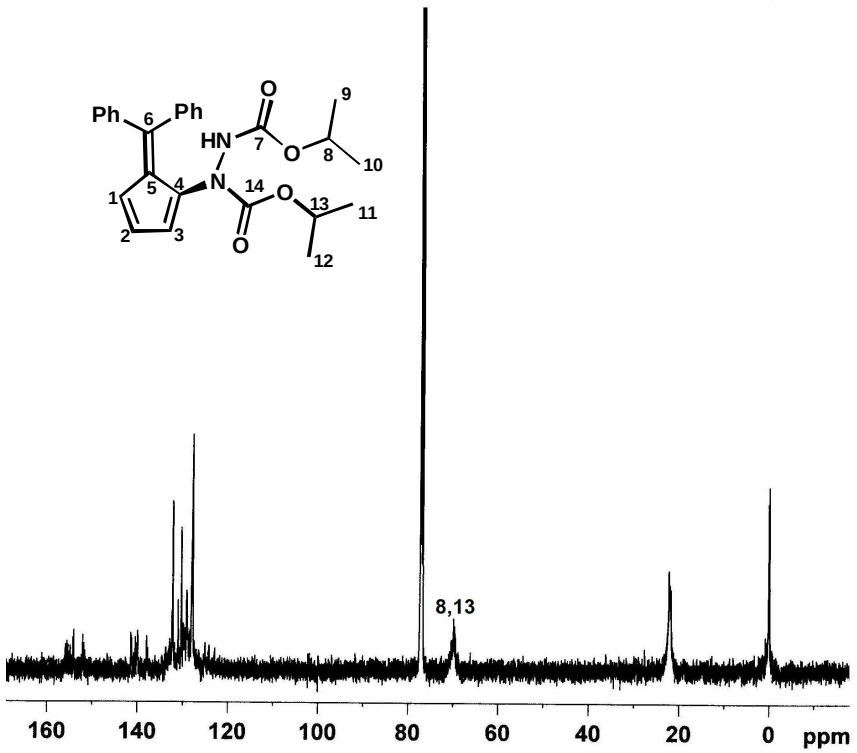


Figure 2.8. ^{1}H NMR spectrum of compound **43**

2.5. Conclusion

In conclusion, we have introduced a facile route towards the synthesis of a new class of disubstituted alkylidene cyclopentenes by the functionalization of pentafulvenes *via*, palladium mediated ring opening of fulvene derived bicyclic hydrazines with a number of soft nucleophiles. The products are obtained in good to excellent yields. The possibility for further functionalization was effectively demonstrated by the synthesis of substituted cyclopentanones and 2-hydrazino fulvenes. It is noteworthy that alkylidene cyclopentanes are key intermediates in the synthesis of a number of biologically active molecules.

2.6. Experimental

All reactions were conducted in oven dried glassware. Solvents used for the experiments were distilled or dried as specified. All reactions were monitored by TLC (Silica gel 60 F254, 0.25 mm, Merck); visualization was effected with UV

and/or by staining with Enholm yellow or with basic $KMnO_4$. Column chromatography was done using 100-200 mesh silica gel and appropriate mixture of petroleum ether and ethyl acetate for elution. The solvents were removed using Buchi E.L rotary evaporator. HPLC analyses were conducted with a LC9101 Recycling Preparative HPLC. The IR spectra were taken on Nicolet FT-IR spectrometer. NMR spectra were recorded at 300 and 500 (^{1}H) and 75 and 125 (^{13}C) MHz respectively on a Bruker DPX-300 and 500 MHz FT-NMR spectrometer. NMR spectra were obtained using $CDCl_3$ as the solvent. Chemical shifts are given in δ scale with TMS as internal standard. Abbreviations used in ^{1}H NMR are **s**: singlet, **brs**: broad singlet, **d**: doublet, **t**: triplet, **m**: multiplet. Mass spectra were recorded by FAB ionization technique using JEOL JMS 600H mass spectrometer.

General Procedure

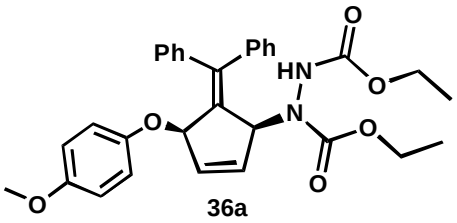
$Pd(PPh_3)_4$ (5 mol%), 1,1'-bis-(diphenylphosphino)-ferrocene (10 mol%) and K_2CO_3 (1 equiv.) were taken in a Schlenk tube, placed under vacuum for 15min. Freshly distilled THF (2 mL) was degassed and then added to the mixture at room temperature. The solution was stirred for 15 min. To the Schlenk tube, phenol (1.0 equiv.) and bicyclic hydrazine (1.5 equiv) dissolved in THF (2 mL) were added and the solution was stirred at room temperature until TLC analysis indicated full conversion. The solvent was removed under reduced pressure and the residue was subjected to chromatography [silica gel (100–200 mesh), EtOAc–hexane, 40:60] to afford the products in good to excellent yields.

Diethyl 1-(5-(diphenylmethylene)-4-(4-methoxyphenoxy)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 36a

Following the general experimental procedure, bicyclic hydrazine **34a** (121 mg, 0.30 mmol), 4-methoxy phenol **35a** (25 mg, 0.20 mmol), dppf (11 mg, 10 mol%), and $Pd(PPh_3)_4$ (12 mg, 5 mol%) and K_2CO_3 (28 mg, 0.20 mmol), in 4 mL

of dry THF at r.t. for 1.5 h gave the product **36a** as a white powder in 96% (102 mg) yield.

Mp 122-124 °C. R_f : 0.52 (6:4 Hexane/ethyl acetate).



36a

IR (KBr)ν_{max}: 3368, 2983, 2928, 1748, 1727, 1599, 1510, 1374, 1231, 1034, 763 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.28 (m, 3H), 7.22-7.12 (m, 7H), 6.68-6.62 (m, 4H), 6.13-6.09 (m, 2H), 5.88-5.82 (m, 1H), 5.60 (s, 1H), 5.11 (m, 1H), 4.10-4.03 (m, 2H), 3.84-3.83 (m, 2H), 3.69 (s, 3H), 1.19-1.16 (m, 3H), 1.05-0.98 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.0, 155.1, 153.7, 149.6, 141.4, 140.0, 138.0, 133.6, 133.0, 132.1, 130.0, 129.4, 129.1, 128.0, 127.8, 124.7, 116.0, 78.3, 62.5, 62.1, 61.8, 55.6, 14.7, 14.4.

MS (FAB): for $C_{31}H_{32}N_2O_6$, Calcd, M^+: 528.23; Found: 528.90.

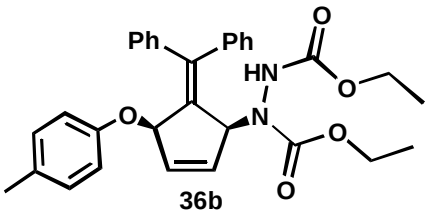
Diethyl 1-(5-(diphenylmethylene)-4-(p-tolyloxy)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 36b

Following the general experimental procedure, bicyclic hydrazine **34a** (137 mg, 0.34 mmol), *p*-cresol **35b** (25 mg, 0.23 mmol), dppf (11 mg, 10 mol%), and $Pd(PPh_3)_4$ (12 mg, 5 mol%) and K_2CO_3 (32 mg, 0.23 mmol), in 4 mL of dry THF at r.t. for 1.5 h gave the product **36b** as light brown powder in 88% (104 mg) yield.

Mp 78-80 °C. R_f : 0.39 (6:4 Hexane/ethyl acetate).

IR (KBr)ν_{max}: 3308, 3055, 2974, 2928, 1750, 1715, 1508, 1412, 1227, 1063, 930, 772 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.10 (m, 10H), 6.94-6.93 (m, 2H), 6.68-6.62 (m, 2H),



36b

6.16-6.08 (m, 2H), 5.89-5.82 (m, 1H), 5.61 (s, 1H), 5.22-5.17 (m, 1H), 4.06-4.01 (m, 2H), 3.83-3.77 (m, 2H), 2.21 (s, 3H), 1.18-0.97 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2, 154.7, 153.7, 141.3, 137.9, 133.7, 132.2, 129.9, 129.5, 129.3, 129.1, 128.0, 127.8, 124.7, 115.1, 79.4, 62.7, 62.3, 61.9, 21.0, 14.5, 14.4.

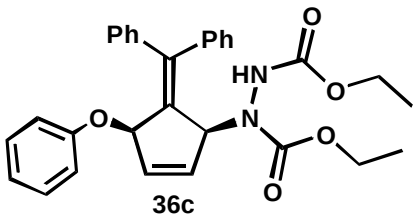
MS (FAB) for $C_{31}H_{32}N_2O_5$, calcd (M^+): 512.23; found: 512.20.

Diethyl 1-(5-diphenylmethylene)-4-phenoxycyclopent-2-enyl)hydrazine-1,2-dicarboxylate 36c

Following the general experimental procedure, bicyclic hydrazine **34a** (162 mg, 0.40 mmol), phenol **35c** (25 mg, 0.27 mmol), dppf (15 mg, 10 mol%), and $Pd(PPh_3)_4$ (12 mg, 5 mol%) and K_2CO_3 (37 mg, 0.27 mmol), in 4 mL of dry THF at r.t. for 1.5 h gave the product **36c** as a light brown powder in 86% (115 mg) yield.

Mp 124-126°C. R_f : 0.53 (6:4 Hexane/ethyl acetate).

IR (KBr)ν_{max}: 3308, 3055, 2978, 2932, 1748, 1715, 1597, 1493, 1383, 1227, 1028, 966, 752 cm^{-1}.



36c

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.16 (m, 12H), 6.95-6.90 (m, 1H), 6.82-6.80 (m, 2H), 6.25-6.21 (m, 2H), 5.98-5.92 (m, 1H), 5.72 (s, 1H), 5.31 (m, 1H), 4.12 (m, 2H), 3.91 (m, 2H), 1.23-1.09 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.9, 156.2, 154.7, 141.1, 140.3, 135.1, 134.9, 134.6, 134.3, 133.0, 132.6, 129.4, 128.6, 128.1, 127.6, 127.5, 127.3, 121.1, 116.1, 78.8, 62.6, 62.3, 61.7, 14.4,

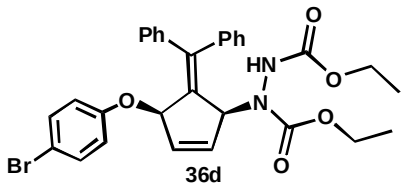
14.2.

MS (FAB) for $C_{30}H_{30}N_2O_5$, calcd (M^+): 498.22; found: 498.58.

Diethyl 1-(4-(4-bromophenoxy)-5-(diphenylmethylene)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 36d

Following the general experimental procedure, bicyclic hydrazine **34a** (85 mg, 0.21 mmol), 4-bromophenol **35d** (25 mg, 0.14 mmol), dppf (8 mg, 10 mol%), and $Pd(PPh_3)_4$ (8 mg, 5 mol%) and K_2CO_3 (20 mg, 0.14 mmol) in 4 mL of dry THF at r.t. for 1.5 h gave the product **36d** as light brown powder in 87% (72 mg) yield.

Mp 130-134 °C. R_f : 0.62 (6:4 Hexane/ethyl acetate).



36d

IR (KBr) ν_{max}: 3308, 3057, 2980, 2859, 1743, 1713, 1585, 1412, 1227, 1063, 930, 772 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.16 (m, 12H), 6.72-6.66 (m, 2H), 6.21-6.15 (m, 2H), 5.97-5.91 (m, 1H), 5.70 (s, 1H), 5.28-5.25 (m, 1H), 4.14-4.06 (m, 2H), 3.95-3.90 (m, 2H), 1.26-1.04 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3, 156.1, 154.7, 147.0, 140.6, 140.1, 135.7, 135.1, 134.0, 133.5, 132.2, 131.9, 128.7, 128.5, 128.1, 127.8, 127.6, 127.5, 127.1, 117.8, 79.3, 63.6, 62.4, 62.2, 14.5, 14.2.

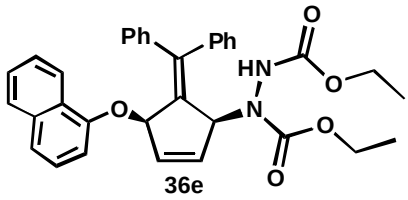
MS (FAB) for $C_{30}H_{29}BrN_2O_5$, calcd (M^+): 576.13; found: (M+2): 578.22.

Diethyl 1-(5-diphenylmethylene)-4-(naphthalen-1-yloxy)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 36e

Following the general experimental procedure, bicyclic hydrazine **34a** (101 mg, 0.25 mmol), α-naphthol **35e** (25 mg, 0.17 mmol), dppf (10 mg, 10 mol%), and

$Pd(PPh_3)_4$ (9 mg, 5 mol%) and K_2CO_3 (24 mg, 0.17 mmol) in 4 mL of dry THF at r.t. for 1.5 h gave the product **36e** as brown powder in 78% (74 mg) yield.

Mp 128-130°C. R_f : 0.60 (6:4 Hexane/ethyl acetate).



36e

IR (KBr) ν_{max}: 3364, 3053, 2982, 2930, 1750, 1719, 1595, 1489, 1381, 1231, 1061, 795, 754, 702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (d, 1H, *J* = 8.0 Hz), 7.81 (d, 1H, *J* = 8.0 Hz), 7.52-7.50 (m, 2H), 7.42-7.38 (m, 5H), 7.32-7.24 (m, 4H), 7.00-6.98 (m, 3H), 6.63 (d, 1H, *J* = 8.0 Hz), 6.36 (bs, 1H), 6.26 (m, 1H), 6.07 (m, 1H), 5.81 (s, 1H), 5.52 (m, 1H), 4.15-4.12 (m, 2H), 3.97 (m, 2H), 1.14-1.09 (m, 6H).

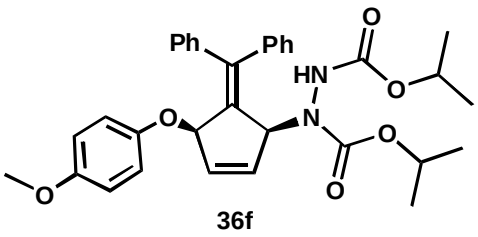
^{13}C NMR (125 MHz, $CDCl_3$): δ 156.5, 156.1, 152.9, 141.1, 140.9, 140.3, 135.4, 134.7, 132.6, 132.1, 128.7, 128.5, 128.0, 127.8, 127.4, 126.2, 125.8, 125.6, 124.9, 122.9, 120.4, 106.3, 79.3, 63.7, 62.6, 61.9, 14.5, 14.3.

MS (FAB) for $C_{34}H_{32}N_2O_5$, calcd (M^+): 548.23; found: 548.71.

Diisopropyl 1-(5-diphenylmethylene)-4-(methoxyphenoxy)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 36f

Following the general experimental procedure, bicyclic hydrazine **34b** (130 mg, 0.30 mmol), 4-methoxy phenol **35a** (25 mg, 0.20 mmol), dppf (11 mg, 10 mol%), $Pd(PPh_3)_4$ (12 mg, 5 mol%) and K_2CO_3 (28 mg, 0.20 mmol), in 4 mL of dry THF at r.t. for 1.5 h gave the product **36f** as a light brown powder in 81% (91 mg) yield.

Mp 148-150 °C. R_f : 0.54 (6:4 Hexane/ethyl acetate).



36f

IR (KBr)ν_{max}: 3323, 3053, 2980, 2934, 1742, 1713, 1466, 1385, 1225, 1036, 966, 826, 750 cm^{-1}.

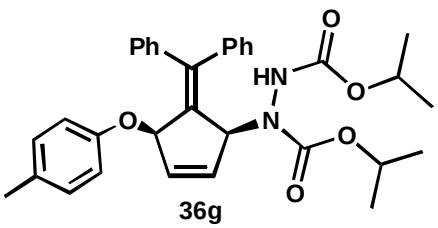
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.20 (m, 3H), 7.18-7.10 (m, 7H), 6.67-6.60 (m, 4H), 6.41 (s, 1H), 6.11-6.05 (m, 2H), 5.87-5.82 (m, 1H), 5.14-5.10 (m, 1H), 4.86-4.82 (m, 1H), 4.54-4.50 (m, 1H), 3.68 (s, 3H), 1.18-0.99 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6, 154.2, 153.9, 140.9, 140.3, 134.9, 134.8, 134.4, 134.0, 132.8, 128.7, 128.0, 127.5, 127.4, 127.3, 114.6, 79.9, 70.2, 69.5, 62.2, 55.3, 22.1, 21.9.

MS (FAB) for $C_{33}H_{36}N_2O_6$, calcd (M^+): 556.26; found: 556.46.

Diisopropyl 1-(5-diphenylmethylene)-4-(p-tolyloxy)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 36g

Following the general experimental procedure, bicyclic hydrazine **34b** (147 mg, 0.34 mmol), *p*-cresol **35b** (25 mg, 0.23 mmol), dppf (11 mg, 10 mol%), $Pd(PPh_3)_4$ (12 mg, 5 mol%) and K_2CO_3 (32 mg, 0.23 mmol), in 4 mL of dry THF at r.t. for 1.5 h gave the product **36g** as light brown powder in 81% (101 mg) yield. Mp 94-96°C. R_f : 0.48 (6:4 Hexane/ethyl acetate).



36g

IR (KBr)ν_{max}: 3325, 3054, 2980, 2939, 1748, 1715, 1612, 1508, 1491, 1468, 1385, 1229, 1036, 963, 752, 702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.09 (m, 10H), 6.94-6.92 (m, 2H), 6.67-6.61 (m, 2H), 6.40 (s, 1H), 6.14-6.06 (m, 2H), 5.88-5.82 (m,

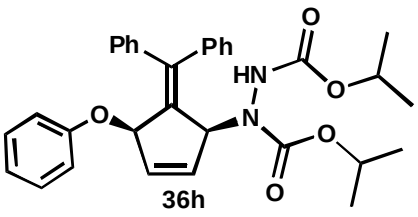
1H), 5.23-5.16 (m, 1H), 4.83-4.82 (m, 1H), 4.53-4.52 (m, 1H), 2.21 (s, 3H), 1.19-0.96 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7, 154.7, 153.5, 140.9, 132.6, 132.1, 130.2, 130.0, 129.7, 128.7, 128.0, 127.7, 127.4, 127.3, 124.6, 115.1, 79.4, 69.7, 69.4, 62.2, 22.0, 21.8, 20.5.

MS (FAB) for $C_{33}H_{36}N_2O_5$, calcd (M^+): 540.26; found: 540.46.

Diisopropyl 1-(5-diphenylmethylene)-4-phenoxycyclopent-2-enyl)hydrazine-1,2-dicarboxylate 36h

Following the general experimental procedure, bicyclic hydrazine **34b** (173 mg, 0.34 mmol), phenol **35c** (25 mg, 0.23 mmol), dppf (11 mg, 10 mol%), $Pd(PPh_3)_4$ (12 mg, 5 mol%) and K_2CO_3 (32 mg, 0.23 mmol), in 4 mL of dry THF at r.t. for 1.5 h gave the product **36h** as light brown powder in 75% (91 mg) yield. Mp 114-116 °C. R_f : 0.43 (6:4 Hexane/ethyl acetate).



36h

IR (KBr)ν_{max}: 3325, 3054, 2980, 2939, 1748, 1715, 1612, 1508, 1491, 1468, 1385, 1229, 1036, 963, 752, 702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43-7.34 (m, 4H), 7.29-7.15 (m, 8H), 6.93-6.90 (m, 1H), 6.85-6.80 (m, 2H), 6.50 (s, 1H), 6.24-6.12 (m, 2H), 5.98-5.92 (m, 1H), 5.34-5.28 (m, 1H), 4.91-4.85 (m, 1H), 4.63-4.59 (m, 1H), 1.32-1.03 (m, 12H).

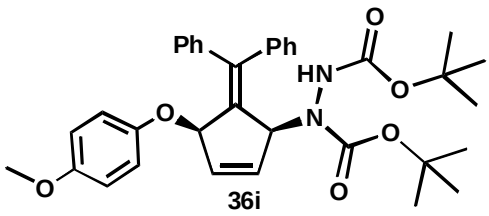
^{13}C NMR (125 MHz, $CDCl_3$): δ 156.9, 155.7, 155.6, 140.9, 135.1, 134.5, 133.9, 132.5, 132.4, 129.2, 128.8, 128.7, 128.2, 128.0, 127.4, 121.0, 78.7, 69.6, 69.4, 62.2, 21.8, 21.7.

MS (FAB) for $C_{32}H_{34}N_2O_5$, calcd (M^+): 526.25; found: 526.46.

Di-*tert*-butyl 1-(5-diphenylmethylene)-4-(4-methoxyphenoxy)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 36i

Following the general experimental procedure, bicyclic hydrazine **34c** (138 mg, 0.30 mmol), 4-methoxy phenol **35a** (25 mg, 0.20 mmol), dppf (11 mg, 10 mol%), $Pd(PPh_3)_4$ (12 mg, 5 mol%) and K_2CO_3 (28 mg, 0.20 mmol), in 4 mL of dry THF at r.t. for 1.5 h gave the product **36i** as light brown powder in 60% (71 mg) yield.

Mp 94-96 °C. R_f : 0.35 (6:4 Hexane/ethyl acetate).



36i

IR (KBr)ν_{max}: 3333, 3057, 2978, 2932, 1748, 1711, 1504, 1393, 1368, 1238, 1157, 1032, 968, 752 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.12 (m, 10H), 6.68-6.66 (m, 4H), 6.35 (s, 1H), 6.09-6.01 (m, 1H), 5.84-5.80 (m, 1H), 5.39 (m, 1H), 5.09-5.06 (m, 1H), 3.68 (s, 3H), 1.34 (s, 9H), 1.21 (s, 9H).

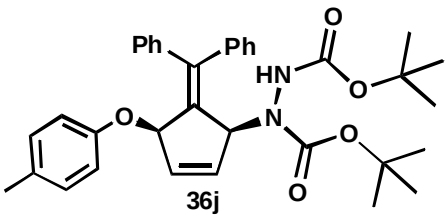
^{13}C NMR (125 MHz, $CDCl_3$): δ 155.8, 155.1, 154.9, 141.1, 140.8, 135.0, 134.8, 132.4, 129.8, 129.7, 128.9, 128.8, 128.7, 128.0, 127.6, 127.4, 116.0, 80.8, 80.0, 61.8, 61.6, 55.6, 28.2, 28.1.

MS (FAB) for $C_{35}H_{40}N_2O_6$, calcd (M^+): 584.29; found: 584.82.

Di-*tert*-butyl 1-(5-(diphenylmethylene)-4-(p-tolyloxy)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 36j

Following the general experimental procedure, bicyclic hydrazine **34c** (157 mg, 0.34 mmol), *p*-cresol **35b** (25 mg, 0.23 mmol), dppf (11 mg, 10 mol%), $Pd(PPh_3)_4$ (12 mg, 5 mol%) and K_2CO_3 (32 mg, 0.23 mmol), in 4 mL of dry THF at r.t. for 1.5 h gave the product **36j** as light brown powder in 55% (72 mg) yield.

Mp 156-158 °C. R_f : 0.54 (6:4 Hexane/ethyl acetate).



36j

IR (KBr)ν_{max}: 3337, 3050, 2984, 2938, 1752, 1717, 1506, 1389, 1371, 1226, 1148, 1031, 961, 751 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44-7.34 (m, 3H), 7.25-7.15 (m, 7H), 7.03-7.00 (m, 2H), 6.75-6.73 (m, 2H), 6.48 (s, 1H), 6.20-6.15 (m, 2H), 5.96-5.88 (m, 1H), 5.28-5.20 (m, 1H), 2.28 (s, 3H), 1.40 (s, 9H), 1.28 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9, 154.8, 153.3, 141.0, 135.1, 135.0, 132.4, 132.2, 130.3, 129.8, 128.9, 128.7, 128.0, 127.7, 127.4, 116.6, 80.4, 79.1, 61.6, 28.2, 21.0.

MS (FAB) for $C_{35}H_{40}N_2O_5$, calcd (M^+): 568.29; found (M+1): 569.01.

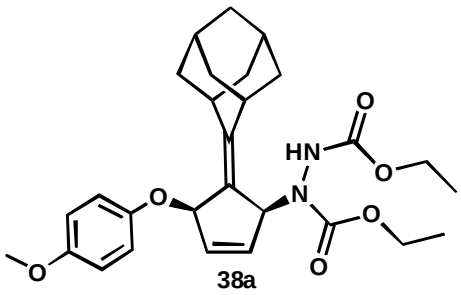
Diethyl 1-(5-adamantalylidene)-4-(4-methoxyphenoxy)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 38a

Following the general experimental procedure, bicyclic hydrazine **37a** (112 mg, 0.30 mmol), 4-methoxy phenol **35a** (25 mg, 0.20 mmol), dppf (11 mg, 10 mol%), and $Pd(PPh_3)_4$ (12 mg, 5 mol%) and K_2CO_3 (28 mg, 0.20 mmol), in 4 mL of dry THF at r.t. for 1.5 h gave the product **38a** as light green viscous liquid in 76% (76 mg) yield.

R_f : 0.54 (6:4 Hexane/ethyl acetate).

IR (KBr)ν_{max}: 3306, 3054, 2909, 2856, 1753, 1707, 1504, 1412, 1302, 1225, 1063, 955, 756 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88-6.76 (m, 4H), 6.57 (s, 1H), 6.25-6.16 (m, 2H), 5.87 (m, 1H), 5.38 (m, 1H), 4.21-4.19 (m, 2H), 4.07-



38a

4.06 (m, 2H), 3.77 (s, 3H), 2.81-2.77 (m, 2H), 1.95-1.92 (m, 12H), 1.27-1.25 (m, 6H).

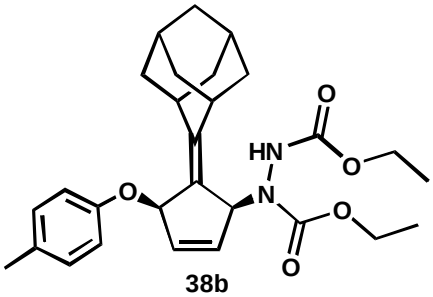
^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 155.8, 153.7, 135.1, 133.3, 130.1, 129.9, 121.9, 115.8, 77.7, 62.4, 61.7, 55.8, 40.2, 39.5, 38.5, 38.3, 36.8, 35.3, 34.8, 28.0, 14.7, 14.3.

MS (FAB): for $C_{28}H_{36}N_2O_6$, Calcd, M^+: 496.26; Found: 496.32.

Diethyl 1-(5-adamantalylidene)-4-(p-tolyloxy)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 38b

Following the general experimental procedure, bicyclic hydrazine **37a** (127 mg, 0.34 mmol), *p*-cresol **35b** (25 mg, 0.23 mmol), dppf (11 mg, 10 mol%), and $Pd(PPh_3)_4$ (12 mg, 5 mol%) and K_2CO_3 (32 mg, 0.23 mmol), in 4 mL of dry THF at r.t. for 1.5 h gave the product **38b** as light green viscous liquid in 73% (81 mg) yield.

R_f : 0.52 (6:4 Hexane/ethyl acetate).



38b

IR (KBr)ν_{max}: 3308, 3057, 2916, 2850, 1758, 1714, 1502, 1414, 1302, 1225, 1063, 968, 750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (d, 2H, *J* = 8.5 Hz), 6.83 (d, 2H, *J* = 8.5 Hz), 6.54 (s, 1H), 6.27-6.26 (m, 1H), 6.17-6.16 (m, 1H), 5.88 (m, 1H), 5.44 (s, 1H), 4.26-4.18 (m, 2H), 4.05-4.04 (m, 2H), 2.80-2.74 (m, 2H), 2.29 (s, 3H), 1.97-1.82 (m, 12H), 1.60-1.26 (m, 4H), 1.13-1.11 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 155.8, 153.7, 135.1, 133.1, 130.0, 129.9, 121.9, 115.8, 77.6, 62.4, 61.7, 61.3, 40.2, 39.5, 38.5, 38.3,

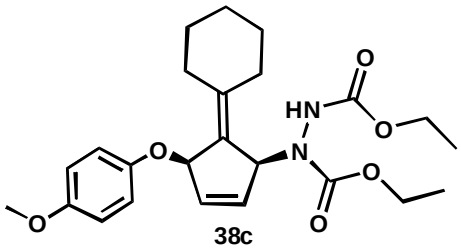
36.8, 35.3, 34.8, 28.0, 20.5, 14.7, 14.3.

MS (FAB) for $C_{28}H_{36}N_2O_5$, calcd (M^+): 480.26; found: 480.32.

Diethyl 1-(5-cyclohexylidene-4-(4-methoxyphenoxy)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 38c

Following the general experimental procedure, bicyclic hydrazine **37b** (109 mg, 0.30 mmol), 4-methoxy phenol **35a** (25 mg, 0.20 mmol), dppf (11 mg, 10 mol%), and $Pd(PPh_3)_4$ (12 mg, 5 mol%) and K_2CO_3 (28 mg, 0.20 mmol), in 4 mL of dry THF at r.t. for 1.5 h gave the product **38c** as light yellow viscous liquid in 78% (70 mg) yield.

R_f : 0.72 (6:4 Hexane/ethyl acetate).



38c

IR (KBr)ν_{max}: 3308, 3057, 2916, 2850, 1758, 1714, 1502, 1414, 1302, 1225, 1063, 968, 750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.87-6.68 (m, 4H), 6.41 (s, 1H), 6.14-6.10 (m, 2H), 5.77-5.71 (m, 1H), 5.29 (s, 1H), 4.17-4.15 (m, 2H), 4.02 (m, 2H), 3.70 (s, 3H), 2.16 (m, 4H), 1.56-1.53 (m, 6H), 1.21-1.09 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.0, 155.7, 153.4, 132.8, 132.6, 127.1, 125.1, 124.8, 116.0, 64.9, 62.8, 61.8, 60.4, 55.6, 26.0, 25.9, 22.6, 22.2, 21.0, 14.6, 14.2.

MS (FAB): for $C_{24}H_{32}N_2O_6$, Calcd, M^+: 444.23; Found (M+1): 445.03.

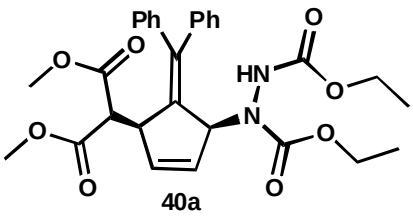
General Experimental Procedure: $[Pd(allyl)Cl]_2$ (5 mol%), 1,1'-bis-(diphenylphosphino)-ferrocene (10 mol%) and NaH (1.0 equiv.) were taken in a Schlenk tube, placed under vacuum for 15min. Freshly distilled THF (2 mL) was degassed and then added to the mixture at room temperature. The solution was stirred for 15 min. Active methylene compound (1.0 equiv.) and bicyclic

hydrazine (1.5 equiv.) dissolved in THF (2 mL) were added and was stirred at room temperature until TLC analysis indicated full conversion. The solvent was removed under reduced pressure and the residue was subjected to chromatography [silica gel (100–200 mesh), EtOAc–hexane, 40:60] to afford the substituted alkylidene cyclopentene in good yields.

Diethyl 1-(4-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-5-(diphenylmethylene)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 40a

Following the general experimental procedure, bicyclic hydrazine **34a** (113 mg, 0.28 mmol), dimethyl malonate **39a** (25 mg, 0.19 mmol), dppf (6 mg, 10 mol%), $[Pd(allyl)Cl]_2$ (4 mg, 5 mol%) and NaH (5 mg, 1.0 equiv.), in 4 mL of dry THF at r.t. for 1.5 h gave the product **40a** as a white solid in 93% (94 mg) yield.

Mp 122-124 °C. R_f : 0.52 (6:4 Hexane/ethyl acetate).



40a

IR (KBr)ν_{max}: 3317, 3049, 2981, 2940, 2900, 1730, 1720, 1601 1489, 1370, 1216, 1061, 750, 705 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.20 (m, 10H), 6.15-6.10 (m, 1H), 5.90 (s, 1H), 5.78 (m, 1H), 4.46 (m, 1H), 4.18-4.10 (m, 4H), 3.67 (s, 6H), 3.28 (m, 1H), 1.26-1.10 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 168.4, 156.5, 156.0, 141.0, 135.1, 134.8, 128.6, 128.1, 127.6, 127.4, 127.0, 126.7, 63.0, 61.7, 61.4, 53.4, 45.2, 28.3, 14.7, 14.5.

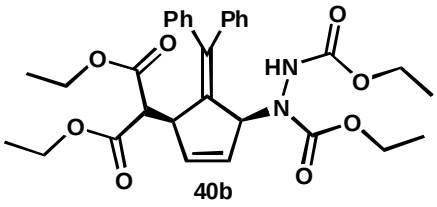
MS (FAB): for $C_{29}H_{32}N_2O_8$, Calcd, M^+: 536.22; Found: 536.30.

Diethyl 1-(4-(1,3-diethoxy-1,3-dioxopropan-2-yl)-5-(diphenylmethylene)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 40b

Following the general experimental procedure, bicyclic hydrazine **34a** (97 mg, 0.24 mmol), diethyl malonate **39b** (25 mg, 0.16 mmol), dppf (6 mg, 10

mol%), $[Pd(allyl)Cl]_2$ (3 mg, 5 mol%) and NaH (4 mg, 1.0 equiv.), in 4 mL of dry THF at r.t. for 1.5 h gave the product **40b** as a white solid in 86% (78 mg) yield.

R_f : 0.50 (6:4 Hexane/ethyl acetate).



40b

IR (KBr)ν_{max}: 3324, 3046, 2975, 2936, 2910, 1730, 1722, 1584, 1493, 1368, 1223, 1061, 760, 705 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.13 (m, 10H), 6.11 (m, 1H), 5.89 (s, 1H), 5.77 (m, 1H), 4.45-4.40 (m, 1H), 4.18-4.10 (m, 4H), 3.93-3.89 (m, 2H), 3.74 (m, 2H), 3.28-3.22 (m, 1H), 1.26-1.19 (m, 6H), 1.05-0.96 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 168.1, 156.4, 154.2, 144.5, 143.8, 142.0, 141.8, 141.3, 141.1, 135.4, 135.1, 135.0, 128.6, 127.0, 62.4, 61.7, 61.3, 53.1, 29.8, 14.5, 14.1.

MS (FAB): for $C_{31}H_{36}N_2O_8$, Calcd, M^+: 564.25; Found: 564.93.

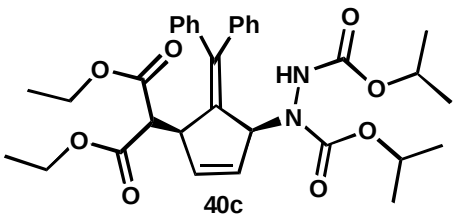
Diisopropyl 1-(4-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-5-(diphenylmethylene)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 40c

Following the general experimental procedure, bicyclic hydrazine **34b** (104 mg, 0.24 mmol), diethyl malonate **39b** (25 mg, 0.16 mmol), dppf (6 mg, 10 mol%), $[Pd(allyl)Cl]_2$ (3 mg, 5 mol%) and NaH (4 mg, 1.0 equiv.), in 4 mL of dry THF at r.t. for 1.5 h gave the product **40c** as a white solid in 76% (70 mg) yield.

Mp 122-124 °C. R_f : 0.63 (6:4 Hexane/ethyl acetate).

IR (KBr)ν_{max}: 3312, 3055, 2981, 2936, 2908, 1726, 1715, 1597, 1489, 1371, 1223, 1061, 754, 705 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20-7.18 (m, 10H), 6.14-6.08 (m, 1H), 5.89-5.88 (m, 1H),



40c

5.80-5.70 (m, 1H), 4.89-4.88 (m, 1H), 4.54-4.40 (m, 2H), 4.13 (m, 2H), 3.94 (m, 2H), 3.29-3.22 (m, 1H), 1.21-0.83 (m, 18H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 167.7, 155.5, 153.6, 141.8, 141.2, 135.1, 134.7, 130.4, 128.7, 128.5, 128.3, 127.9, 127.2, 126.9, 126.6, 69.5, 69.3, 63.9, 61.1, 60.9, 45.4, 26.9, 22.1, 21.9, 14.0, 13.7.

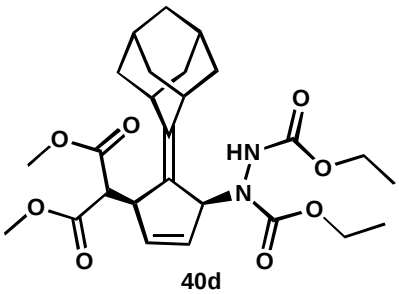
MS (FAB): for $C_{33}H_{40}N_2O_8$, Calcd, M^+: 592.28; Found: 592.93

Diethyl 1-(4-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-5-(adamantalylidene)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 40d

Following the general experimental procedure, bicyclic hydrazine **37a** (108 mg, 0.29 mmol), dimethyl malonate **39a** (25 mg, 0.19 mmol), dppf (4 mg, 10 mol%), $[Pd(allyl)Cl]_2$ (6 mg, 5 mol%) and NaH (5 mg, 1.0 equiv.), in 4 mL of dry THF at r.t. for 1.5 h gave the product **40d** as viscous liquid in 79% (76 mg) yield. R_f : 0.50 (6:4 Hexane/ethyl acetate).

IR (KBr)ν_{max}: 3308, 2980, 2907, 2849, 1728, 1711, 1694, 1504, 1412, 1306, 1219, 1061, 959, 812 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.05-6.01 (m, 1H), 5.92 (s, 1H), 5.79-5.76 (m, 1H), 4.19-4.16 (m, 4H), 3.92 (d, 1H, *J* = 9.0 Hz), 3.75 (s, 6H), 3.42-3.40 (m, 1H), 2.79-2.75 (m, 1H), 2.54-2.50 (m, 1H), 1.92-1.80 (m, 12H), 1.25 (s, 6H).



40d

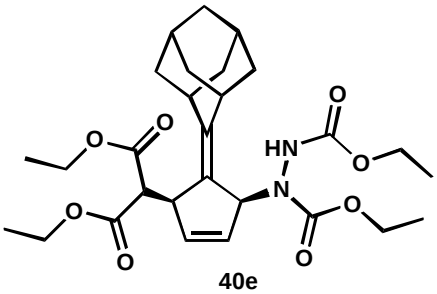
^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 168.7, 156.0, 155.2, 150.8, 137.1, 130.5, 121.8, 62.4, 61.7, 57.4, 52.4, 44.9, 39.2, 38.8, 38.6, 36.7, 35.0, 34.5, 27.7, 14.6, 14.5.

MS (FAB): for $C_{26}H_{36}N_2O_8$, Calcd, M^+: 504.25; Found (M+1): 505.05.

Diethyl 1-(4-(1,3-diethoxy-1,3-dioxopropan-2-yl)-5-(adamantalylidene)cyclopent-2-enyl)hydrazine-1,2-dicarboxylate 40e

Following the general experimental procedure, bicyclic hydrazine **37a** (89 mg, 0.24 mmol), diethyl malonate **39b** (25 mg, 0.16 mmol), dppf (6 mg, 10 mol%), $[Pd(allyl)Cl]_2$ (3 mg, 5 mol%) and NaH (4 mg, 1.0 equiv.), in 4 mL of dry THF at r.t. for 1.5 h gave the product **40e** as a light brown viscous liquid in 70% (60 mg) yield.

R_f : 0.63 (6:4 Hexane/ethyl acetate).



40e

IR (KBr)ν_{max}: 3311, 2975, 2910, 2849, 1730, 1715, 1698, 1510, 1414, 1306, 1225, 1064, 950, 754 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.07-6.04 (m, 1H), 5.91 (s, 1H), 5.79-5.76 (m, 1H), 4.32-4.14 (m, 8H), 3.93-3.91 (m, 1H), 3.47-3.35 (m, 1H), 2.80-2.77 (m, 1H), 2.57-2.54 (m, 1H), 1.94-1.62 (m, 12H), 1.27-1.26 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 168.4, 155.9, 155.2, 150.7, 137.3, 130.2, 121.9, 62.8, 62.3, 61.6, 61.3, 57.8, 44.6, 39.2, 39.0, 38.7, 36.7, 34.9, 34.5, 27.7, 14.5, 14.0

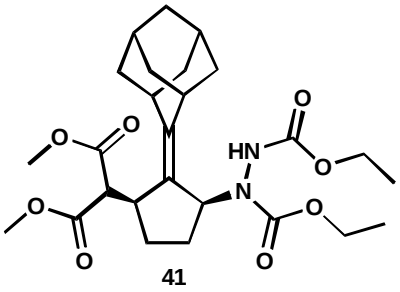
MS (FAB): for $C_{28}H_{40}N_2O_8$, Calcd, M^+: 532.28; Found: 533.09.

Diethyl 1-(3-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-2-(adamentylidene)cyclopentyl)hydrazine-1,2-dicarboxylate 41

The compound **40d** (300.0 mg, 0.59 mmol) was dissolved in anhydrous ethyl acetate. Pd/C (10% on carbon) (catalytic) was added and the reaction mixture was stirred under 1 atm pressure of H_2 at room temperature for 6 h. After the completion of the reaction as indicated by TLC, the reaction mixture was filtered through a pad of celite. The solvent was removed under reduced pressure and the

residue was subjected to chromatography [silica gel (100–200 mesh), EtOAc–hexane, 30:70] to afford **41** as colorless viscous liquid (298.6 mg, 100%).

Mp 136 °C . R_f 0. 51 (6:4 Hexane/ethyl acetate).



41

IR (KBr)ν_{max}: 3312, 2978, 2907, 2849, 1732, 1697, 1616, 1416, 1384, 1220, 1126, 1061, 925, 758 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.25-4.11 (m, 5H), 3.74 (s, 6H), 3.50-3.40 (m, 2H), 2.68-2.63 (m, 2H), 2.52-2.50 (m, 1H), 2.32-2.26 (m, 1H), 2.04 (m, 1H), 1.81-1.56 (m, 14H), 1.30-1.23 (m, 6H).

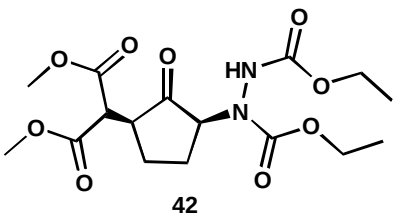
^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 168.4, 156.3, 155.2, 150.6, 128.3, 62.3, 61.8, 61.1, 53.6, 52.4, 40.8, 39.2, 38.4, 36.7, 35.2, 33.6, 29.6, 28.9, 22.5, 14.4, 14.2.

MS (FAB): for $C_{26}H_{38}N_2O_8$, Calcd, M^+: 506.26; Found (M+1): 506.81.

Diethyl 1-(3-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-2-oxocyclopentyl)hydrazine-1,2-dicarboxylate 42

Compound **41** (160.0 mg, 0.32 mmol) was dissolved in a 1:1 mixture of CH_3CN and CCl_4 (10 mL). Sodium periodate (409.0 mg, 1.92 mmol) was added to the solution and the mixture was stirred. A solution of ruthenium trichloride (7.8 mg, 0.03 mmol) in water (5 mL) was added in one portion, and vigorous stirring was continued for 5 h. The reaction mixture was diluted with water (10 mL) and was extracted with CH_2Cl_2 (3x20 mL) and filtered through a pad of celite. The filtrate was concentrated under reduced pressure and the residue was subjected to chromatography on a silica gel (100–200 mesh) column using ethyl acetate/hexanes mixture as eluent afforded **42** as colorless viscous liquid (92.0 mg, 74%).

R_f 0. 65 (6:4 Hexane/ethyl acetate).



42

IR (KBr)ν_{max}: 3308, 2984, 2957, 1744, 1713, 1506, 1435, 1415, 1383, 1228, 1161, 1059, 926, 762cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.21-4.10 (m, 4H), 3.93-3.92 (m, 1H), 3.77 (s, 6H), 2.73 (m, 1H), 2.45 (bs, 1H), 2.22-2.05 (m, 2H), 1.86-1.85 (m, 2H), 1.28-1.26 (m, 6H).

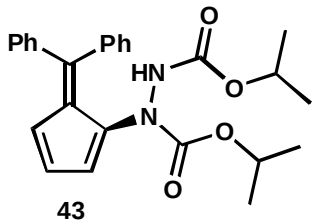
^{13}C NMR (125 MHz, $CDCl_3$): δ 211.7, 168.5, 168.0, 156.3, 155.4, 62.9, 62.3, 60.4, 52.8, 29.7, 24.3, 22.0, 14.4, 14.2.

MS (FAB): for $C_{16}H_{24}N_2O_9$, Calcd, M^+: 388.15; Found: 388.17.

Diisopropyl 1-(5-(diphenylmethylene)cyclopenta-1,3-dienyl)hydrazine-1,2-dicarboxylate 43

Compound **36f** (53.0 mg, 0.10 mmol) and chloranil (73.8 mg, 0.3 mmol) were dissolved in xylene and heated at 110 ^{o}C for 3 h. The solvent was removed under reduced pressure and the residue was subjected to chromatography [silica gel (60–120 mesh)], EtOAc–hexane, 20:80] to afford the product **43** in good yield (30.0 mg, 74%).

R_f 0. 39 (6:4 Hexane/ethyl acetate).



43

IR (KBr)ν_{max}: 3312, 3055, 2981, 2936, 2908, 1726, 1715, 1597, 1489, 1371, 1223, 1061, 754, 705 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.24 (m, 10H), 6.80-6.66 (m, 1H), 6.40-6.39 (m, 1H), 6.14-6.12 (m, 1H), 4.90-4.83 (m, 2H), 1.27-1.12 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 154.3, 141.5, 140.5, 138.0, 132.4, 131.8, 130.3, 129.1, 128.4, 127.8, 125.0, 124.2, 70.0, 69.7, 22.2, 22.0.

MS (FAB) for $C_{26}H_{28}N_2O_4$, calcd (M^+): 432.20; found: 432.86.

2.7. References

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Chapter 3

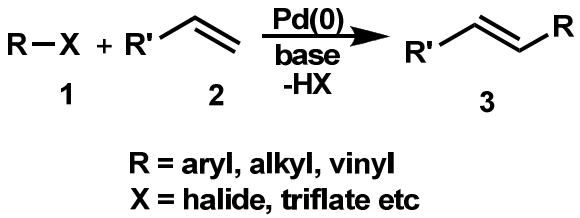
Palladium Catalyzed Ring Opening of Fulvene Derived Azabicyclic Olefins with Aryl Halides: An Efficient Synthesis of Functionalized Cyclopentenes

3.1. Introduction

Transition-metal-catalyzed reactions provide efficient and powerful methods for the synthesis of carbo- and heterocyclic molecules[1]and have played an enormously decisive and important role in modern organic synthesis. It enabled the synthetic organic chemist to construct increasingly complex carbon frame works and thus, facilitated the syntheses of a myriad of organic compounds. Among the transition metals, palladium is arguably the most versatile and ubiquitous metal in modern organic synthesis.[2] Palladium-mediated processes have become essential tools, spanning countless applications in the syntheses of natural products, polymers, agrochemicals, and pharmaceuticals. There are a number of well-known name reactions that feature this metal, including the Heck, Suzuki, Stille, and Buchwald-Hartwig cross-couplings; the Wacker process[3] and the Tsuji-Trost allylation.[4] In addition, Pd also enables hydrogenation; hydrogenolysis; carbonylation; the formation of C–C, C–O, C–N, and C–S bonds; cycloisomerization; and even pericyclic reactions.[4] This chapter deals with the palladium catalyzed ring opening of pentafulvene derived azabicyclic olefins with aryl halides leading to the stereoselective synthesis of substituted cyclopentenes.

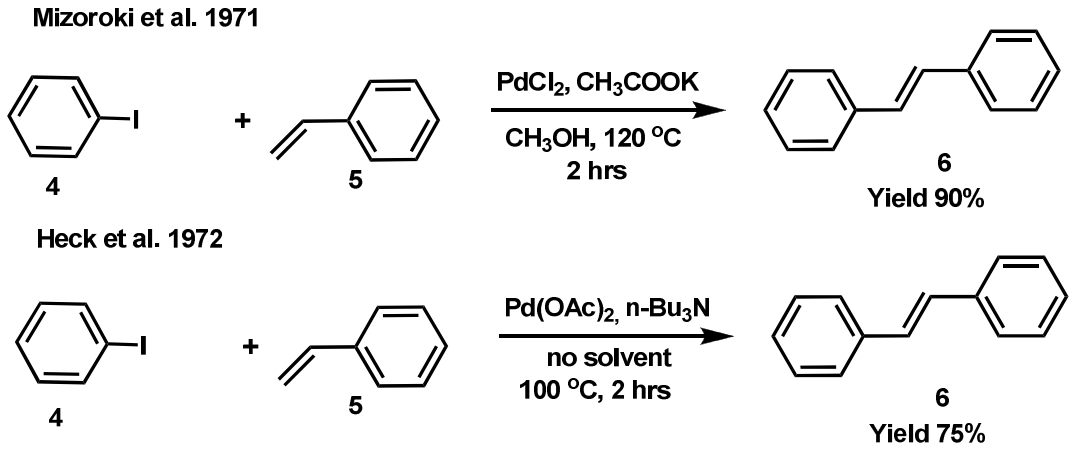
3.2. Heck Coupling or Mizoroki Heck reaction

The Heck reaction (Scheme 3.1) (also called the Mizoroki-Heck reaction) is the palladium-catalyzed C-C coupling between aryl halides or vinyl halides and activated alkenes in the presence of a base to form a substituted alkene.



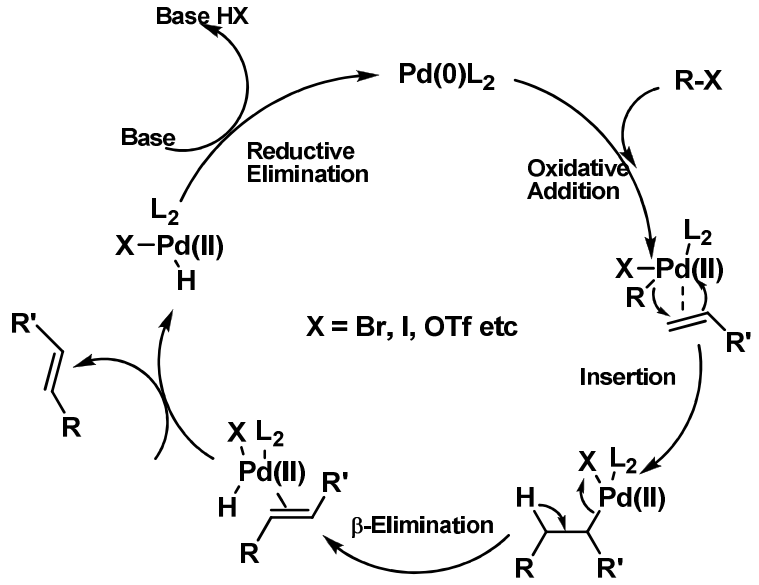
Scheme 3.1

The first examples of this reaction as we would recognize it today were reported independently by Mizoroki (1971)[5] and, in an improved form, by Heck (1972)[6] (Scheme 3.2).



Scheme 3.2

The Heck reaction now stands as a remarkably robust and efficient method for carbon–carbon bond formation, particularly in the generation of tertiary and quaternary stereocenters and intramolecular ring formation, and remains a flourishing area of research. The mechanism of the Heck reaction is shown in Scheme 3.3.



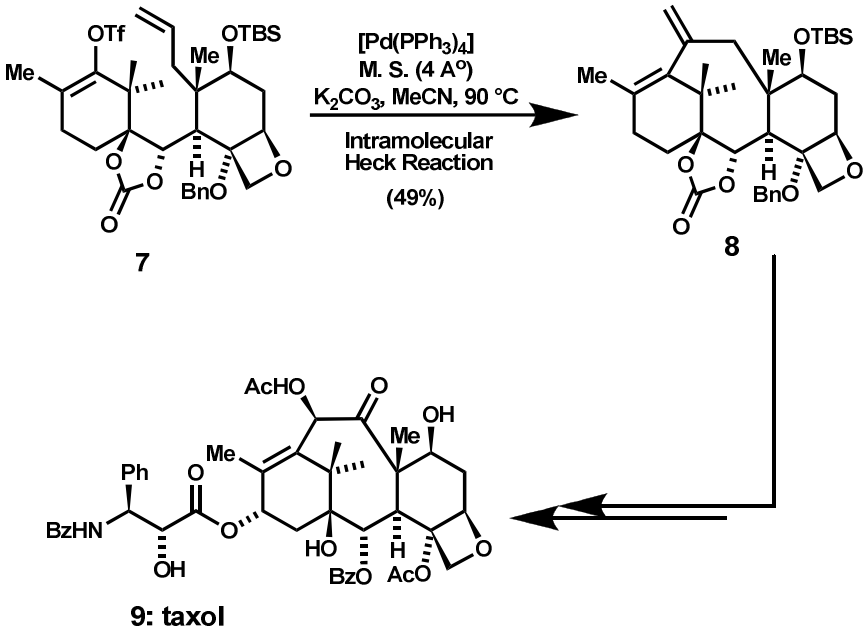
Scheme 3.3

The reaction begins when the active Pd(0) catalyst reacts with the organo halide RX in a so-called oxidative addition. In this reaction the oxidation state of palladium formally changes from Pd(0) to Pd(II) with the formation of an organopalladium compound RPdX. In this process a new palladium-carbon bond is formed. In the next step the olefin co-ordinates to palladium, and the olefin and the R group are now assembled on the metal and can react with one another. In the next step the R group on palladium migrates to one of the carbons of the co-ordinated olefin and palladium will shift to the other carbon of the olefin. This process is called a migratory insertion and generates the carbon-carbon bond. Finally, the release of the organic group occurs *via* a β-hydride elimination which forms the new olefin in which the R group from the organohalide RX has replaced a hydrogen atom on the substrate olefin. In this step a short-lived HPdX species is formed, which loses HX to give Pd(0). The Pd(0) species formed is now ready to enter another catalytic cycle.

A great advantage of the Heck reaction is the wide substrate scope ranging from simple olefin to activated alkenes. It has been used for the syntheses of number of different natural products and biologically active compounds.

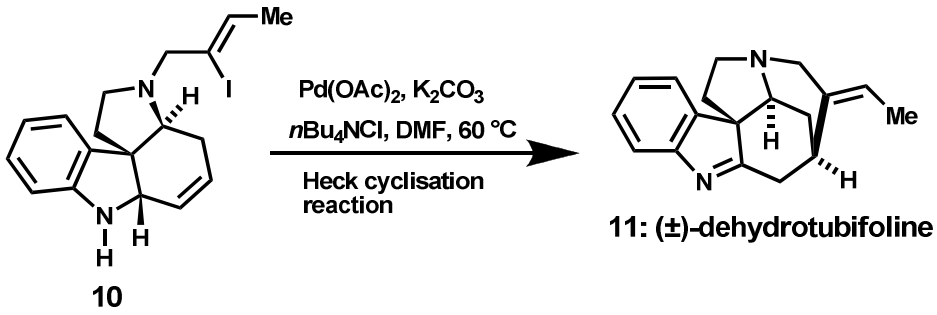
3.3. Heck reaction in total synthesis

The intermolecular and intramolecular variants of Heck reaction has been widely applied in more than 100 different syntheses of natural products and biologically active compounds. The first example for the applications of intramolecular Heck reaction was in the total synthesis of the natural product taxol by Danishefsky and co-workers (Scheme 3.4).[7] The intramolecular cyclization of the cyclohexene moiety of triflate **7** onto the pendant terminal alkene was brought about by treatment with $[Pd(PPh_3)_4]$ and K_2CO_3 in refluxing MeCN, thus effecting the closure of the central eight-membered ring to generate the tetracyclic product **9** in 49% yield.



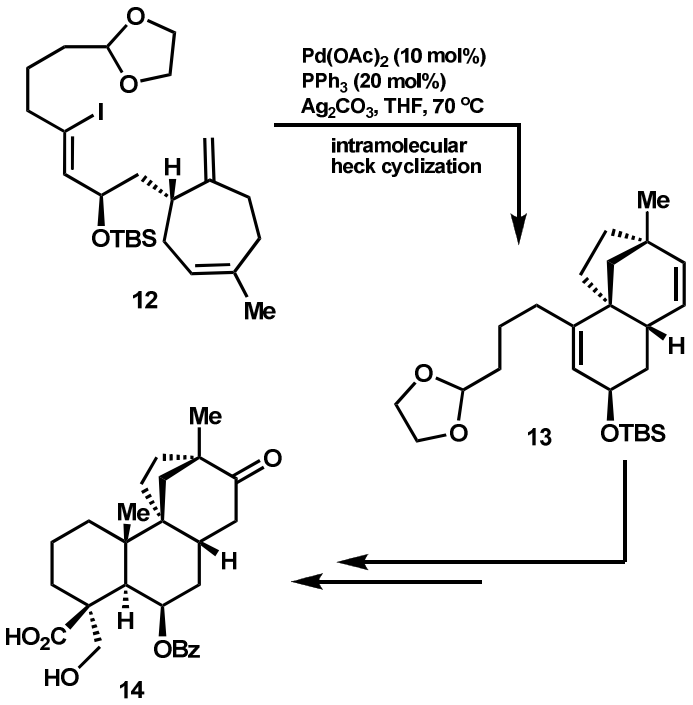
Scheme 3.4

Rawal and coworkers employed the Heck reaction for total syntheses of the alkaloid dehydrotubifoline, **11**. In this instance, the palladium-catalyzed process was used to forge the final carbon–carbon bond and cast the final ring of the polycyclic structure of the target in 79% yield Scheme 3.5.[8]



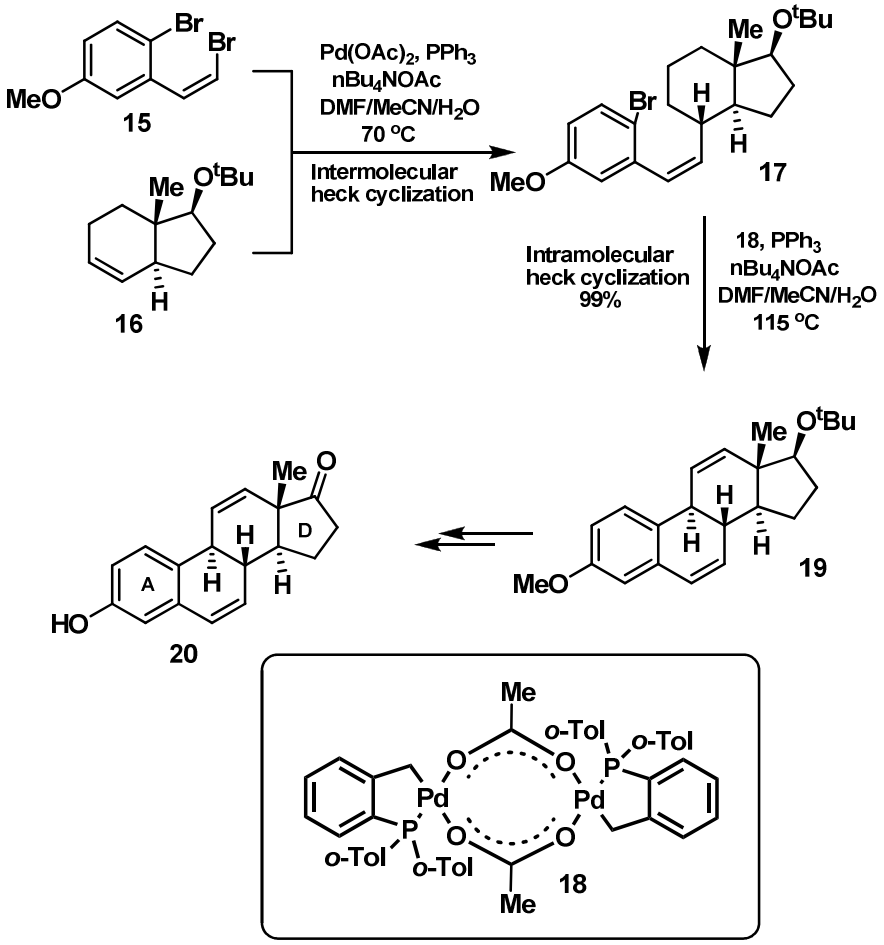
Scheme 3.5

Overman and co-workers have successfully utilized the palladium-catalyzed reactions in the synthesis of the scopadulcic acid family of diterpenes. The intramolecular Heck cyclization of substituted cycloheptene **12** was triggered by the addition of $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), and Ag_2CO_3 to a refluxing solution of iodide **12** in THF. This intermediate could then be elaborated in a number of steps to complete the total synthesis of scopadulcic acid B, **14** (Scheme 3.6).[9]



Scheme 3.6

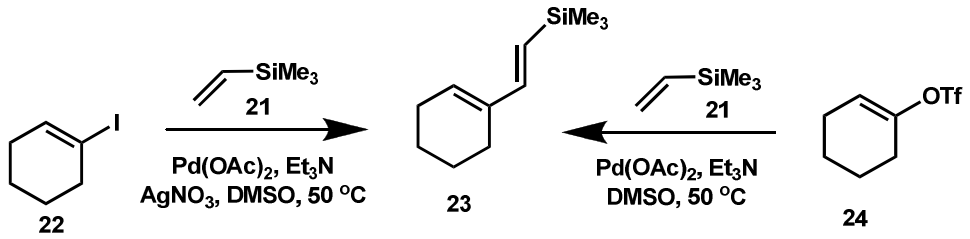
Steroid research can be regarded as one of the triumphs of 20th century science. An alternative approach to the steroid skeleton, based on palladium-catalyzed Heck reactions, was recently introduced by Tietze and co-workers by an elegant, enantioselective total synthesis of the female sex hormone estrone (Scheme 3.7). Specifically, these researchers discovered that treatment of **15** and **16** with catalytic amounts of $Pd(OAc)_2$ and PPh_3 in the presence of nBu$_4$NOAc in a mixed DMF/MeCN/H_2O solvent system at 70 ^oC led to the selective formation of the intermolecular Heck reaction product **17.** The Heck reaction product **17** on treatment with a catalytic amount of the novel palladacycle **18** in the same solvent system, but at a slightly higher temperature (115 ^oC), led to the generation of the estrone core structure **20** in quantitative yield.[10]



Scheme 3.7

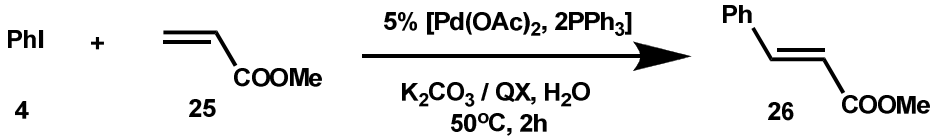
3.4. Reactivity of Aryl halides towards Alkenes

The Pd -catalysed arylation or vinylation of alkenes, generally referred to as the Heck reaction, should in principle serve as an attractive alternative preparative route to some of the important dienes with regioselectivity, and the concomitant desilylation reaction can be suppressed. In 1988, Hallberg *et al.* reported the synthesis of a series of 1-trimethylsilyl-1,3-dienes by the palladium-catalyzed coupling of trimethylvinylsilane, with vinyl halides or triflates in presence of silver salts (Scheme 3.8).[11]



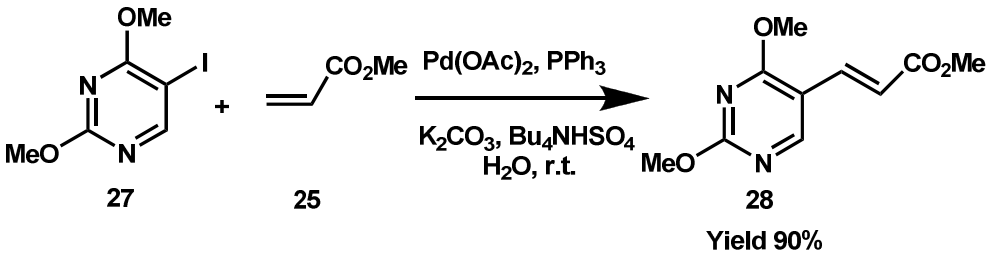
Scheme 3.8

Palladium-catalyzed carbomethoxyvinylation of iodobenzene in water in the presence of a base and a phase-transfer catalyst (PTC) provided *trans*-methyl cinnamate in 98% yield. The presence of water determines the efficiency of quaternary ammonium salt (QX) in palladium-catalysed vinylation of organic halides using an alkali metal carbonate as the base, in which QX could be a chloride, a bromide or a hydrogensulfate. The [Pd/M_2CO_3/QX] catalyst system was even used for performing the reactions in water, without organic solvent (Scheme 3.9).[12]



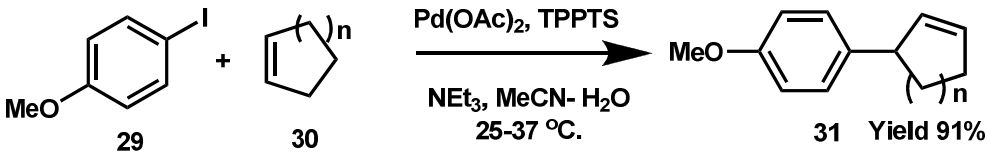
Scheme 3.9

In 1997, Walker and coworkers reported a heterogenous Heck-reaction of methyl acrylate **25** with 5-iodo-2,4-dimethoxypyrimidine **27** under aqueous phase-transfer conditions at room temperature (Scheme 3.10).[13]



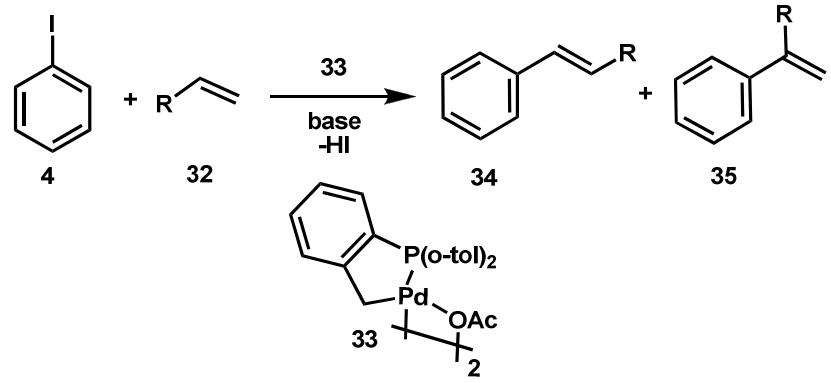
Scheme 3.10

Heck reactions have been conducted in homogeneous aqueous systems in the presence of water soluble phosphines TPPMS and TPPTS. Reactions of iodoarenes and iodoalkenes in aqueous MeCN could be conducted under very mild conditions at temperatures not exceeding 40°C [$Pd(OAc)_2$ (2.5 mol %), 2 TPPTS, NEt_3, MeCN-H_2O (15:1), 25-40 °C]. Notable is the ease and high regioselectivity of reaction with cycloalkenes, giving exclusively 3-arylcycloalkenes **31** (Scheme 3.11).[14]



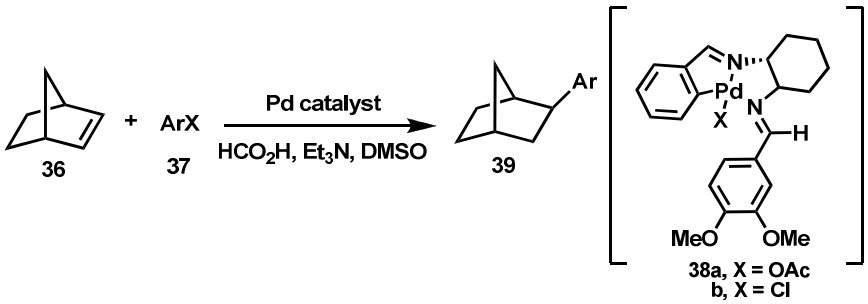
Scheme 3.11

In 1995, Herrmann and co-workers reported the highest activity of Pd complex **33** and related species in the Heck coupling of aryl halides with simple alkenes (Scheme 3.12).[15]



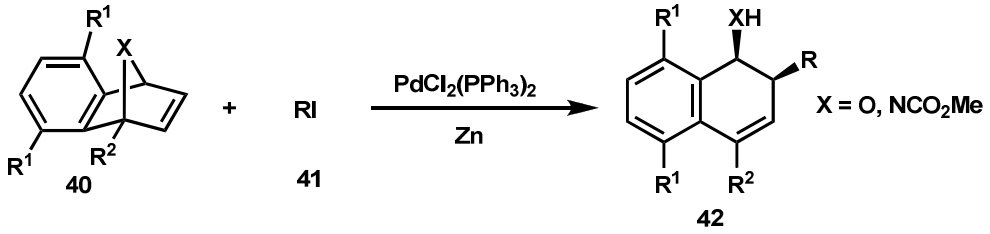
Scheme 3.12

Recently Nevarro and co-workers synthesised the chiral *N*,*N*,*C*-complexes **38**, based on (1*R*,2*R*)-1,2-diaminocyclohexane and applied them to Heck-type coupling reactions (Scheme 3.13).[16] Attempts to apply these catalysts to the asymmetric hydroarylation of norbornene **36** (Scheme 3.13) showed no enantioselectivity.



Scheme 3.13

The reaction of organic halides with 7-heteroatom benzonorbornadiene derivatives in the presence of $Pd(PPh_3)_2Cl_2$ and zinc powder yielded *cis*-1,2-dihydro-1-naphthol or methyl N-(*cis*-1,2-dihydro-l-naphthyl) carbamate derivatives stereoselectively (Scheme 3.14).[17]

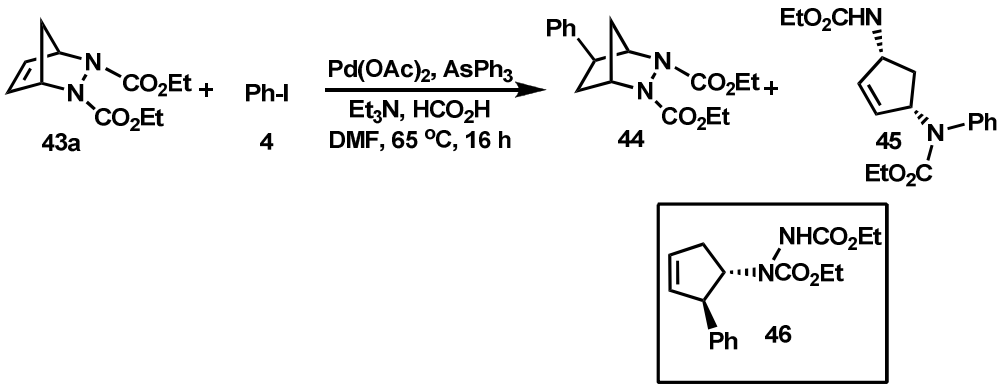


Scheme 3.14

3.5. Background to the present work

Kaufmann and co-workers reported the first palladium catalyzed hydroarylation of the N,N'-diethoxycarbonyl-substituted derivative with triethyl amine as a base. It gave the hydroarylated product **44** with N-arylated 3,5-disubstituted cyclopentene **45** as a side product (Scheme 3.15).[18] The proposed structure of **45** appeared to be incorrect and it is probably the fragmentation

product of general structure **46**, as proposed by the same authors in a subsequent patent.[19]



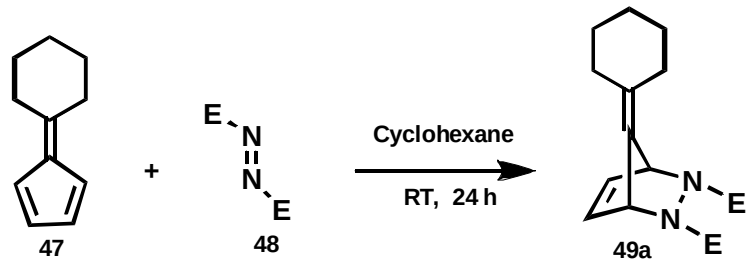
Scheme 3.15

Further investigations from the same group showed that sterically more hindered and more rigid tri- and tetracyclic substrates also afforded hydroarylated products along with 3,4-disubstituted cyclopentenes in minor amounts.[20]

We have recently developed the stereoselective synthesis of cyclopentene-annulated benzofuran and indole derivatives by the palladium catalyzed tandem ring opening and ring closing of cyclopentadiene derived azabicyclic alkenes with 2-iodophenol or 2-iodoaniline.[21] The reaction was effectively tuned towards the exclusive formation of either cyclopentannulated product or substituted cyclopentene. This was the first report on the exclusive formation of *trans*-3,4-disubtituted cyclopentenes by the palladium catalyzed ring opening of azabicyclic olefins with *ortho* functionalized aryl halides. Unfortunately it was general only for 2-iodoanilines and 2-iodophenols. The reaction was not working with other unsubstituted aryl halides and hetero aryl halides. This made us to investigate the reactivity of various aryl iodides with fulvene derived azabicyclic olefins by changing the reaction conditions which resulted in developing an exclusive synthesis of functionalized cyclopentenes.

3.6. Results and discussion

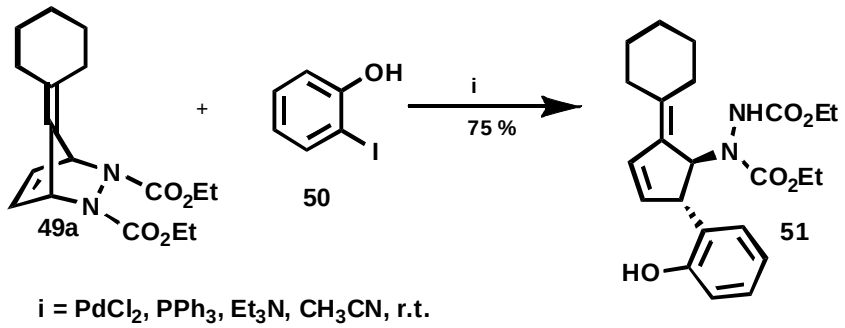
The starting materials for our investigations were prepared according to the literature procedures.[22] For example, the 2,3-diazabicyclo[2.2.1]hept-5-ene **49a** was synthesized by the Diels-Alder cycloaddition of pentafulvene **47** with dialkyl azodicarboxylate **48** (Scheme 3.16).



Scheme 3.16

3.6.1. Reactions of pentafulvene derived bicyclic hydazines with aryl halides

We initiated our experiments with the reaction of diethyl 7-cyclohexylidene 2,3-diazabicyclo[2.2.1]hept-5-ene-2,3 dicarboxylate **49a** with 2-iodophenol **50** in the presence of $PdCl_2/PPh_3/Et_3N$ in CH_3CN at 80 ^oC (Scheme 3.17). This experiment resulted in a sluggish reaction. Lowering the reaction temperature increased the yield of the reaction. The reaction at room temperature afforded substituted alkylidene cyclopentene **51** in 75% yield. The structure of the product was assigned with the help of various spectroscopic techniques**.**



Scheme 3.17

The structure of **51** was assigned based on spectral analysis and by comparison to the literature report. IR spectrum of **51** showed a strong absorption due to the carbonyls at 1740 and 1720 $cm.^{-1}$ In ^{1}H NMR spectrum of **51** (Figure 3.1), the olefinic protons at C-1 and C-2 resonated as multiplet at δ 6.35-6.25 ppm and δ 5.91 ppm. The multiplet at δ 5.09 ppm was assigned to the proton at C-4, while the proton at C-3, appeared at δ 4.41-4.32 ppm along with the four methylene protons of the carboethoxy group respectively. The aromatic protons were observed in the region δ 7.15-6.48 ppm.

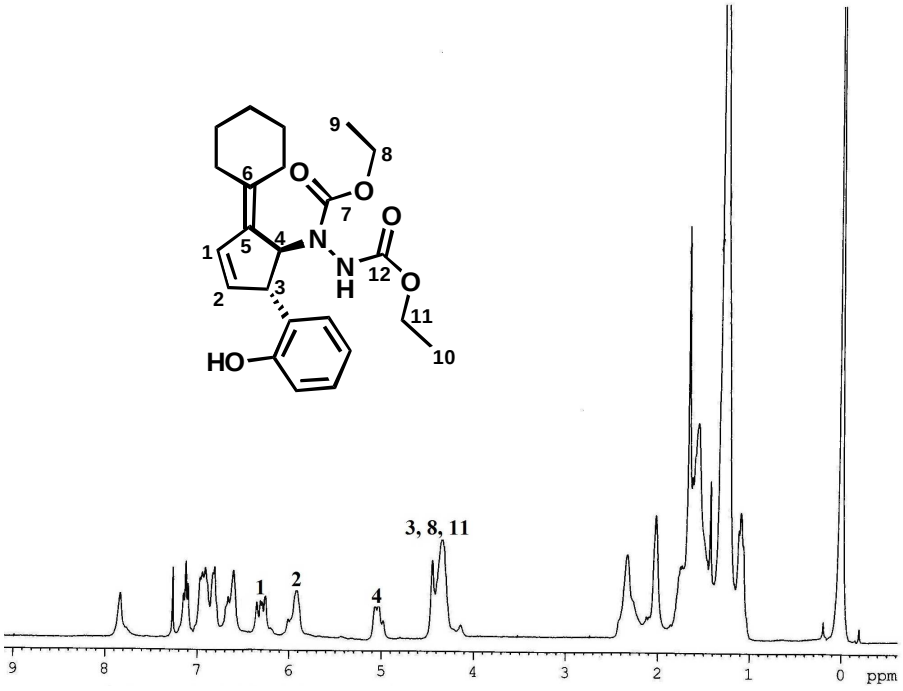


Figure 3.1. ^{1}H NMR spectrum of **51**

The ^{13}C NMR spectrum (Figure 3.2) of **51** positioned the characteristic carbonyl absorptions at δ 156.2 and 156.0 ppm. The carbons C-4 attached to nitrogen resonated at δ 60.4 ppm. High resolution mass spectral analysis also supported the structure assignment with the molecular ion peak at *m/z* 414.15.

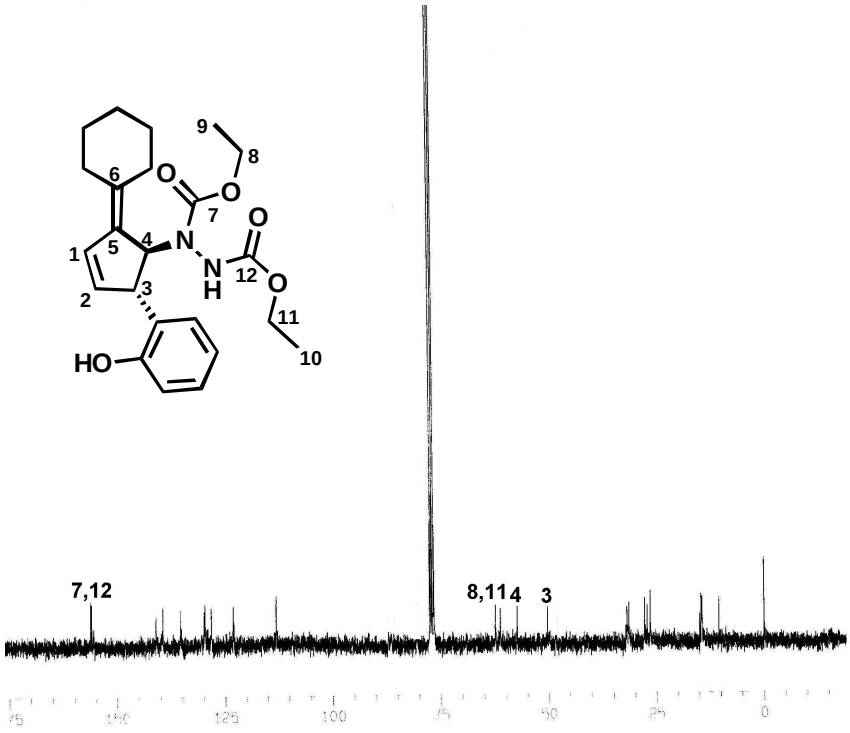
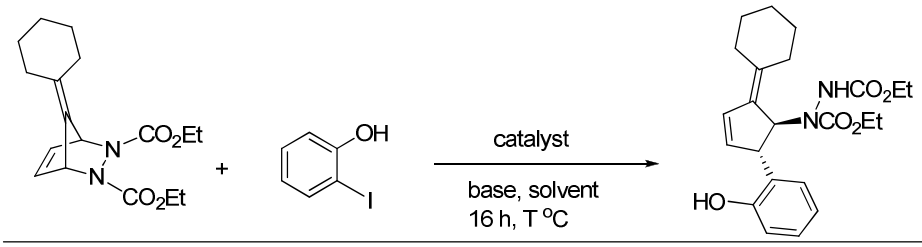


Figure 3.2. ^{13}C NMR spectrum of **51**

Detailed optimization studies (Table 3.1) were carried out with substrates **49a** and **50** to find out the best condition for the reaction. Different organic and inorganic bases were examined and Et_3N was found to be the best for the exclusive formation of alkylidene cyclopentene. The reactions with bases such as NaOAc and K_2CO_3 failed to afford the product (Table 1, entry 7-8). Other organic bases such as DIEA and DIPA could only effect the formation of the product in lower yields (Table 1, entry 5-6). Various catalysts such as $PdCl_2$, $[Pd(allyl)Cl]_2$, $Pd(PPh_3)_4$ were screened from which $PdCl_2$ gave the highest yield (Table 1, entry 4, 9-11). Among the different solvents examined, CH_3CN was found to be the best (Table 1, entry 4, 12-15). On the basis of these investigations, the optimal conditions for this reaction are as follows: 1:3 mixture of iodophenol/olefin with 10 mol% $PdCl_2$, 1.5 equiv. of Et_3N and 3 mL of CH_3CN for 16 h.



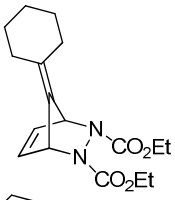
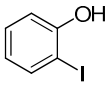
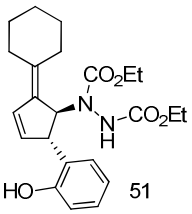
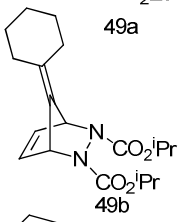
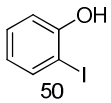
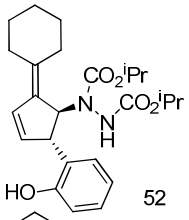
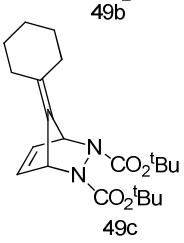
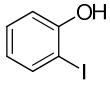
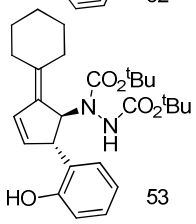
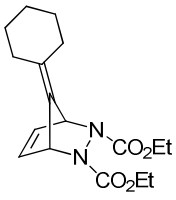
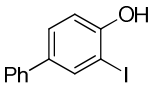
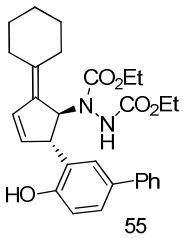
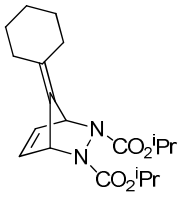
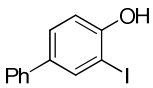
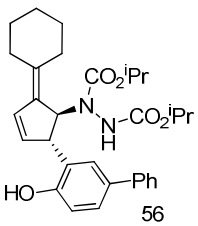
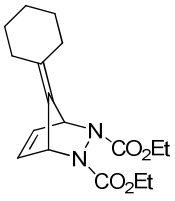
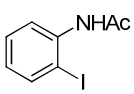
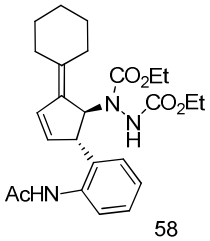
Entry	Catalyst/ Ligand	Solvent	Base	T (°C)	Yield (%)[a]
1	$PdCl_2/PPh_3$	CH_3CN	Et_3N	80	0
2	$PdCl_2/PPh_3$	CH_3CN	Et_3N	50	49
3	$PdCl_2/PPh_3$	CH_3CN	Et_3N	r.t.	75
4	$PdCl_2$	CH_3CN	Et_3N	r.t.	90
5	"	"	DIEA	"	63
6	"	"	DIPA	"	11
7	"	"	NaOAc	"	no reaction
8	"	"	K_2CO_3	"	no reaction
9	$Pd(OAc)_2$	"	Et_3N	"	16
10	$[Pd(allyl)Cl]_2$	"	"	"	trace
11	$Pd(PPh_3)_4$	"	"	"	no reaction
12	$PdCl_2$	DMF	Et_3N	"	72
13	$PdCl_2$	THF	"	"	trace
14	"	Toluene	"	"	9
15	"	Dioxane	"	"	10

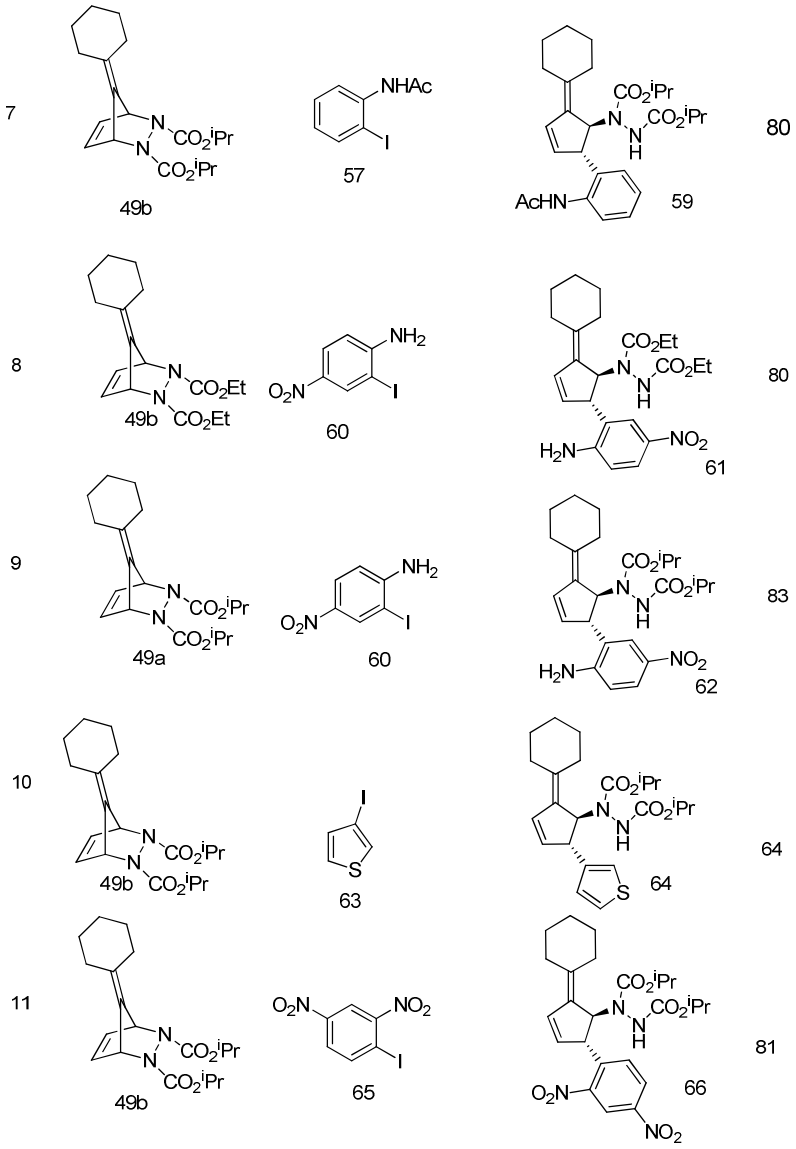
Reaction Conditions:alkene(3.0 equiv.), aryl halide (1.0 equiv.),catalyst (10 mol%), base (1.5 equiv.), solvent (3 mL),temp, 16h.a Isolated yield

To explore the scope and generality of the method, the reaction was repeated using different fulvene derived bicyclic hydrazine and aryl halides. The results of the investigations are summarized in table 3.2.

Table 3.2. Palladium catalyzed ring opening of fulvene derived bicyclic hydrazines with aryl halides.

Table 3.2. Palladium catalyzed ring opening of fulvene derived bicyclic hydrazines with aryl halides

Entry	Bicyclic olefin	Aryl halide	Product	Yield (%)[a]
1	 49a	 50	 51	90
2	 49b	 50	 52	86
3	 49c	 50	 53	78
4	 49a	 54	 55	91
5	 49b	 54	 56	86
6	 49a	 57	 58	96



Reaction Conditions:alkene (3.0 equiv.), aryl halide (1.0 equiv.), catalyst (10 mol%), base (1.5 equiv.), solvent (3 mL), temp, 16 h.[a] Isolated yield

The products were characterized by usual spectroscopic analysis which provided adequate support for the assigned structures. IR spectra of all the products presented a broad absorption band in the region 1750-1710 cm^{-1}, matching the carbonyl absorptions. In all the cases, ^{13}C NMR spectra spotted the carbonyl peaks in the region δ 150-156 ppm.

In the proton NMR spectrum of **52**, the methine protons of isopropyl moiety appeared as singlet at δ 4.91 and as multiplet at δ 4.85-4.80 ppm. In the ^{13}C NMR spectrum, the methine carbons appeared at δ 70.0 and 69.0 ppm and the carbon bearing hydrazine moiety was spotted at δ 61.9 ppm. In **53**, ^{1}H NMR spectrum located the methyl protons of the *tert*-butyl group as two distinct singlet at δ 1.49 ppm and δ 1.42 ppm. In the ^{13}C NMR spectrum, the two less intense peaks at δ 82.1 and 80.7 ppm corresponds to the quaternary carbons of the *tert*-butyl group and the carbon bearing phenyl substituent was discernible at δ 57.2 ppm. The ^{1}H NMR spectrum of **55** positioned the aromatic protons at δ 7.59 (m, 3H), 7.51-7.39 (m, 1H), 7.35-7.30 (m, 1H), 7.06-6.89 (m, 2H), 6.76-6.71 (m, 1H) ppm. The proton attached to the carbon bearing the phenyl ring appeared as multiplet δ 4.24-4.03 ppm along with the methylene protons of carboethoxy group. In the ^{13}C NMR spectrum, the methylene carbon was spotted at δ 62.5 and 61.3 ppm. The ^{1}H NMR spectrum of **56** located the methine protons as multiplets at δ 5.80 and δ 5.53-5.51 ppm and the corresponding carbon at δ 70.0 and 68.7 ppm in the ^{13}C NMR spectrum.

In **58** the CH_3-CO- singlet at δ 2.20 ppm and the proton on the carbon bearing hydrazine substituent at δ 5.00-4.95 ppm respectively. In the ^{13}C NMR spectrum, the carbon bearing the hydrazine group was spotted at δ 61.9 ppm. In **59** the methine protons of the isopropyl moiety and the proton on the carbon bearing hydrazine moiety resonated as multiplets δ 4.99-4.88 ppm. In the ^{13}C NMR spectrum, these methine carbons were observed at δ 71.3 and 70.8 ppm and the carbon bearing the hydrazine group was spotted at δ 64.5 ppm.

The ^{1}H NMR spectrum of **61** the alkene protons were seen as two distinct multiplet at δ 6.75 ppm and 6.22 ppm. In the ^{13}C NMR spectrum, the carbonyl carbons appeared at δ 156.2 and 155.9 ppm. In the ^{1}H NMR spectrum of compound **62** the alkene protons were seen as multiplets at δ 6.76-6.75 and δ 6.19-

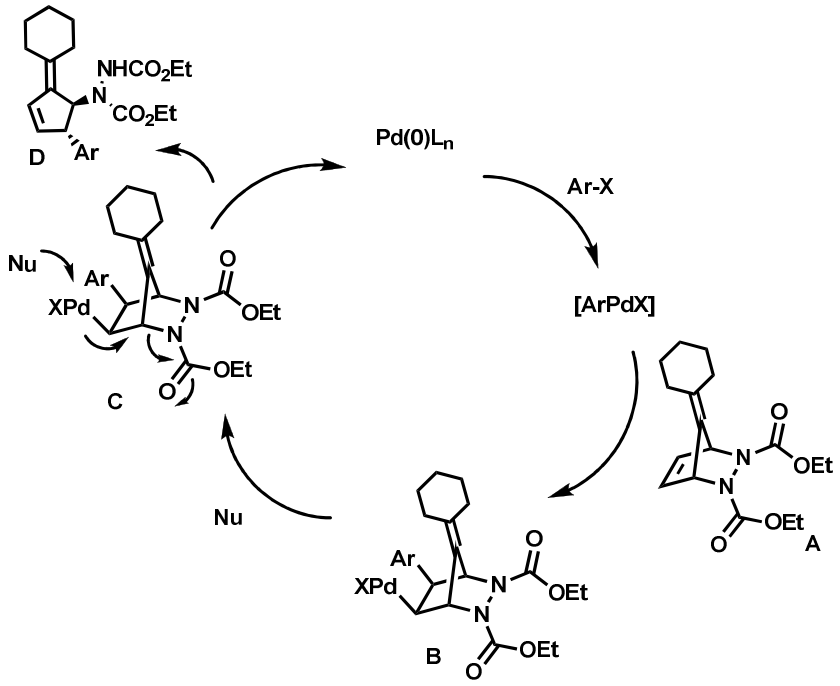
6.13 ppm. In the ^{13}C NMR spectrum, the carbonyl carbons were seen at δ 157.0 and 156.8 ppm.

The proton NMR spectrum of **64** showed the olefinic protons at δ 6.16 and δ 5.92-5.78 ppm as multiplet. The signal at δ 4.90 ppm was assigned to proton on the carbon bearing hydrazine moiety and the methine protons of isopropyl moiety. The ^{13}C NMR spectrum showed the carbon bearing the hydrazine moiety at δ 62.0 ppm. The signal at δ 48.0 was allocated to the carbon having the phenyl ring. In the ^{1}H NMR spectrum of **66** the aromatic protons were discernible at δ 8.76 (singlet), 8.35 (doublet), and 7.60 (singlet) ppm. The two olefinic protons were resonated as multiplet at δ 6.59-6.40 and as singlet at δ 5.77 ppm. In the ^{13}C NMR spectrum, the carbon bearing hydrazine substituent was discernible at δ 61.4 ppm and the cyclohexyl carbons were observed between δ 31.9-26.4 ppm.

In all the cases, the structures of the products were further confirmed by mass spectral analysis, which cited the molecular ion peaks within the approved limits.

3.6.2. Mechanism of the reaction

The first step of the catalytic cycle involves oxidative addition of Pd(0) into aryl iodide to form Ar-PdL_2X. In the next step the [ArPdX] adds to the C-C double bond giving **B**. Attack of the nucleophile and successive elimination of L_nPdNu along with the ring opening results in the formation of the hydrazine cyclopentene **D**. The addition of the species $RPdL_n$ to the double bond is a *syn* addition which results in the formation of the *trans*-3,4-disubstituted alkylidene cyclopentene as the product.



Scheme 3.18

3.7. Conclusion

In conclusion, we have developed a mild, simple and efficient strategy for the exclusive synthesis of alkylidene cyclopentenes. The generality of the method was established by the reactions of various bicyclic hydrazines with aryl and heteroaryl iodides.The products of the developed methodology can be used as potential intermediates towards a number of biologically relevant molecules.

3.8. Experimental Details

General information about the experiments is given in Section 2.6 of Chapter 2.

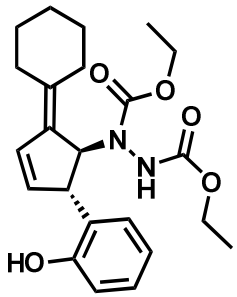
General experimental procedure: Bicyclic hydrazine (3.0 equiv.), aryl halide (1.0 equiv.) and $PdCl_2$ (10 mol%) were charged in a Schlenk tube and degassed. The mixture was dissolved in acetonitrile (3.0 mL) and Et_3N (1.5 equiv.) was added and allowed to stir at room temperature for 16 hours under argon atmosphere. The extent of reaction was monitored by TLC and on completion the reaction mixture was evaporated and the residue was subjected to column

chromatography on silica gel (100-200 mesh) using ethyl acetate/hexane mixture as eluent to afford the product in good to excellent yields.

Diethyl 1-(2-cyclohexylidene-5-(2-hydroxyphenyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 51

Following the general experimental procedure, bicyclic hydrazine **49a** (221 mg, 0.69 mmol), 2-iodophenol **50** (50 mg, 0.23 mmol), $PdCl_2$ (4 mg, 10 mol%) and Et_3N (0.04 mL, 0.35 mmol), in 3 mL of dry CH_3CN at r.t. for 16 h gave the product **51** as a colourless viscous liquid in 90% (86 mg) yield.

R_f: 0.52 (6:4 Hexane/ethyl acetate).



51

IR (KBr)ν_{max}: 3452, 3286, 2934, 2844, 1740, 1720, 1465, 1410, 1366, 1130, 1055, 920, 751, 700 $cm.^{-1}$

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.15-7.10 (m, 1H), 6.94-6.81 (m, 3H), 6.67-6.48 (m, 1H), 6.35-6.25 (m, 1H), 5.91 (m, 1H), 5.09 (m, 1H), 4.41-4.32 (m, 5H), 2.34 (m, 2H), 2.03 (m, 2H), 1.67-1.56 (m, 4H), 1.43 (m, 1H), 1.29-1.27 (m, 5H), 1.12-1.10 (m, 2H).

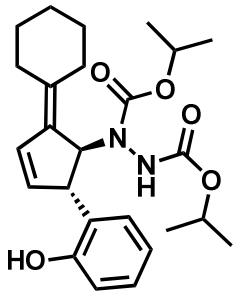
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 156.0, 141.0, 139.4, 135.4, 129.9, 129.7, 128.3, 123.0, 113.1, 62.4, 61.3, 60.4, 50.3, 31.9, 31.4, 27.8, 27.3, 26.5, 14.9, 14.6.

MS (FAB): for $C_{23}H_{30}N_2O_5$, Calcd, M^+: 414.22; Found: 414.15.

Diisopropyl 1-(2-cyclohexylidene-5-(2-hydroxyphenyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 52

Following the general experimental procedure, bicyclic hydrazine **49b** (240 mg, 0.69 mmol), 2-iodophenol **50** (50 mg, 0.23 mmol), $PdCl_2$ (4 mg, 10 mol%) and Et_3N (0.04 mL, 0.35 mmol), in 3 mL of dry CH_3CN at r.t. for 16 h gave the product **52** as colourless viscous liquid in 86% (87 mg) yield.

R_f: 0.56 (hexane/ethyl acetate = 6:4).



52

IR (KBr)ν_{max}: 3444, 3268, 2920, 2844, 1733, 1714, 1465, 1408, 1236, 1116, 1032, 919, 751 cm.$^{-1}$

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.30-7.27 (m, 2H), 6.92 (m, 1H), 6.40-6.35 (m, 1H), 5.98 (m, 1H), 5.06 (m, 1H), 4.91 (s, 1H), 4.85-4.80 (m, 1H), 4.45-4.30 (m, 1H), 2.49-2.42 (m, 2H), 2.36 (m, 2H), 1.68-1.62 (m, 2H), 1.53 (m, 2H), 1.42-1.40 (m, 2H), 1.23-1.16 (m, 12H).

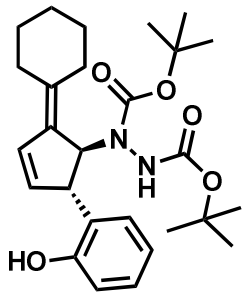
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 155.4, 140.7, 139.8, 139.2, 135.2, 134.7, 130.1, 129.5, 128.4, 123.0, 112.9, 70.0, 69.0, 61.9, 57.2, 32.1, 31.8, 31.5, 28.1, 27.2, 26.7, 22.3, 21.9.

MS (FAB): for $C_{25}H_{34}N_2O_5$, Calcd, M^+: 442.25; Found: 442.20.

Di-tert-butyl 1-(2-cyclohexylidene-5-(2-hydroxyphenyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 53

Following the general experimental procedure, bicyclic hydrazine **49c** (259 mg, 0.69 mmol), 2-iodophenol **50** (50 mg, 0.23 mmol), $PdCl_2$ (4 mg, 10 mol%) and Et_3N (0.04 mL, 0.35 mmol), in 3 mL of dry CH_3CN at r.t. for 16 h gave the product **53** as a colourless viscous liquid in 78% (84 mg) yield.

R_f : 0.48 (hexane/ethyl acetate = 6:4).



53

IR (KBr)ν_{max}: 3458, 3300, 2914, 2854, 1725, 1710, 1414, 1352, 1220, 1056, 951, 751, cm.$^{-1}$

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (m, 2H), 6.94-6.79 (m, 2H), 6.59 (s, 2H), 6.19-6.15 (m, 1H), 5.90 (m, 1H), 5.04 (s, 1H), 4.41-4.34 (m, 1H), 2.35 (m, 2H), 2.03 (m, 2H), 1.49 (s, 9H), 1.42 (s, 9H), 1.29 (m, 6H).

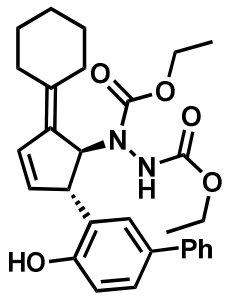
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 154.9, 140.6, , 139.4, 136.2, 133.8, 133.1, 131.3, 129.7, 127.9, 123.0, 112.4, 82.1, 80.7, 64.6, 57.2, 32.0, 30.7, 29.6, 28.1, 27.8, 26.8, 26.4.

MS (FAB): for $C_{27}H_{38}N_2O_5$, Calcd, M^+: 470.28; Found: 470.25.

Diethyl 1-(2-cyclohexylidene-5-(4-hydroxybiphenyl-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 55

Following the general experimental procedure, bicyclic hydrazine **49a** (163 mg, 0.51 mmol),) 2-hydroxy-iodobyphenyl **54** (50 mg, 0.17 mmol), $PdCl_2$ (3 mg, 10 mol%) and Et_3N (0.04 mL, 0.26 mmol), in 3 mL of dry CH_3CN at r.t. for 16 h gave the product **55** as a colourless viscous liquid in 91% (76 mg) yield.

Rf : 0.54 (hexane/ethyl acetate = 6:4).



55

IR (KBr)ν_{max}: 3457, 3204, 2934, 2818, 1736, 1717, 1501, 1432, 1233, 1078, 867, 752 cm.$^{-1}$

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.59 (m, 3H), 7.51-7.39 (m, 1H), 7.35-7.30 (m, 1H), 7.06-6.89 (m, 2H), 6.76-6.71 (m, 1H), 5.99 (s, 1H), 5.81-5.79 (m, 1H), 5.53-5.52 (m, 1H), 4.24-4.03 (m, 5H), 2.65-2.51 (m, 2H), 2.17-2.11 (m, 2H), 1.57-1.42 (m, 6H), 1.25-1.22 (m, 6H).

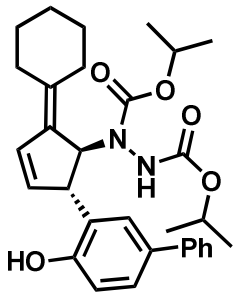
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 155.5, 139.2, 137.9, 135.5, 128.9, 128.2, 127.3, 126.8, 112.8, 107.3, 65.8, 62.5, 61.3, 57.4, 32.0, 31.5, 27.8, 27.3, 26.5, 14.6.

MS (FAB): for $C_{29}H_{34}N_2O_5$, Calcd, M^+: 490.25; Found: 490.28.

Diisopropyl 1-(2-cyclohexylidene-5-(4-hydroxybiphenyl-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 56

Following the general experimental procedure, bicyclic hydrazine **49b** (177 mg, 0.51mmol), 2-hydroxy-iodobiphenyl **54** (50 mg, 0.17 mmol), $PdCl_2$ (3 mg, 10 mol%) and Et_3N (0.04 mL, 0.35 mmol), in 3 mL of dry CH_3CN at r.t. for 16 h gave the product **56** as a colourless viscous liquid in 86% (76 mg) yield.

Rf : 0.56 (hexane/ethyl acetate = 6:4).



56

IR (KBr)ν_{max}: 3452, 3206, 2934, 2822, 1741, 1712, 1501, 1352, 1252, 1091, 878, 767 cm.$^{-1}$

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.51-7.32 (m, 6H), 7.00-6.97 (m, 1H), 6.77-6.67 (m, 2H), 5.99 (m, 1H), 5.80 (m, 1H), 5.53-5.51 (m, 1H), 4.26-4.22 (m, 1H), 2.44 (m, 2H), 2.17 (m, 2H), 1.64-1.61 (m, 6H), 1.46-1.41 (m, 6H), 1.22-1.16 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0, 155.5, 139.2, 137.8, 135.3, 130.1, 128.8, 128.3, 127.3, 126.7, 113.0, 70.0, 68.7, 62.1, 57.1, 31.9, 31.5, 27.8, 27.2, 26.4, 21.9.

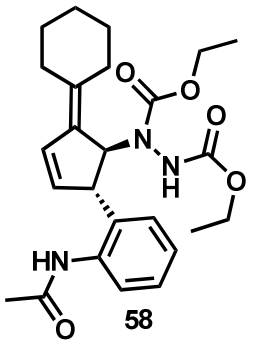
MS (FAB): for $C_{31}H_{38}N_2O_5$, Calcd, M^+: 518.28; Found: 518.24.

Diethyl 1-(2-(2-acetamidophenyl)-5-cyclohexylidenecyclopent-3-enyl)hydrazine-1,2-dicarboxylate 58

Following the general experimental procedure, bicyclic hydrazine **49a** (182 mg, 0.57 mmol), N-(2-iodophenyl)acetamide **57** (50 mg, 0.19 mmol), $PdCl_2$ (3mg, 10 mol%) and Et_3N (0.04 mL, 0.29 mmol), in 3 mL of dry CH_3CN at r.t. for 16 h gave the product **58** as a colourless viscous liquid in 96% (82 mg) yield.

Rf : 0.44 (hexane/ethyl acetate = 6:4).

IR (KBr)ν_{max}: 3433, 3206, 2928, 2824, 1750, 1717, 15`4, 1320, 1252, 1065, 928, 821 cm.$^{-1}$



58

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (s, 1H), 7.24-7.22 (m, 1H), 7.00-6.95 (m, 2H), 6.62 (m, 1H), 6.47-6.36 (m, 1H), 5.88 (m, 1H), 5.00-4.95 (m, 1H), 4.33-4.01 (m, 5H), 2.33 (m, 2H), 2.20 (s, 3H), 2.03-1.99 (m, 2H), 1.89 (s, 2H), 1.29-1.24 (m, 4H), 1.12-1.07 (m, 6H).

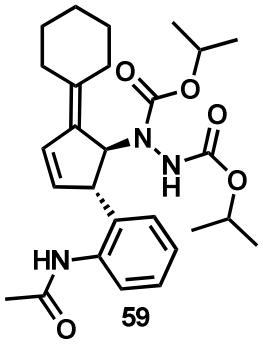
^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 156.7, 156.0, 136.4, 135.8, 133.8, 131.5, 127.6, 127.2, 125.8, 124.9, 123.9, 110.9, 62.8, 62.4, 61.9, 49.5, 30.4, 28.2, 26.4, 25.6, 24.8, 23.9, 14.4.

MS (FAB): for $C_{25}H_{33}N_3O_5$, Calcd, M^+: 455.24; Found: 455.19.

Diisopropyl 1-(2-(2-acetamidophenyl)-5-cyclohexylidenecyclopent-3-enyl)hydrazine-1,2-dicarboxylate 59

Following the general experimental procedure, bicyclic hydrazine **49b** (198 mg, 0.57 mmol), N-(2-iodophenyl)acetamide **57** (50 mg, 0.19 mmol), $PdCl_2$ (3 mg, 10 mol%) and Et_3N (0.04 mL, 0.29 mmol), in 3 mL of dry CH_3CN at r.t. for 16 h gave the product **59** as a colourless viscous liquid in 83% (102 mg) yield.

R_f: 0.48 (6:4 Hexane/ethyl acetate).



59

IR (KBr)ν_{max}: 3399, 3278, 2902, 2813, 1744, 1720, 1463, 1415, 1256, 1134, 1055, 920, 751 $cm.^{-1}$

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22-7.06 (m, 1H), 7.03-6.94 (m, 2H), 6.62 (m, 1H), 6.21 (m, 1H), 5.91-5.87 (m, 1H), 4.99-4.88 (m, 3H), 4.33-4.24 (m, 1H), 2.33 (m, 2H), 2.22 (s, 3H), 1.66-1.61 (m, 2H), 1.47-1.42 (m, 4H), 1.24-1.22 (m, 4H), 2.00 (m, 2H), 1.64-1.55 (m, 6H), 1.32-1.23 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 156.0, 141.0, 139.4, 136.5, 135.1, 134.0, 131.4, 127.2, 124.6,

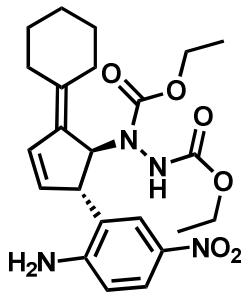
123.7, 71.3, 70.8, 64.5, 49.8, 32.1, 30.3, 29.7, 28.1, 27.8, 22.1, 21.8.

MS (FAB): for $C_{27}H_{37}N_3O_5$, Calcd, M^+: 483.27; Found: 483.22.

Diethyl 1-(2-(2-amino-5-nitrophenyl)-5-cyclohexylidenecyclopent-3-enyl)hydrazine-1,2-dicarboxylate 61

Following the general experimental procedure, bicyclic hydrazine **49a** (182 mg, 0.57 mmol), 2-iodo-4-nitroaniline **60** (50 mg, 0.19 mmol), $PdCl_2$ (3 mg, 10 mol%) and Et_3N (0.04 mL, 0.29 mmol), in 3 mL of dry CH_3CN at r.t. for 16 h gave the product **61** as a colourless viscous liquid in 80% (70 mg) yield.

R_f: 0.60 (6:4 Hexane/ethyl acetate).



61

IR (KBr)ν_{max}: 3345, 3052, 2876, 2634, 1740, 1726, 1698, 1516, 1254, 1112, 1058, 965, 758 $cm.^{-1}$

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.18 (s, 1H), 7.29 (s, 1H), 7.06-7.03 (m, 1H), 6.75 (m, 1H), 6.22 (m, 1H), 5.94 (s, 1H), 5.03-4.87 (m, 2H), 4.26-4.25 (m, 5H), 2.37 (s, 2H), 2.20-2.17 (m, 2H), 1.65-1.62 (m, 6H), 1.32-1.15 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): 156.2, 155.9, 154.8, 138.5, 132.4, 131.0, 127.3, 125.5, 124.1, 113.8, 70.7, 69.5, 63.3, 49.0, 36.1, 35.4, 31.6, 22.0, 21.9, 14.6, 14.2.

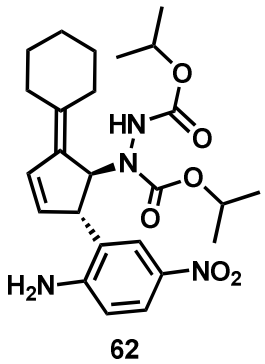
MS (FAB): for $C_{23}H_{30}N_4O_6$, Calcd, M^+: 458.22; Found: 458.22.

Diisopropyl 1-(2-(2-amino-5-nitrophenyl)-5-cyclohexylidenecyclopent-3-enyl)hydrazine-1,2-dicarboxylate 62

Following the general experimental procedure, bicyclic hydrazine **49b** (198 mg, 0.57 mmol), 2-iodo-4-nitroaniline **60** (50 mg, 0.19 mmol), $PdCl_2$ (3 mg, 10

mol%) and Et_3N (0.04 mL, 0.29 mmol), in 3 mL of dry CH_3CN at r.t. for 16 h gave the product **62** as a colourless viscous liquid in 83% (76 mg) yield.

R_f: 0.60 (6:4 Hexane/ethyl acetate).



62

IR (KBr)ν_{max}: 3350, 3052, 2965, 2934, 1730, 1698, 1607, 1500, 1254, 1202, 1055, 978, 753 $cm.^{-1}$

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.21-8.18 (m, 1H), 7.29 (s, 1H), 7.10-7.07 (m, 1H), 6.76-6.75 (m, 1H), 6.19-6.13 (m, 1H), 5.94 (s, 1H), 5.77 (s, 1H), 5.11-4.89 (m, 3H), 4.19 (s, 1H), 2.36 (s, 2H), 2.09 (s, 2H), 1.64 (m, 6H), 1.33-1.28 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): 157.0, 156.8, 150.9, 138.7, 135.0, 132.1, 126.2, 112.2, 106.7, 70.5, 70.1, 63.2, 50.1, 31.4, 31.1, 29.7, 28.3, 26.3, 22.0.

MS (FAB): for $C_{25}H_{34}N_4O_6$, Calcd, M^+: 486.25; Found: 486.20.

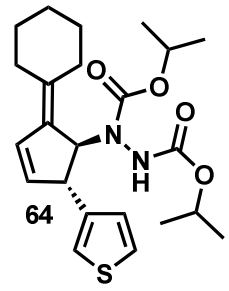
Diisopropyl 1-(2-cyclohexylidene-5-(thiophen-3-yl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 64

Following the general experimental procedure, bicyclic hydrazine **49b** (250 mg, 0.72 mmol), 3-iodothiophene **63** (50 mg, 0.24 mmol), $PdCl_2$ (4 mg, 10 mol%) and Et_3N (0.04 mL, 0.36 mmol), in 3 mL of dry CH_3CN at r.t. for 16 h gave the product **64** as a colourless viscous liquid in 64% (67 mg) yield.

R_f: 0.64 (6:4 Hexane/ethyl acetate).

IR (KBr)ν_{max}: 3366, 2980, 1748, 1716, 1676, 1577, 1444, 1386, 1223, 1105, 1065, 754, 702 $cm.^{-1}$

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.01 (s, 1H), 6.65-6.47 (m, 2H), 6.16 (s, 1H), 5.92-5.78 (m, 1H), 4.90 (m, 3H), 4.46-4.37 (m, 1H), 2.43-2.03 (m,



64

4H), 1.63-1.55 (m, 2H), 1.45-1.40 (m, 2H), 1.28-1.22 (m, 12H).

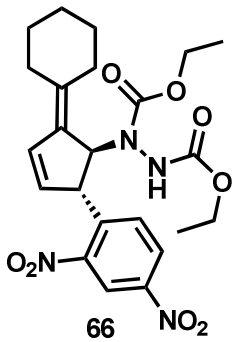
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0, 155.1, 140.1. 134.7, 128.8, 127.3, 127.0, 126.8, 123.7, 71.7, 70.8, 62.0, 48.0, 32.0, 29.7, 28.0, 27.1, 26.0, 22.0.

MS (FAB): for $C_{23}H_{32}N_2O_4S$, Calcd, M^+: 432.21; Found: 432.19.

Diethyl 1-(2-cyclohexylidene-5-(2,4-dinitrophenyl)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 66

Following the general experimental procedure, bicyclic hydrazine **49a** (163 mg, 0.51 mmol), 2,4-dinitroiodobenzene **65** (50 mg, 0.17 mmol), $PdCl_2$ (3 mg, 10 mol%) and Et_3N (0.04 mL, 0.26 mmol), in 3 mL of dry CH_3CN at r.t. for 16 h gave the product **66** as a colourless viscous liquid in 81% (67 mg) yield.

R_f: 0.50 (6:4 Hexane/ethyl acetate).



66

IR (KBr)ν_{max}: 3330, 3118, 2967, 1724, 1704, 1523, 1412, 1320, 1236, 1056, 1079, 947, 754 cm.$^{-1}$

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.76 (s, 1H), 8.35 (d, J = 8.10 Hz, 1H), 7.60 (s, 1H), 6.92 (s, 1H), 6.59-6.40 (m, 1H), 5.77 (s, 1H), 5.70 (brs, 1H), 4.15-4.00 (m, 5H), 2.34-2.20 (m, 4H), 1.61-1.59 (m, 6H), 1.32-1.24 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.6, 156.0, 155.4, 149.0, 139.4, 135.3, 129.6, 128.2, 123.0, 116.0, 62.6, 61.6, 61.4, 48.4, 31.9, 31.4, 27.7, 27.2, 26.4, 14.5, 14.3

MS (FAB): for $C_{23}H_{28}N_4O_8$, Calcd, M^+: 488.19; Found: 488.28.

3.9. References

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Chapter 4

Synthesis of Highly Functionalized Heterocycles by Palladium Mediated Reactions of Pentafulvene Derived Bicyclic Hydrazines

4.1.Introduction

The development of new methods for carbon-carbon bond formation is a prime topic inorganic chemistry. In the past three decades, tremendous effort has been devoted into the transition-metal catalyzed reactions,[1] which permits the formation of carbon-carbon or carbon-heteroatom bonds in a way that is not accessible through traditional methods. Among the myriad of important transition metal catalyzed synthetic transformations, palladium-catalyzed processes[2]has gained widespread use in industrial and academic synthetic chemistry. Among various types of palladium-catalyzed transformations, the annulation reaction and related chemistry occupy a special place. Annulation processes have proven quite valuable inorganic synthesis because of the ease with which a variety of complicated hetero- and carbocycles can be rapidly constructed.[3] Combining two or more independent acyclic moieties to form several bonds in one process potentially provides an opportunity to rapidly synthesize complex molecules without having to spend time and resources on the isolation of intermediates and their reintroduction in subsequent steps. This is especially attractive in this age of high-throughput and combinatorial chemistry.[4] Equally important is the minimization of waste brought about by a decrease in the amounts of reagents and solvents required for a single-step operation as opposed to a multistep endeavor.[5]

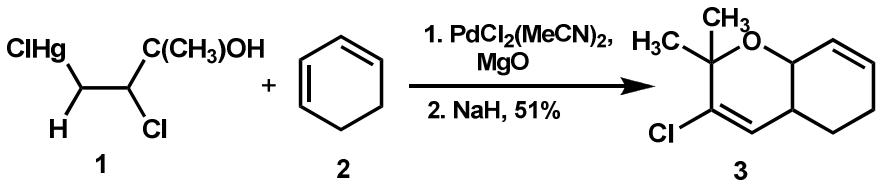
Palladium reagents have been used extensively to prepare various carbo- and heterocyclic compounds,[6] by both cyclic carbopalladation and annulation.[7] One of

the most important factors contributing to such widespread application of palladium catalysts is their tolerance of most important organic functional groups. In these processes only catalytic amounts of palladium are employed, and the palladium catalyst is quite stable to air and moisture. The present chapter discloses a simple, one pot strategy for the carboannulation of fulvene derived azabicyclichydrazines with 2-iodophenol under palladium catalysis.

4.2. Palladium catalyzed annulation reactions

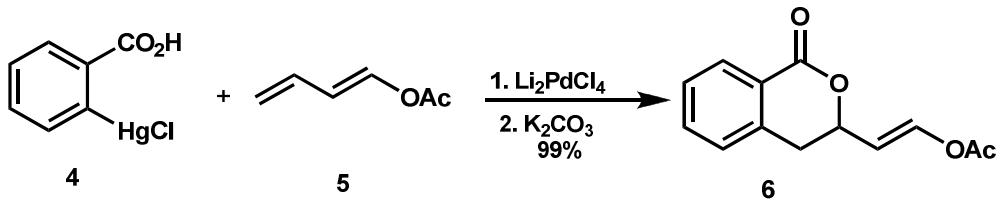
In recent years, a number of novel new routes to heterocycles and carbocycles that involve the heteroannulation or carboannulation of appropriately functionalized aryl or vinylic halides or triflates onto carbon-carbon unsaturation have been developed.[6]The following section discusses in brief, the development and application of Pd-catalyzed annulation chemistry.

Larock *et al.* reported the synthesis of a variety of heterocycles by a two step process. The first step involves the palladium mediated reaction of functionalized aryl or vinyl mercurials with 1,3- and 1,4-dienes as well as vinyliccyclopropanes which is followed by base promoted cyclisation of the initially formed π-allyl palladium intermediate (Scheme 4.1).[7]



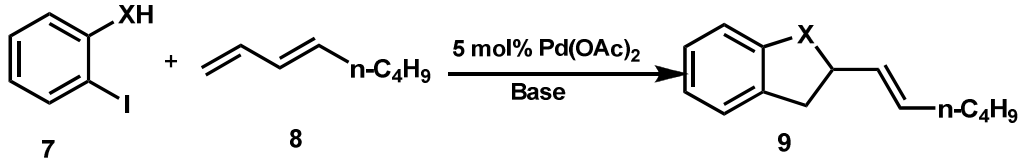
Scheme 4.1

A variety of five and six-membered lactones, 2,3-dihydrobenzofurans, benzopyrans and 2,3-dihydroindoles were prepared in this manner. This chemistry was subsequently extended to acetoxy-substituted 1,3-dienes (Scheme 4.2).[8] The major drawback to this approach was the use of stoichiometric amounts of palladium salts and toxic organomercurials.



Scheme 4.2

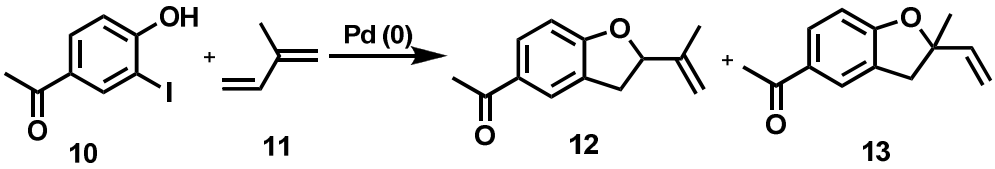
Later Larock and co-workers have expanded the heteroannulation to a wide range of cyclic and acyclic 1,3-dienes using appropriately functionalized aryl iodides and 5 mol% of a suitable palladium catalyst (Scheme 4.3).[9] 2-Iodophenols afforded 2,3-dihydrobenzofurans, *o*-iodobenzylicalcohols produce benzopyrans, and *o*-iodoaniline and *o*-benzylic amine derivatives generate the corresponding nitrogen heterocycles.



X	Yield (%)
O	75
CH_2O	56
NAc	63
NTs	84
CH_2NTs	81

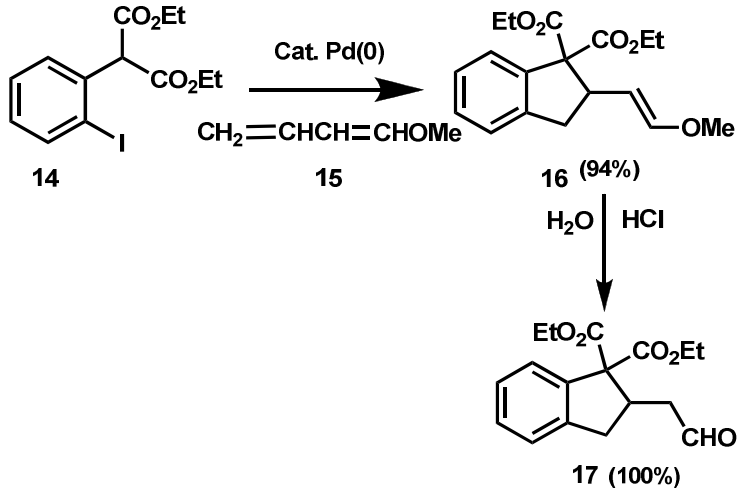
Scheme 4.3

The palladium catalyzed heteroannulation chemistry has provided a most direct route to naturally occurring 2,3-dihydrobenzofurans like Tremetone **13** (Scheme 4.4).[9]



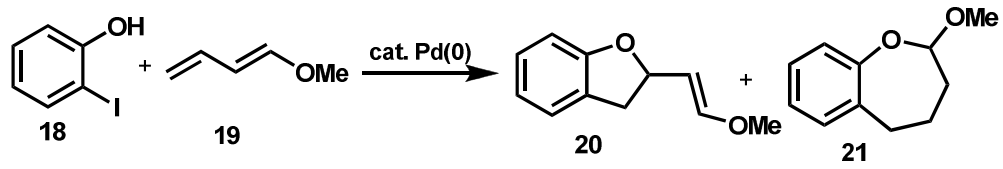
Scheme 4.4

The palladium catalyzed annulations of oxygen substituted 1,3-dienes **15** with different *o*-functionalized aryl halides **14** was reported by the same group. The products easily undergo hydrolysis to form carbonyl compounds (Scheme 4.5).[10]



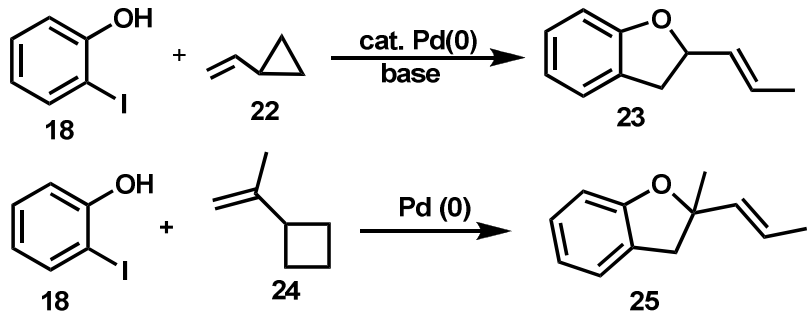
Scheme 4.5

The heteroannulation chemistry also afforded the first examples of 1,4-annulation of a 1,3-diene as minor products (Scheme 4.6). Apparently, the directing effect of the oxygensubstituent is powerful enough to produce a product **21** of a less favourable larger ring size.[10]



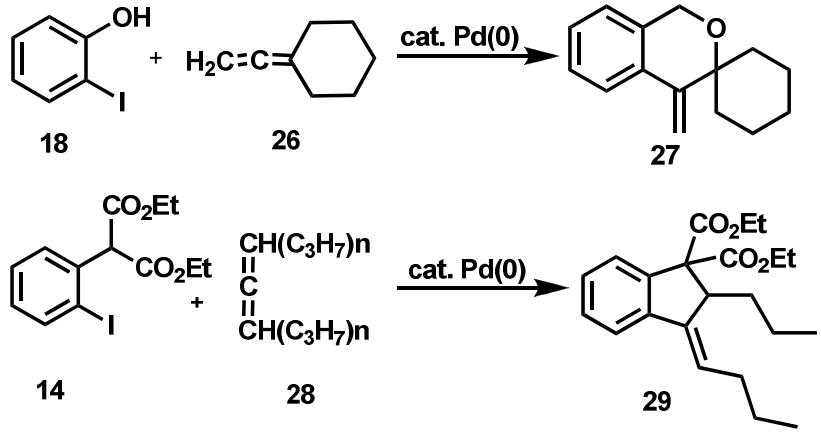
Scheme 4.6

The palladium-catalyzed hetero- and carboannulation of unsaturated cyclopropanes and cyclobutanes by aryl halides bearing *ortho* functionality were also reported by Larock and co-workers. They have shown that these olefinic substrates that produce π-allyl palladium intermediates on annulations could lead to interesting carbocycles (Scheme 4.7).[11]



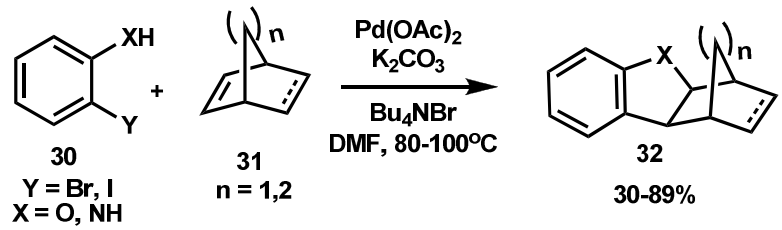
Scheme 4.7

Larock and co-workers extended the annulation methodology to allenes. Aryl halides bearing heteroatom- or potential carbanion-containing functionality in the *ortho* position react regioselectively with 1,2-dienes in the presence of a palladium catalyst and a carbonate base to afforded carbocycles. An array of acyclic and cyclic 1,2-dienes have been successfully annulated by a variety of functionalized aryl iodides as depicted in scheme 4.8.[12]



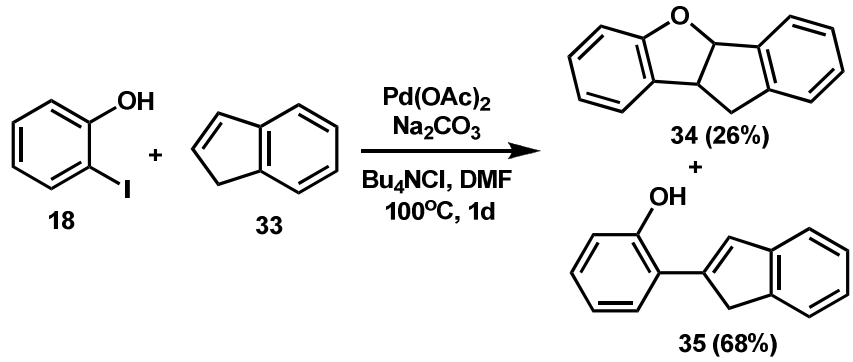
Scheme 4.8

In 1998 Catellani and Del Rio reported several examples for the formation of oxygen- and nitrogen-containing heterocycles by the palladium-catalyzed heteroannulation of norbornene, norbornadiene and bicyclo[2.2.2]octene by *o*-halophenols and -anilines (Scheme 4.9).[13]



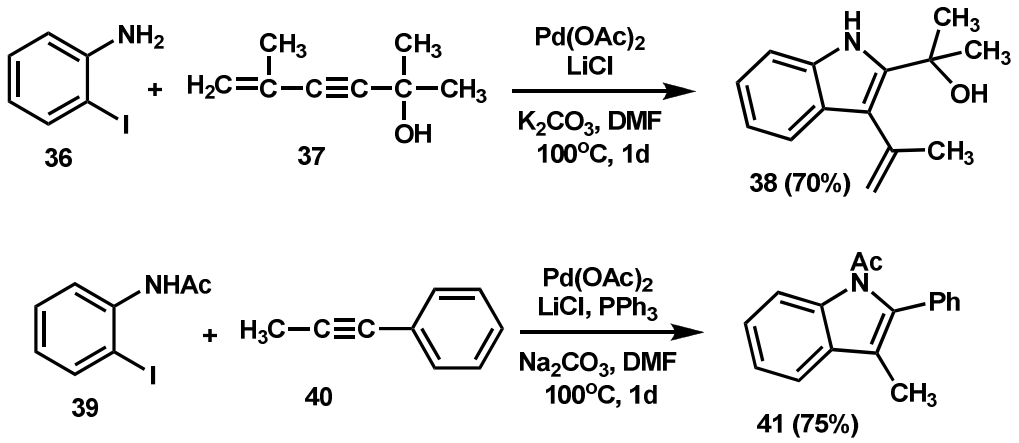
Scheme 4.9

At the same time Larock and co-workers also brought out the heteroannulation of norbornene and bicyclo[2.2.2]octane. They also extended the annulation chemistry to other bicyclic alkenes like indenes under the conditions used for the annulation of norbornene. They obtained two products, the desired heteroannulated product **34** and undesired Heck product **35** as shown in scheme 4.10.[14]



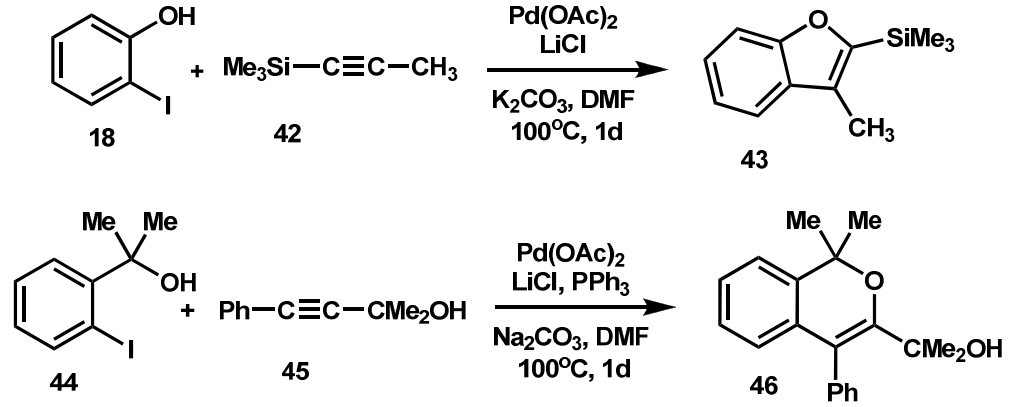
Scheme 4.10

The palladium catalyzed coupling of *o*-iodoaniline and the corresponding N-methyl, acetyl and tosyl derivatives with a wide variety of alkynes were examined by Larock *et al*. By these reactions, they introduced a valuable route towards substituted indoles (Scheme 4.11).[15]



Scheme 4.11

Later the same group extended the scope of alkyne annulation chemistry to the synthesis of a wide variety of oxygen heterocycles like benzofurans, benzopyrans etc (Scheme 4.12).[16]



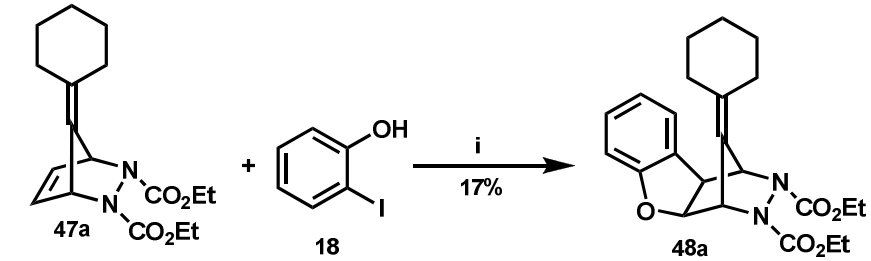
Scheme 4.12

These are some of the available reports on palladium catalyzed annulations of different *o*-functionalized aryl halides with unsaturated substrates. The reactivity of azabicyclic alkenes, have been extensively investigated with monocentered nucleophiles.[17, 18] These investigations resulted in the formation of either 3,4- or 3,5-disubstituted cyclopentenes. The easy availability and well documented reactivity of various *o*-functionalized aryl halides prompted us to investigate the reactivity of these bicentered nucleophiles towards fulvene derived azabicyclic olefins under palladium catalysis.

4.3. Results and discussion

4.3.1. Palladium catalyzed reaction of azabicyclic alkenes with 2-iodophenols

Our studies commenced with the reaction of 2-iodophenol **18** with the cyclohexylfulvene derived bicyclic olefin **47a** in the presence of $Pd(OAc)_2$-Bu_4NCl-K_2CO_3 catalyst system in DMF at 60 ^oC. The reaction afforded functionalized benzofuran **48a** in 17% yield (Scheme 4.13).



Scheme 4.13

The structure of **48a** was assigned through a detailed spectral analysis. The IR spectrum showed the characteristic carbonyl absorptions at 1747 and 1702 cm^{-1}. ^1H NMR spectrum of **48a** (Figure 3.1) located the proton at C-2 and the two ring junction protons at C-3 and C-4 as muliplet in the region δ 5.04-4.89 ppm. The proton on the carbon C-1 appeared as broad singlet at δ 3.93 ppm. The methylene protons at C-7 and C-10 resonated as multiplet in the region δ 4.27-4.13 ppm, whereas the multiplets from δ 2.31-1.20 ppm were assigned to the methyl protons of the carboethoxy group and the methylene protons of cyclohexyl ring. The aromatic protons resonated between δ 7.19-6.68 ppm.

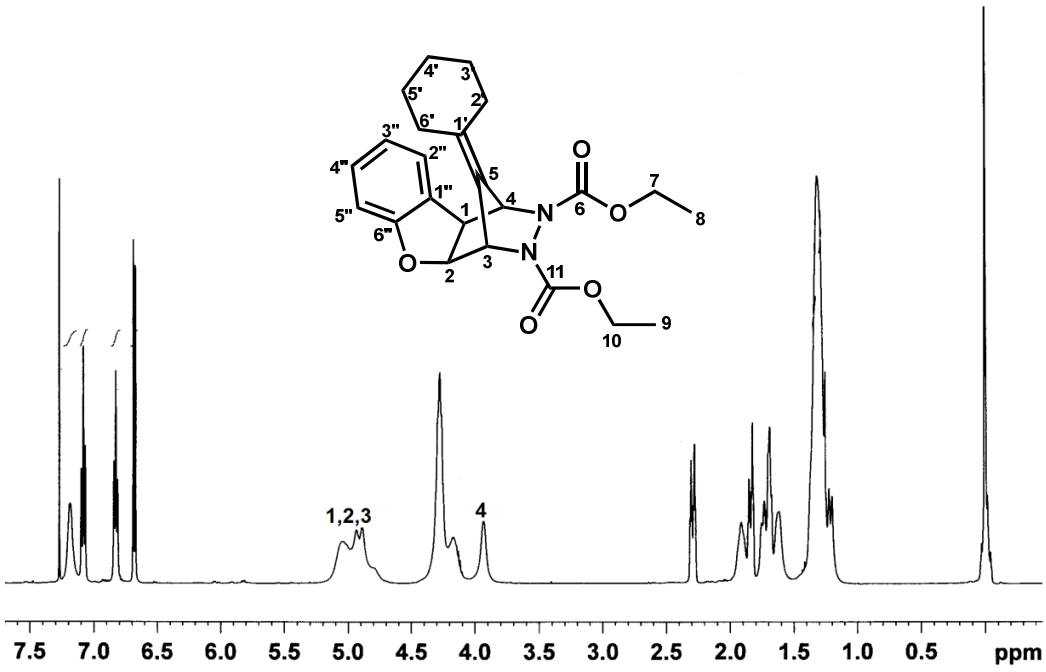


Figure 3.1^{1}H NMR spectrum of **48a**

The ^{13}C NMR spectrum (Figure 3.2) showed the characteristic peak of carbonyl group at δ 161.5 ppm. The carbons at C-1, C-2, C-3 and C-4 of the cyclopentane ring appeared at δ 49.7 80.6, 71.6, 63.5 ppm respectively. The methylene carbons of the carboethoxy group resonated at δ 62.7 ppm, while the methyl carbons showed their signals at δ 14.5 ppm. The signals at 32.1-26.0 were of the carbons of cyclohexyl ring.Mass spectrum well supported the structure with the molecular ion peak at *m/z* (M+1): 413.23.

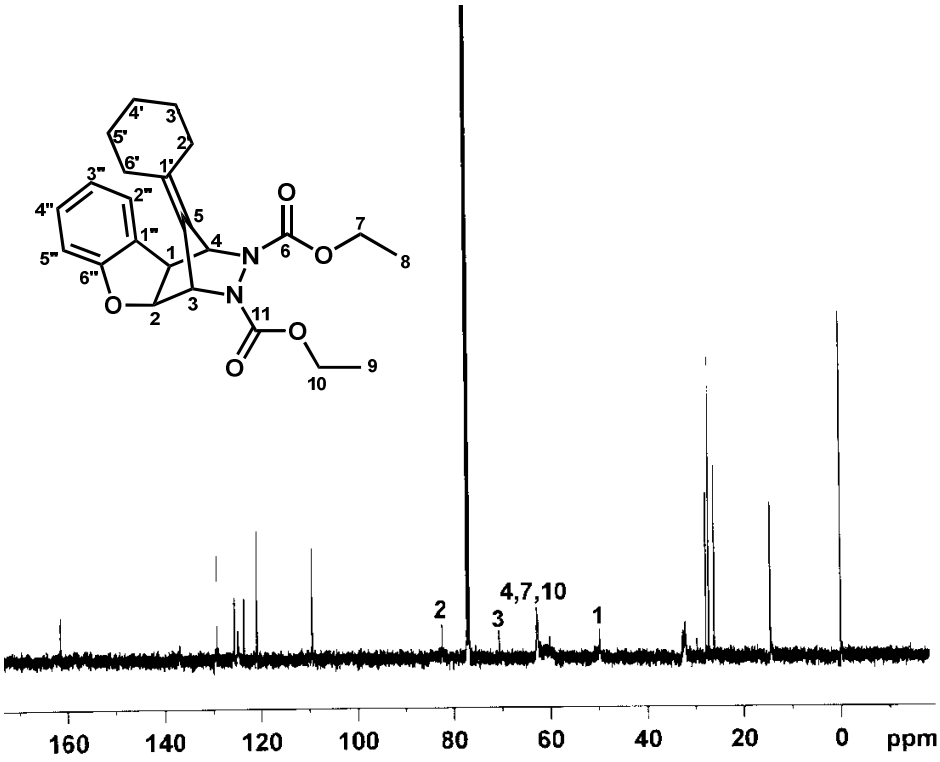


Figure 3.2 ^{13}C NMR spectrum of **48a**

Unambiguous evidence for the structure and stereochemistry of the product **48a** was obtained by single crystal X-ray analysis (Figure 3.3).

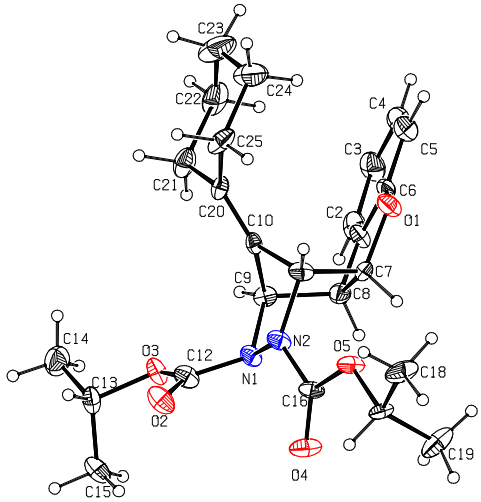


Figure 3.3. Single crystal X-ray structure of compound **48a**

Detailed optimization studies were carried out to find out the best catalyst system. Among the different catalysts (see Table 4.1) screened, $PdCl_2/Bu_4NCl//K_2CO_3$was found to be the best catalyst system and under these conditions,product **48a** was obtained in 88% yield.

Table 4.1: Optimization studies for suitable catalyst system

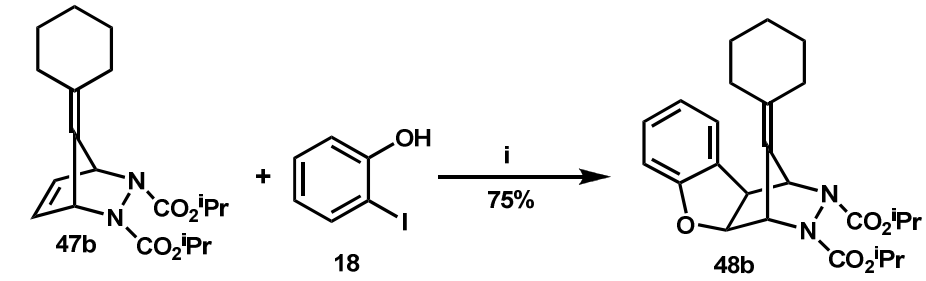
Entry	Catalyst	Solvent	Base	Additive	Yield (%)[a]
1	$Pd(OAc)_2$	DMF	K_2CO_3	Bu_4NCl	17[b]
2	$Pd(OAc)_2$	"	"	"	25
3	$Pd(OAc)_2$	"	"	"	33
4	$PdCl_2$	"	"	"	88
5	$[Pd(allyl)Cl]_2$	"	"	"	-
6	$Pd(PPh_3)_4$	"	"	"	-
7	$PdCl_2(PPh_3)_2$	"	"	"	-
8	$PdCl_2$	"	"	Bu_4NBr	15
9	$PdCl_2$	"	"	Bu_4NI	8
10	$PdCl_2$	"	"	LiCl	7
11	$PdCl_2$	"	"	Bu_4NCl	trace
12	$PdCl_2$	"	Et_3N	Bu_4NCl	-
13	$PdCl_2$	"	Cs_2CO_3	Bu_4NCl	24
14	$PdCl_2$	CH_3CN	K_2CO_3	"	65
15	$PdCl_2$	THF	"	"	45

Reaction Conditions: bicyclic alkene (3.0 equiv.), 2- iodophenol (1.0 equiv.), catalyst (10 mol%), base (1.0 equiv.), additive (1.0 equiv.), solvent (3 mL), r.t., 16 h. [a] Isolated yield, [b] 60 °C.

The generality of the method was proved by the reaction of 2-iodophenol with a number of bicyclichydrazines derived from 6,6-cyclohexylfulvene and various dialkylazodicarboxylates. The details of these investigations are described below.

When the bicyclic hydrazine **47b** derived from 6,6-cyclohexylidene fulvene and diisopropyl azodicarboxylate was subjected to palladium catalyzed ring

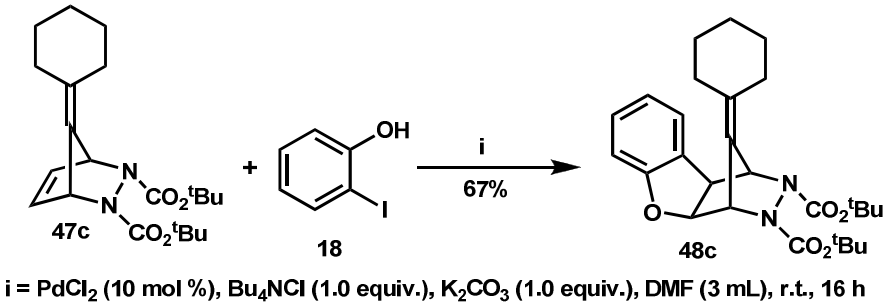
opening with 2-iodophenol **18**, benzofuran derivative **48b** was obtained in 75% yield (Scheme 4.14).



Scheme 4.14

The product **48b** was characterized on the basis of spectral data. IR spectrum confirmed the carbonyl absorptions in the region 1749-1725 cm.$^{-1}$ ^{1}H NMR spectrum marked the methine protons of isopropyl moiety along with the two ring junction protons and the proton near to oxygen in the region δ 5.01-4.86 ppm as multiplet. ^{13}C NMR spectrum gave the carbonyl signal at δ 157.3 ppm. Further evidence for the structure was obtained from mass spectral analysis which showed a molecular ion peak at *m/z* (M+1): 441.21.

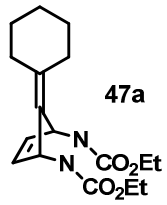
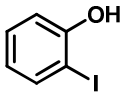
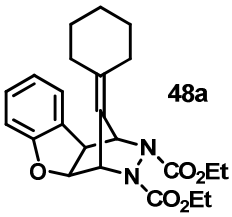
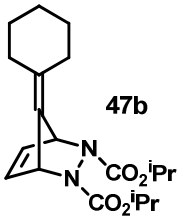
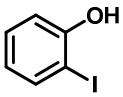
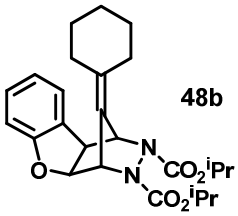
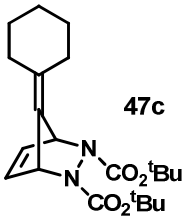
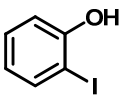
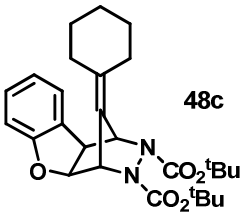
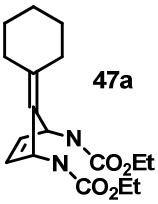
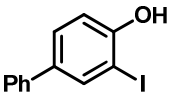
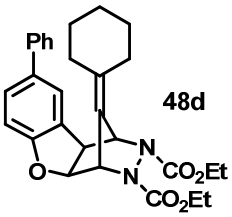
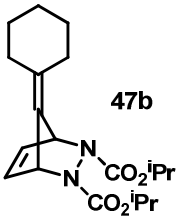
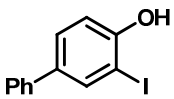
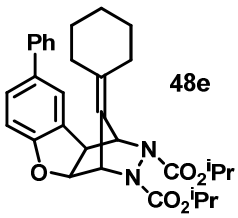
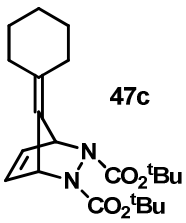
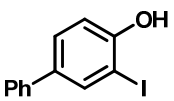
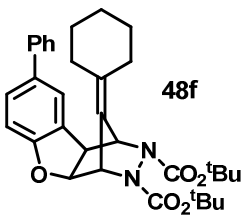
The bicyclic hydrazine **47c** prepared from 6,6-cyclohexylidenefulvene and di-*tert*-butyl azodicarboxylate followed similar reaction pathway under same conditions as mentioned above. The product **48c** was isolated in 67% yield and the reaction is presented in scheme 4.15.



Scheme 4.15

Spectral analysis was carried out for the structure elucidation. In the ^{1}H NMR spectrum of **48c** the methyl protons of the *tert*-butyl group resonated as two distinct singlet at δ 1.53 ppm and δ 1.46 ppm.^{13}C NMR spectrum positioned the carbonyl groups at δ 161.4 ppm. The less intense peaks at δ 82.1 ppm correspond to the quaternary carbons of the *tert*-butyl group. All other signals in ^{1}H, ^{13}C NMR and mass spectra well supported the structure assignment. The results obtained with different bicyclic hydrazinesare summarized in table 4.2.

Table 4.2: Reaction of cyclohexyl fulvene derived bicyclic hydrazine with different 2-iodophenols

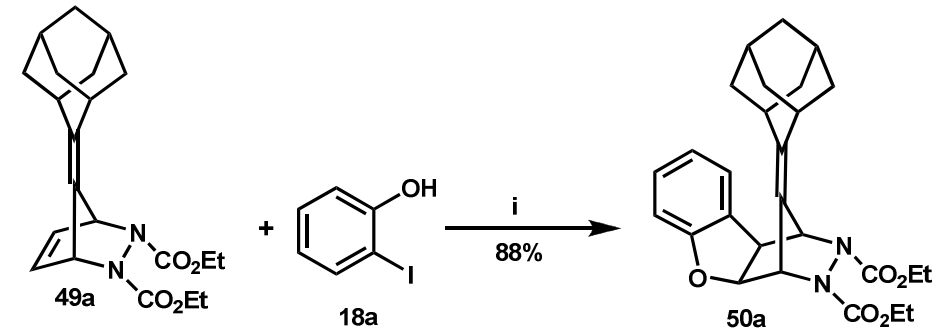
Entry	Alkene	2-iodophenol	Product	Yield (%)
1	 47a	 18a	 48a	88
2	 47b	 18a	 48b	75
3	 47c	 18a	 48c	67
4	 47a	 18b	 48d	63
5	 47b	 18b	 48e	60
6	 47c	 18b	 48f	58

Usual spectral analysis was carried out for the structure elucidation. In the ^{1}H NMR spectrum of **48d,** the characteristic aromatic protons resonated in the region δ 7.48-6.75 ppm. The two ring junction protons along with the proton near to oxygen appeared as multiplet at δ 5.08-4.94 ppm.^{13}C NMR spectrum positioned the carbonyl groups at δ 161.1 ppm. In the ^{1}H NMR spectrum of **48e** the 5 proton multiplet in the region δ 5.07-4.81 ppm includes the methine protons of the isopropyl moiety, the two ring junction protons and the proton near to oxygen. The aromatic protons resonated in the region δ 7.49-6.75 ppm. ^{13}C NMR spectrum positioned the carbonyl groups at δ 161.1 ppm. The signal at δ 71.5 ppm corresponds to the methine carbons of the isopropyl group. In the ^{1}H NMR spectrum of **48f** the methyl protons of the *tert*-butyl group resonated as two distinct singlet at δ 1.53 ppm and δ 1.48 ppm.^{13}C NMR spectrum placed the carbonyl carbon at δ 161.4 ppm. The less intense peaks at δ 82.1 ppm correspond to the quaternary carbons of the *tert*-butyl group. All other signals in ^{1}H, ^{13}C NMR and mass spectra well supported the structure assignment.

4.3.2. Reactions of 6,6-adamantylidene fulvene derived bicyclic hydrazines

In the next phase of the present investigation, we have checked the reactivity of 2-iodophenol with adamantylidene fulvene derived bicyclic hydrazines and the results of these experiments are discussed in the following section.

When the reaction was carried out using 6,6-adamantylidene fulvene derived adduct **49a** and 2-iodophenol **18a,** the substituted dihydrobenzofuran **50a** was obtained in 70% yield. The reaction is presented in the following scheme.

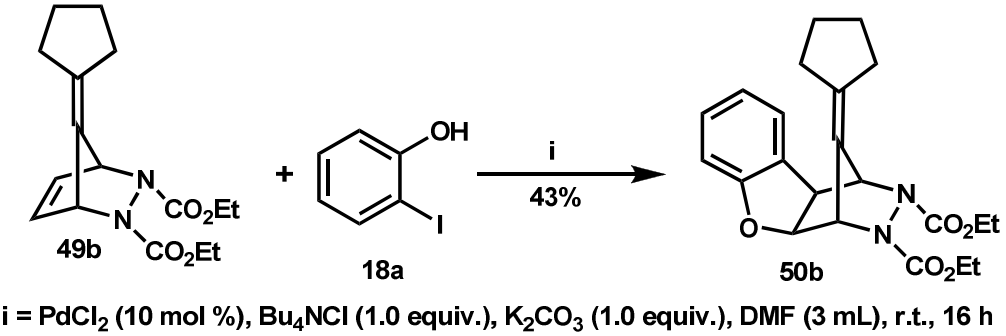


Scheme 4.16

The structure of the product **50a** was assigned by spectroscopic analysis. IR spectrum confirmed the carbonyl absorptions in the region 1752-1703 cm.$^{-1}$ The characteristic adamantyl protons resonated as two singlets at δ 2.65 and δ 2.26 ppm in the ^{1}H NMR spectrum. The carbonyl groups resonated at δ 161.4 ppm in the ^{13}C NMR spectrum. The peaks corresponding to the adamantyl carbons were located in the region δ 38.9-27.8 ppm. A well defined molecular ion peak at *m/z* 465.20 (M+1) provided another convincing evidence for the structure.

4.3.3. Reactions of 6,6-cyclopentyl fulvene derived bicyclic hydrazines

The bicyclic hydrazine **49b** prepared from 6,6-cyclopentylfulvene and diethyl azodicarboxylate also reacted similarly to produce the compound **50b** in 43% yield. The reaction is depicted in scheme 4.17.

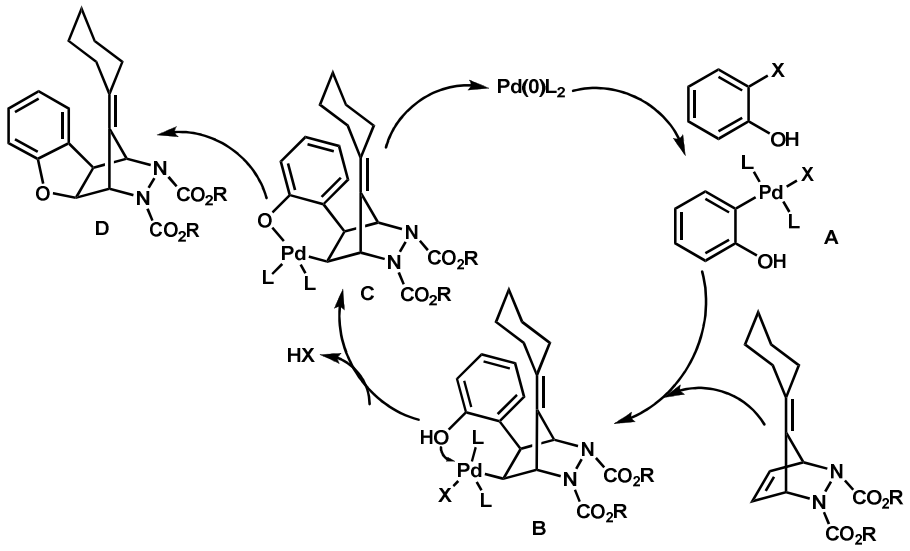


Scheme 4.17

Usual spectral analysis was employed to establish the structure of the product **50b**. IR spectrum presented the carbonyl peak at 1749 and 1717 cm.$^{-1}$ In ^{1}H NMR spectrum, the aromatic protons resonated in between δ 7.17 and δ 6.60 ppm and the signal referring to the methylene protons of carboethoxy groups were appeared as a multiplet in the region δ 4.27-4.13 ppm. ^{13}C NMR spectrum of **50b** showed the carbonyl peak at δ 158.7 ppm, and the cycloalkyl carbons produced its signals within the permissible region. Mass spectrum well supported the structure assignment by providing a molecular ion peak at *m/z* 399.20 (M+1).

4.4.Mechanistic Pathway

The mechanism of heteroannulation of the fulvene derived azabicycle is similar to that of heteroannulation of norbornene and related systems.[19] The mechanism starts with the oxidativeaddition of carbon-halogen bond of aryl iodide to palladium catalyst (intermediate **A**). This is followed by the aryl palladation of double bond through the *exo* phase of the alkene to form intermediate **B**. Oxypalladation result in the formation of the six membered palladacycle intermediate **C**, which undergoes reductive elimination of the palladium species to generate the heteroannulated product **D** and regenerate the Pd(0) to continue the catalytic cycle (Scheme 4.18).



Scheme 4.18

4.5. Conclusion

In conclusion, we have developed a simple and efficient strategy for the exclusive synthesis of dihydrobenzofuran annulated bicyclic compounds. The generality of the method was established by carrying out the reactions of various bicyclic hydrazines with different 2-iodophenols. The products with multiple points of functionalization can be easily manipulated to biologically important molecule.

4.6. Experimental details

General information about the experiments is given in Section 2.6 of Chapter 2.

4.6.1 General experimental procedure for the reaction of fulvenederived bicyclic hydrazine with 2-iodophenol.

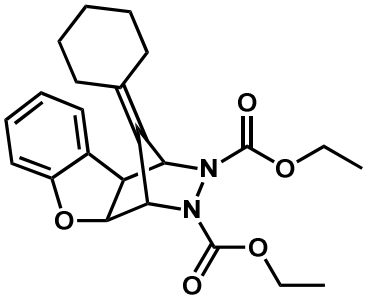
Bicyclic hydrazine (3.0 equiv.), 2-iodophenol (1.0 equiv.), Bu_4NCl (1.0 equiv.), K_2CO_3 (2.0 equiv.) and $PdCl_2$ (10 mol%) were taken in a Schlenk tube. The mixture was dissolved in DMF (2 mL) and stirred at room temperature for 16 hours under argon atmosphere. After the completion of the reaction, the reaction mixture was extracted with ethylacetate, dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue on silica gel (100-200 mesh) column chromatography using 15% ethyl acetate in hexane afforded the product in good yield.

Compound 48a

Following the general experimental procedure, the bicyclic hydrazine **47a** (221 mg, 0.69 mmol) 2-iodophenol **18a** (50 mg, 0.23 mmol), Bu_4NCl (54mg, 1.0 equiv.), K_2CO_3 (63 mg, 2.0 equiv.) and $PdCl_2$ (4 mg, 10 mol%) were taken in a Schlenk tube. The mixture was dissolved in DMF (2.0 mL) and stirred at room temperature for 16 hours under argon atmosphere gave the product **48a** as white solid (83 mg, 88%).

R_f: 0.66 (hexane/ethyl acetate = 8:2)

Mp:118-119 ^oC.



IR (KBr) ν_{max}: 2936, 2927, 2857, 1747, 1702, 1481, 1307, 1325, 1243, 1191, 1017, 914, 862, 777 cm.$^{-1}$

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (brs, 1H), 7.08 (t, 1H, *J* = 7.50 Hz), 6.83 (t, 1H, *J* = 7.50 Hz), 6.68 (d, 1H, *J* = 8.00 Hz), 5.04-4.89 (m, 3H), 4.27-4.13 (m, 4H), 3.93 (brs, 1H), 2.31-2.27 (m, 1H), 1.91-1.83 (m, 2H), 1.75-1.62 (m, 3H), 1.32-1.20 (m, 10H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.5, 136.9, 129.1, 125.5, 124.8, 123.7, 120.7, 109.4, 80.6, 71.6, 63.5, 62.7, 49.7, 32.1, 27.9, 27.1, 26.0, 14.5.

HRMS (FAB) for $C_{23}H_{28}N_2O_5$, cacld (M^+): 412.23; Found (M+1): 413.23.

Compound 48b

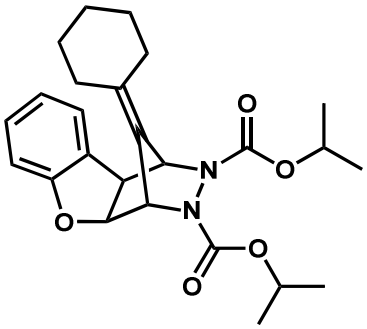
Following the general experimental procedure, the bicyclic hydrazine **47b** (240 mg, 0.69 mmol) 2-iodophenol **18a** (50 mg, 0.23 mmol), Bu_4NCl (64 mg, 1.0 equiv.), K_2CO_3 (63 mg, 2.0 equiv.) and $PdCl_2$ (4.0 mg, 10 mol%) were taken in a Schlenk tube. The mixture was dissolved in DMF (2.0 mL) and stirred at room temperature for 16 hours under argon atmosphere gave the product **48b** as colorless viscous liquid (76 mg, 75%).

R_f: 0.56 (hexane/ethyl acetate = 8:2).

IR (neat) ν_{max}: 2980, 2944, 2854, 1749, 1725, 1475, 1368, 1262, 1110, 914, 824, 778cm.$^{-1}$

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (brs, 1H), 7.11-7.06 (m, 1H), 6.85-6.83 (m, 1H), 6.69-6.68 (m, 1H), 5.01-4.86 (m, 5H), 3.94 (brs, 1H), 2.31-2.27 (m, 2H), 1.92-1.81 (m, 2H), 1.31 (m, 6H), 1.29-1.14 (m, 12H)

^{13}C NMR (125 MHz, $CDCl_3$):δ 157.3, 155.3, 140.6,



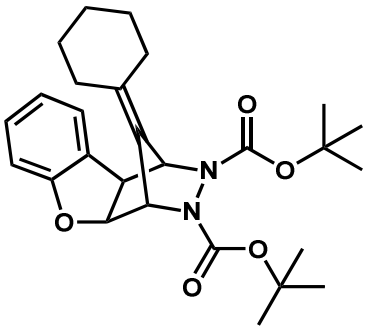
139.0, 134.7, 134.2, 133.7, 133.2, 130.0, 128.5, 128.1, 127.9, 127.7, 127.1, 126.8, 69.8, 69.1, 61.6, 55.3, 22.1, 21.5.

HRMS (FAB) for $C_{25}H_{32}N_2O_5$, calcd (M+): 440.23; Found (M+1): 441.21

Compound 48c

Following the general experimental procedure, the bicyclic hydrazine **47c** (260 mg, 0.69 mmol) 2-iodophenol **18a** (50 mg, 0.23 mmol), Bu_4NCl (64 mg, 1.0 equiv.), K_2CO_3 (63 mg, 2.0 equiv.) and $PdCl_2$ (4.0 mg, 10 mol%) were taken in a Schlenk tube. The mixture was dissolved in DMF (2.0 mL) and stirred at room temperature for 16 hours under argon atmosphere gave the product **48c** as colorless viscous liquid (72 mg, 67%).

R_f: 0.44 (hexane/ethyl acetate = 8:2).



IR (neat) ν_{max}: 2981, 2934, 2856, 1744, 1725, 1479, 1369, 1329, 1232, 1158, 1006, 852, 745 $cm.^{-1}$

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (brs, 1H), 7.09-7.06 (m, 1H), 6.82 (s, 1H), 6.67 (d, 1H, *J* = 8.00 Hz), 5.09-4.97 (m, 1H), 4.84-4.72 (m, 2H), 3.93 (brs, 1H), 2.29-2.27 (m, 1H), 1.94-1.67 (m, 4H), 1.53 (s, 9H), 1.46 (s, 9H), 1.34-1.13 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4, 136.1, 129.1, 125.7, 124.8, 124.0, 120.7, 109.3, 82.1, 81.8, 72.0, 65.4, 49.7, 31.9, 28.1, 27.2, 26.9.

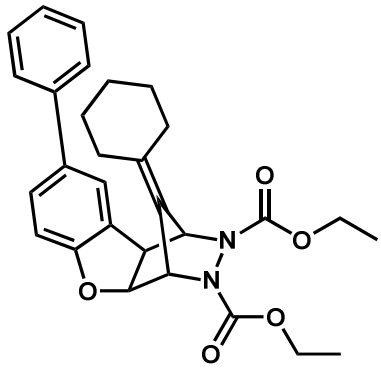
HRMS (FAB) for $C_{27}H_{36}N_2O_5$, calcd (M^+): 468.26; Found (M+1): 469.27.

Compound 48d

Following the general experimental procedure, the bicyclic hydrazine **47a** (163 mg, 0.51 mmol) 2-hydroxy-iodobyphenyl **18b** (50 mg, 0.17 mmol), Bu_4NCl

(47 mg, 1.0 equiv.), K_2CO_3 (47 mg, 2.0 equiv.) and $PdCl_2$ (3.0 mg, 10 mol%) were taken in a Schlenk tube. The mixture was dissolved in DMF (2.0 mL) and stirred at room temperature for 16 hours under argon atmosphere gave the product **48d** as colorless viscous liquid (52 mg, 63%).

R_f: 0.68 (hexane/ethyl acetate = 8:2).



IR (neat) ν_{max}:2982, 2934, 2856, 1748, 1710, 1478, 1374, 1277, 1191, 1046, 914, 863, 766 cm.$^{-1}$

^{1}H NMR(500 MHz, $CDCl_3$): δ 7.48 (d, 2H, *J* = 7.50 Hz), 7.41 (t, 3H, *J* = 8.00 Hz), 7.32-7.29 (m, 2H), 6.75 (d, 1H, *J* = 8.50 Hz), 5.08-4.94 (m, 3H), 4.28-4.17 (m, 4H), 4.00 (brs, 1H), 2.34-2.30 (m, 1H), 1.91-1.86 (m, 2H), 1.73-1.39 (m, 3H), 1.29-1.14 (m, 10H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.1, 141.1, 134.7, 128.8, 128.3, 126.8, 126.4, 123.5, 109.6, 80.6, 70.6, 63.7, 62.8, 49.7, 32.6, 32.2, 29.7, 27.9, 27.0, 26.0, 14.5

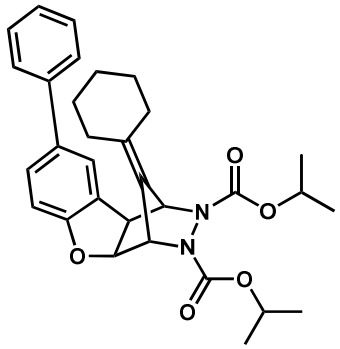
HRMS (FAB) for $C_{29}H_{32}N_2O_5$, calcd (M^+):488.23; found (M+1): 489.20.

Compound 48e

Following the general experimental procedure, the bicyclic hydrazine **47b** (178 mg, 0.51 mmol) 2-hydroxy-iodobyphenyl **18b** (50 mg, 0.17 mmol), Bu_4NCl (47 mg, 1.0 equiv.), K_2CO_3 (47 mg, 2.0 equiv.) and $PdCl_2$ (3.0 mg, 10 mol%) were taken in a Schlenk tube. The mixture was dissolved in DMF (2.0 mL) and stirred at room temperature for 16 hours under argon atmosphere gave the product **48e** as colorless viscous liquid (53 mg, 60%).

R_f: 0.59 (hexane/ethyl acetate = 8:2).

IR (neat) ν_{max}: 2977, 2933, 2858, 1746, 1719, 1478, 1375, 1277, 1103, 1008, 913, 823, 765 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$):δ 7.49-7.48 (m, 2H), 7.42 (t, 3H, *J* = 7.50 Hz), 7.33-7.31 (m, 2H), 6.75 (d, 1H, *J* = 8.50 Hz), 5.07-4.81 (m, 5H), 4.00 (brs, 1H), 2.33-2.30 (m, 1H), 1.94-1.85 (m, 2H), 1.72 (m, 2H), 1.33-1.24 (m, 17H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.1, 141.1, 134.7, 128.8, 128.3, 126.9, 126.8, 123.7, 109.5, 80.5, 71.5, 70.5, 64.0, 49.9, 32.0, 29.7, 28.0, 27.1, 26.0, 22.0.

HRMS (FAB) for $C_{31}H_{36}N_2O_5$, calcd (M^+): 516.26; found (M+1): 517.24.

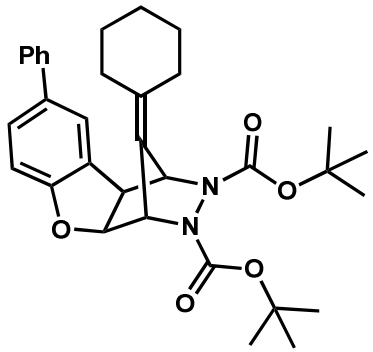
Compound 48f

Following the general experimental procedure, the bicyclic hydrazine **47c** (192 mg, 0.25 mmol) 2-hydroxy-iodobyphenyl **18b** (30 mg, 0.25 mmol), Bu_4NCl (64 mg, 1.0 equiv.), K_2CO_3 (2.0 equiv.) and $PdCl_2$ (10 mol%) were taken in a Schlenk tube. The mixture was dissolved in DMF (2.0 mL) and stirred at room temperature for 16 hours under argon atmosphere gave the product **48f** as colorless viscous liquid (54 mg, 58%).

R_f: 0.44 (hexane/ethyl acetate = 8:2).

IR (neat)ν_{max}: 2981, 2934, 2856, 1744, 1725, 1479, 1369, 1329, 1232, 1158, 1006, 852, 745 cm.$^{-1}$

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48-7.46 (m, 2H), 7.40 (t, 3H, *J* = 7.5 Hz), 7.33-7.30 (m, 2H), 6.67 (d, 1H, *J* = 8.00 Hz), 5.07-4.95 (m, 1H), 4.84-4.72 (m, 2H), 3.95 (br s, 1H), 2.29-2.26 (m, 1H), 1.92-1.65 (m, 4H), 1.53 (s, 9H), 1.48 (s, 9H), 1.34-1.13 (m, 5H).



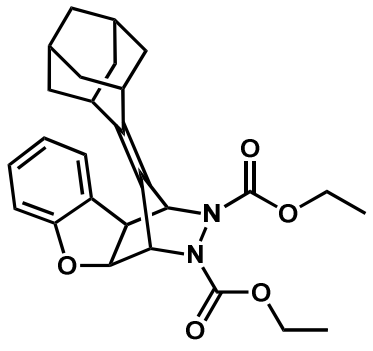
^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4, 136.1, 129.1, 125.7, 124.8, 124.0, 120.7, 109.3, 82.1, 81.8, 72.0, 65.4, 49.7, 31.9, 28.1, 27.2, 26.9.

HRMS (FAB) for $C_{33}H_{40}N_2O_5$, Calcd (M+): 544.68; Found (M+1): 545.71.

Compound 50a

Following the general experimental procedure, the bicyclic hydrazine **49a** (257 mg, 0.69 mmol) 2-iodophenol **18a** (50 mg, 0.23 mmol), Bu_4NCl (64 mg, 1.0 equiv.), K_2CO_3 (63 mg, 2.0 equiv.) and $PdCl_2$ (4.0 mg, 10 mol%) were taken in a Schlenk tube. The mixture was dissolved in DMF (2.0 mL) and stirred at room temperature for 16 hours under argon atmosphere gave the product **50a** as colorless viscous liquid (56 mg, 70%).

R_f: 0.63 (hexane/ethyl acetate = 8:2).



IR (neat) ν_{max}: 2980, 2912, 2851, 1752, 1703, 1596, 1463, 1306, 1223, 1116, 1014, 936, 871, 751cm.$^{-1}$

^{1}H NMR(500 MHz, $CDCl_3$): δ 7.16 (brs, 1H), 7.05 (t, 1H, *J* = 7.50 Hz), 6.80 (t, 1H, *J* = 7.50 Hz), 6.65 (d, 1H, *J* = 8.00 Hz), 5.03-4.92 (m, 3H), 4.25 (m, 4H), 3.91 (brs, 1H), 2.65 (s, 1H), 2.26 (s, 1H), 1.86-1.81 (m, 2H), 1.75-1.67 (m, 5H), 1.60 (brs, 1H), 1.39-1.25 (m, 10H).

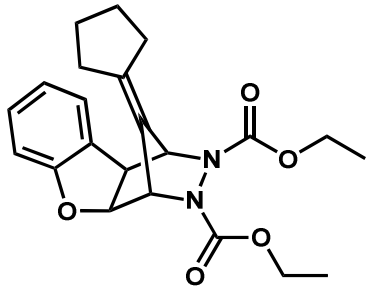
^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4, 144.2, 129.0, 125.6, 124.7, 120.7, 119.3, 109.4, 82.4, 69.6, 62.7, 61.9, 49.6, 38.9, 36.8, 31.5, 27.8, 14.5, 14.0.

HRMS (FAB) for $C_{27}H_{32}N_2O_5$, calcd (M^+):464.23; Found (M+1): 465.20.

Compound 50b

Following the general experimental procedure, the bicyclic hydrazine **49b** (156 mg, 0.69 mmol) 2-iodophenol **18a** (50 mg, 0.23 mmol), Bu_4NCl (64 mg, 1.0 equiv.), K_2CO_3 (63 mg, 2.0 equiv.) and $PdCl_2$ (4.0 mg, 10 mol%) were taken in a Schlenk tube. The mixture was dissolved in DMF (2.0 mL) and stirred at room temperature for 16 hours under argon atmosphere gave the product **50b** as colorless viscous liquid (29 mg, 43%).

R_f: 0.36 (hexane/ethyl acetate = 8:2).



IR (neat) ν_{max}: 2982, 2918,2854, 1749, 1717, 1595, 1465, 1307, 1244, 1120, 909, 836 $cm.^{-1}$

^{1}H NMR(500 MHz, $CDCl_3$): δ 7.17 (br s, 1H), 7.12 (t, 1H, *J* =7.50 Hz), 6.87 (t, 1H, *J* = 7.50 Hz), 6.60 (d, 1H, *J* = 8.00 Hz), 5.06-4.89 (m, 3H), 4.27-4.13 (m, 4H), 3.97 (brs, 1H), 2.60 (s,1H), 2.31-2.27 (m, 1H), 1.93-1.84 (m, 2H), 1.75-1.64 (m, 4H), 1.31-1.23 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7, 154.1, 141.8, 137.2, 136.7, 135.7, 133.7, 133.1, 129.8, 129.6, 128.7,128.2, 128.1, 127.7, 110.3, 105.7, 64.8, 63.2, 56.2, 49.2, 14.3.

HRMS (FAB) for $C_{22}H_{26}N_2O_5$, calcd (M^+):398.18; Found (M+1): 399.20.

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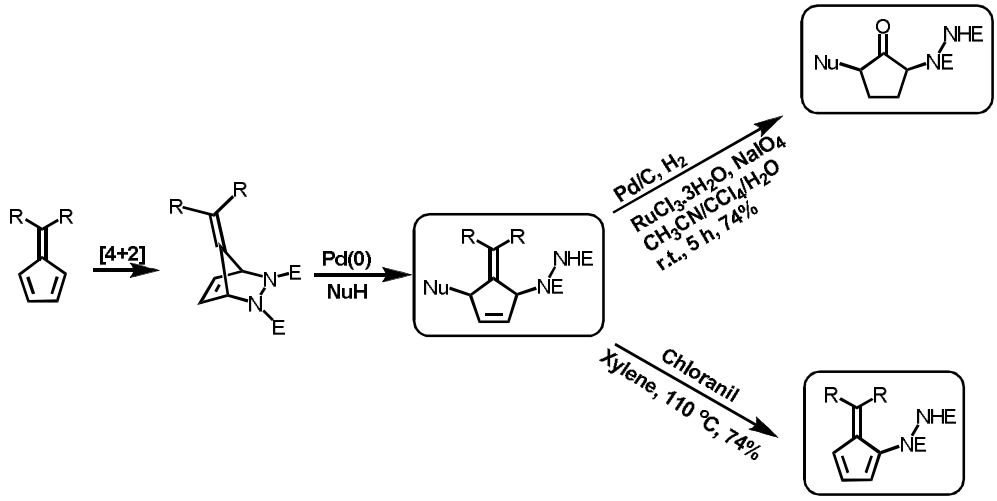
SUMMARY

The thesis entitled "**PALLADIUM CATALYZED CARBON-CARBON/CARBON-HETEROATOM BOND FORMATION REACTIONS UTILIZING PENTAFULVENE DERIVED BICYCLIC HYDRAZINES**" embodies the results of our investigations in the area of palladium catalyzed desymmetrization of pentafulvene derived bicyclic hydrazines.

The introductory chapter presents an overview of pentafulvenes with special emphasis on synthetic applications of their cycloadducts. A definition of the present work is also incorporated in the chapter.

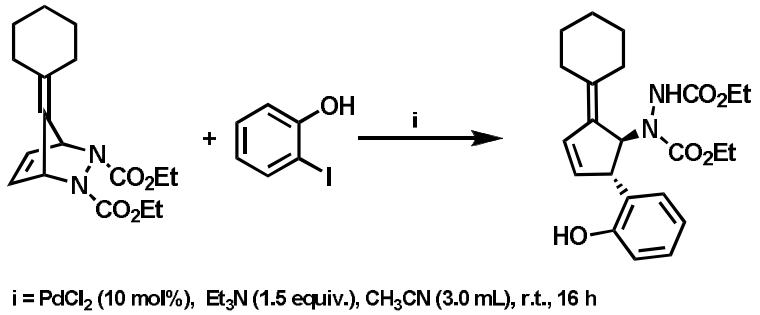
The second chapter describes the palladium mediated ring opening of pentafulvene derived bicyclic hydrazine using various soft nucleophiles *viz* phenols and active methylene compounds resulting in the synthesis of *cis*-1,2-disubstituted alkylidene cyclopentenes. The possibility for further functionalization was effectively demonstrated by the synthesis of substituted cyclopentanones and 2-hydrazino fulvenes (Scheme 1). This has been published in *Synthesis* 2010(21): 3649-3656.



Scheme 1

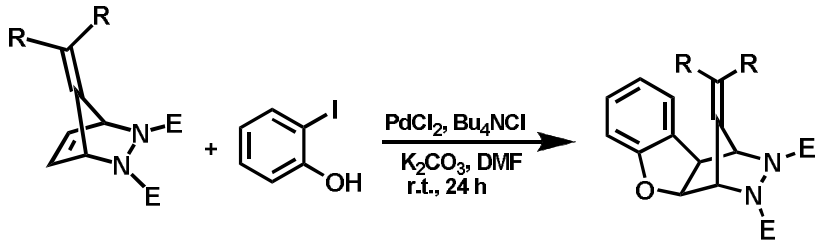
The third chapter of the thesis describes a novel synthesis of *trans*-disubstituted cyclopentenes *via* palladium catalyzed desymmetrization of fulvene derived

azabicyclic olefins with various aryl halides. By utilizing the developed strategy we could introduce different functionalities like aryl, heteroaryl and aryl groups with different functional groups to the cyclopentane skeleton. An illustrative example is presented in scheme 2 and these results are published in RSC Advances 2013, 00.



Scheme 2

The last part of the thesis describes the palladium catalyzed cyclopentannulation of pentafulvene derived bicyclic hydrazines with 2-iodophenols towards the synthesis of benzofuran fused bicyclic hydrazines (Scheme 3). The generality of the methodology was established by the reactions of various fulvene derived bicyclic hydrazines with differently substituted 2-iodophenols and these investigations are published as a full paper in *Tetrahedron*, 2012, 69, 152-159.



Scheme 3

In conclusion, we have unraveled a novel reactivity pattern of pentafulvene derived azabicyclic olefins with soft nucleophiles, mono and bicentered nulceophiles. Our investigations in this line have resulted in the development of general methodologies for the stereoselective synthesis of substituted alkylidene cyclopentenes. We have also developed a novel palladium catalyzed protocol for

the synthesis of benzofuran fused bicyclic hydrazines from fulvene derived bicyclic hydrazines and 2-iodophenols.

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