NOVEL SYNTHETIC TRANSFORMATIONS OF PENTAFULVENES TOWARDS ALKYLIDENE CYCLOPENTENES AND AZAPOLYCYCLES

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BY

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JUNE, 2008

.....To My Parents and Teachers

DECLARATION

*I hereby declare that the matter embodied in the thesis entitled "**Novel Synthetic Transformations of Pentafulvenes Towards Alkylidene Cyclopentenes and Azapolycycles**" is the result of the investigations carried out by me at the Organic Chemistry Section of National Institute for Interdisciplinary Science and Technology (CSIR), Trivandrum, under the supervision of **Dr. K. V. Radhakrishnan** and the same has not been submitted elsewhere for any other degree.*

Anas S.

Trivandrum
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CERTIFICATE

*This is to certify that the work embodied in the thesis entitled "**Novel Synthetic Transformations of Pentafulvenes Towards Alkylidene Cyclopentenes and Azapolycycles**" has been carried out by **Mr. Anas S.** under my supervision at the Organic Chemistry Section of National Institute for Interdisciplinary Science and Technology (CSIR), Trivandrum and the same has not been submitted elsewhere for any other degree.*

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Anas S.

CONTENTS

PREFACE

The reactions involving fulvenes and its derivatives have been the focus of intensive research in synthetic organic chemistry. Functionalization of fulvenes is a major synthetic tool for accessing valuable building blocks like polycyclic cyclopentanoids. 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.

Although the addition of hetero dienophiles to fulvenes was reported as early as 1968, to date, there is no detailed study on the synthetic utility of these adducts. In light of these and as part of our continuing interest in the chemistry of bicyclic hydrazines, we decided to explore the synthetic utility 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 organometallic reagents 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 "***Novel Synthetic Transformations of Pentafulvenes Towards Alkylidene Cyclopentenes and Azapolycycles***".

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/Lewis acid mediated ring opening of pentafulvene derived bicyclic

hydrazine with organostannanes, allylsilane and allylindium reagents leading to the novel synthesis of *trans*-disubstituted alkylidene cyclopentenes. It is noteworthy that alkylidene cyclopentenes are key intermediates in the synthesis of a number of biologically active molecules.

We have also unraveled a novel reactivity of organoboronic acids with fulvene derived bicyclic hydrazines leading to the stereoselective synthesis of alkylidene cyclopentenes. The generality of the methodology was established by carrying out the reactions of fulvene derived bicyclic hydrazines with aryl, heteroaryl and alkenyl boronic acids and these investigations are discussed in the third chapter.

After establishing a successful strategy for the desymmetrization of fulvene derived bicyclic hydrazines, our next aim was to elaborate the methodology using the cycloadduct from pentafulvenes and 1,2,4-triazoline-3,5-diones. Interestingly, the reaction between 6,6-diphenyl fulvene and 4-phenyl-1,2,4-triazoline-3,5-dione afforded a mixture of azapolycycles rather than the normal Diels-Alder adduct. The unusual reactivity between pentafulvenes and triazolinediones prompted us for a detailed investigation and the results constitute the subject matter of final chapter of the thesis. The observed reactivity is rationalized using systematic experimental and theoretical investigations. In addition, a detailed study on the host-guest complexation observed in the crystal structure of one of the product is also included in this chapter.

It may be mentioned that each chapter of the thesis is presented as an independent unit and therefore the structural formulae, schemes and figures are numbered chapter wise.

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

ABBREVIATIONS

Ac	: acetyl	dppf	: bis(diphenylphosphino)ferrocene
AcOH	: acetic acid	dppm	: bis(diphenylphosphino)methane
Ad	: adamantyl	dppp	: bis(diphenylphosphino)propane
AI	: aziridinium imide	EDG	: electron donating group
Ar	: argon	EWG	: electron withdrawing group
aq	: aqueous	EI	: electron impact
BINAP	: 2,2'-bis(dphenylphosphino)-1,1' binaphthyl	Et	: ethyl
		FAB	: fast atom bombardment
Bn	: benzyl	FMO	: frontier molecular orbital
Boc	: tertiary butyloxycarbonyl	h	: hour
^{t}Bu	: tertiary butyl	HMPA	: hexamethylphosphoramide
calcd	: calculated	HOMO	: highest occupied molecular orbital
cod	: 1,5-cyclooctadiene	HRMS	: high resolution mass spectra
Cpd	: cyclopentadiene	Hz	: hertz
Cy	: cyclohexyl	IMDA	: intramolecular Diels-Alder
d	: doublet	IR	: infrared
dba	: dibenzylidene acetone	*J*	: coupling constant
dd	: doublet of a doublet	LA	: Lewis acid
DDQ	: dichlorodicyanobenzoquinone	LDA	: lithium diisopropylamine
DBU	: 1,8-diazabicyclo[5.4.0]undec-7-ene	LUMO	: lowest unoccupied molecular orbital
DCM	: dichloromethane	m	: multiplet
DMF	: dimethyl formamide	Me	: methyl
dppb	: bis(diphenylphosphino)butane	MESP	: molecular electrostatic potential
dppe	: bis(diphenylphosphino)ethane	mg	: milligram

mL : millilitre

Mp : melting point

MS : mass spectroscopy

NBD : norbornadiene

NMR : nuclear magnetic resonance

Nu : nucleophile

o : ortho

p : para

PDC : pyridinium dichromate

Ph : phenyl

PhH : benzene

PMB : *para*-methoxy benzene

^{i}Pr : isopropyl

PTAD : 4-phenyl-1,2,4-triazoline-3,5-dione

q : quartet

R_f : retention factor

RT : room temperature

s : singlet

t : triplet

TAD : 1,2,4-triazoline-3,5-dione

Tf : triflyl(trifluoromethane sulfonyl)

TFA : trifluoroacetic acid

THF : tetrahydrofuran

TLC : thin layer chromatography

TMM : trimethylenemethane

TMS : trimethylsilyl

Tol : tolyl

TS : transition state

TsOH : toluene sulphonic acid

tert : tertiary

UV : ultra violet

Chapter 1

Pentafulvenes: Versatile Synthons in Organic Synthesis

1.1. Introduction

The non-functionalized carbon-carbon multiple bond systems are recognized as latent functional groups; however they are generally unreactive towards carbon nucleophiles due to their electron rich π-orbitals. Fulvenes, cyclic molecules with odd number of carbon atoms in the ring belong to the category of non-functionalized carbon-carbon double bonds.[1] They are the prototype of cyclic cross-conjugated molecules and possess a particular type of polar system with a unique π-electron display. Based on their dipole moments as well as on their reactivity patterns, fulvenes would occupy an intermediate position between the open chain olefinic and aromatic compounds.

The reactions involving fulvenes and their derivatives have intrigued chemists for more than a century due to their theoretical, mechanistic, and synthetic importance. Among various fulvenes, pentafulvenes enjoy a coveted status owing to its unique reactivity pattern and the versatility of the reaction products.[2] Pentafulvenes are mainly utilized as versatile intermediates to access new carbo as well as 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,[3] capnellene,[4] β-vetivone,[5] hinesol,[6] silphinene,[7] viburtinal,[8] longifolene[9] etc (Figure 1.1). Fulvenes have also been utilized for the synthesis of titanocene anticancer drugs[10] and various aminocyclopentitols with

glycosidase inhibitory activity.[11] Fulvenes and benzofulvenes have been patented as anti-inflammatory agents having antipyretic and analgesic activity.[12]

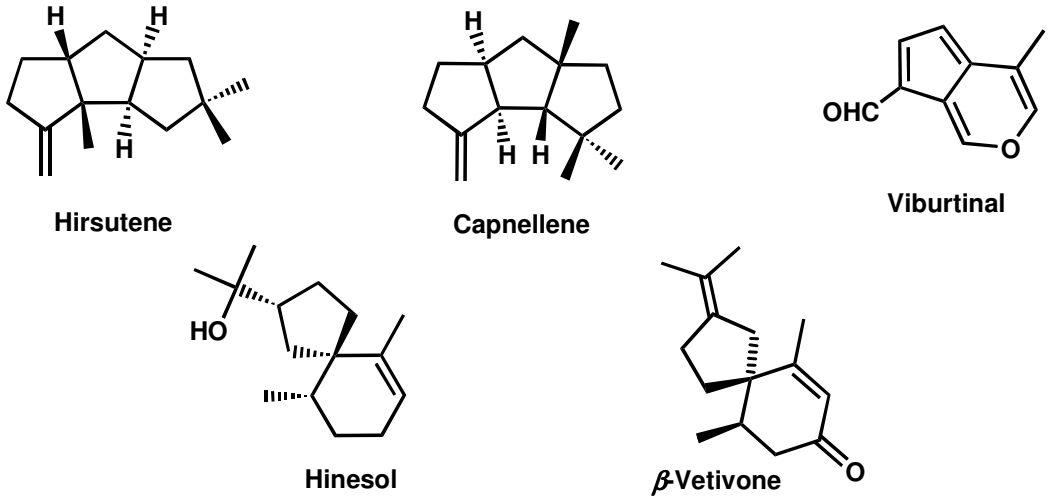


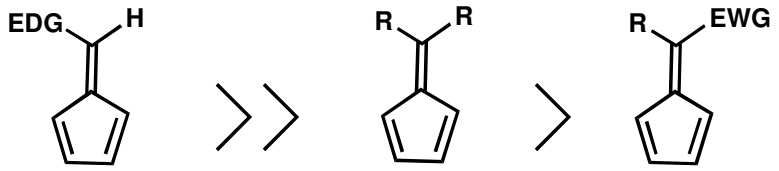
Figure 1.1 Some natural products synthesized from pentafulvenes

1.2. Pentafulvenes: Some important aspects

Pentafulvenes, the first synthetic colored hydrocarbons, exhibit unique physical and chemical properties, depending on the type of substituent at the exocyclic carbon atom. These cyclic cross-conjugated systems possess high polarizability and non-benzenoid aromaticity. The dipole moment of fulvenes is mainly attributed to the polarity of the exocyclic double bond. Therefore pentafulvenes may be regarded as all carbon analogues of the organic carbonyl compounds.

Due to chemical instability, they have been considered for a long time as non-aromatic.[13] The ground state of fulvenes presents a strong polyolefinic character as compared to the aromaticity exhibited by benzene ring. The electronic nature of substituents at the exocyclic position markedly influence the aromatic character of pentafulvenes.[14] The presence of electron donating groups at the exocyclic position of the pentafulvene strongly stabilize the ring system, leading to a substantial increase in aromatic character. For example, the N,N-dimethyl

aminofulvene is more aromatic than 6,6-dialkyl or diaryl fulvenes and shows remarkable differences in their reactivity.[15]



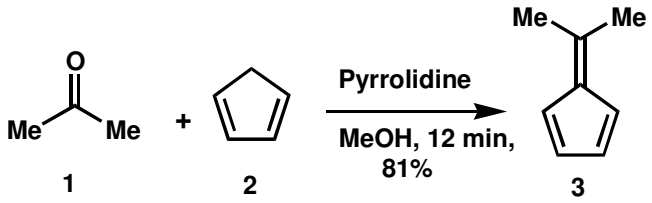
EDG = Electron donating groups **EWG = Electron withdrawing groups**

Scheme 1.1 Order of aromaticity of pentafulvenes

1.3. Synthesis of pentafulvenes

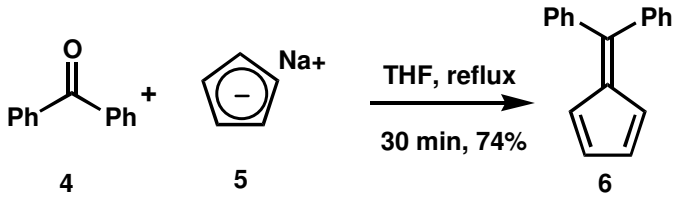
Pentafulvene was first synthesized and named (Latin, *fulvus,* meaning yellow) by Thiele in 1900.[16] This method involved the condensation of cyclopentadiene with ketones or aldehydes using an alkali metal base in an alcohol, providing the product in modest to good yields. The scope and limitation of this method depends on the reactivity of the carbonyl compound and on the stability of the fulvene formed. However, the yields for these reactions averaged 50% for bases like alkoxides and alcoholic solutions of hydroxides. In this scenario, Freiesleben suggested a modified procedure to improve the yield of the reacton by using primary or secondary amines as bases.[17]

In 1983, Stone and Little developed a more versatile and convenient synthesis of pentafulvenes.[18] They showed that pyrrolidine efficiently promotes fulvene formation from cyclopentadiene and corresponding carbonyl compounds (Scheme 1.2). 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 1.2

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.[19] 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 1.3).[20]



Scheme 1.3

1.4. Reactivity of pentafulvenes

Different aspects of the reactivity of pentafulvenes have been reported during the last decade. These fascinating molecules display a wide range of reactions with nucleophiles, electrophiles and various cycloaddition partners.[21] 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.[22] 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.[23] However, the synthetic potential of pentafulvenes were mainly exploited in periselective cycloaddition reactions.

1.5. Cycloaddition reactions of pentafulvenes

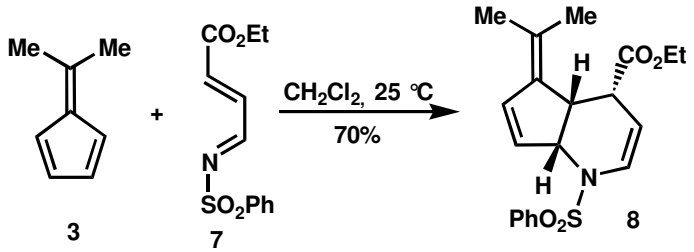
Cycloadditions of fulvenes provide versatile and powerful approaches to various natural products and biologically active molecules.[24] Because of its diverse reactivity profile in cycloadditions, pentafulvenes have received remarkable attention both from the synthetic and theoretical point.[25] In cycloadditions,

pentafulvenes can participate as a 2π, 4π, or 6π component, depending on the number of electrons furnished by the competing partner.[26] The periselectivity of these reactions is controlled by the substituents on the fulvene and the other substrate.[27] Many intermolecular and intramolecular cycloaddition reactions of fulvenes that illustrate their versatility have been unraveled and are well documented in literature.

1.5.1. Intermolecular cycloaddition reactions

Intermolecular cycloaddition reactions are the most widely exploited reactivity profile of pentafulvenes. Pentafulvenes behave as 2π components with electron deficient dienes, 4π component with dienophiles and as 6π components with electron-rich dienes.[28] The addition of relatively electron deficient 4π systems occur across the endocylic alkene moiety of pentafulvenes, while in few reports the exocyclic double bond acting as 2π component has been described.[29] In presence of strongly electron donating substituents at exocyclic carbon, fulvenes prefer to act as 6π components with electron deficient diene systems.[28b]

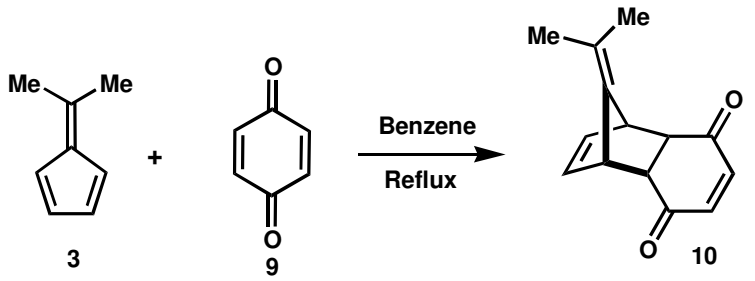
Hong and co-workers have demonstrated a highly regio- and stereoselective inverse electron demand Diels-Alder cycloaddition of pentafulvenes, acting as 2π components with azadienes. The [2+4] cycloaddition of dimethyl fulvene **3** and N-sulfonyl-1-aza-1,3-butadiene **7** afforded the tetrahydro-[1]-pyrindine derivative **8** in good yield (Scheme 1.4).[30]



Scheme 1.4

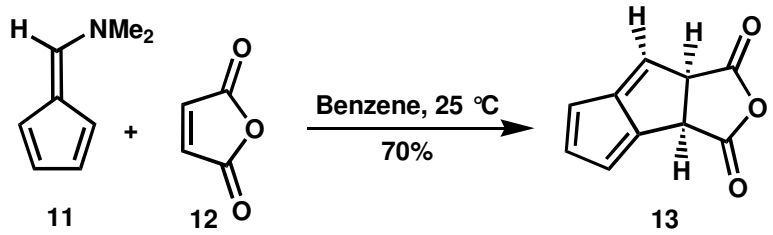
In addition to the reaction with various hetero and homo dienes, pentafulvenes can function as highly reactive dienes with various dienophiles.

Pentafulvenes undergo smooth Diels-Alder reaction with dienophiles like maleimide, maleic anhydride, *p*-quinone and dialkyl azodicarboxylates to afford the corresponding bicyclic adducts in good yields.[31] A typical Diels-Alder cycoaddition of pentafulvene **3** with quinone **9** is presented in scheme 1.5.



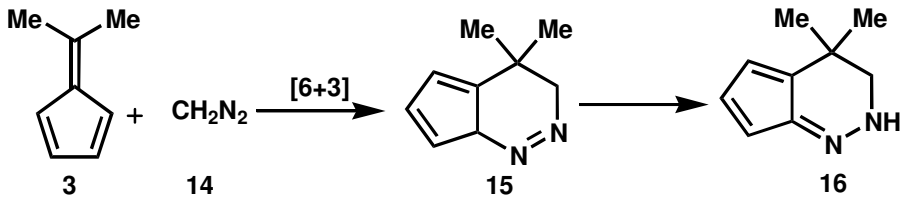
Scheme 1.5

As mentioned earlier, the reactivity of fulvenes mainly depends on the polarity of the exocyclic double bond. Therefore more electron rich fulvenes show different behaviour towards dienophiles. For example, 6-(N,N-dimethylamino) fulvene **11** undergoes a [6+2] cycloaddition with maleic anhydride **12** to produce a novel pentalene derivative **13** in 70% yield (Scheme 1.6).[32]



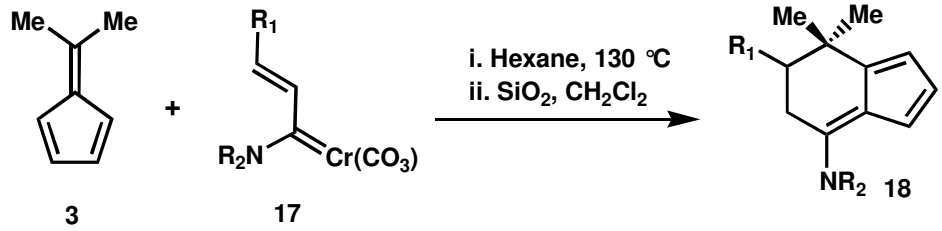
Scheme 1.6

The reactions of pentafulvenes with various dipoles are also exploited for the construction of many biologically important polycycles.[33] Diazomethane**,** a 1,3-dipole with well established nucleophilic character adds to 6,6-dimethyl fulvene **3** exclusively in a [6+3] fashion to give the product **16**, after tautomerization of the initially formed cycloadduct **15**.[34]



Scheme 1.7

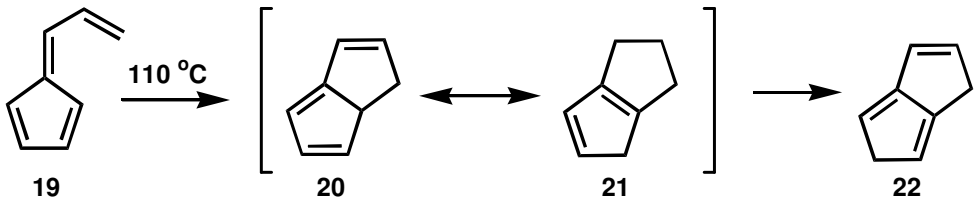
Recently, Barluenga and co-workers have disclosed a novel reactivity of pentafulvenes with Fischer carbene complexes. Scheme 1.8 represents an example for the [6+3] cycloaddition of pentafulvenes with alkenyl carbene complexe **17** to produce amino indene derivatives and the strategy is outlined in Scheme 1.8.[35]



Scheme 1.8

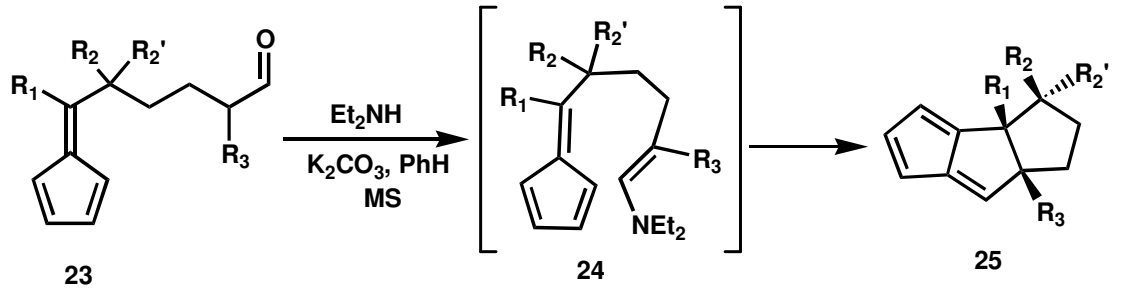
1.5.2. Intramolecular cycloaddition reactions

Intramolecular cycloaddition, one of the powerful strategies for construction of polycyclic molecules, have been applied to a variety of fulvene containing substrates. In 1971, Gajewski and Cavender reported a facile thermal intramolecular cyclization of 6-vinyl fulvene **19** to produce dihydropentalene **22** (Scheme 1.9).[36]



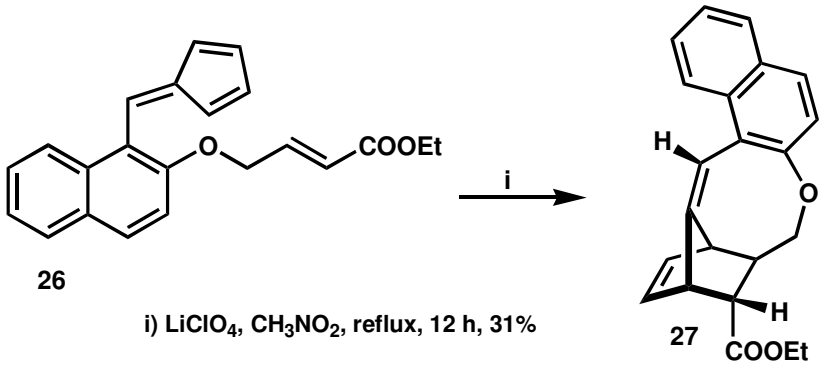
Scheme 1.9

An intramolecular cyclization of fulvene **24** to form tricyclopentanoid skeleton **25** was described by Houk and co-workers in 1985.[37] The reaction goes through a [6+2] cycloaddition pathway and is illustrated in scheme 1.10.



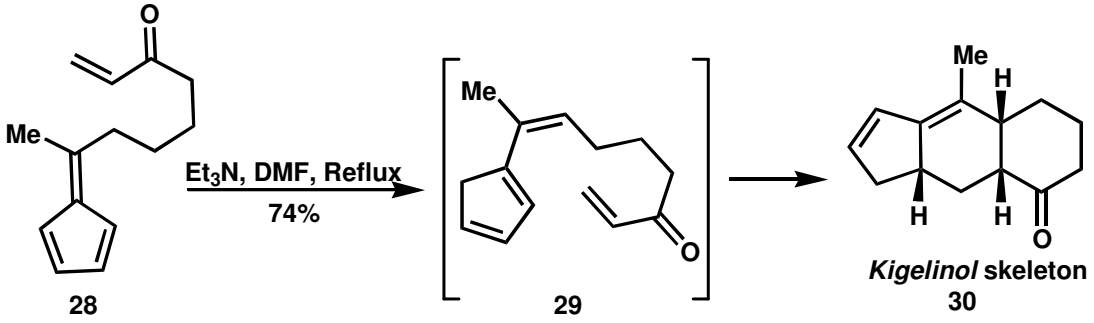
Scheme 1.10

Raghunathan *et al.* have reported an interesting intramolecular [4+2] cyloaddition of fulvene **26**, leading to the formation of 6-oxatricyclo-[6.4.0.0]-dodeca-2,11-diene ring systems (Scheme 1.11).[38]



Scheme 1.11

Recently, Hong and co-workers have described an alternative and elegant Intramolecular Diels-Alder (IMDA) cycloaddition in simple acyclic fulvenes towards a variety of polycyclic ring skeletons such as kigelinol, neoamphilactane, kempane *etc.* An example for the synthesis of kigelinol skeleton **30** from the fulvene **28** is depicted in scheme 1.12.[39]

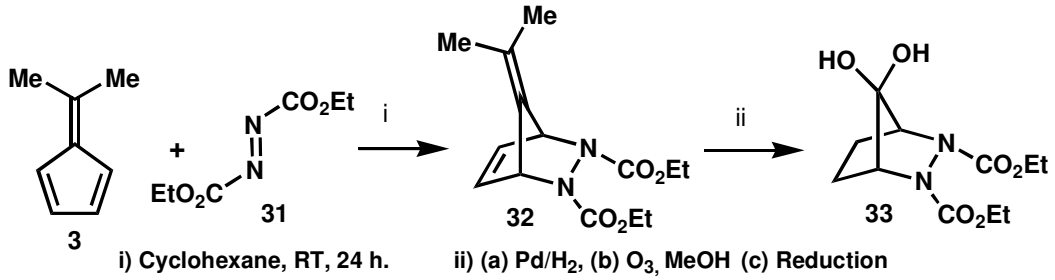


Scheme 1.12

1.6. Synthetic utilization of pentafulvene adducts

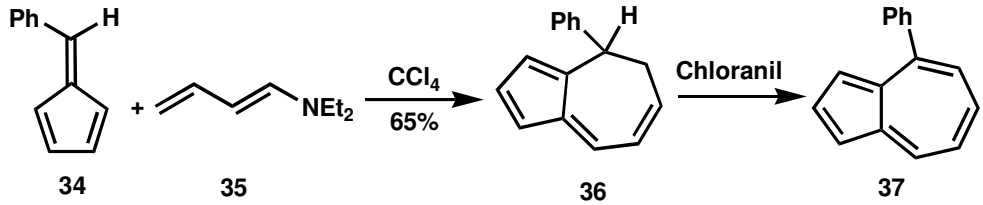
Compared to the rich literature in the area of cycloaddition chemistry of pentafulvenes, much less attention has been paid to the synthetic utilization of their cycloadducts. Tactical manipulations on the chosen adduct offer the prospects for designing a variety of molecular skeletons that are important in biological systems. In this perspective, a brief review on the synthetic modifications of pentafulvene derived adducts are given in the following section.

The pioneering report on the synthetic modification of a pentafulvene derived adduct can be tracked back to the work of Alford *et al.* in 1968.[40] After establishing a novel Diels-Alder cycloaddition between dimethyl fulvene **3** and diethyl azodicarboxylate **31**, they have efficiently modified the resulting bicyclic adduct **32** into a stable ketone hydrate **33** (Scheme 1.13).



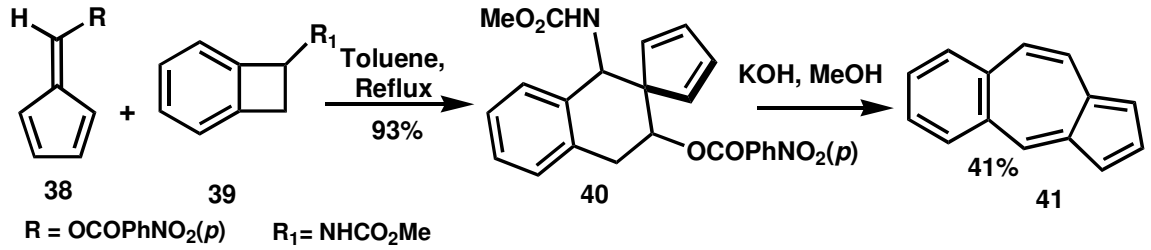
Scheme 1.13

Houk and co-workers have evolved a new strategy for the synthesis of azulenes *via* a single step conversion of the initially formed [6+4] cycloadduct from pentafulvenes and electron rich dienes. The cyclization of 6-phenyl fulvene **34** with 1-diethylamino butadiene **35** afforded the hydrazulene derivative **36** in 65% yield and the product was converted to azulene **37** on treatment with chloranil (Scheme 1.14).[41]



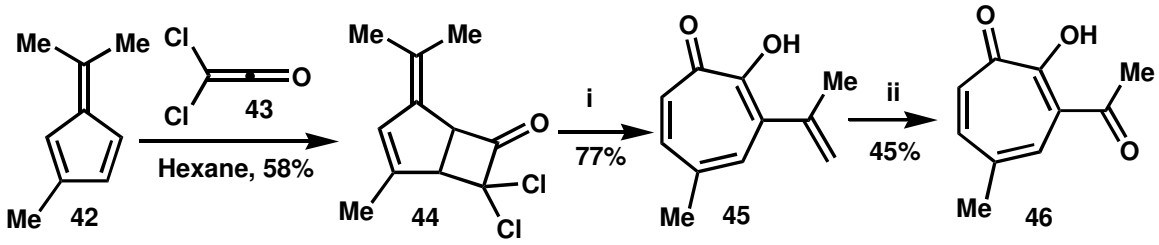
Scheme 1.14

The same group have unraveled a novel reactivity of 6-[(*p*-nitrobenzoyl)oxy]-fulvene **38** with [(methoxycarbonyl)amino]benzocyclobutene **39**, leading to the formation of the spiro adduct **40** in 93% yield, which can be converted to the benzoazulene **41.**[42] The strategy is delineated in scheme 1.15.



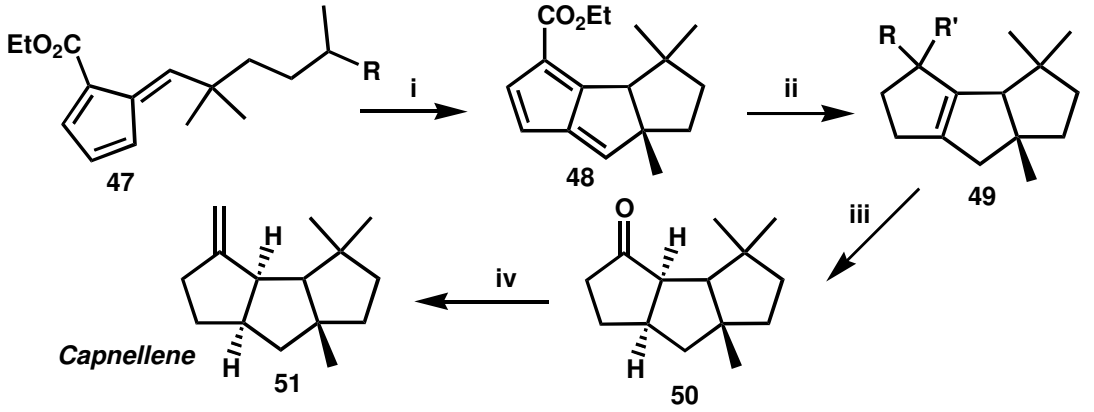
Scheme 1.15

Imafuku and Arai developed a route towards substituted tropolone derivatives *via* synthetic modification of the cyloadduct from 2,6,6-trimethylfulvene **42** and dichloroketene **43**. The hydrolysis of the cycloadduct **44** followed by the treatment with hydrazoic acid afforded 5-alkyl-3-acetyl tropolone **46** (Scheme 1.16).[43]



Scheme 1.16

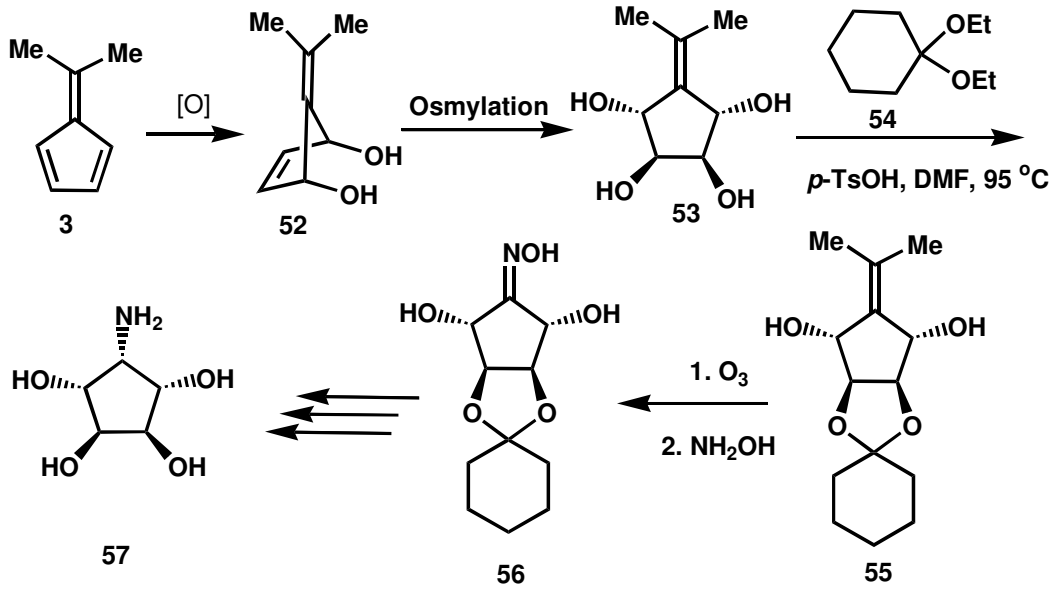
In his seminal work in 1990, Houk *et al.* described the synthesis and regioselective intramolecular cycloaddition of ester substituted fulvenes into synthetically useful tricyclopentanoid skeletons. They have further extended the synthetic potential of this molecule **48**, towards the total synthesis of capnellene **51**. The synthetic route is outlined in scheme 1.17.[44]



(i) N-Methylaniline, 4 A^0 MS; (ii) a) Mg, MeOH, RT, 64%, b) 10% NaOH, 60 ^{0}C, 100%, c) LDA, -78 ^{0}C, THF, HMPA, d) O_2, RT, H_3O^+, e) $Pb(OAc)_4$, 57%; (iii) a) Li, NH_3, b) PDC, DCM, 62% overall; (iv) CH_2=PPh_3

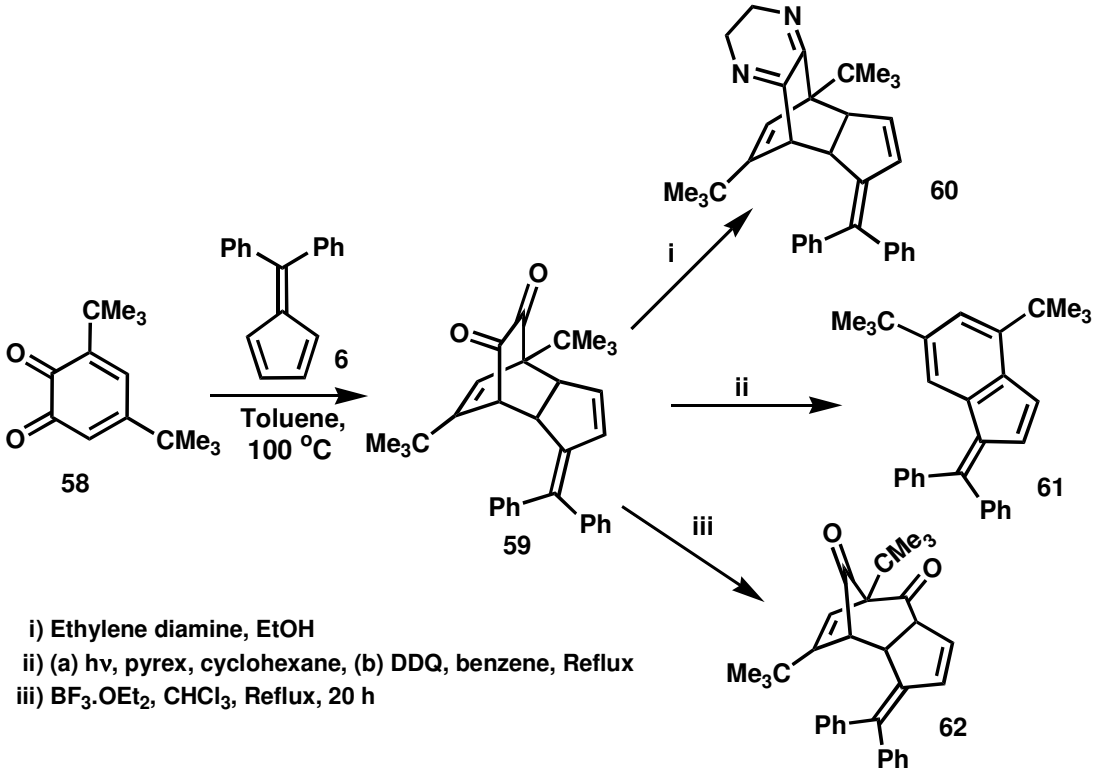
Scheme 1.17

Ganem and colleagues proposed a novel route to various aminocyclopentitols with glycosidase inhibitory activity from fulvene.[11] The reaction sequence starts with the sensitized photo-oxygenation of fulvene **3** to produce 1,4-ketol **52,** which on catalytic osmylation resulted in the formation of tetraol **53**. The protected syn-diol **55** was converted to trehazoline and other cyclopentanoids of biological interest.



Scheme 1.18

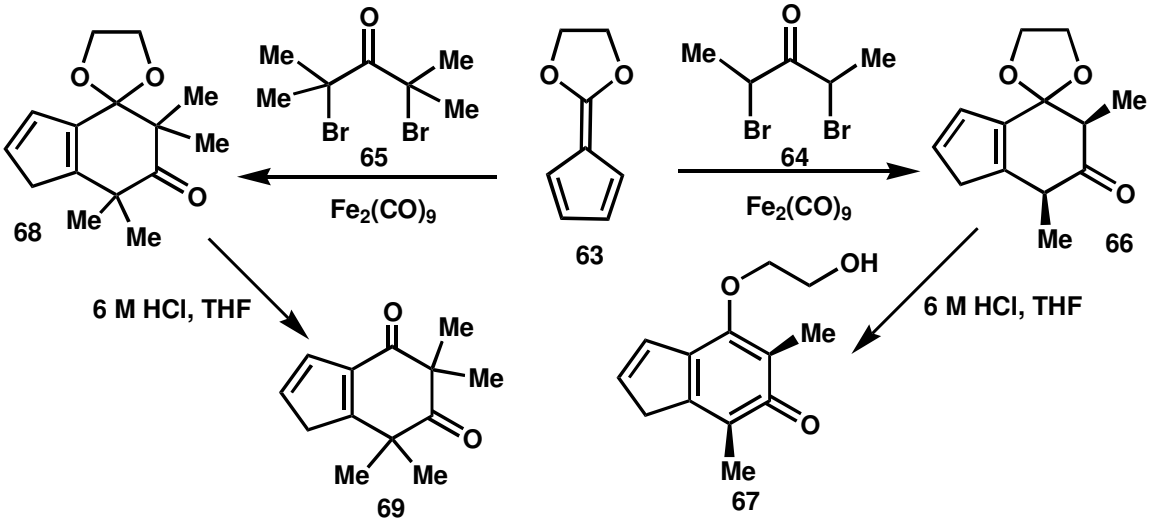
Studies from our laboratory have uncovered some novel facets in the cycloaddition reactions of pentafulvenes with *o*-quinones.[45] The bicyclo[2.2.2]octen-7,8-dione adduct **59** was isolated in excellent yield from the reaction of 6,6-diphenyl fulvene **6** with the substituted 1,2-benzoquinone **58**. The adduct **59** undergo facile double decarbonylation reaction on photolysis providing an efficient route towards highly substituted indene and benzene derivatives.[46] The condensation of the adduct **59** with 1,2-diamines smoothly afforded pyrazino barrelene derivative **60**, while the Lewis acid catalyzed rearrangement of the bicyclo[2.2.2] adduct **59** afforded bicyclo[3.2.1] systems (Scheme 1.19).[47]



Scheme 1.19

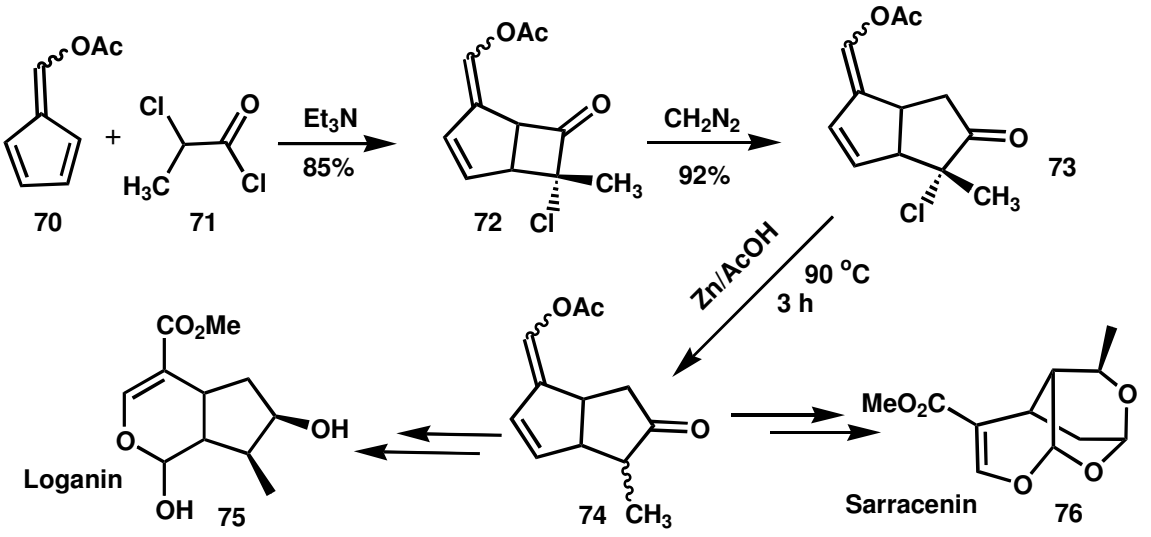
B. -C. Hong and co-workers described a novel approach to indane systems by utilizing the metal mediated [6+3] cycloaddition reactions of fulvenes with di- and tetra- substituted oxyallyl cations.[48] The reaction of fulvene ketene acetal **63** with the oxyallyl cations **64** and **65** in presence of $Fe_2(CO)_9$, yielded the corresponding cycloadducts in good yields. Direct hydrolysis of these ketal adducts gave

different products; tetrasubstituted adduct afforded the diketone **69**, while disubstituted ketal gave indene **67** (Scheme 1.20).



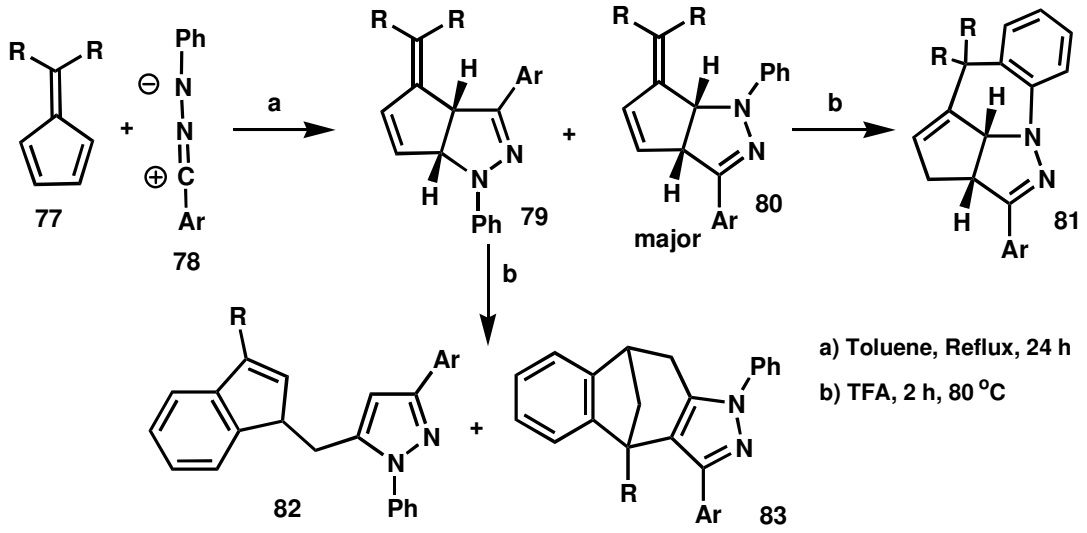
Scheme 1.20

The total synthesis of Iridoid natural products Loganin and Sarracenin was reported by N. C. Chang and co-workers by utilizing the cycloadduct from 6-acetoxyfulvene **70** and *in situ* generated methyl chloroketenes. The key step in the synthesis was the conversion of the cycloadduct **72** into an intermediate diquinane **73** (Scheme 1.21).[49]



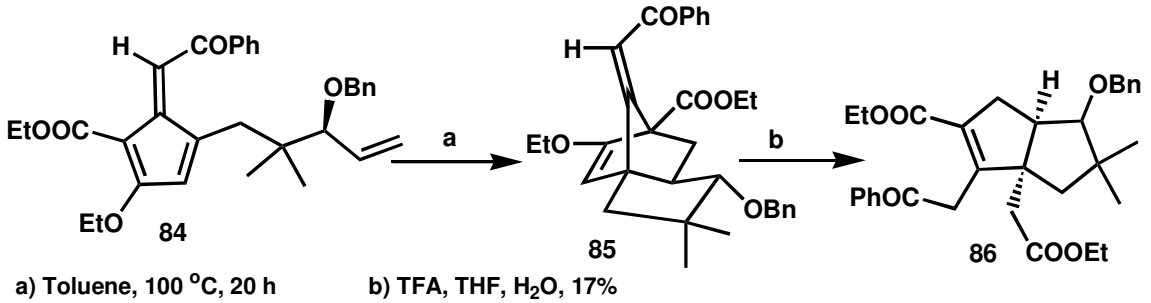
Scheme 1.21

Ciamala *et al.* have demonstrated the [3+2] dipolar cycloaddition reactions of diphenyl fulvene with various diaryl-nitrilimines **78** leading to regioisomeric pyrazoline derivatives. The acid promoted intramolecular rearrangement of the cycloadducts **79** and **80** provided a novel entry into substituted quinoline and pyrazole derivatives (Scheme 1.22). [50]



Scheme 1.22

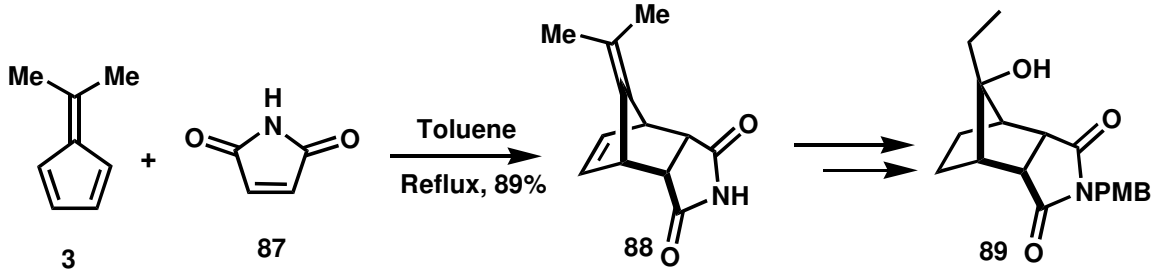
Hatanaka and co-workers have described a highly regio and stereoselective intramolecular [4+2] cycloaddition of 4-alkenyl fulvene **84** prepared from 1,4-ynedione and allylidene phosphorane. The resulting [4+2] adduct on treatment with TFA gave bicyclo[3.3.0]octane skeleton **86**. [51]



Scheme 1.23

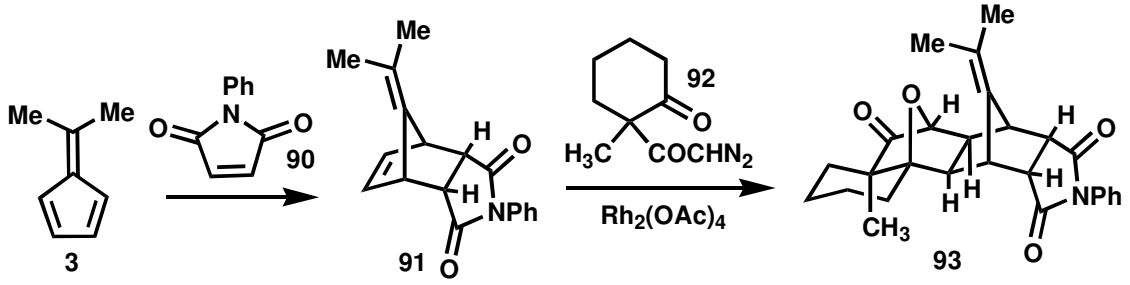
The reaction of 6,6-dimethyl fulvene **3** and maleimide **87** in refluxing toluene produced [4+2] cycloadducts as an 8:1 mixture of *exo* and *endo* isomers. The

major *exo* isomer **88** was easily converted into the module **89**, which is used as abiotic receptors toward neutral organic guest molecules (Scheme 1.24).[52]



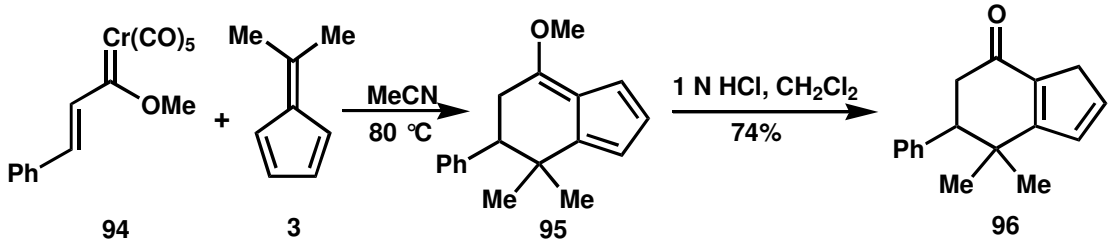
Scheme 1.24

Muthusamy *et al.* have evolved an efficient and stereoselective protocol for the construction of *syn*-facially bridged norbornane frameworks **93** from pentafulvene derived norbornene derivatives *via* reactions with rhodium carbenoids generated from diazo ketones (Scheme 1.25).[53]



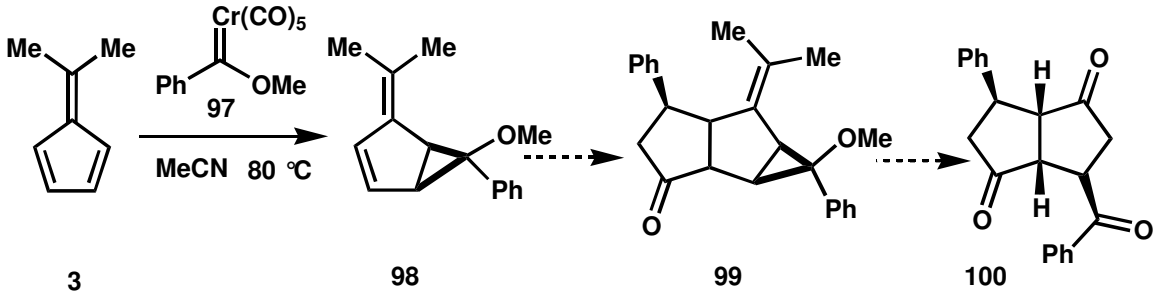
Scheme 1.25

Jose Barluenga and co-workers recently developed a novel and easy access to indane and dihydroindene derivatives *via* [6+3] cycloaddition reaction of pentafulvenes with alkenyl alkoxycarbene complex **94** (Scheme 1.26).[54]



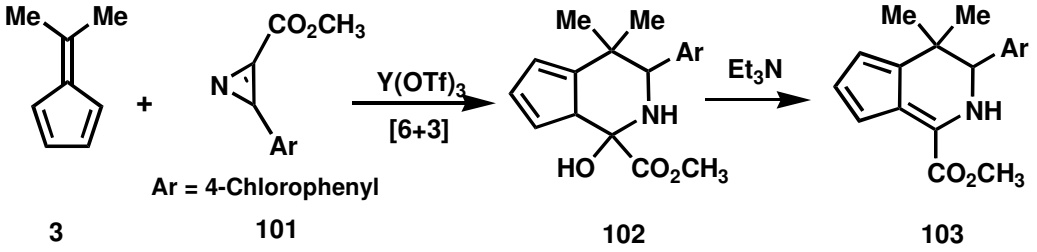
Scheme 1.26

Modification of the above methodology using chromium alkoxycarbene complex **97** provided a novel strategy for annulated cyclopentanone or diquinane systems and the synthetic strategy is depicted in scheme 1.27.[55]



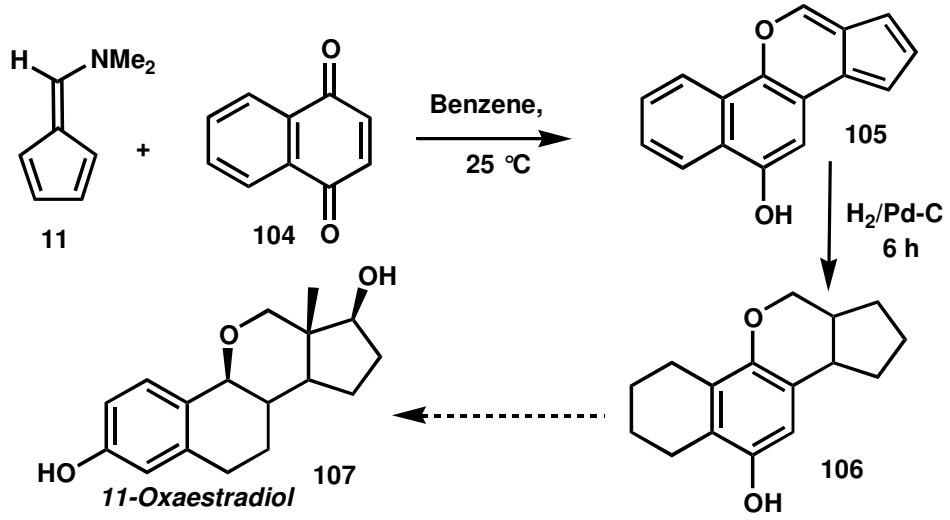
Scheme 1.27

Hong *et al.* have found that in the presence of a Lewis acid, 2H-azirine **101** react with fulvenes through a formal regioselective [6+3] cycloaddition pathway and the treatment of the resulting adduct **102** with Et_3N afforded [2]pyrindine derivative **103** (Scheme 1.28). [56]



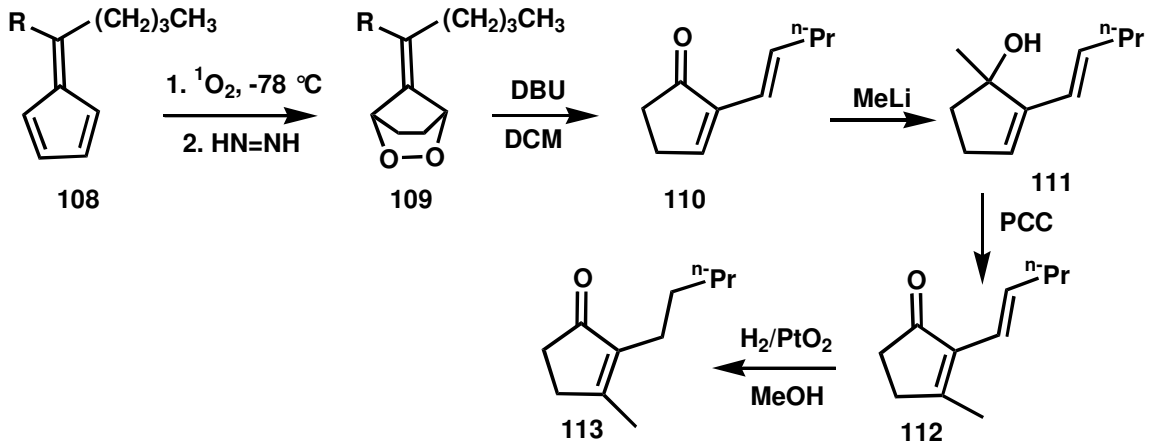
Scheme 1.28

Same authors have recently reported a novel hetero [6+3] cycloaddition of fulvenes towards the synthesis of 11-oxasteroids.[57] 6-(N,N-dimethylamino)fulvene **11** reacts with quinone **104** in a [6+3] fashion to afford the oxa-tricyclic product **102**, which on catalytic hydrogenation for 6 hours afforded 11-oxaesteroid framework **107** (Scheme 1.29).



Scheme 1.29

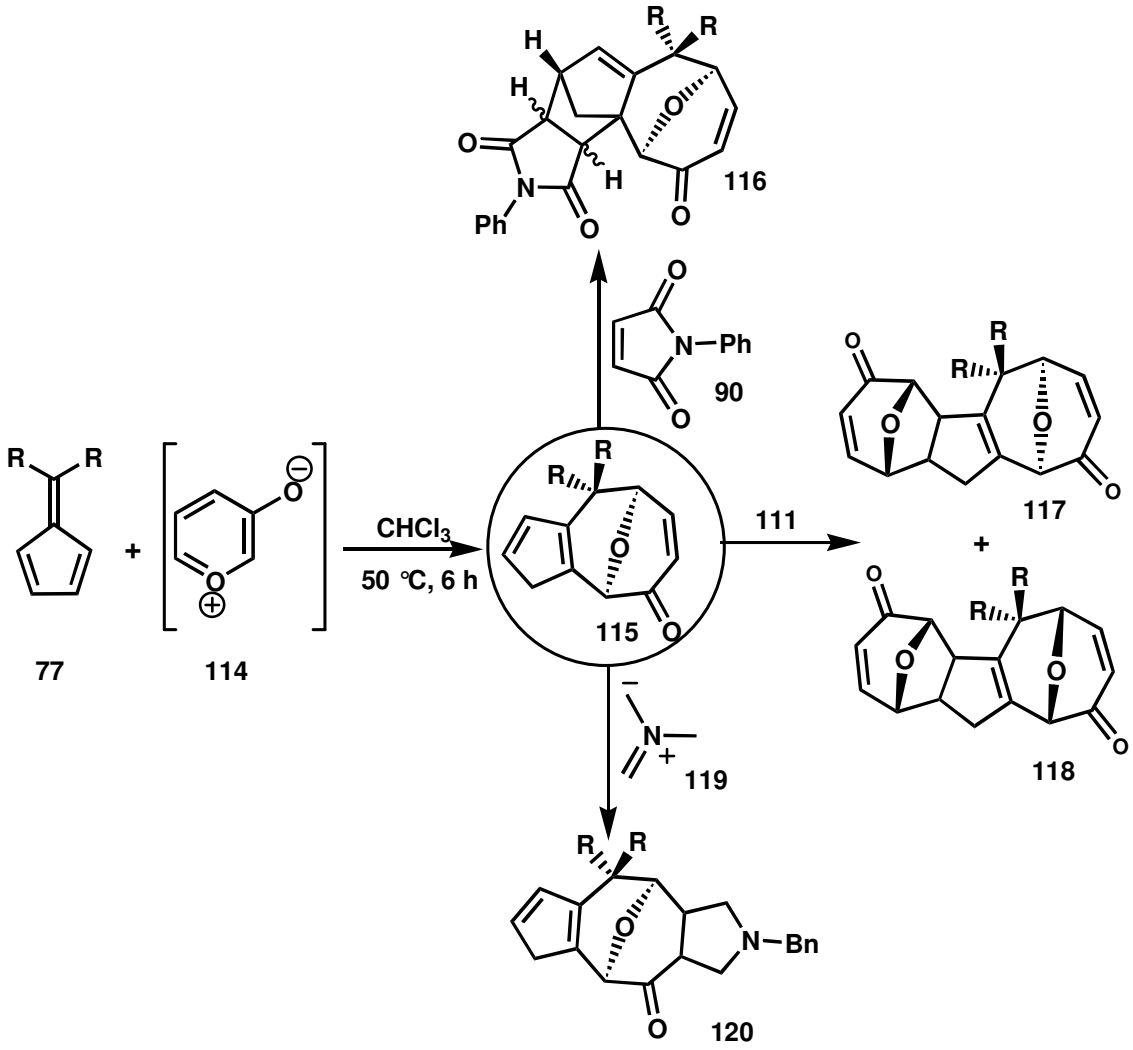
The saturated endoperoxides derived from fulvene **108** undergo an unusual base promoted isomerization in one pot to afford 2-vinyl-2-cyclopentenone **110**.[58] This methodology, developed by Erden *et al.* was implemented in the short synthesis of a naturally occurring fragrant compound, dihydrojasmone and the strategy is illustrated in scheme 1.30.



Scheme 1.30

Recent investigations from our own laboratory have unraveled a novel [6+3] cycloaddition profile of pentafulvenes with 3-oxidopyrylium betaines leading to 5-8 fused cyclooctanoids **115** and the synthetic versatility of these products were enhanced by further useful transformations.[59] For example, the adduct **115** undergo

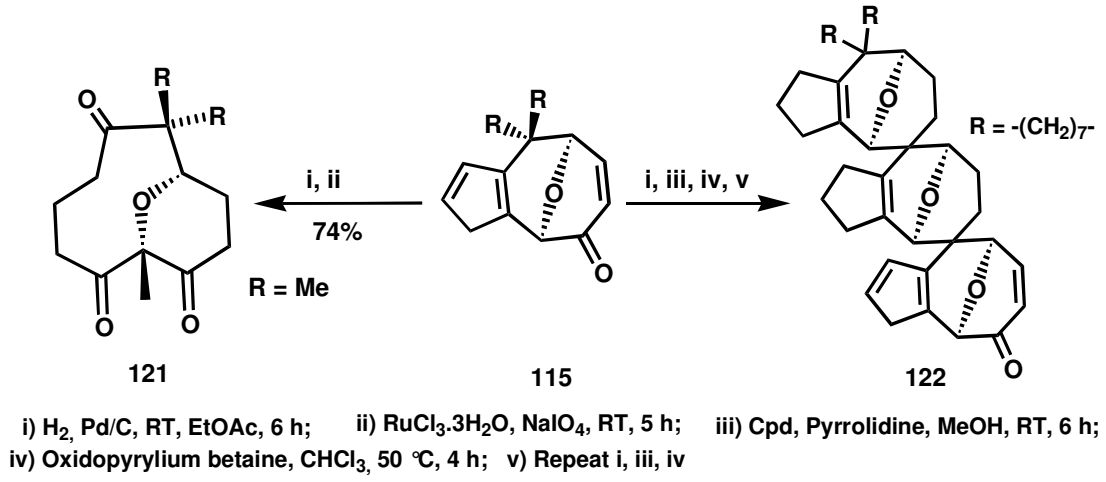
facile Diels-Alder reaction with dienophile like **90** and dipolar cycloaddition with azomethine ylide **119** to afford the polycycles **116** and **120**.[60] The carbon frame work of **115** was further expanded through the cycloaddition reaction with another molecule of 3-oxidopyrylium betaines and a variety of 7-5-8 fused oxa-bridged cyclooctanoids of the type **117** and **118** were synthesized in excellent yields (Scheme 1.31).[61]



Scheme 1.31

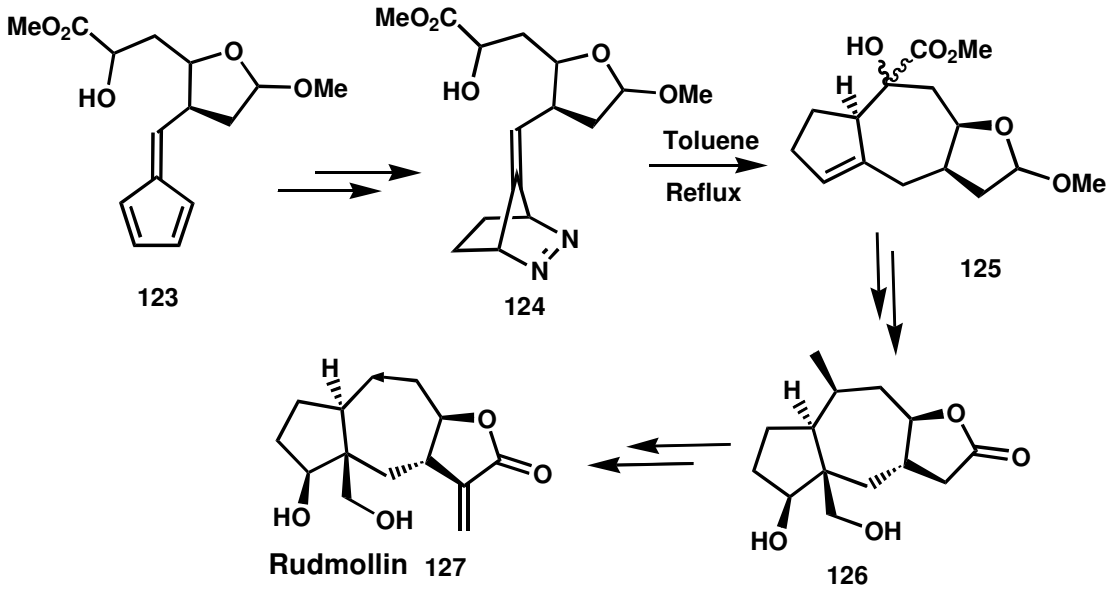
Recently, our studies have further elaborated the synthetic utility of the adduct **115**, by converting it into synthetically and biologically useful molecular

frameworks such as 11-membered carbocycles and spirocyclic cycloooctanoids (Scheme 1.32).[62]



Scheme 1.32

Little and co-workers have utilized the azabicyclic adduct derived from pentafulvene **123,** towards the total synthesis of *rudmollin,* which displays *in vivo* activity against P-388 lymphoid leukemia. The key step in the synthesis involves the conversion of the modified cycloadduct **124** in to the tricycle **125**, through an atom transfer cyclization (Scheme 1.33).[63]



Scheme 1.33

1.7. Conclusion and present work

From the above discussions it is clear that a variety of useful molecular skeletons have been synthesized through short and easy chemical manipulations of pentafulvene derived adducts. Although, the addition of heterodienophiles to fulvenes was reported as early as 1968,[39] to date, there is no serious attempt to study the synthetic utility of the resulting adduct. In light of these and as part of our continuing interest in the chemistry of bicyclic hydrazines,[64] we decided to explore the synthetic potential of pentafulvene derived azabicyclic olefins. The investigations along this line form the focal theme of the thesis.

Our attention was drawn to 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 organometallic reagents, will provide a novel access to biologically important alkylidene cyclopentenes. Given the ubiquitous nature of alkylidene cyclopentenes in biologically active molecules and in natural products, a method to access these molecules would be useful in synthetic organic chemistry. The details of these investigations describing the synthesis of allyl, vinyl, heteroaryl and hetero atom substituted alkylidene cyclopentenes using various organostannanes/silane/indium reagents are presented in the second chapter of the thesis.

We have also unraveled a novel reactivity of organoboronic acids with pentafulvene derived bicyclic hydrazines leading to the stereoselective synthesis of *trans*-vicinal disubstituted alkylidene cyclopentenes and these investigations are discussed in the third chapter.

The fourth and final chapter deals with the detailed investigations on the interesting reactivity of pentafulvenes with triazolinediones, affording novel azapolycycles. The observed reactivity is rationalized using detailed theoretical investigations, which revealed that both cycloaddition and nucleophilic mechanisms are operative in the reaction conditions.

1.8. References

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Chapter 2

Facile Synthesis of Alkylidene Cyclopentenes *via* Palladium/Lewis Acid Mediated Desymmetrization of Fulvene Derived Bicyclic Hydrazines

2.1. Introduction

Transition metal-catalyzed reactions have revolutionized the art and practice of organic synthesis over the past few decades and emerged as the most widely applicable protocol for the construction of many important molecular skeletons.[1] The formation of carbon-carbon or carbon-hetero atom bonds in this fashion has undergone significant development in recent years. One of the recent interests in this area is the generation of multiple stereocenters through the addition of nucleophiles to heterobicyclic alkenes, with concomitant ring opening.[2] The present chapter describes the palladium catalyzed desymmetrization of pentafulvene derived bicyclic hydrazines with various organometallic reagents leading to the stereoselective synthesis of alkylidene cyclopentenes. Before going into the details, a brief introduction about alkylidene cyclopentanes is presented in the following section.

2.2. Alkylidene cyclopentanes

The widespread occurrence and interesting biological activities of substituted cyclopentane derivatives in nature make them important targets for synthesis.[3] Among various cyclopentane derivatives, alkylidene cyclopentanes hold special attention as intermediates in the construction of biologically interesting molecules including (+) and (-)-nigellamine A_2,[4] guanacastepene A[5] etc. Trost's synthesis of

(+)-allocyathin B_2 which has interesting biological activities, involves an alkylidene cyclopentenone as the key intermediate.[6] Alkylidene cyclopentanes can easily be converted to piperidine alkaloids like streptazolins,[7] odoriferous compounds like β-vetivone,[8] α-vetispirene,[9] hirsutene,[10] liseaverticillols[11] etc. Some of the structurally related compounds are shown in figure 2.1.

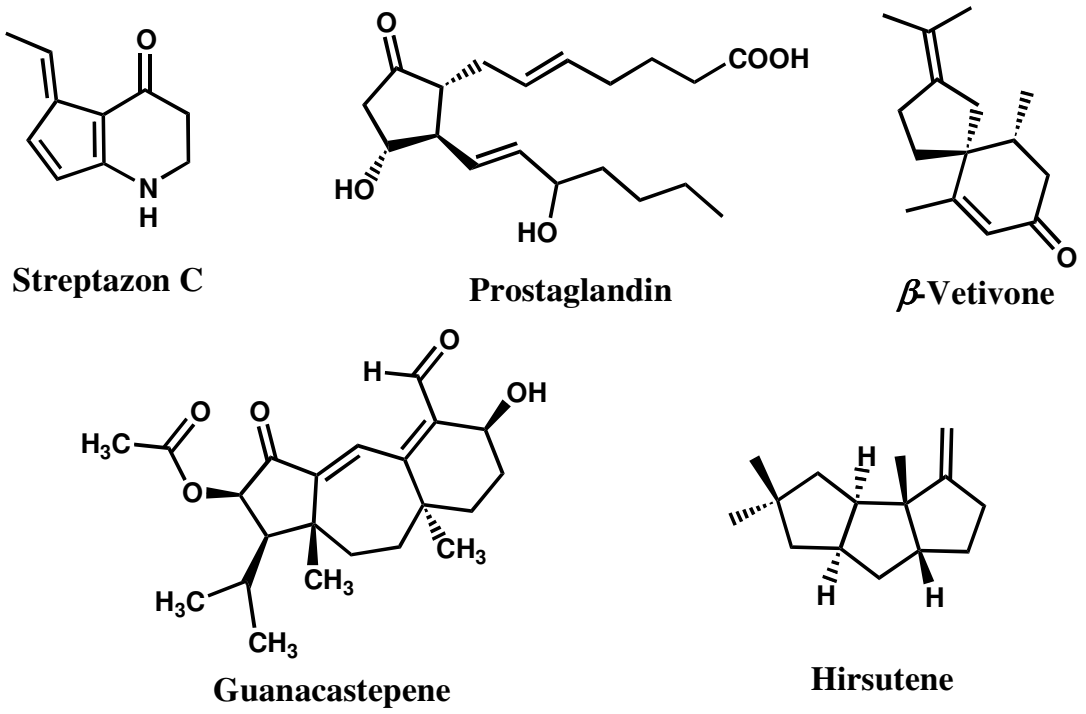
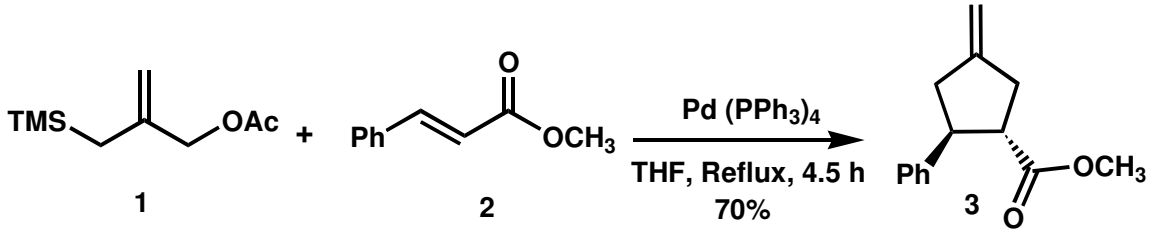


Figure 2.1. Natural products containing alkylidene cyclopentane skeleton

2.2.1. Synthesis of alkylidene cyclopentanes

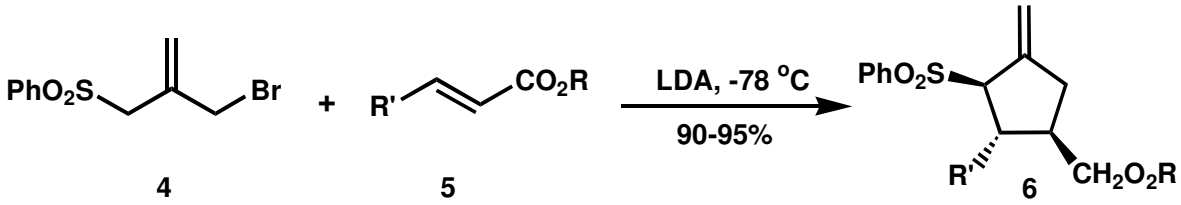
Though a number of reports are known[12] toward the synthesis of substituted cyclopentene derivatives, there is only scant information available for the direct access to alkylidene cyclopentenes and its derivatives. Trost and co-workers have elegantly utilized the trimethylenemethane (TMM) chemistry for the introduction of various substituents to the cyclopentane core.[13] 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).[13a]



1 2 3

Scheme 2.1

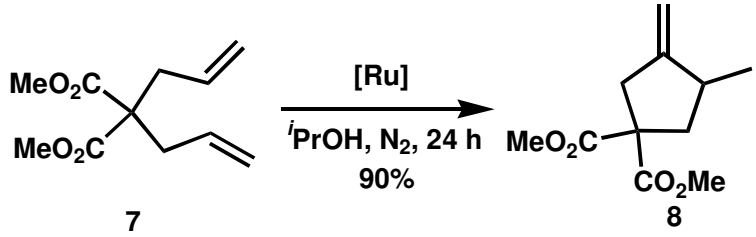
Hassner and co-workers have elaborated this methodology by using 2-bromomethyl-3-phenylsulfonyl-l-propene **4** as the TMM precursor and synthesized the trisubstituted methylidene cyclopentane **6** in good yields.[14] The reaction is outlined in scheme 2.2.



4 5 6

Scheme 2.2

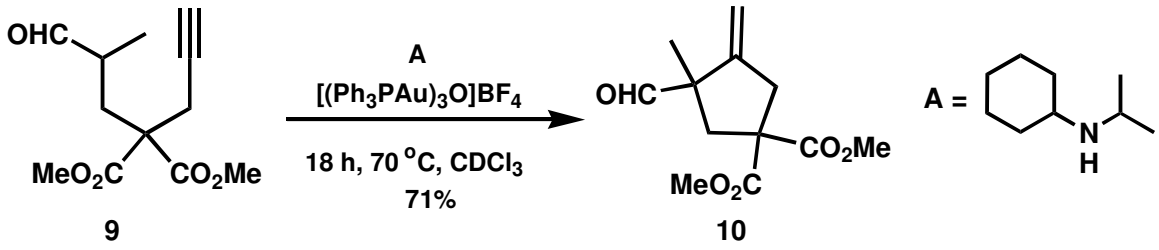
Itoh *et al.* have provided[15] another interesting and more versatile protocol for the construction of these molecules by a ruthenium catalyzed regioselective cycloisomerization of 1,6-heptadiene **7** (Scheme 2.3).



7 8

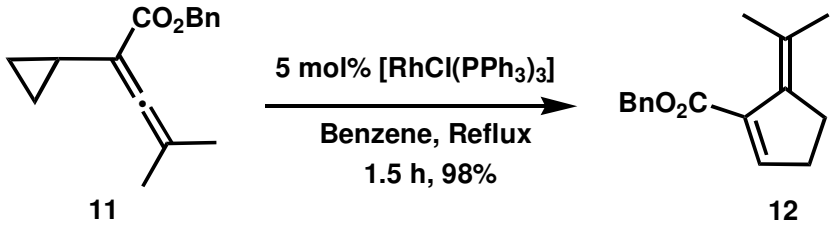
Scheme 2.3

Stefan F. Kirsch has shown that formyl alkyne **9** undergo cyclizations on activation with catalytic amounts of a Au(I) complex and a secondary amine, leading to the synthesis of highly functionalized methylidene cyclopentane **10**. The synthetic protocol is illustrated in Scheme 2.4.[16]



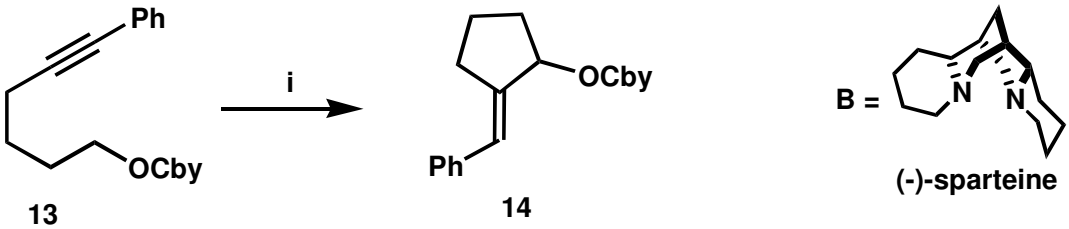
Scheme 2.4

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.[17] For example, heating allenylcyclopropane **11** in refluxing benzene for 1.5 h in the presence of $[RhCl(PPh_3)_3]$ gave the corresponding methylene cyclopentene **12** in 88% yield. (Scheme 2.5).



Scheme 2.5

D. Hoppe adopted a (-)-sparteine mediated stereoselective intramolecular carbolithiation strategy for the enantiopure synthesis of functionalized alkylidene cyclopentane **14** from substituted hexynyl carbamate **13** (Scheme 2.6).[18]

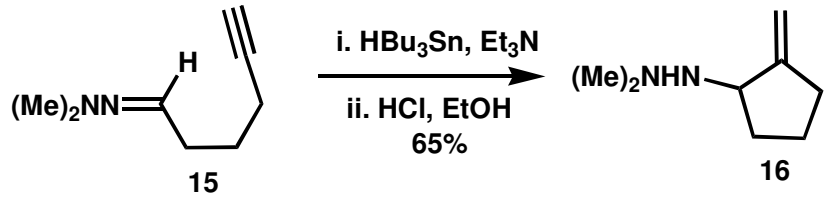


i = 1) *s*-BuLi, (-)-sparteine, Et_2O, -78 °C; 2) MeOH, -78 °C

Scheme 2.6

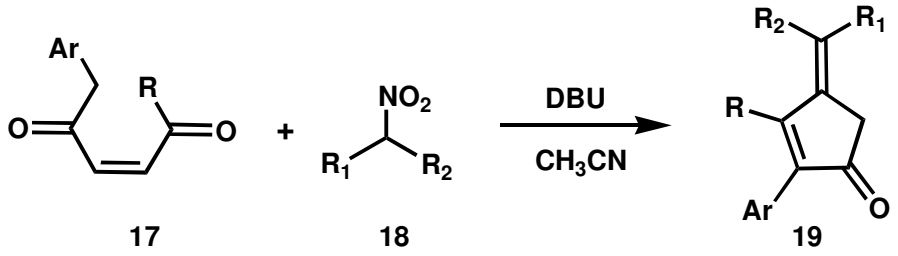
Jose Marco-Contelles described an interesting synthesis of methylidene cyclopentenes *via* 5-exo-trig free radical cyclization of alkyne tethered multiple

carbon-nitrogen molecule **15** in presence of tributyltinhydride and triethylamine. The reaction sequence is delineated in Scheme 2.7.[19]



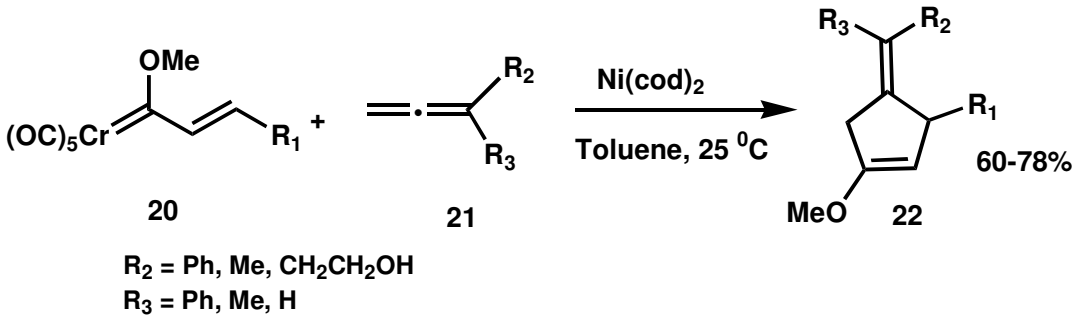
Scheme 2.7

Stereoselective synthesis of 4-alkylidene cyclopentenones **19** was reported by Petrini *et al.* by the reaction of 1,4-diketone **17** with various functionalized nitro alkenes **18** in presence of DBU (Scheme 2.8).[20]



Scheme 2.8

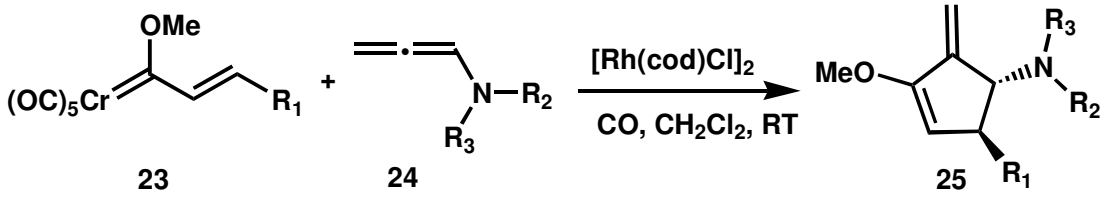
In 2004, Barluenga and co-workers have unraveled a novel synthesis of alkylidene cyclopentenes by a nickel (0) mediated [3+2] cyclization of chromium alkenyl carbene complex **20** with 1,1-disubstituted allenes **21** (Scheme 2.9).[21]



Scheme 2.9

Recently, 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 **23** with aminoallene **24** in the presence of 10 mol% of

$[Rh(cod)Cl]_2$ resulted in the formation 5-methylidene cyclopentene derivatives **25**, in good yields (60-99%). The reaction is presented in Scheme 2.10.



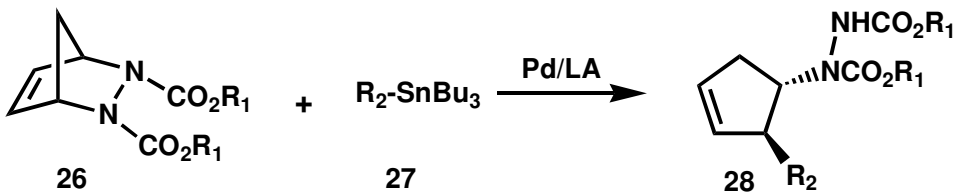
23 **24** **25**

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. Statement of the Problem

One of the ultimate goal and challenge in synthetic organic chemistry is to develop novel and efficient transformations for the creation of functionalized molecules with structural diversity. In this context, the transition metal-catalyzed transformations of heterobicyclic alkenes have great potential to achieve these targets.[23] Recent investigations from our laboratory have shown that cyclopentadiene derived bicyclic hydrazines **26** undergo ring opening with organostannanes leading to the synthesis of *trans*-vicinal disubstituted hydrazino-cyclopentenes **28** (Scheme 2.11).[24]



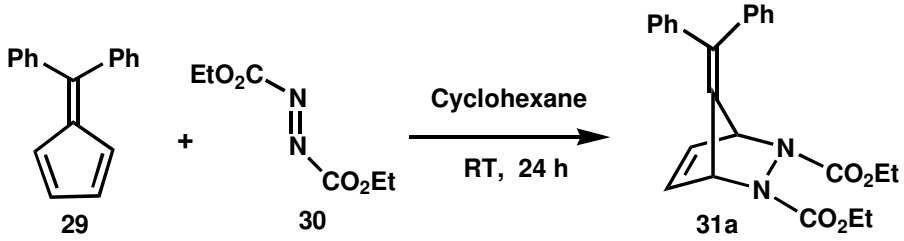
26 **27** **28**

Scheme 2.11

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

2.4. Results and discussion

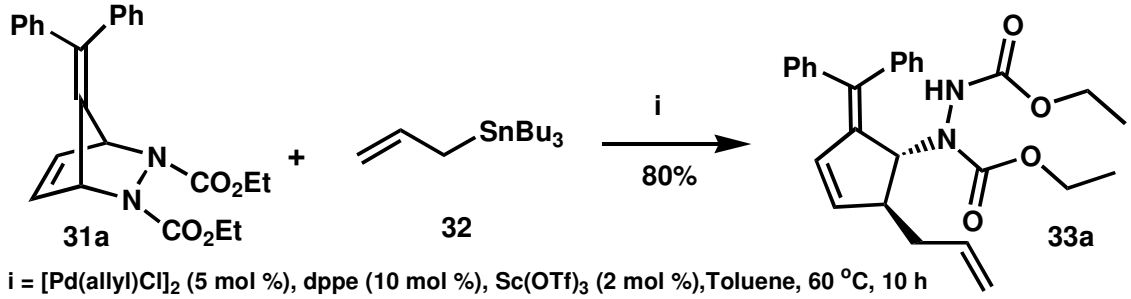
The azabicyclic olefins required for our investigations were prepared as per the literature procedures.[25] For example, the 2,3-diazabicyclo[2.2.1]hept-5-ene **31a** was synthesized by the Diels-Alder cycloaddition of pentafulvene **29** with diethyl azodicarboxylate **30** (Scheme 2.11).



Scheme 2.12

2.4.1. Desymmetrization reactions using allylstannane

Our experiments started with the reaction of 2,3-carbethoxy-7-diphenylmethylene-2,3-diazabicyclo[2.2.1]hept-5-ene **31a**, with allyltributyltin **32** in presence of $[Pd(allyl)Cl]_2$, dppe and $Sc(OTf)_3$ in toluene. The reaction afforded the substituted alkylidene cyclopentene **33a** in 80% yield (Scheme 2.12).



i = $[Pd(allyl)Cl]_2$ (5 mol %), dppe (10 mol %), $Sc(OTf)_3$ (2 mol %),Toluene, 60 ^oC, 10 h

Scheme 2.13

The structure of the compound **33a** was established by spectroscopic analysis. In the IR spectrum, the signals at 1742 and 1713 cm^{-1} were diagnostic of the carboethoxy group, whereas NH absorption was discernible at 3302 cm^{-1}. In the ^{1}H NMR spectrum (Figure 2.2), the two ring olefinic protons were observed as a multiplet in the region δ 6.34-6.31 ppm and as a doublet at δ 6.06 ppm respectively. A broad multiplet centered at δ 5.82 ppm and another multiplet centered at δ 5.13 ppm was assigned to the olefinic methine and methylene protons of the allylic group. The protons on C-3 and C-4 were observed as multiplets in the region δ 3.31-3.18 and 5.56-5.46 ppm, respectively. The two independent multiplets resonated in the regions δ 2.58-2.43 ppm and δ 2.30-2.20 ppm were indicative of protons on the C-7 carbon.

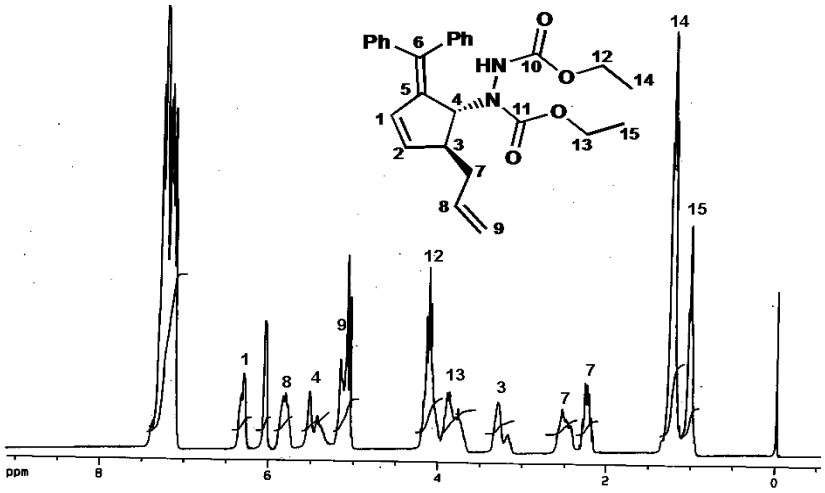


Figure 2.2. ^{1}H NMR spectrum of compound **33a**

^{13}C NMR spectrum of **33a** (Figure 2.3) positioned the two carbonyl peaks at δ 155.3 ppm and δ 153.4 ppm, while the signal due to methylene carbons of the carboethoxy groups appeared at δ 62.1 and 61.9 ppm. The characteristic allylic carbons were discernible at δ 136.5, 116.9 and 37.5 ppm. The C-3 and C-4 carbons were observed at δ 49.4 and 61.3 ppm respectively. All other signals were in good agreement with the proposed structure. Finally, the structure of the

compound was further confirmed by mass spectral analysis, HOMO-COSY NMR studies and by comparison to literature data.[22,24]

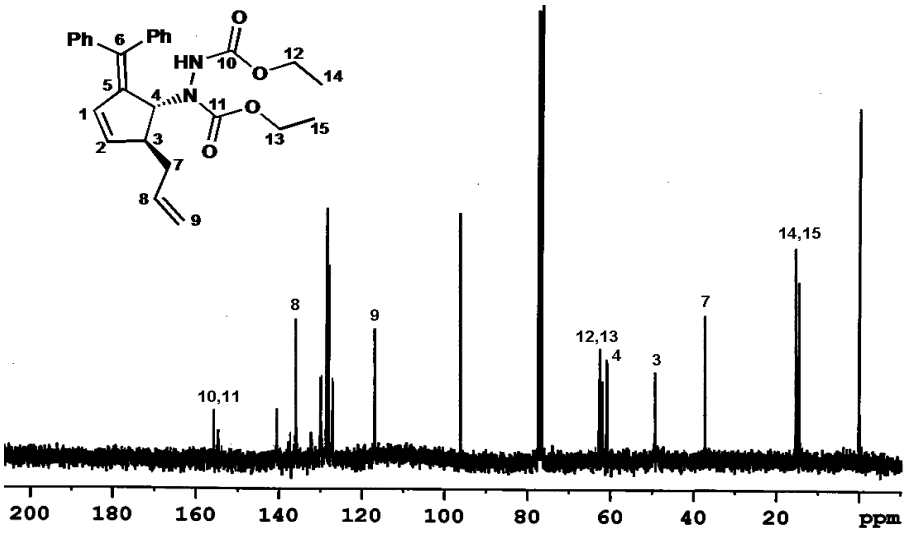


Figure 2.3. ^{13}C NMR spectrum of compound **33a**

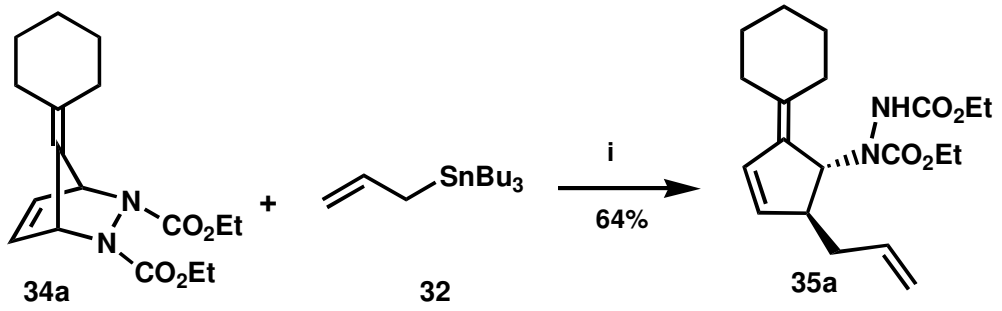
In order to develop a suitable catalytic system for this transformation, we undertook detailed optimization studies using different catalyst/ ligand/ Lewis acid systems and the details are given in table 2.1. After a series of experiments, 5 mol % $Pd_2(dba)_3.CHCl_3$ along with 20 mol % PPh_3 as ligand and 2 mol % $Sc(OTf)_3$ as Lewis acid was found to be the best condition for this transformation with toluene (at 60 ^{o}C) as the solvent.

Table 2.1 Optimization studies using different catalysts / ligands/Lewis acids

Entry	Catalyst	Ligand	Lewis acid	Yield (%)
1	$[Pd(allyl)Cl]_2$	dppe	$Sc(OTf)_3$	80
2	$[Pd(allyl)Cl]_2$	dppm	$Sc(OTf)_3$	56
3	$[Pd(allyl)Cl]_2$	dppb	$Sc(OTf)_3$	61
4	$[Pd(allyl)Cl]_2$	dppf	$Sc(OTf)_3$	46
5	$Pd_2(dba)_3.CHCl_3$	dppe	$Sc(OTf)_3$	65
6	$Pd_2(dba)_3.CHCl_3$	dppm	$Sc(OTf)_3$	56
7	$Pd_2(dba)_3.CHCl_3$	dppb	$Sc(OTf)_3$	62
8	$Pd_2(dba)_3.CHCl_3$	dppf	$Sc(OTf)_3$	64
9	$Pd_2(dba)_3.CHCl_3$	PPh_3	$Sc(OTf)_3$	88[a]
10	$Pd_2(dba)_3.CHCl_3$	P(*o*-Tol)$_3$	$Sc(OTf)_3$	67[a]
11	$Pd(OAc)_2$	dppe	$Sc(OTf)_3$	32
12	$Pd(OAc)_2$	dppf	$Sc(OTf)_3$	13
13	$Pd(OAc)_2$	PPh_3	$Sc(OTf)_3$	28[a]
14	$PdCl_2$	dppe	$Sc(OTf)_3$	30
15	$Pd_2(dba)_3.CHCl_3$	PPh_3	$Yb(OTf)_3$	77[a]
16	$Pd_2(dba)_3.CHCl_3$	PPh_3	$Cu(OTf)_2$	66[a]
17	$Pd_2(dba)_3.CHCl_3$	PPh_3	$Sn(OTf)_2$	78[a]
18	$Pd_2(dba)_3.CHCl_3$	PPh_3	I_2	60[a]

Conditions: Adduct (2 equiv.), Allylstannane (1 equiv.), Catalyst (5 mol %), Ligand (10 mol %), Lewis acid (2 mol %), Toluene, 60 °C, 10 h, [a]20 mol % Ligand was used.

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-pentamethylene fulvene derived bicyclic hydrazine **34a** and allyltributyltin **32** under the optimized conditions, afforded the corresponding cycloalkylidene cyclopentene **35a** in 64% yield. The reaction is illustrated in Scheme 2.14.

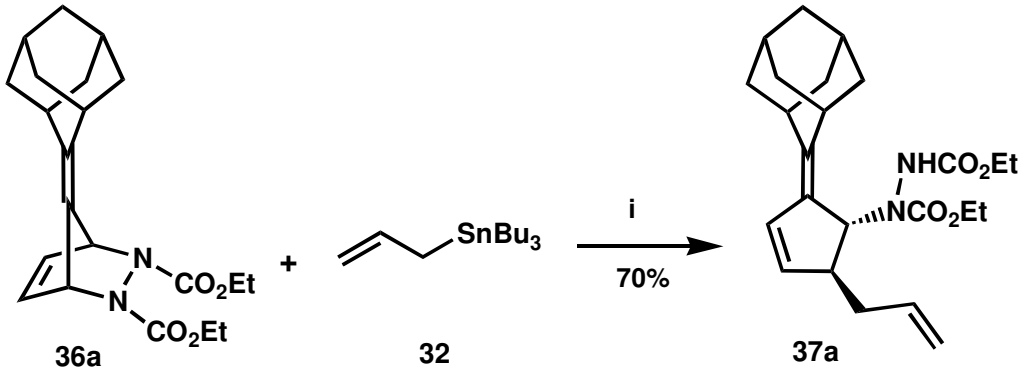


i = $Pd_2(dba)_3.CHCl_3$ (5 mol %), PPh_3 (20 mol %), $Sc(OTf)_3$ (2 mol %), Toluene, 60 ^oC, 10 h

Scheme 2.14

As usual the product **35a** was analyzed on the basis of spectral data. IR spectrum confirmed the carbonyl absorptions in the region 1751-1714 cm^{-1} and the signal due to NH absorption was seen at 3295 cm^{-1}. ^1H NMR spectrum located characteristic cycloalkyl protons as three independent multiplets in the region δ 2.36-2.20, 2.15-2.11 and 1.83-1.40 ppm. The multiplets found around δ 4.25-4.10 and 1.31-1.22 ppm were indicative of the presence of carboethoxy group. The carbonyl groups resonated at δ 156.0 and 155.5 ppm in the ^{13}C NMR spectrum. The cycloalkyl carbons were located in the region δ 32.1-26.8 ppm. A well defined molecular ion peak at *m/z* 385.12 $(M+Na)^+$ provided another convincing evidence for the structure.

The scope of this reaction was further tested by carrying out the reaction with the bicyclic hydrazine **36a** prepared from 6-adamantylidene fulvene and diethyl azodicarboxylate. This substrate also underwent smooth ring opening reaction with allyltributyltin **32** under similar conditions and furnished the product **37a** in 70% yield (Scheme 2.15).



36a **32** **37a**

i = $Pd_2(dba)_3.CHCl_3$ (5 mol %), PPh_3 (20 mol %), $Sc(OTf)_3$ (2 mol %), Toluene, 60 ^oC, 10 h

Scheme 2.15

As in the previous cases, the characterization of the product **37a** was accomplished by spectroscopic analysis. The IR spectrum displayed absorption at 3329 cm^{-1} corresponding to the NH functionality; the carbonyls absorbed at 1755 and 1705 cm^{-1}. In the ^1H NMR spectrum, the signal due to the NH proton was discernible as a broad singlet at δ 6.06 ppm (exchangeable with D_2O). The multiplets in the region δ 2.35-2.09 (2H) and 1.96-1.56 (12H) ppm were indicative of the adamantyl protons. ^{13}C NMR spectrum located the carbonyl signals at δ 156.2 and 155.1 ppm. The adamantyl carbons were visible in the region δ 39.5-28.1 ppm. The molecular ion peak at *m/z* 414.2520, observed in the mass spectrum provided backing information for the proposed structure.

The results of the desymmetrization reactions of various pentafulvene derived bicyclic hydrazines with allyltributyltin are summarized in the table 2.2.

Table 2.2 Reaction of various pentafulvene derived bicyclic hydrazines with allylstannane

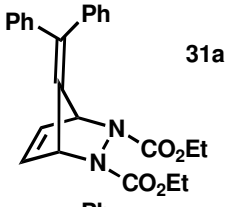
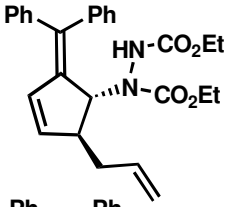
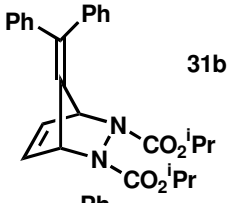
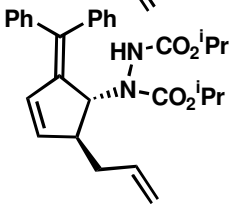
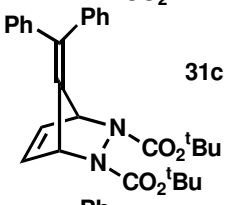
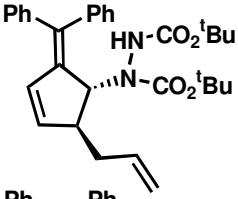
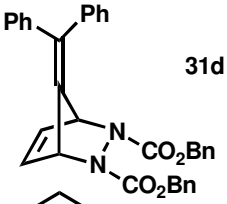
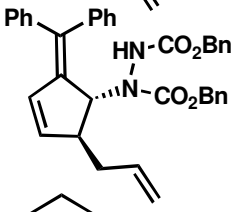
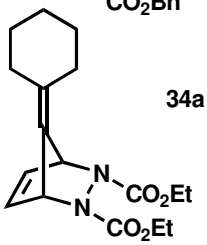
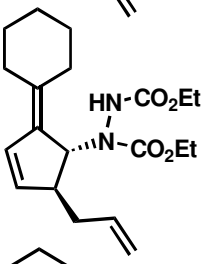
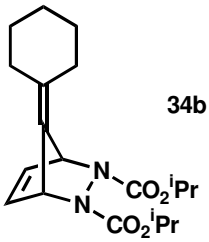
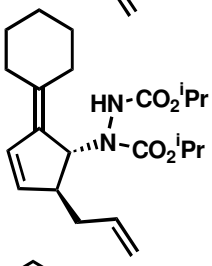
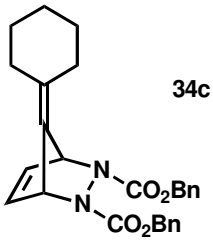
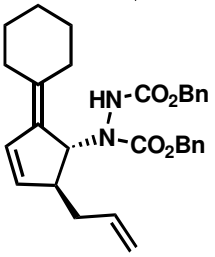
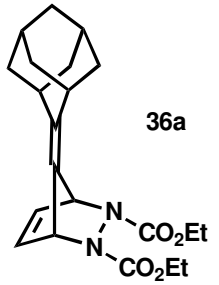
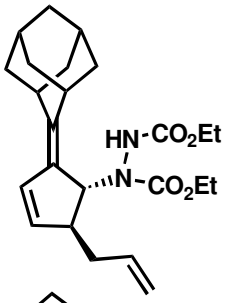
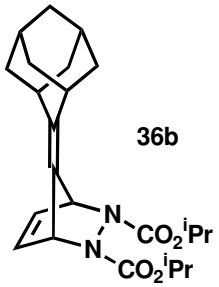
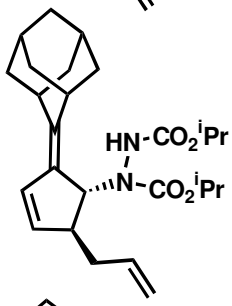
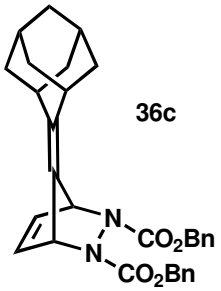
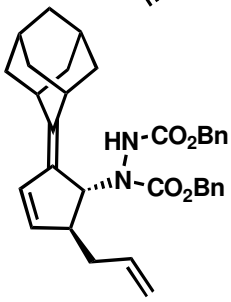
Entry	Bicyclic hydrazine		Product		Yield (%)
1		31a		33a	88
2		31b		33b	64
3		31c		33c	43
4		31d		33d	80
5		34a		35a	64
6		34b		35b	74
7		34c		35c	56

Table 2.2 Continues....

Entry	Bicyclic hydrazine		Product		Yield(%)
8		36a		37a	70
9		36b		37b	88
10		36c		37c	63

Reaction conditions: Adduct (2 equiv.), Allylstannane (1 equiv.), $Pd_2(dba)_3.CHCl_3$ (5 mol %), PPh_3 (20 mol %), $Sc(OTf)_3$ (2 mol %), Toluene, 60 ° C, 10 h

As usual the products shown in table 2.2 were characterized by spectroscopic methods. In all the cases carbonyl absorptions were confirmed by IR and ^{13}C NMR spectra. In the ^{1}H NMR spectrum of **33b**, the methine protons of the isopropyl moiety appeared as two distinct multiplets in the regions δ 4.87-4.78 ppm and δ 4.65-4.59 ppm. In the ^{13}C NMR spectrum, these methine carbons were observed at δ 70.3 and 69.8 ppm and the carbon bearing the hydrazine group was spotted at δ 61.6 ppm. In **33c**, ^{1}H NMR spectrum located the methyl protons of the *tert*-butyl group as a complex multiplet in the region δ 1.56-1.22 ppm. In the ^{13}C NMR spectrum, the two less intense peaks at δ 80.9 and 80.6 ppm corresponds to

the quaternary carbons of the *tert*-butyl group and the carbon bearing hydrazine substituent was discernible at δ 64.1 ppm. In the ^{1}H NMR spectrum of **33d**, the benzylic protons were detected as a broad multiplet at around δ 5.18-4.68 ppm along with the terminal olefinic protons of the allyl group. ^{13}C NMR spectrum presented the benzylic carbons at δ 68.3 and 68.0 ppm.

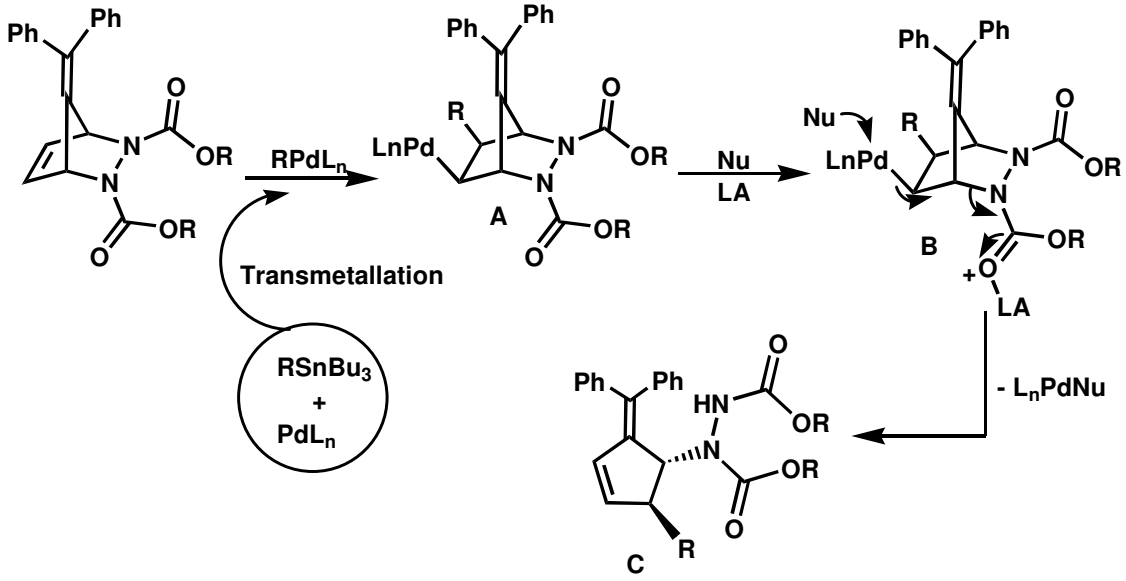
^{1}H NMR spectrum of the **35b** located the N-H proton as a broad singlet at δ 5.98 ppm. The ring olefinic proton adjacent to the exocyclic double bond resonated as a doublet at δ 6.32 ppm and as in the case of **35a**, the cycloalkyl protons were observed between δ 2.35-1.40 ppm. In the ^{13}C NMR spectrum, the carbon bearing allyl moiety was discernible at δ 49.9 ppm. In the case of **35c**, ^{13}C NMR produced two signals at δ 68.0 and 67.5 ppm for the benzylic carbons, while the carbon carrying hydrazine group was located at δ 62.1 ppm.

In the ^{1}H NMR spectrum of **37b**, the signal corresponding to the N-H proton was discernible as a singlet at δ 6.04 (exchangeable with D_2O). In the ^{13}C NMR spectrum, the adamantyl carbons were observed between δ 39.5 and 28.1 ppm. Compound **37c** located the characteristic aromatic signals in the region δ 7.33-7.20 ppm, while the N-H proton was detected as a broad singlet (exchangeable with D_2O) at δ 6.01 ppm. The adamantyl protons gave the signal as multiplets within the allowed limits. In ^{13}C NMR spectrum, the benzylic carbons were observed at δ 69.5 and 67.6 ppm and the carbon attached to the hydrazine group was discernible at δ 61.8 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

Mechanism of the reaction was found to be similar to the one proposed for the ring opening of cyclopentadiene derived bicyclic hydrazines on reaction with organostannanes.[24] First step involves the transmetallation of organostannane with

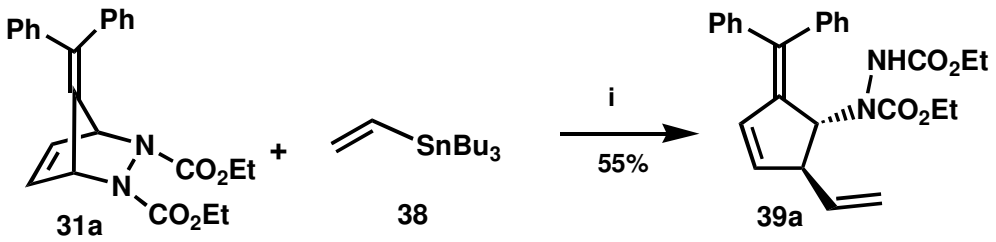
palladium forming the active palladium species R-Pd-L_n. Next step is the co-ordination followed by the addition of this species into the endocyclic C-C double bond to form the intermediate **A**. In the final step, the Lewis acid assisted ring opening of intermediate **B** along with the elimination of L_n-Pd-Nu gives the product **C** (Scheme 2.16). The Lewis acid assists the C-N bond cleavage by getting coordinated to the carboethoxy group. The addition of the species R-Pd-L_n to the double bond is a *syn* addition which results in the formation of the *trans*-disubstituted alkylidene cyclopentene as the product.



Scheme 2.16 Proposed mechanism of the reaction

2.4.2. Reactions using vinylstannane

Encouraged by the results obtained with allylstannane, we decided to extend the scope of the reaction using other organostannanes. Next part our investigation involved the palladium/Lewis acid mediated ring opening of bicycle hydrazines using vinylstannane. Diphenyl fulvene derived bicyclic hydrazine **31a** with vinyl tributyltin **38** under the optimized conditions showed similar reactivity and gave the corresponding vinyl substituted alkylidene cyclopentene **39a** in 55% yield (Scheme 2.17).



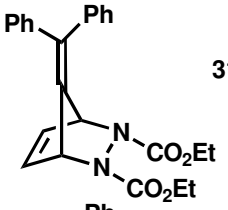
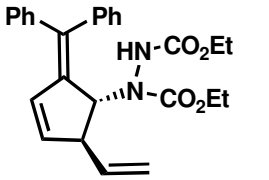
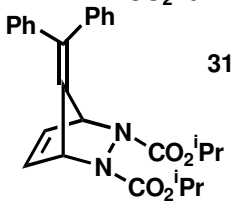
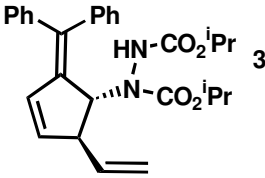
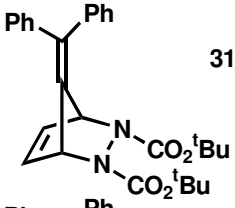
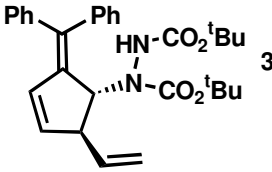
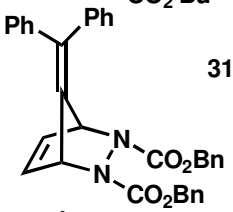
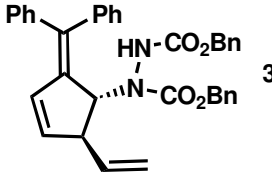
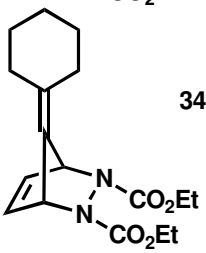
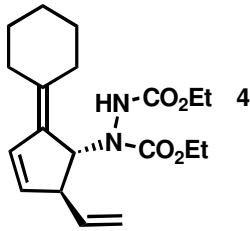
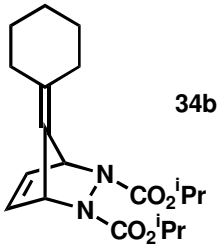
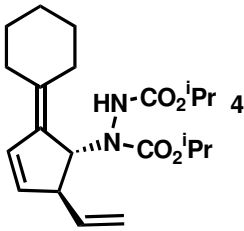
i = $Pd_2(dba)_3.CHCl_3$ (5 mol %), PPh_3 (20 mol %), $Sc(OTf)_3$ (2 mol %),Toluene, 60 ^oC, 10 h

Scheme 2.17

The structure of the product **39a** was established by spectroscopic analysis. The IR spectrum of **39a** confirmed the N-H absorption at 3302 cm^{-1}, while the stretching vibrations due to the carbonyls were observed at 1744 and 1716 cm^{-1}. In the ^1H NMR spectrum signal due to terminal vinyl protons appeared as a multiplet at δ 5.19-5.06 ppm. The protons attached to the carbon bearing the vinyl group resonated as a multiplet centered at δ 3.85 ppm. In the ^{13}C NMR spectrum, the ester carbonyls were positioned at δ 156.9 and 155.0 ppm and the carbon carrying the vinyl group was identified at δ 53.7 ppm. All other signals were in good agreement with the proposed structure. The molecular ion peak observed at *m/z* 455.45 $(M+Na)^+$, in the mass spectrum provided further evidence for the structure assignment.

Analogous reactivity was observed with a range of bicyclic hydrazines and corresponding vinyl substituted alkylidene cyclopentenes were isolated in good yields. The bicyclic hydrazines selected were from the cycloaddition of 6,6-diphenyl and cyclohexyl fulvenes with ethyl, isopropyl, *tert*-butyl and benzyl azodicarboxylates. The results of these investigations are compiled in table 2.3.

Table 2.3 Reaction of various pentafulvene derived bicyclic hydrazines with vinylstannane

Entry	Bicyclic hydrazine	Product	Yield (%)
1	 31a	 39a	55
2	 31b	 39b	53
3	 31c	 39c	51
4	 31d	 39d	68
5	 34a	 40a	52
6	 34b	 40b	64

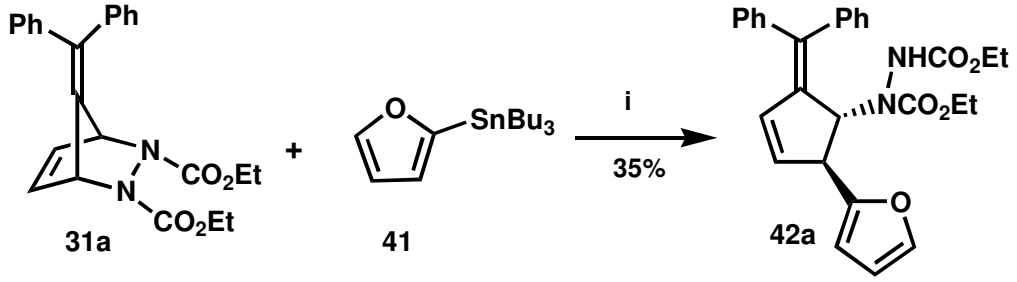
Reaction conditions: Adduct (2 equiv.), Vinylstannane (1 equiv.), $Pd_2(dba)_3.CHCl_3$ (5 mol %), PPh_3 (20 mol %), $Sc(OTf)_3$ (2 mol %), Toluene, 60 °C, 10 h

Usual spectral analyses were employed to establish the structures of the products. In the ^1H NMR spectrum of the product **39b**, the two isopropyl methine protons were observed as multiplets in the region δ 4.91-4.86 ppm and δ 4.64-4.55

ppm, respectively. ^{13}C NMR spectrum positioned the terminal vinylic carbon at δ 115.0 ppm and the carbon bearing hydrazine moiety at 61.6 ppm. The complex multiplet observed in the region δ 1.46-1.25 ppm, in the ^{1}H NMR spectrum of **39c** is characteristic of the *tert*-butyl group. In the ^{13}C NMR spectrum, quaternary carbons of the *tert*-butyl moiety were visible at δ 80.7 and 80.5 ppm and the methyl carbons were identified at δ 30.1, 29.7, 29.5, and 28.1 ppm. The ^{1}H NMR spectrum of **39d** presented the benzylic protons in the region δ 5.26-4.73 ppm along with the signals of the vinyl proton. ^{13}C NMR spectrum marked a signal at δ 53.2 ppm corresponding to the carbon carrying the vinyl substituent. The structures were further confirmed by mass spectral analysis which showed molecular ion peaks within the permissible limits.

2.4.3. Reactions using heteroaryl stannanes

Our next attempt was to study the reactivity of heteroaryl stannanes in the palladium catalyzed ring opening reactions of these bicyclic substrates. A model reaction using 2-(tributylstannyl)furan **41** and bicyclic hydrazine **31a** resulted in the formation of the product **42a** in 35% yield (Scheme 2.18).



i = $Pd_2(dba)_3.CHCl_3$ (5 mol %), PPh_3 (20 mol %), $Sc(OTf)_3$ (2 mol %), Toluene, 60 ^{o}C, 10 h

Scheme 2.18

The structure of the product **42a** was assigned on the basis of spectral analysis. The signals at 1753 and 1722 cm^{-1} were diagnostic of the carbonyl groups and the N-H absorption was found as a broad band at around 3300-3400 cm^{-1}. The characteristic furan protons were found to resonate along with the aromatic and olefinic protons, in convincing regions. The proton on the carbon

bearing the furan ring was identified as a multiplet centered at δ 4.51 ppm. The signals observed at δ 110.3 and 105.6 ppm in the ^{13}C NMR spectrum, was due to the aromatic furan carbons; while the carbon carrying furyl substituent was detected at δ 49.2 ppm. Mass spectrum gave a well defined molecular ion peak at *m/z* 472.1986.

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 2.4.

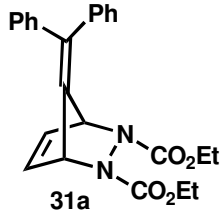
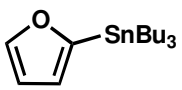
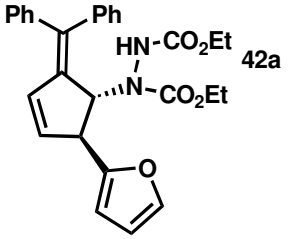
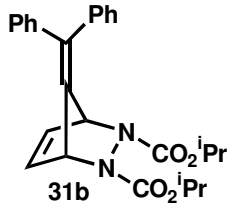
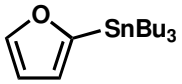
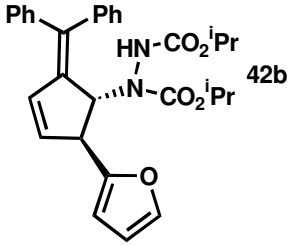
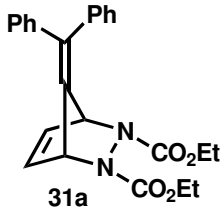
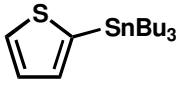
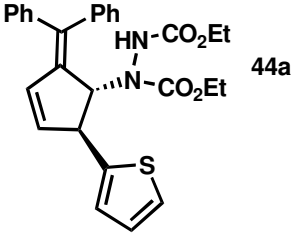
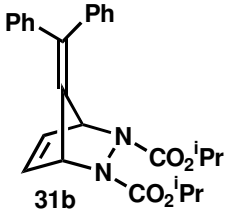
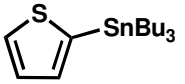
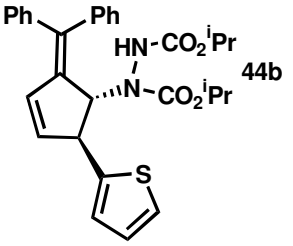
Table 2.4 Optimization studies using different catalysts/ligands/LA

Entry	Catalyst	Ligand	Lewis acid	Yield (%)
1	$Pd_2(dba)_3.CHCl_3$	PPh_3	$Sc(OTf)_3$	35
2	$Pd_2(dba)_3.CHCl_3$	dppe	$Sc(OTf)_3$	33
3	$Pd_2(dba)_3.CHCl_3$	dppm	$Sc(OTf)_3$	26
4	$Pd_2(dba)_3.CHCl_3$	dppf	$Sc(OTf)_3$	24
5	$Pd(OAc)_2$	PPh_3	$Sc(OTf)_3$	38
6	$Pd(OAc)_2$	dppe	$Sc(OTf)_3$	29
7	$Pd(OAc)_2$	dppm	$Sc(OTf)_3$	27
8	$Pd(OAc)_2$	PPh_3	$Yb(OTf)_3$	26
9	$Pd(OAc)_2$	PPh_3	$Sn(OTf)_3$	37
10	$Pd(OAc)_2$	PPh_3	$Cu(OTf)_3$	23
11	$Pd(OAc)_2$	PPh_3	I_2	25

Reaction conditions: 29a (2 equiv.), 39 (1 equiv.), Catalyst (5 mol %), Ligand (10 mol %), Lewis acid (2 mol %),Toluene, 60 ° C, 10 h

After the optimization studies, the combination of 5 mol % $Pd(OAc)_2$, 10 mol% PPh_3 and 2 mol % $Sc(OTf)_3$ was found to be the best condition for this transformation. Under this condition, the reaction was repeated using 2-(tributylstannyl)thiophene **43** and other bicyclic olefins. To our dismay, the reaction afforded the products in only 38-47% yield. The results of these investigations are summarized in table 2.5.

Table 2.5 : Reaction of various pentafulvene derived bicyclic hydrazines with heteroaryl stannanes

Entry	Bicyclic hydrazine	Stannane	Product	Yield (%)
1	 31a	 41	 42a	38
2	 31b	 41	 42b	47
3	 31a	 43	 44a	47
4	 31b	 43	 44b	38

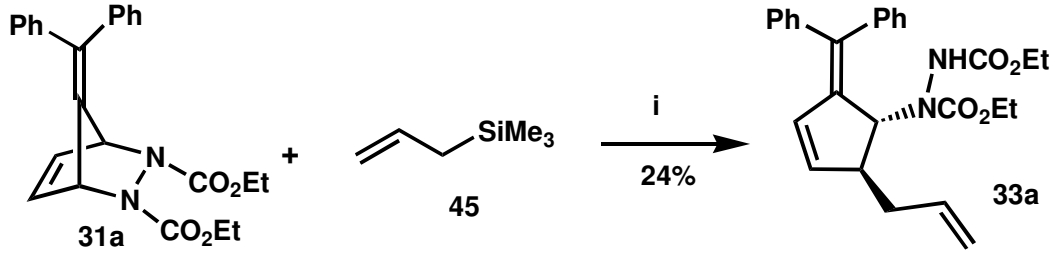
Reaction conditions: Adduct (2 equiv.), Heteroarylstannane (1 equiv.), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), $Sc(OTf)_3$ (2 mol %), Toluene, 60 °C, 10 h

The structures of heteroaryl substituted alkylidene cyclopentenes **42b**, **44a** and **44b** were established by means of detailed spectral analysis. In the ^{1}H NMR spectrum of **42b**, the methyl protons of the isopropyl group appeared as a multiplet in the region δ 1.24-0.86 ppm. ^{13}C NMR spectrum produced the methine signals of isopropyl functionality at δ 70.1 and 69.8 ppm. In the ^{1}H NMR spectrum of **44a**, the methylene protons resonated as multiplets in the regions δ 4.30-4.12 ppm and δ 3.86-3.76 ppm, whereas the multiplet observed around δ 1.42-1.25 ppm is

characteristic of the methyl protons. ^{13}C NMR spectrum spotted the thiophene bearing carbon at δ 49.0 ppm. The ^{1}H NMR spectrum of **44b** displayed a multiplet at around δ 4.67-4.57 ppm representing the proton on the carbon carrying the thiophene substituent. In the ^{13}C NMR spectrum, the signal at δ 66.3 was attributed to the carbon bearing the hydrazino group. All other signals in ^{1}H NMR and ^{13}C NMR spectra supported the structure assignment. Further proofs for the structures were obtained from mass spectral analysis which gave well defined molecular ion peaks within the allowed range.

2.4.4. Reactions using allylsilane

Organometals containing relatively electronegative metals such as organosilanes are also known to participate in palladium-catalyzed cross-coupling reactions.[26] These reactions are thought to proceed *via* transmetallation on palladium. The carbon-silicon bond of allyltrimethylsilane, although less polarized, has sufficient nucleophilicity to react with palladium complexes. Next phase of our work involved the palladium/Lewis acid mediated ring opening of azabicyclic olefins with allyltrimethylsilane. Allyltributyltin, is a toxic chemical and hence it is desirable to replace it with allyltrimethylsilane. With this aim in mind, we have carried out the above transformations with allyltrimethylsilane as the allylating agent. As expected, the reaction of bicyclic hydrazine **31a** with allyltrimethylsilane **45** in the presence of Pd/Lewis acid catalyst afforded allyl substituted alkylidene cyclopentene **33a** in 24% yield (Scheme 2.19).



i = $Pd_2(dba)_3.CHCl_3$ (5 mol %), PPh_3 (20 mol %), $Sc(OTf)_3$ (2 mol %), Toluene, 60 ^{o}C, 10 h

Scheme 2.19

When the reaction was repeated using a number of fulvene derived bicyclic hydrazines, corresponding alkylidene cyclopentenes were obtained in low yields. The results are summarized in table 2.6.

Table 2.6 : Reaction of various Pentafulvene derived bicyclic hydrazines with allyltrimethyl silane

Entry	Bicyclic hydrazine	Product	Yield (%)
1	31a	33a	24
2	31b	33b	16
3	31c	33c	trace
4	31d	33d	22
5	34a	35a	13
6	34b	35b	15
7	34c	35c	13
8	36a	37a	23
9	36b	37b	15
10	36c	37c	12

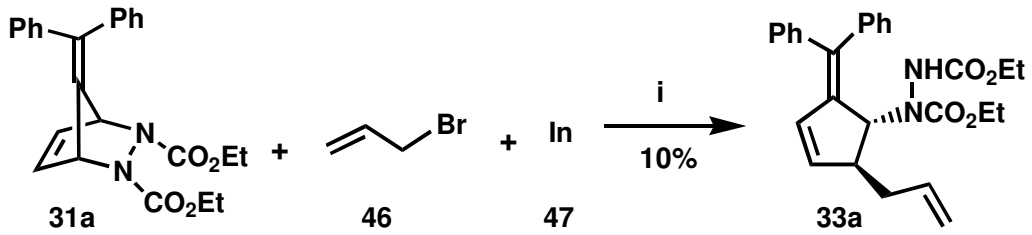
Reaction conditions: Bicyclic hydrazine (2 equiv.), Allylsilane (1 equiv.), PPh_3 (20 mol %), $Pd_2(dba)_3.CHCl_3$ (5 mol %), $Sc(OTf)_3$ (2 mol %), Toluene, 60 ^oC, 10 h

2.4.5. Reactions using allylindium reagents

Among organometallic reagents, organoindium reagents have gained increasing popularity in organic synthesis.[27] Indium metal exhibits low heterophilicity and can be handled with ease as it is unaffected by air or oxygen. Reactions of organoindium proceeds with exceptional regio and stereoselectivity.[28] In addition, organoindium compounds tolerate many functional groups and are less toxic than other organometallic reagents.

It was reported that allylindium reagents can be effectively used for the regio and stereoselective allylation of alkynes[29] and allenes.[30] However, the reactivity of these reagents towards carbon-carbon double bonds has received only scant attention.[31] In this context, our laboratory have recently reported[32] a novel reactivity of organoindium reagents with azabicyclic olefins under palladium

catalysis. Intrigued by this observation, we undertook an investigation on the palladium catalyzed reactions of organoindium reagents with fulvene derived bicyclic hydrazines. Our studies were initiated by the reaction of allylindium, generated *in situ* from allyl bromide **46** and indium **47**, with azabicyclic olefin **31a** in THF in presence of Pd[(allyl)Cl]$_2$/dppe/Yb(OTf)$_3$ catalyst system. The reaction afforded alkylidene cyclopentene **33a** in 10% yield (Scheme 2.20).



i = Pd[(allyl)Cl]$_2$ (5 mol %), dppe (10 mol %), Yb(OTf)$_3$ (2 mol %), THF, 60 ^{o}C, 24 h

Scheme 2.20

After a series of optimization reactions, the best condition for this reaction was found to be 1 equiv. of bicyclic hydrazine, 3 equiv. of allyl bromide, 2 equiv. of indium, 5 mol % $Pd_2(dba)_3.CHCl_3$ along with 20 mol % PPh_3 as ligand and 2 mol % Yb(OTf)$_3$ in THF as solvent. The results of optimization studies are shown in table 2.7.

Table 2.7: Optimization studies using different catalysts/ligands/Lewis acids

Entry	Catalyst	Ligand	Lewis acid	Yield (%)
1	$[Pd(allyl)Cl]_2$	PPh_3	$Sc(OTf)_3$	10
2	$Pd(OAc)_2$	PPh_3	$Yb(OTf)_3$	25
3	$PdCl_2$	PPh_3	$Yb(OTf)_3$	No reaction
4	$PdCl_2(PPh_3)_2$	PPh_3	$Yb(OTf)_3$	No reaction
5	$Pd_2(dba)_3.CHCl_3$	PPh_3	$Yb(OTf)_3$	40
6	$Pd_2(dba)_3.CHCl_3$	PPh_3	I_2	No reaction
7	$Pd_2(dba)_3.CHCl_3$	PPh_3	$Yb(OTf)_3$	No reaction[a]

bicyclic hydrazine (1 equiv.), Allyl bromide (3 equiv.), Indium powder (2 equiv.), Catalyst (5 mol%), Ligand (20 mol%), $Sc(OTf)_3$ (2 mol%),Toluene, 60 °C, 24 h

[a]DMF was used as the solvent

The generality of the method was exemplified by the reactions of other pentafulvene derived bicyclic hydrazines with allyltrimethylsilane and the results are summarized in table 2.8.

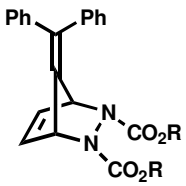
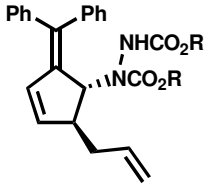
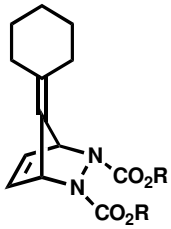
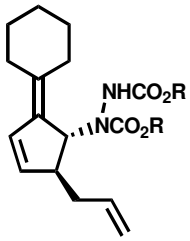
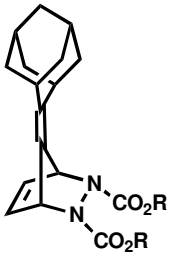
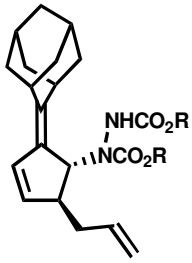
Table 2.8: Reaction of various pentafulvene derived bicyclic hydrazines with allylindium reagent

Entry	Bicyclic hydrazine	Product	Yield (%)
1	31a	33a	40
2	31b	33b	35
3	31c	33c	trace
4	31d	33d	35
5	34a	35a	38
6	34b	35b	45
7	34c	35c	trace
8	36a	37a	trace
9	36b	37b	42
10	36c	37c	50

Reaction conditions: Bicyclic hydrazine (1 equiv.), Allyl bromide (3 equiv.), In (2 equiv.), PPh_3 (20 mol%), $Pd_2(dba)_3.CHCl_3$ (5 mol%), $Yb(OTf)_3$ (2 mol%), THF, 60 ^oC, 24 h

Thus, we have synthesized substituted alkylidene cyclopentenes from fulvene derived bicyclic hydrazines using various organometallic reagents like organostannanes, silanes and indium reagents, among which stannanes gave better yields. This can be attributed to the difference in the efficiency of transmetallation in various organometallic reagents. Organostannanes are known to undergo an easy transmetallation with palladium compared to the organoindium and organosilicon reagents. The summary of the results obtained with the reactions of allylstannane, allylsilane and allylindium reagents with various pentafulvene derived bicyclic hydrazines are presented in table 2.9.

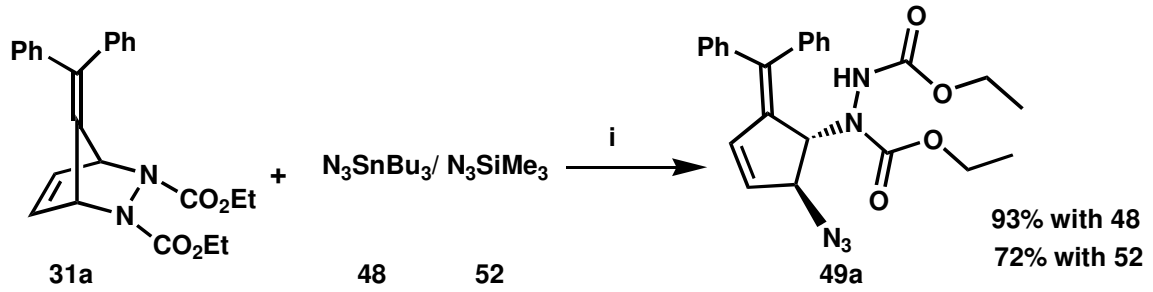
Table 2.9: Summary of the reactions with allylstannane/silane/indium reagents

Entry	Bicyclic hydrazine		Product		Yield (%)		
					Stannane	Silane	Indium
1		31a R = Et		33a	88	24	40
2		31b R = ^{i}Pr		33b	64	16	35
3		31c R = ^{t}Bu		33c	43	trace	trace
4		31d R = Bn		33d	80	22	35
5		34a R = Et		35a	64	13	38
6		34b R = ^{i}Pr		35b	74	15	45
7		34c R = ^{t}Bu		35c	56	13	trace
8		36a R = Et		37a	70	23	trace
9		36b R = ^{i}pr		37b	88	15	42
10		36c R = Bn		37c	63	12	50

2.4.6. Reactions using azidostannane/silane

In the next phase of our work, encouraged by the possibility of converting azido and hydrazino groups into amines, we decided to explore the scope of this reaction using oragnic azides. So far we were using carbon nucleophiles in the desymmetrization of bicyclic hydrazines. Heteroatom nucleophiles like azide, which can be generated from azidostannane/silane seemed to be a good substrate for the palladium/Lewis acid mediated ring opening of bicyclic hydrazines.

We started our experiments with $Pd_2(dba)_3.CHCl_3$ /PPh_3/$Sc(OTf)_3$ catalyst system in dry toluene as the solvent. Under this condition, the reaction between bicyclic hydrazine **31a** and azidostannane **48**, afforded 3-azido-4-hydrazino alkylidene cyclopentene **49a** in excellent yield. Similar reactivity was observed with trimethylsilylazide **52** leading to the product **49a** in 72% yield (Scheme 2.21).



Scheme 2.21

The structure of the product **49a** was established based on spectroscopic analysis. IR spectrum showed absorptions at 3312 cm^{-1} and 1742 cm^{-1} indicating the presence of N-H and C=O functionalities. Azide group presented its absorption at 2102 cm^{-1} as a sharp signal. ^{1}H NMR spectrum (Figure 2.4) located the olefinic protons at C-1 and C-2 as a double doublet and a singlet at δ 6.52 and 5.99 ppm respectively. The N-H proton was found to be merged with the multiplet signal due to proton at C-3 in the region δ 5.67-5.45 ppm. The multiplets observed in the regions δ 4.19-4.09 and 4.03-3.92 ppm were attributed to the protons at C-9 and C-10.

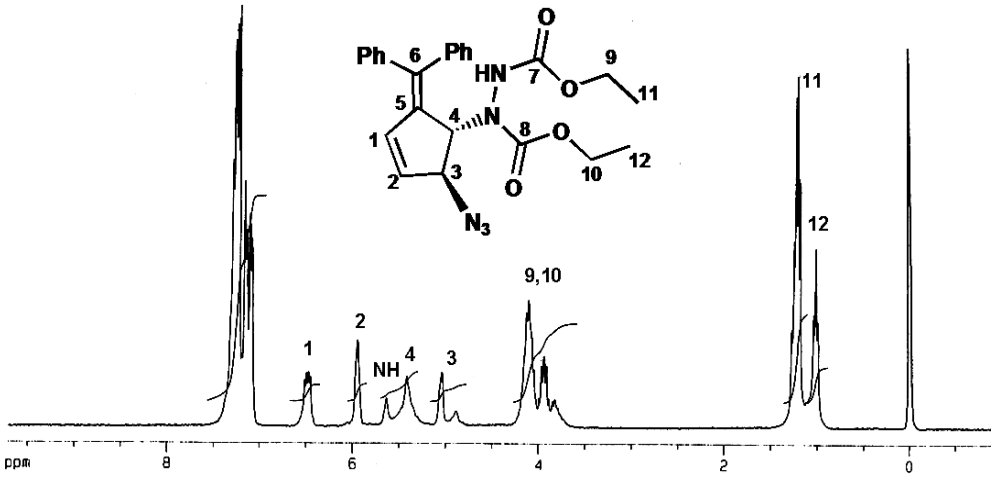


Figure 2.4. ^{1}HNMR spectrum of compound **49a**

^{13}C NMR spectrum of **49a** (Figure 2.5) marked carbonyl signals at δ 156.2 and 154.4 ppm. Carbon carrying the azide group C-3 appeared at δ 70.3 ppm,

while the C-4 carbon was found to resonate at δ 67.8 ppm. The signals at δ 62.7 and 62.2 ppm were assigned to the ethoxy carbons C-9 and C-10. The methyl carbons C-11 and C-12 were visible at δ 14.4 and 14.1 ppm. Mass spectra identified the molecular ion peak at *m/z* 447.2017 and provided additional evidence for the structure.

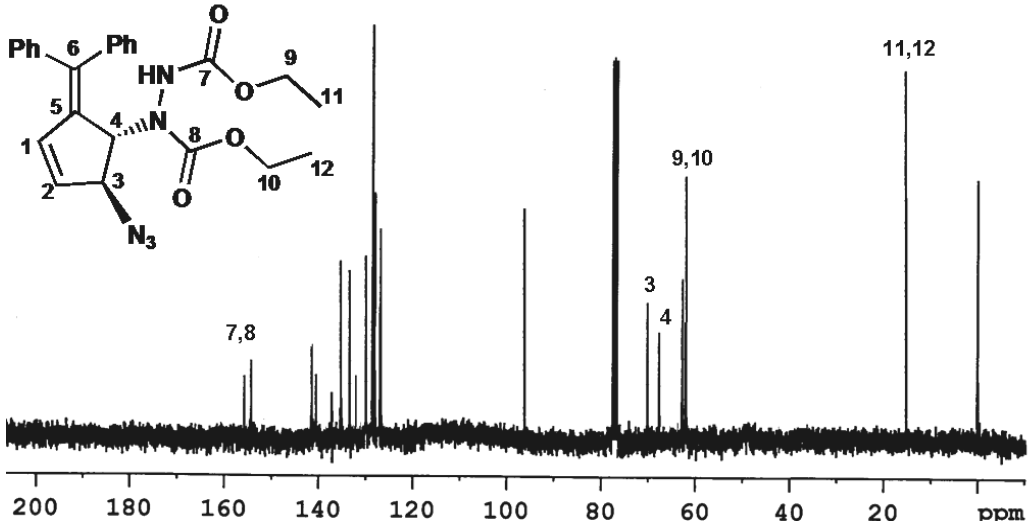


Figure 2.5. ^{13}C NMR spectrum of compound **49a**

The generality of this method was exemplified by the reaction of **46** and **50** with a number of pentafulvene derived bicyclic hydrazines and the results are summarized in table 2.10. The reactions using the azidosilane were found to be cleaner when compared to azidostannane. Moreover we could replace the toxic stannanes with less toxic silanes.

Table 2.10: Reaction of various pentafulvene derived bicyclic hydrazines with azidostannanes

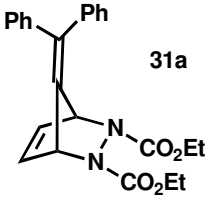
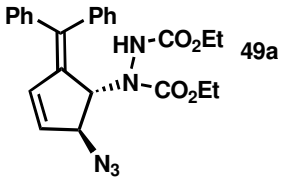
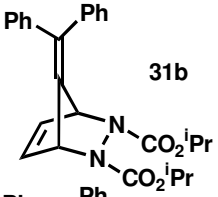
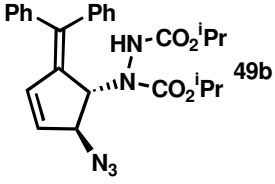
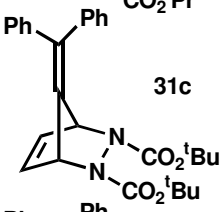
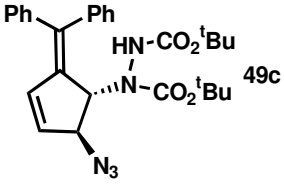
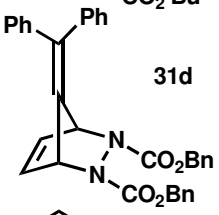
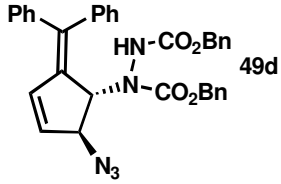
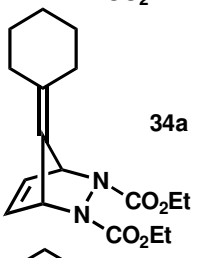
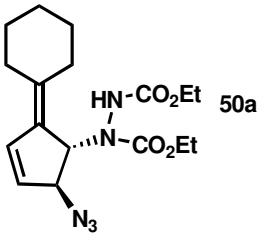
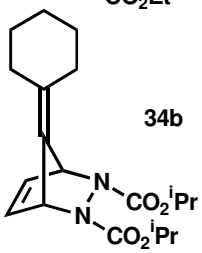
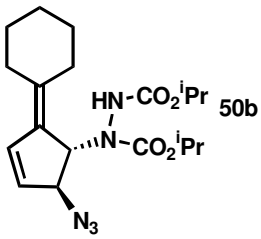
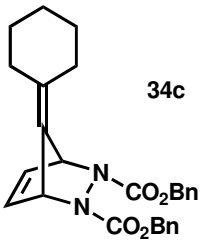
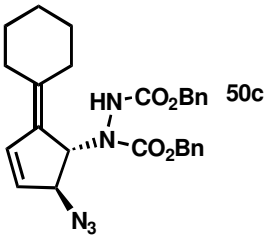
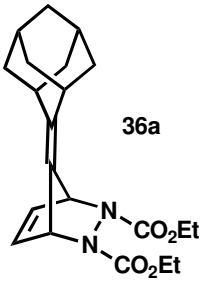
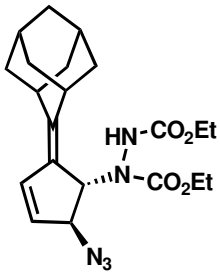
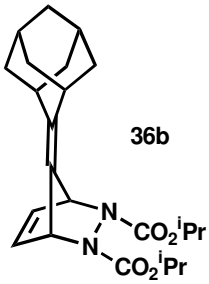
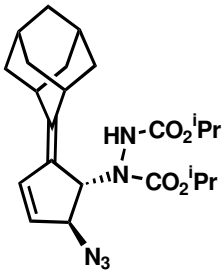
Entry	Bicyclic hydrazine	Product	Yield (%)	
			Stannane	Silane
1	 31a	 49a	93	72
2	 31b	 49b	70	75
3	 31c	 49c	83	46
4	 31d	 49d	67	81
5	 34a	 50a	54	43
6	 34b	 50b	61	58
7	 34c	 50c	60	55

Table 2.10. Continues....

Entry	Bicyclic hydrazine	Product	Yield (%) with	
			Stannane	Silane
8	 36a	 51a	70	64
9	 36b	 51b	84	77

Reaction conditions: Adduct (2 equiv.), Azidostannane (1 equiv.), $Pd_2(dba)_3.CHCl_3$ (5 mol %), PPh_3 (20 mol %), $Sc(OTf)_3$ (2 mol %), Toluene, 60 °C, 10 h

The alkylidene cyclopentenes shown in table 2.9 were characterized by means of spectroscopic analysis. For all the compounds, IR and ^{13}C NMR spectra provided sufficient evidences for the carbonyl absorptions. In the IR spectra, the carbonyl absorptions were found in the region 1750-1710 cm^{-1}, while the presence of azide group was confirmed by a sharp signal observed around 2100 cm^{-1}. In the ^{1}H NMR spectrum of **49b**, the methine protons of the isopropyl groups resonated along with the signals of the proton on carbon carrying the hydrazine group as a broad multiplet in the region δ 5.10-4.67 ppm. In the ^{13}C NMR spectrum, the carbons bearing the azido and hydrazino groups gave signals at δ 70.9 and 70.2 ppm. For compound **49c**, the ^{1}H NMR spectrum positioned the proton on the carbon attached to the hydrazine group as a multiplet at around δ 5.10-4.97 ppm, whereas the methyl protons of *tert*-butyl substituent presented a multiplet at δ 1.48-1.22 ppm. In ^{13}C NMR spectrum, tetra substituted carbons of the *tert*-butyl group appeared at δ 82.3 and 81.2 ppm. ^{1}H NMR spectrum of **49d** showed the

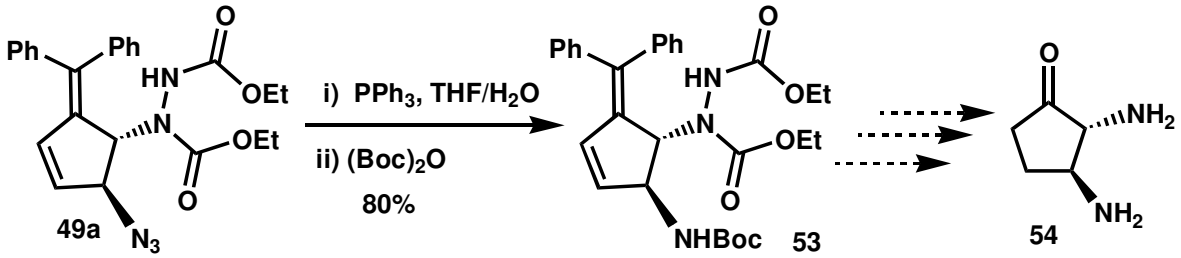
characteristic aromatic signals in the region δ 7.40-7.05 ppm. In the ^{13}C NMR spectrum, the peak at δ 65.4 ppm was assigned to the carbon carrying the hydrazine substituent and signals observed at δ 68.3 and 68.0 ppm were attributed to the benzylic carbons.

In the ^{1}H NMR spectrum of **50a**, the N-H proton was identified as a singlet at δ 6.15 ppm and the proton on the carbon with the azide group produced its signal as a multiplet at δ 5.33-5.03 ppm. ^{13}C NMR spectrum positioned the ethoxy carbons at δ 63.4, 61.2, 14.5 and 14.4 ppm, whereas the cycloalkyl carbons resonated between δ 31.0 and 25.0 ppm. ^{1}H NMR spectrum of **50b**, marked two well distinct multiplets centered at δ 2.20 and 1.63 ppm for the cycloalkyl protons. The ^{13}C NMR spectrum spotted the azide carrying carbon at δ 69.4 ppm, while the methine carbons of the isopropyl group identified its signals at δ 70.6 and 70.2 ppm. In compound **50c**, ^{1}H NMR spectrum assigned the multiplet in the region δ 5.16-4.78 ppm to the benzylic protons and the multiplets centered at δ 2.15 and 1.40 ppm to cycloalkyl protons. In the ^{13}C NMR spectrum, the carbons carrying the nitrogen substituents resonated in the region δ 69.0-68.0 ppm along with the signals of the benzylic carbons.

In the ^{1}H NMR spectrum of **51a**, the ring junction protons of the adamantyl group adjacent to the exocyclic double bond were discernible as singlets at δ 2.94 and 2.58 ppm. The rest of the adamantyl protons was observed as a broad multiplet in the region δ 4.24-4.11 ppm. ^{13}C NMR spectrum positioned the carbon bearing azide functionality at δ 70.1 ppm, whereas the adamantyl carbons resonated between δ 40.0 and 30.0 ppm. ^{1}H NMR spectrum of **51b** identified the methyl protons of the isopropyl groups as a multiplet in the region δ 1.37-1.25 ppm, while the methine protons of the ester group resonated around δ 69.0 ppm in the ^{13}C NMR spectrum of the compound **51b**.

2.4.7. Reduction of the azide moiety in 49a

In order to explore the synthetic utility of 3-azido-4-hydrazino-alkylidene cyclopentenes and also to get further confirmation of the assigned structure, we have carried out the reduction of the azide moiety in **49a**. The resulting amino compound was Boc protected and isolated the product **53** in 80% yield. The reaction sequence is described in scheme 2.22.



Scheme 2.22

The characterization of the product **53** was accomplished by means of usual spectroscopic analysis. In the IR spectrum, the carbonyl and N-H absorptions were observed in the region 1734-1710 cm^{-1} and 3362-3322 cm^{-1} respectively. The reduction of the azide moiety in **49a** was confirmed by the absence of sharp signal at 2100 cm^{-1} in the IR spectrum of **53**. ^{1}H NMR spectrum located the two N-H protons at δ 6.38 and 5.18 ppm as broad singlets. The nine proton singlet observed at δ 1.45 ppm was attributed to the *tert*-butyl protons. ^{13}C NMR spectrum supported the assigned structure of **53**, by providing three carbonyl signals in the region δ 156.0-154.0 ppm. The molecular ion peak observed at *m/z* 544.84 $(M+Na)^{+}$ in the mass spectrum, gave additional evidence to the proposed structure.

The molecule **53** can be converted to synthetically and biologically useful *trans*-cyclopentane-1,2-diamine[33] derivative **54** by simple synthetic modifications. The scarcity of efficient routes as well as the complexity of the existing methodologies[34] for the synthesis of vicinal diamines makes our strategy more appealing.

2.5. Conclusions

In summary, we have unraveled a facile method for the functionalization of pentafulvenes *via,* Pd/Lewis acid mediated ring opening of fulvene derived bicyclic hydrazines with a number of organometallic reagents. Among the various organometals studied, organostannanes were more reactive than the corresponding silanes and indium reagents. The described methodology offers a conceptually new approach towards the synthesis of allyl, vinyl, heteroaryl and hetero atom substituted alkylidene cyclopentenes. 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 carried out in oven dried Wheaton vial under nitrogen atmosphere. Progress of the reaction was monitored by Thin Layer Chromatography, which was performed on Merck precoated plates (silica gel. 60 F_{254}, 0.25 mm) and was visualized by fluorescence quenching under UV light or by staining with Enholm yellow solution. Column chromatography was done using 60-120 mesh silica gel and appropriate mixture of petroleum ether (60-80 ^{o}C) and ethyl acetate for elution. The solvents were removed using Buchi rotary evaporator. The IR spectra were recorded on Nicolet FT-IR spectrometer. NMR spectra were recorded on Bruker FT-NMR spectrometer using $CDCl_3$ or $CDCl_3$-CCl_4 mixture (7:3) as solvent. TMS was used as the internal standard and chemical shifts are in δ-scale. High resolution mass spectra were recorded under EI/HRMS (at 5000 resolution) using JEOL JMS 600H mass spectrometer. Abbreviations used in ^{1}H NMR are **s**-singlet, **brs**-broad singlet, **d**-doublet, **dd**-doublet of doublet, **q**-quartet and **m**-multiplet.

General Procedure for the synthesis of allyl/vinyl alkylidene cyclopentenes

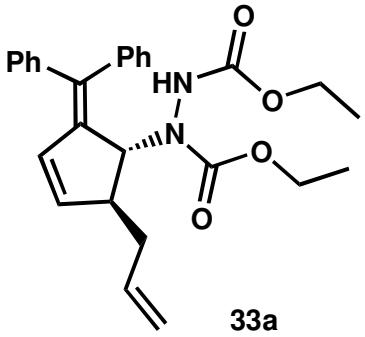
Bicyclic hydrazine (2 equiv.) and stannane/silane (1 equiv.) were taken in a wheaton vial, and dissolved in dry toluene (4 mL). PPh_3 (20 mol%),

$Pd_2(dba)_3.CHCl_3$ (5 mol %) were added to the reaction mixture followed by the addition of $Sc(OTf)_3$ (2 mol %). The reaction mixture was stirred at 60 ^oC for 10 h. Completion of the reaction was monitored by TLC and the reaction mixture was subjected to silica gel column chromatography (20% ethyl acetate in hexane) and afforded the products in good to excellent yields.

Diethyl - 1- ((2-allyl- 5-diphenylmethylene) cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 33a

Following the general experimental procedure, bicyclic hydrazine **31a** (122 mg, 0.30 mmol), allyltributyltin **32** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%), in 4 mL of dry toluene at 60 °C for 10 h gave the product **33a** as a white solid in 88% (60 mg) yield.

Mp 135-137 °C. R_f 0.60 (3:1 Hexane/ethyl acetate).



33a

IR (KBr)ν_{max}: 3302, 3057, 2978, 1742, 1713, 1489, 1412, 1300, 1220, 1124, 751, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.14 (m, 10H), 6.34-6.31 (m, 1H), 6.06 (d, *J* = 3.9 Hz, 1H), 5.84-5.78 (m, 1H), 5.56-5.46 (m, 1H), 5.17-5.06 (m, 2H), 4.15-4.11 (m, 2H), 3.89-3.88 (m, 2H), 3.31-3.18 (m, 1H), 2.58-2.43 (m, 1H), 2.30-2.20 (m, 1H), 1.24 (t, *J* = 6.9 Hz, 3H), 1.03 (t, *J* = 6.6 Hz, 3H).

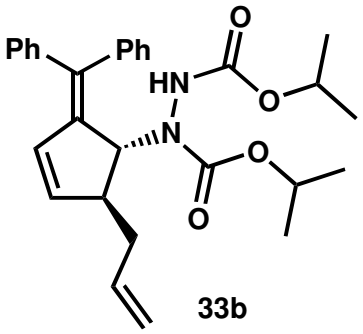
^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 153.5, 140.7, 138.2, 136.5, 135.9, 132.2, 130.0, 129.7, 128.6, 128.0, 127.1, 116.9, 62.1, 61.9, 61.3, 49.4, 37.5, 14.9, 14.5.

LRMS (FAB) for $C_{27}H_{30}N_2O_4$, calcd (M^+): 446.2206; found: 469.97$(M+Na)^+$.

Diisopropyl 1-((2-allyl-5-diphenylmethylene)cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 33b

Following the general experimental procedure, bicyclic hydrazine **31b** (131 mg, 0.30 mmol), allyltributyltin **32** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%), in 4 mL of dry toluene at 60 °C for 10 h gave the product **33b** as a white solid in 64% (46 mg) yield.

Mp 126-128 °C. R_f 0.39 (3:1 Hexane/ethyl acetate).



33b

IR (KBr)ν_{max}: 3308, 2982, 2936, 1728, 1715, 1588, 1469, 1375, 1229, 1181, 1145, 1109, 1034, 921, 760, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.19 (m, 10H), 6.32-6.29 (m, 1H), 6.05 (s, 1H), 5.85-5.75 (m, 1H), 5.55-5.44 (m, 2H), 5.17-5.08 (m, 2H), 4.87-4.78 (m, 1H), 4.65-4.59 (m, 1H), 3.28-3.15 (m, 1H), 2.52-2.50 (m, 1H), 2.23-2.15 (m, 1H), 1.25-1.20 (m, 6H), 1.07-0.88 (m, 6H).

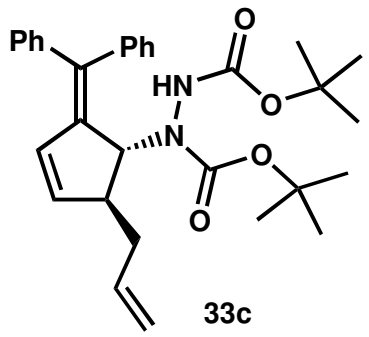
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 155.9, 139.4, 133.0, 132.5, 132.1, 130.5, 130.3, 129.7, 129.3, 128.9, 128.4, 128.1, 127.9, 124.8, 118.6, 70.3, 69.8, 61.6, 53.2, 41.8, 22.3, 22.0, 21.5, 21.0

LRMS (FAB) for $C_{29}H_{34}N_2O_4$, calcd (M^+): 474.2519; found: 475.04 (M+1).

Di *tert*-butyl 1-((2-allyl-5-diphenylmethylene)cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 33c

Following the general experimental procedure, bicyclic hydrazine **31c** (139 mg, 0.30 mmol), allyltributyltin **32** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **33c** as a light yellow solid in 43% (33 mg) yield.

Mp 104-105 °C. R_f 0.53 (3:1 Hexane/ethyl acetate).



33c

IR (KBr)ν_{max}: 3330, 2923, 1742, 1725, 1392, 1366, 1257, 1158, 1021, 913, 752 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.14 (m, 10H), 6.38-6.29 (m, 1H), 6.08-6.05 (m, 1H), 5.92-5.70 (m, 1H), 5.53-5.25 (m, 2H), 5.10-5.04 (m, 2H), 3.39-3.27 (m, 1H), 2.57-2.49 (m, 1H), 2.27-2.17 (m, 1H), 1.56-1.22 (m, 18H).

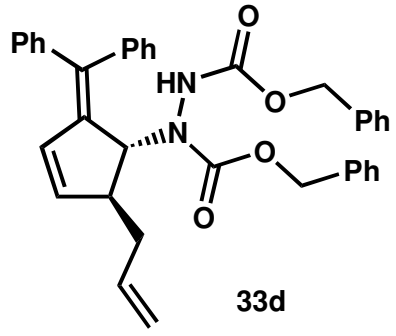
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 155.3, 142.9, 140.9, 139.5, 136.4, 136.2, 133.3, 132.5, 130.7, 130.2, 129.1, 128.8, 128.7, 127.5, 116.9, 80.9, 80.6, 64.1, 49.4, 37.6, 31.1, 29.9, 28.4, 27.7.

LRMS (FAB) for $C_{31}H_{38}N_2O_4$, calcd (M^+): 502.2832; found: 525.19 $(M+Na)^+$.

Dibenzyl 1-((2-allyl-5-diphenylmethylene)cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 33d

Following the general experimental procedure, bicyclic hydrazine **31d** (160 mg, 0.30 mmol), allyltributyltin **32** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **33d** as a white solid in 80% (69 mg) yield.

Mp 139-142 °C. R_f 0.31 (3:1 Hexane/ethyl acetate).



33d

IR (KBr)ν_{max}: 3298, 2974, 1742, 1694, 1504, 1423, 1308, 1219, 1139, 756, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.13 (m, 20H), 6.31 (d, J = 4.5 Hz, 1H), 6.08-6.05 (m, 1H), 5.96-5.70 (m, 2H), 5.58-5.50 (m, 1H), 5.18-4.68 (m, 6H), 3.35 (s, 1H), 2.55-2.40 (m, 1H), 2.35-2.23 (m, 1H).

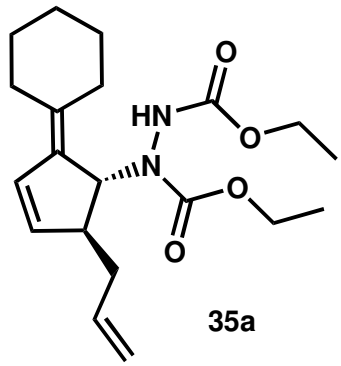
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 154.8, 140.5, 139.2, 136.0, 135.6, 133.8, 130.0, 129.8, 128.8, 128.7, 128.6, 128.3, 128.1, 127.9, 127.8, 116.0, 68.3, 68.0, 67.4, 53.2, 40.6.

LRMS (FAB) for $C_{37}H_{34}N_2O_4$, calcd (M^+): 570.2519; found: 593.30 $(M+Na)^+$.

Diethyl 1-((2-allyl-5-cyclohexylidene)cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 35a

Following the general experimental procedure, bicyclic hydrazine **34a** (97 mg, 0.30 mmol), allyltributyltin **32** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **35a** as an yellow viscous liquid in 64% (35 mg) yield.

R_f 0.41 (3:1 Hexane/ethyl acetate).



35a

IR (neat) ν_{max}: 3295, 2928, 2854, 1751, 1714, 1517, 1416, 1384, 1228, 1178, 1124, 1063, 913, 758 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.33 (d, J = 5.7 Hz, 1H), 6.11 (s, 1H), 5.88-5.75 (m, 2H), 5.10-4.85 (m, 3H), 4.25-4.10 (m, 4H), 3.16-2.95 (m, 1H), 2.36-2.20 (m, 3H), 2.15-2.11 (m, 3H), 1.83-1.40 (m, 6H), 1.31-1.22 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0, 155.5, 137.1, 136.4, 133.7, 129.8, 127.3, 116.5, 62.5, 62.0, 61.7, 50.0, 39.1, 32.1, 31.3, 28.3, 27.1, 26.8, 14.9, 14.7.

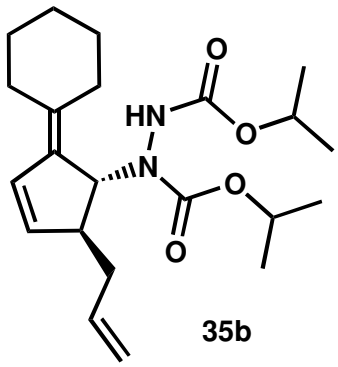
LRMS (FAB) for $C_{20}H_{30}N_2O_4$, calcd (M^+): 362.2206; found: 385.12 $(M+Na)^+$.

Diisopropyl 1-((2-allyl-5-cyclohexylidene)cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 35b

Following the general experimental procedure, bicyclic hydrazine **34b** (105 mg, 0.30 mmol), allyltributyltin **32** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%),

$Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **35b** as an yellow viscous liquid in 74% (44 mg) yield.

R_f 0.38 (3:1 Hexane/ethyl acetate).



35b

IR (neat) ν_{max}: 3292, 2980, 2854, 1752, 1705, 1468, 1385, 1297, 1232, 1180, 1109, 1036, 912, 758 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.32 (d, *J* =5.7 Hz, 1H), 5.98 (brs, 1H), 5.86-5.74 (m, 2H), 5.10-4.75 (m, 5H), 3.09-3.05 (m, 1H) 2.35-2.25 (m, 3H), 2.16-2.11 (m, 3H) 1.85-1.40 (m, 6H), 1.33-1.19 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 154.9, 136.9, 135.9, 134.0, 130.1, 129.7, 116.5, 69.9, 69.5, 61.9, 49.9, 39.1, 32.1, 31.3, 29.9, 28.5, 26.8, 22.9, 22.4, 22.2.

LRMS (FAB) for $C_{22}H_{34}N_2O_4$, calcd (M^+): 390.2519; found: 413.37 $(M+Na)^+$.

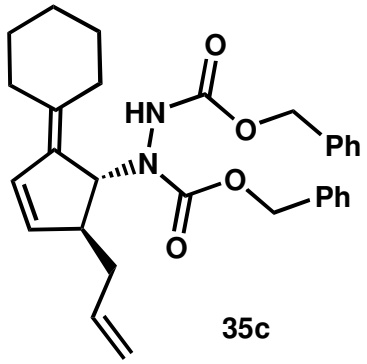
Dibenzyl 1-((2-allyl-5-cyclohexylidene)cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 35c

Following the general experimental procedure, bicyclic hydrazine **34c** (134 mg, 0.30 mmol), allyltributyltin **32** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **35c** as an yellow solid in 56% (41 mg) yield.

Mp 81-83 °C. R_f 0.41 (3:1 Hexane/ethyl acetate).

IR (KBr) ν_{max}: 3296, 2926, 1750, 1710, 1413, 1377, 1311, 1229, 1059, 916, 752, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.20 (m, 10H), 6.29-6.21 (m, 2H), 5.84-5.58 (m, 2H), 5.20-5.02 (m,



35c

8H), 2.89-2.76, (m, 1H), 2.61-2.56 (m, 1H), 2.25-1.86 (m, 4H), 1.62-1.25 (m, 6H).

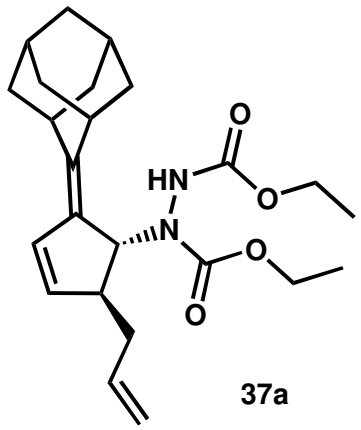
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 154.4, 143.3, 142.6, 135.9, 134.8, 132.3, 130.1, 128.5, 128.3, 128.2, 120.9, 116.4, 68.0, 67.5, 62.1, 51.0, 38.9, 35.8, 31.8, 30.4, 28.2, 26.5.

LRMS (FAB) for $C_{30}H_{34}N_2O$, calcd (M^+): 486.2519; found: 486.43.

Diethyl 1-((2-allyl-5-adamantylidene)cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 37a

Following the general experimental procedure, bicyclic hydrazine **36a** (112 mg, 0.30 mmol), allyltributyltin **32** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **37a** as a brownish yellow viscous liquid in 70% (44 mg) yield.

R_f 0.33 (3:1 Hexane/ethyl acetate).



37a

IR (neat) ν_{max}: 3294, 2908, 2849, 1755, 1705, 1412, 1302, 1214, 1119, 1062, 910, 757 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.32 (d, J = 5.8 Hz, 1H), 6.06 (brs, 1H), 5.92-5.72 (m, 2H), 5.10-4.99 (m, 3H) 4.19-4.12 (m, 4H) 3.17-3.09 (m, 1H), 2.91 (s, 1H), 2.74-2.59 (m, 1H), 2.35-2.09 (m, 2H), 1.96-1.56 (m, 12H), 1.25 (t, 6H).

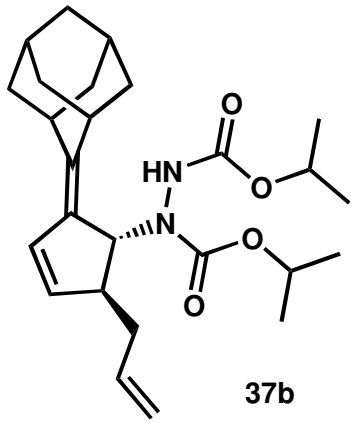
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 155.1, 143.7, 136.1, 135.8, 129.6, 129.1, 116.3, 62.2, 61.8, 61.6, 49.4, 39.9, 39.5, 39.0, 38.8, 37.0, 34.9, 34.7, 28.1, 14.7, 14.5.

HRMS (EI) for $C_{24}H_{34}N_2O_4$, calcd (M^+): 414.2519; found: 414.2520.

Diisopropyl 1-((2-allyl-5-adamantylidene)cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 37b

Following the general experimental procedure, bicyclic hydrazine **36b** (121 mg, 0.30 mmol), allyltributyltin **32** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **37b** as light yellow viscous liquid in 88% (55 mg) yield.

R_f 0.46 (3:1 Hexane/ethyl acetate).



37b

IR (neat) ν_{max}: 3290, 3073, 2849, 1750, 1714, 1468, 1404, 1295, 1231, 1110, 1036, 912, 758, 735, 647 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.34-6.32 (d, *J* = 6.0 Hz, 1H), 6.04 (brs, 1H), 5.88-5.77 (m, 2H), 5.11-4.95 (m, 5H), 3.14-3.09 (m, 1H), 2.89 (s, 1H), 2.72-2.60 (m, 1H), 2.48-2.14 (m, 2H), 1.96-1.77 (m, 12H) 1.35-1.22 (m, 12H).

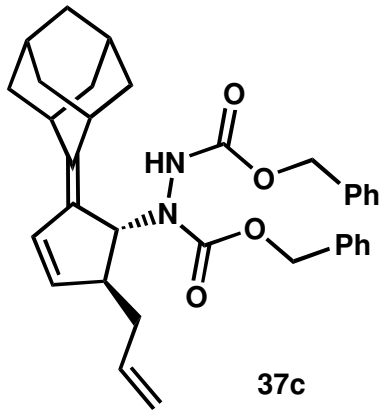
^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 154.6, 143.9, 136.2, 130.1, 129.4, 129.0, 116.1, 69.7, 69.4, 61.9, 49.2, 39.5, 38.9, 38.7, 36.9, 34.9, 34.1, 28.1, 27.9, 26.8, 22.1, 21.9.

HRMS (EI) for $C_{26}H_{38}N_2O_4$, calcd (M^+): 442.2832; found: 442.2851.

Dibenzyl 1-((2-allyl-5-adamantylidene)cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 37c

Following the general experimental procedure, bicyclic hydrazine **36c** (150 mg, 0.30 mmol), allyltributyltin **32** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **37c** as light yellow viscous liquid in 63% (51 mg) yield.

R_f 0.56 (3:1 Hexane/ethyl acetate).



37c

IR (neat) ν_{max}: 3291, 2908, 2848, 1755, 1713, 1449, 1407, 1297, 1214, 1123, 1046, 912, 753, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.20 (m, 10H), 6.28-6.20 (m, 2H), 6.01 (brs, 1H), 5.83-5.69 (m, 3H), 5.12-4.85 (m, 6H), 3.11 (s, 1H), 2.86 (s, 1H), 2.56-2.40 (m, 1H), 2.20-2.16 (m, 1H), 1.96-1.60 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 155.8, 141.2, 140.1, 139.4, 138.5, 136.4, 135.9, 130.2, 128.5, 128.3, 128.2, 126.8, 124.5, 116.4, 69.5, 67.6, 61.8, 49.8, 39.7, 39.4, 39.1, 36.9, 34.9, 34.3, 28.0.

LRMS (FAB) for $C_{34}H_{38}N_2O_4$, cacld (M^+): 538.2832; found: 561.03 $(M+Na)^+$.

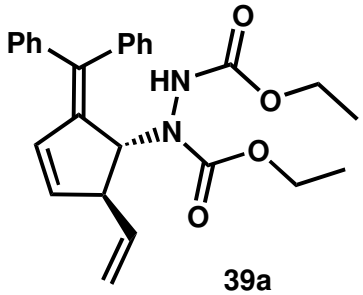
Diethyl 1-((2-diphenylmethylene-5-vinyl)cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 39a

Following the general experimental procedure, bicyclic hydrazine **31a** (127.4 mg, 0.32 mmol), vinyltributyltin **38** (50 mg, 0.16 mmol), PPh_3 (9 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (9 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **39a** as a brownish yellow solid in 55% (38 mg) yield.

Mp 85-87 °C. R_f 0.55 (3:1 Hexane/ethyl acetate).

IR (KBr) ν_{max}: 3302, 3065, 2980, 1744, 1716, 1594, 1489, 1443, 1413, 1382, 1303, 1267, 1219, 1171, 1026, 918, 756, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.29 (m, 10H), 6.37-6.35 (m, 1H), 6.03-6.01 (m, 2H), 5.54-5.51 (m, 2H), 5.19-5.06 (m, 2H), 4.15-4.13 (m, 2H), 3.89-



39a

3.87 (m, 2H), 3.86-3.85 (m, 1H), 1.25 (t, *J* = 6.9 Hz, 3H), 1.03 (t, *J* = 6.5 Hz, 3H).

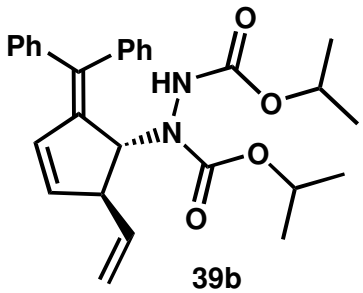
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9, 155.0, 142.5, 141.6, 139.4, 138.9, 135.1, 134.3, 133.2, 130.1, 128.7, 127.3, 126.6, 123.1, 115.6, 67.1, 62.7, 62.1, 53.7, 14.6, 13.9.

LRMS (FAB) for $C_{26}H_{28}N_2O_4$, calcd (M^+): 432.2049; found: 455.45 $(M+Na)^+$.

Diisopropyl 1-((2-diphenylmethylene-5-vinyl)cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 39b

Following the general experimental procedure, bicyclic hydrazine **31b** (137 mg, 0.32 mmol), vinyltributyltin **38** (50 mg, 0.16 mmol), PPh_3 (9 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (9 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **39b** as a brownish yellow viscous liquid in 53% (39 mg) yield.

R_f 0.40 (3:1 Hexane/ethyl acetate).



39b

IR (neat)ν_{max}: 3368, 2980, 2932, 1750, 1716, 1469, 1386, 1301, 1269, 1181, 1109, 1032, 917, 757, 701 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.15 (m, 10H), 6.37-6.35 (m, 1H), 6.05-5.98 (m, 2H), 5.63-5.35 (m, 2H), 5.23-5.07 (m, 2H), 4.91-4.86 (m, 1H), 4.64-4.55 (m, 1H), 3.91-3.81 (m, 1H), 1.28-1.22 (m, 8H), 1.20-0.95 (m, 4H).

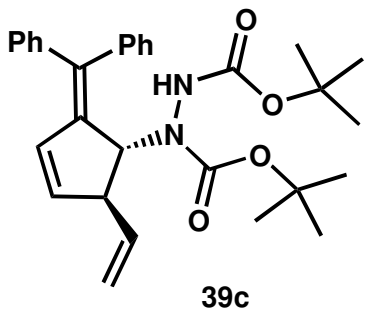
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 155.3, 140.3, 139.2, 138.6, 135.4, 134.6, 133.0, 130.5, 129.1, 128.0, 127.3, 126.6, 123.2, 115.0, 69.8, 69.5, 61.6, 53.2, 22.8, 22.3, 21.7.

LRMS (FAB) for $C_{28}H_{32}N_2O_4$, calcd (M^+): 460.2362; found: 483.54 $(M+Na)^+$.

Di *tert* butyl 1-((2-diphenylmethylene-5-vinyl) cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 39c

Following the general experimental procedure, bicyclic hydrazine **31c** (145.5 mg, 0.32 mmol), vinyltributyltin **32** (50 mg, 0.16 mmol), PPh_3 (9 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (9 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **39c** as an yellow solid in 51% (39 mg) yield.

Mp 106-108 °C. R_f 0.44 (3:1 Hexane/ethyl acetate).



39c

IR (KBr)ν_{max}: 3368, 3058, 2927, 1745, 1713, 1622, 1452, 1392, 1336, 1246, 1158, 1018, 917, 767, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.20 (m, 10H), 6.40-6.31 (m, 1H), 6.18-5.99 (m, 2H), 5.59-5.38 (m, 2H), 5.21-5.05 (m, 2H), 3.95-3.86 (m, 1H), 1.46-1.25 (m, 18H).

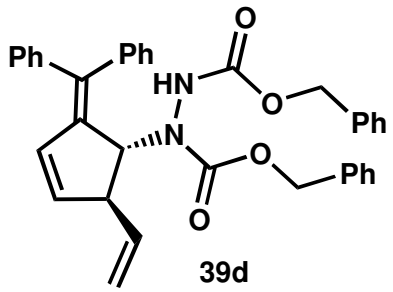
^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 155.2, 139.8, 139.1, 138.2, 134.8, 133.1, 130.5, 129.9, 129.6, 129.5, 128.9, 128.5, 128.3, 127.6, 127.0, 126.9, 125.4, 114.8, 80.7, 80.5, 65.4, 53.0, 30.1, 29.7, 29.5, 28.1.

LRMS (FAB) for $C_{30}H_{36}N_2O_4$, calcd (M^+): 488.2675; found: 511.10 $(M+Na)^+$.

Dibenzyl 1-((2-diphenylmethylene-5-vinyl)cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 39d

Following the general experimental procedure, bicyclic hydrazine **31d** (166.9 mg, 0.32 mmol), vinyltributyltin **38** (50 mg, 0.16 mmol), PPh_3 (9 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (9 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **39d** as an off white solid in 68% (60 mg) yield.

Mp 158-159 °C. R_f 0.34 (3:1 Hexane/ethyl acetate).



39d

IR (KBr)ν_{max}: 3310, 3065, 2927, 1739, 1697, 1596, 1504, 1419, 1314, 1218, 1134, 1046, 916, 755, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.13 (m, 20H), 6.34 (s, 1H), 6.05-5.81 (m, 2H), 5.70-5.52 (m, 1H), 5.26-4.73 (m, 7H), 3.91 (s, 1H).

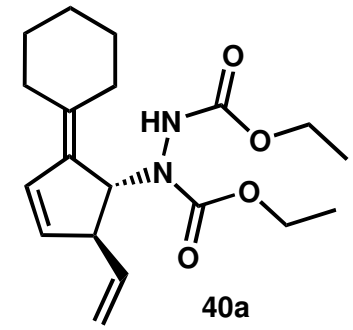
^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 154.1, 140.5, 139.6, 136.0, 135.6, 135.2, 133.8, 130.0, 129.8, 128.8, 128.7, 128.6, 128.3, 128.1, 127.9, 127.8, 127.6, 127.4, 124.2, 115.7, 68.4, 67.6, 67.4, 53.2.

LRMS (FAB) for $C_{36}H_{32}N_2O_4$, calcd (M^+): 556.2362; found: 579.25 $(M+Na)^+$.

Diethyl 1-((2-cyclohexylidene-5-vinyl)cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 40a

Following the general experimental procedure, bicyclic hydrazine **34a** (101 mg, 0.32 mmol), vinyltributyltin **38** (50 mg, 0.16 mmol), PPh_3 (9 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (9 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **40a** as an yellow viscous liquid in 52% (29 mg) yield.

R_f 0.37 (3:1 Hexane/ethyl acetate).



40a

IR (neat)ν_{max}: 3296, 2926, 1750, 1710, 1413, 1377, 1311, 1229, 1059, 916, 752 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.39 (d, J = 5.7 Hz, 1H), 6.20-6.09 (m, 1H), 5.88-5.82 (m, 2H), 5.08-4.98 (m, 3H), 4.23-4.19 (m, 4H), 3.67-3.64 (m, 1H), 2.35-2.10 (m, 4H), 1.80-1.40 (m, 6H), 1.31-1.25 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 155.7, 139.3, 136.3, 129.2, 124.3, 124.1, 114.6, 62.4, 62.0, 61.8, 50.5, 31.5, 30.3, 29.4, 28.2, 26.6, 14.7, 14.2.

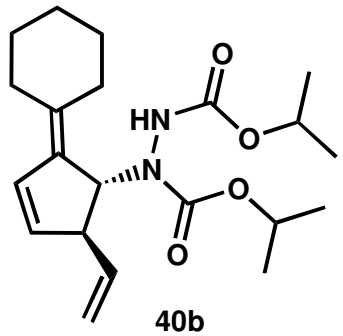
LRMS (FAB) for $C_{19}H_{28}N_2O_4$, calcd (M^+): 348.2049; found: 371.13 $(M+Na)^+$.

Diisopropyl 1-((2-cyclohexylidene-5-vinyl)cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 40b

Following the general experimental procedure, bicyclic hydrazine **34b** (110.03 mg, 0.32 mmol), vinyltributyltin **38** (50 mg, 0.16 mmol), PPh_3 (9 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (9 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **40b** as an yellow viscous liquid in 64% (38 mg) yield.

R_f 0.44 (3:1 Hexane/ethyl acetate).

IR (neat) ν_{max}: 3296, 2926, 1750, 1710, 1413, 1377, 1311, 1229, 1059, 916, 752 cm^{-1}.



40b

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.39 (d, J = 5.6 Hz, 1H), 6.01 (brs, 1H), 5.84-5.80 (m, 3H), 5.07-4.98 (m, 4H), 3.64-3.50 (m, 1H), 2.30-2.08 (m, 4H), 1.79-1.40 (m, 6H), 1.38-1.19 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 155.8, 139.4, 136.4, 128.8, 124.3, 124.1, 114.1, 70.1, 69.8, 62.1, 53.2, 31.9, 30.3, 29.4, 28.2, 26.6, 22.9, 22.4, 22.2.

LRMS (FAB) for $C_{21}H_{32}N_2O_4$, calcd (M^+): 376.2362; found: 399.14 $(M+Na)^+$.

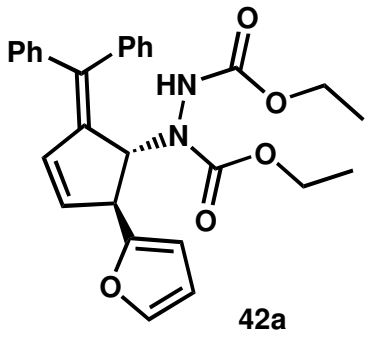
General Experimental Procedure for 42a-b, 44a-b: Bicyclic hydrazine (2 equiv.) and heteroaryl stannane (1 equiv.) were taken in a wheaton vial, and dissolved in dry toluene (4 mL). PPh_3 (10 mol%) and $Pd(OAc)_2$ (5 mol%) were added to the reaction mixture followed by the addition of $Sc(OTf)_3$ (2 mol%). The reaction mixture was stirred at 60 ^oC for 10 h. Completion of the reaction was monitored by TLC and the reaction mixture on silica gel (60-120 mesh) column

chromatography using 20% ethyl acetate in hexane afforded the product in moderate to low yield.

Diethyl 1-(2-(diphenylmethylene)-5-(furan-2-yl) cyclopent-3-enyl) hydrazine -1, 2-dicarboxylate 42a

Following the general experimental procedure, bicyclic hydrazine **31a** (113 mg, 0.28 mmol), 2-tributylstannylfuran **41** (50 mg, 0.14 mmol), PPh_3 (4 mg, 10 mol%), $Pd(OAc)_2$ (2 mg, 5 mol%) and $Sc(OTf)_3$ (1 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **42a** as light brown viscous liquid in 38% (25 mg) yield.

R_f 0.36 (3:1 Hexane/ethyl acetate).



42a

IR (neat)ν_{max}: 3374, 2924, 2852, 1753, 1722, 1487, 1409, 1380, 1218, 1124, 1060, 971, 754, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.16 (m, 12H), 6.49-6.46 (m, 1H), 6.29 (s, 1H), 6.26-6.11 (m, 2H), 5.68-5.50 (m, 1H), 4.53-4.51 (m, 1H), 4.17-4.13 (m, 2H), 3.96-3.78 (m, 2H), 1.28-1.24 (m, 3H), 1.09-0.98 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 154.1, 141.8, 141.7, 137.2, 136.7, 136.5, 135.7, 135.6, 133.7, 133.1, 129.8, 129.6, 128.7, 128.5, 128.2, 128.1, 127.7, 110.3, 105.6, 63.2, 62.2, 62.0, 49.2, 14.3, 14.2.

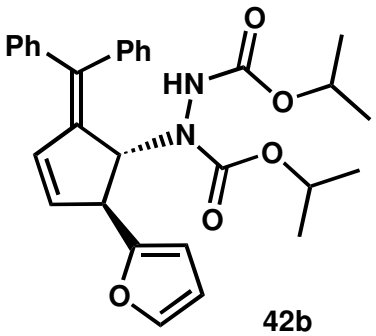
HRMS (EI) for $C_{28}H_{28}N_2O_5$, calcd (M^+): 472.1998; found: 472.1986.

Diisopropyl 1-(2-(diphenylmethylene)-5-(furan-2-yl) cyclopent-3-enyl) hydrazine -1, 2-dicarboxylate 42b

Following the general experimental procedure, bicyclic hydrazine **31b** (121 mg, 0.28 mmol), 2-tributylstannylfuran **41** (50 mg, 0.14 mmol), PPh_3 (4 mg, 10 mol%), $Pd(OAc)_2$ (2 mg, 5 mol%) and $Sc(OTf)_3$ (1 mg, 2 mol%) in 4 mL of dry

toluene at 60 °C for 10 h gave the product **42b** as light brown viscous liquid in 47% (33 mg) yield.

R_f 0.47 (3:1 Hexane/ethyl acetate).



42b

IR (neat)ν_{max}: 3368, 2981, 2934, 1750, 1715, 1597, 1443, 1385, 1298, 1227, 1178, 1108, 1031, 957, 756, 701, 598 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.19 (m, 12H), 6.46-6.44 (m, 1H), 6.30-6.21 (m, 2H), 6.13-6.00 (m, 1H), 5.77-5.53 (m, 2H), 4.90-4.88 (m, 1H), 4.61-4.56 (m, 1H), 1.24-0.86 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 155.3, 141.5, 140.8, 137.2, 136.9, 136.5, 135.2, 132.9, 132.1, 130.2, 129.9, 128.2, 127.9, 127.7, 127.5, 127.3, 127.1, 126.8, 110.2, 105.3, 70.1, 69.8, 64.4, 49.5, 22.6, 21.9.

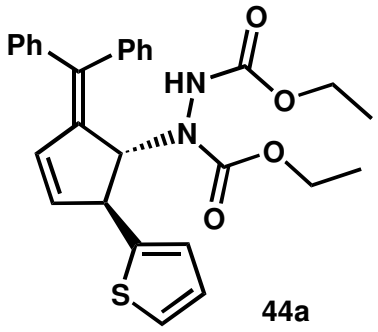
LRMS (FAB) for $C_{30}H_{32}N_2O_5$, calcd (M^+): 500.2311; found: 523.35 ($M+Na^+$).

Diethyl 1-(2-(diphenylmethylene)-5-(thiophen-2-yl) cyclopent-3-enyl) hydrazine -1, 2-dicarboxylate 44a

Following the general experimental procedure, bicyclic hydrazine **31a** (108 mg, 0.26 mmol), 2-tributylstannylthiophene **43** (50 mg, 0.13 mmol), PPh_3 (4 mg, 10 mol%), $Pd(OAc)_2$ (2 mg, 5 mol%) and $Sc(OTf)_3$ (1 mg, 2 mol%) in 4 mL of dry toluene at 60 °C for 10 h gave the product **44a** as light brown viscous liquid in 47% (31 mg) yield.

R_f 0.24 (3:1 Hexane/ethyl acetate).

IR (neat)ν_{max}: 3363, 3291, 2924, 2851, 1722, 1596, 1484, 1407, 1381, 1300, 1223, 1119, 1059, 1028, 756, 701 cm^{-1}.



44a

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.18 (m, 12H), 6.96 (m, 1H), 6.50 (s, 1H), 6.17-6.11 (m, 1H), 5.89-5.40 (m, 2H), 5.03-4.90 (m, 1H), 4.30-4.12 (m, 2H), 3.86-3.76 (m, 2H), 1.42-1.25 (m, 6H).

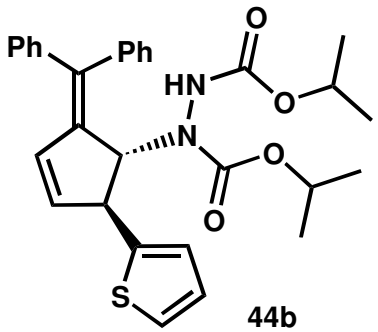
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 154.4, 141.3, 140.7, 139.5, 137.6, 137.2, 134.3, 129.8, 129.7, 128.7, 128.2, 127.6, 126.7, 123.8, 70.6, 62.5, 62.0, 49.0, 14.3, 14.0.

LRMS (FAB) for $C_{28}H_{28}N_2O_4S$, calcd (M^+): 488.1770; found: 511.06 $(M+Na)^+$.

Diisopropyl 1-(2-(diphenylmethylene)-5-(thiophen-2-yl) cyclopent-3-enyl) hydrazine -1, 2-dicarboxylate 44b

Following the general experimental procedure, bicyclic hydrazine **31b** (116 mg, 0.26 mmol), 2-tributylstannylthiophene **43** (50 mg, 0.13 mmol), PPh_3 (4 mg, 10 mol %), $Pd(OAc)_2$ (2 mg, 5 mol %) and $Sc(OTf)_3$ (1 mg, 2 mol %) in 4 mL of dry toluene at 60 °C for 10 h gave the product **44b** as light brown viscous liquid in 38% (26 mg) yield. Light brown viscous liquid.

R_f 0.33 (3:1 Hexane-EtOAc).



44b

IR (neat)ν_{max}: 3368, 2978, 1748, 1716, 1682, 1597, 1468, 1386, 1314, 1234, 1105, 1028, 754, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.09 (m, 12H), 6.95 (m, 1H), 6.50-6.48 (m, 1H), 6.27-6.14 (m, 1H), 5.60-5.47 (m, 2H), 5.11-4.92 (m, 2H), 4.67-4.57 (m, 1H), 1.28-1.21 (m, 6H), 1.06-0.91 (m, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 154.0, 141.6, 140.8, 136.2, 135.7, 133.6, 133.0, 129.8, 129.6, 128.9, 128.7, 128.5, 128.4, 128.2, 128.0, 127.6, 127.5, 127.4, 127.0, 123.3, 70.9, 70.2, 66.3, 48.6, 21.8, 21.7.

LRMS (FAB) for $C_{30}H_{32}N_2O_4S$, calcd (M^+): 516.2083; found: 538.99 $(M+Na)^+$.

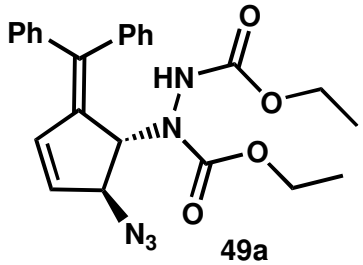
General procedure for the synthesis of azido-hydrazino substituted alkylidene cyclopentenes 49a-d, 50a-c, 51a-b

Bicyclic hydrazine (2 equiv.), stannyl/silyl azide (1 equiv.), PPh_3 (20 mol%), $Pd_2(dba)_3.CHCl_3$ (5 mo%) and $Sc(OTf)_3$ (2 mol %) were taken in a wheaton reactor. The mixture was dissolved in dry toluene (4 mL) and stirred at 60 °C for 12 hours. After the completion of the reaction, the mixture on silica gel (60-120 mesh) column chromatography using 15% ethyl acetate in hexane afforded the products in good to excellent yield.

Diethyl 1-(2-azido-5-(diphenylmethylene)cyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 49a

Following the general experimental procedure, bicyclic hydrazine **31a** (122 mg, 0.30 mmol), azidotributyltin **48** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%), in 4 mL of dry toluene at 60 °C for 12 h gave the product **49a** as a white solid in 93% (63 mg) yield.

Mp 119-121 °C. R_f 0.45 (3:1 Hexane/ethyl acetate).



49a

IR (KBr) ν_{max}: 3312, 2981, 2102, 1742, 1698, 1598, 1492, 1418, 1384, 1305, 1222, 1134, 1061, 954, 756, 703 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.12 (m, 10H), 6.52 (dd, J_1 = 5.6 Hz, J_2 = 12.4 Hz, 1H), 5.99 (s, 1H), 5.67-5.45 (m, 2H), 5.08-4.93 (m, 1H), 4.19-4.09 (m, 2H), 4.03-3.92 (m, 2H), 1.32-1.23 (m, 4H), 1.06 (t, J = 6.9 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 154.4, 141.5, 140.7, 138.2, 136.5, 135.8, 135.6, 133.7, 129.8, 129.7, 128.6, 128.4, 128.3, 128.1, 127.6, 70.3, 67.8,

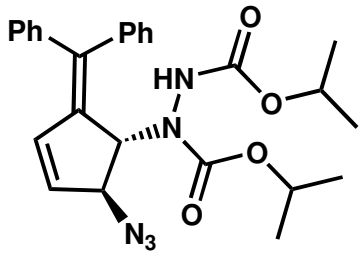
62.7, 62.2, 14.4, 14.1.

HRMS (EI) for $C_{24}H_{25}N_5O_4$, calcd (M^+): 447.1907; found: 447.2017.

Diisopropyl 1-(2-azido-5-(diphenylmethylene)cyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 49b

Following the general experimental procedure, bicyclic hydrazine **31b** (131 mg, 0.30 mmol), azidotributyltin **48** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%), in 4 mL of dry toluene at 60 °C for 12 h gave the product **49b** as a light yellow solid. in 70% (50mg) yield.

Mp 91-93 °C. R_f 0.55 (3:1 Hexane/ethyl acetate).



49b

IR (KBr) ν_{max}: 3362, 2981, 2100, 1725, 1593, 1467, 1385, 1302, 1228, 1108, 1031, 961, 757, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.13 (m, 10H), 6.51(d, *J* = 5.4 Hz, 1H), 5.98-5.83 (m, 1H), 5.61-5.44 (m, 2H), 5.10-4.67 (m, 3H), 1.28-1.22 (m, 8H), 1.09-0.95 (m, 4H).

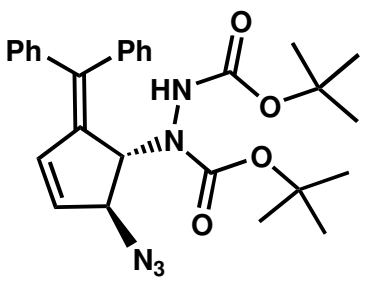
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 154.0, 141.6, 140.8, 136.2, 135.7, 133.6, 132.9, 129.8, 129.7, 128.9, 128.7, 128.5, 128.2, 128.1, 127.6, 70.9, 70.2, 67.9, 66.3, 22.6, 22.1, 21.9.

HRMS (EI) for $C_{26}H_{29}N_5O_4$, calcd (M^+): 475.2220; found: 475.2252.

Di*tert*-butyl 1-(2-azido-5-(diphenylmethylene)cyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 49c

Following the general experimental procedure, bicyclic hydrazine **31c** (139 mg, 0.30 mmol), azidotributyltin **48** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%), in 4 mL of dry toluene at 60 °C for 12 h gave the product **49c** as a white solid in 83% (63 mg) yield.

Mp. 97-99 °C. R_f 0.65 (3:1 Hexane/ethyl acetate).



49c

IR (KBr) ν_{max}: 3375, 2978, 2931, 2100, 1716, 1599, 1477, 1368, 1307, 1252, 1155, 1026, 955, 854, 756, 702, 536 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.14 (m, 10H), 6.58-6.49 (m, 1H), 5.98 (d, *J* = 3.6 Hz, 1H), 5.38-5.30 (m, 2H), 5.10-4.97 (m, 1H), 1.48-1.22 (m, 18H).

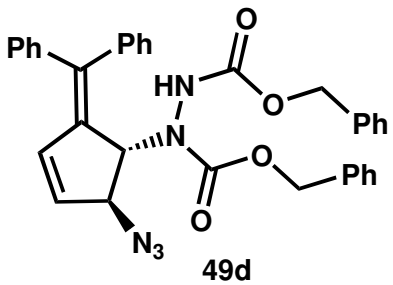
^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 153.4, 141.7, 141.0, 136.6, 135.7, 133.7, 132.8, 129.8, 129.6, 128.7, 128.5, 128.4, 128.1, 128.0, 127.6, 127.5, 82.3, 81.2, 70.2, 65.5, 28.2, 28.1, 28.0.

LRMS (FAB) for $C_{28}H_{33}N_5O_4$, calcd (M^+): 503.25; found: 503.31.

Dibenzyl 1-(2-azido-5-(diphenylmethylene)cyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 49d

Following the general experimental procedure, bicyclic hydrazine **31d** (159 mg, 0.30 mmol), azidotributyltin **48** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%), in 4 mL of dry toluene at 60 °C for 12 h gave the product **49d** as a white solid in 67% (58 mg) yield.

Mp 161-163 °C. R_f 0.48 (3:1 Hexane/ethyl acetate).



49d

IR (KBr) ν_{max}: 3302, 2917, 2104, 1737, 1695, 1526, 1500, 1418, 1303, 1216, 1133, 1021, 752, 695 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.05 (m, 20H), 6.52-6.47 (m, 1H), 6.03-6.01(m, 1H), 5.93-5.81(m, 1H), 5.70-5.50(m, 1H), 5.14-4.93(m, 4H), 4.82-4.78 (m, 1H).

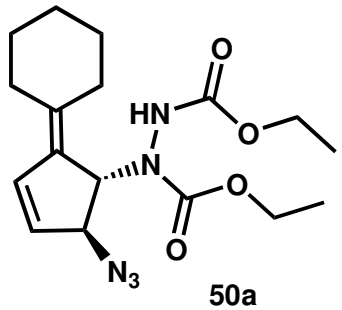
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 154.8, 141.6, 136.0, 135.6, 133.8, 130.0, 129.8, 128.8, 128.7, 128.6, 128.3, 128.1, 127.9, 127.8, 70.6, 68.3, 68.0, 65.4.

LRMS (FAB) for $C_{34}H_{29}N_5O_4$, calcd (M^+): 571.22; found: 593.91 $(M+Na)^+$.

Diethyl 1-(2-azido-5-(cyclohexylidene)cyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 50a

Following the general experimental procedure, bicyclic hydrazine **34a** (96 mg, 0.30 mmol), azidotributyltin **48** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%), in 4 mL of dry toluene at 60 °C for 12 h gave the product **50a** as a brown viscous liquid in 54% (19 mg) yield.

R_f 0.43 (3:1 Hexane/ethyl acetate).



50a

IR (neat) ν_{max}: 3285, 2925, 2857, 2097, 1715, 1410, 1380, 1300, 1230, 1125, 1059, 966, 760 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (d, J = 5.7 Hz, 1H), 6.15 (s, 1H), 5.87 (s, 1H), 5.33-5.03 (m, 1H), 4.78 (s, 1H), 4.30-4.13 (m, 4H), 2.36-2.08 (m, 4H), 1.80-1.50 (m, 6H), 1.42-1.22 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.6, 155.4, 141.6, 135.0, 131.0, 129.4, 70.7, 63.4, 62.4, 61.2, 31.5, 30.5, 29.9, 28.2, 25.7, 14.5, 14.4.

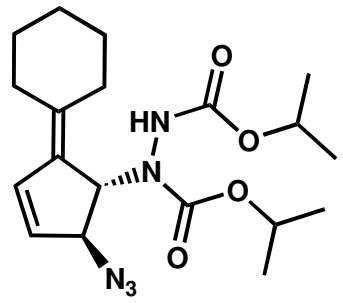
LRMS (FAB) for $C_{17}H_{25}N_5O_4$, calcd (M^+): 363.19; found: 386.11$(M+Na)^+$.

Diisopropyl 1-(2-azido-5-(cyclohexylidene)cyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 50b

Following the general experimental procedure, bicyclic hydrazine **34b** (105 mg, 0.30 mmol), azidotributyltin **48** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%), in 4 mL of dry

toluene at 60 °C for 12 h gave the product **50b** as a brown viscous liquid in 61% (36 mg) yield.

R_f 0.50 (3:1 Hexane/ethyl acetate).



50b

IR (neat) ν_{max}: 3306, 2982, 2936, 2103, 1715, 1468, 1375, 1240, 1181, 1107, 1041, 762 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (s, 1H), 6.31-6.12 (m, 1H), 5.86 (s, 1H), 5.20-4.80(m, 4H), 2.34-2.14 (m, 4H), 1.66-1.58 (m, 6H), 1.30-1.20 (m, 12H).

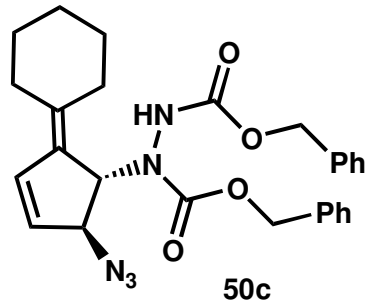
^{13}C NMR (75 MHz, $CDCl_3$): δ 155.0, 153.3, 140.8, 135.0, 131.1, 129.7, 70.6, 70.2, 69.4, 61.9, 32.0, 31.5, 29.9, 28.2, 26.5, 22.8, 22.4, 21.6.

HRMS (EI) for $C_{19}H_{29}N_5O_4$, calcd (M^+): 391.2220; found: 391.2335.

Dibenzyl 1-(2-azido-5-(cyclohexylidene)cyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 50c

Following the general experimental procedure, bicyclic hydrazine **34c** (134 mg, 0.30 mmol), azidotributyltin **48** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%), in 4 mL of dry toluene at 60 °C for 12 h gave the product **50c** as light yellow viscous liquid in 60% (44 mg) yield.

R_f 0.53 (3:1 Hexane/ethyl acetate).



50c

IR (neat) ν_{max}: 3296, 2927, 2834, 2100, 1729, 1428, 1388, 1302, 1218, 1050, 1017, 755 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.10 (m, 10H), 6.60 (s, 1H), 6.22 (s, 1H), 5.83(s, 1H), 5.53-5.33 (m, 1H), 5.16-4.78 (m, 4H), 4.67 (s, 1H), 2.31-1.99 (m, 4H), 1.58-1.23 (m, 6H).

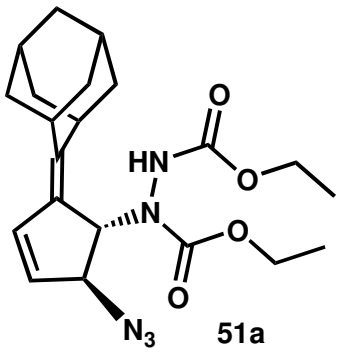
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 155.1, 140.3, 135.9, 135.7, 134.9, 131.0, 130.1, 129.7, 128.7, 128.5, 128.4, 128.3, 127.9, 69.3, 68.7, 68.3, 68.0, 31.5, 29.9, 28.2, 28.0, 26.5.

LRMS (FAB) for $C_{27}H_{29}N_5O_4$, calcd (M^+): 487.22; found: 487.37.

Diethyl 1-(2-azido-5-(adamantalylidene)cyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 51a

Following the general experimental procedure, bicyclic hydrazine **36a** (112 mg, 0.30 mmol), azidotributyltin **48** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%), $Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%), in 4 mL of dry toluene at 60 °C for 12 h gave the product **51a** as a light yellow viscous liquid in 70% (44 mg) yield.

R_f 0.46 (3:1 Hexane/ethyl acetate).



51a

IR (neat) ν_{max}: 3296, 2912, 2851, 2095, 1747, 1714, 1449, 1409, 1382, 1229, 1171, 1061, 942, 750 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (d, J = 5.3 Hz, 1H), 6.15 (s, 1H), 5.87-5.85 (m, 1H), 5.20-4.97 (m, 1H), 4.81-4.56 (m, 1H), 4.24-4.11 (m, 4H), 2.94 (s, 1H), 2.58 (s, 1H), 1.98-1.55 (m, 12H), 1.40-1.23 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 155.0, 147.4, 134.4, 129.2, 127.1, 70.1, 63.7, 62.8, 62.1, 40.3, 39.6, 38.9, 36.8, 35.0, 34.7, 30.8, 27.8, 14.6, 14.4.

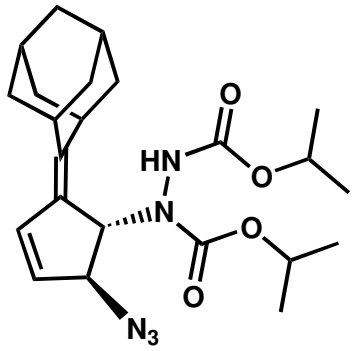
LRMS (FAB) for $C_{21}H_{29}N_5O_4$, calcd (M^+): 415.2220; found: 438.91 $(M+Na)^+$.

Diisopropyl 1-(2-azido-5-(adamantalylidene)cyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 51b

Following the general experimental procedure, bicyclic hydrazine **36b** (120 mg, 0.30 mmol), azidotributyltin **48** (50 mg, 0.15 mmol), PPh_3 (8 mg, 20 mol%),

$Pd_2(dba)_3.CHCl_3$ (8 mg, 5 mol%) and $Sc(OTf)_3$ (2 mg, 2 mol%), in 4 mL of dry toluene at 60 °C for 12 h gave the product **51b** as a light yellow viscous liquid in 84% (56 mg) yield.

R_f 0.50 (3:1 Hexane/ethyl acetate).



51b

IR (neat) ν_{max}: 3301, 2917, 2859, 2099, 1750, 1716, 1448, 1382, 1308, 1235, 1184, 1062, 948, 758 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (s, 1H), 6.15-6.06 (m, 1H), 5.85 (s, 1H), 5.22-5.18 (m, 1H), 5.00-4.80 (m, 3H), 2.94 (s, 1H), 2.59 (s, 1H), 1.98-1.42 (m, 12H), 1.37-1.25 (m, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7, 155.0, 147.1, 135.3, 129.4, 127.9, 70.8, 69.6, 69.3, 66.9, 40.8, 39.7, 38.8, 37.6, 36.7, 35.7, 35.6, 33.6, 26.8, 22.7, 21.7, 21.1.

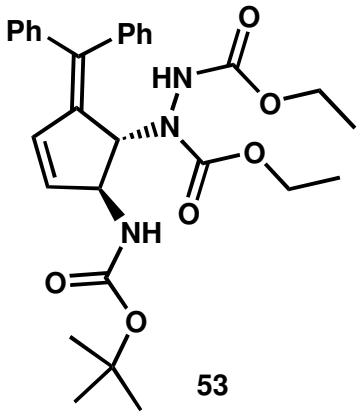
LRMS (FAB) for $C_{23}H_{33}N_5O_4$, calcd (M^+): 443.2533; found: 466.34 $(M+Na)^+$.

Diethyl 1-(2-(*tert*-butoxycarbonylamino)-5-(diphenylmethylene) cyclopent-3-enyl)hydrazine-1,2-dicarboxylate 53

Azido compound **49a** (75 mg, 0.17 mmol) is dissolved in 3 mL THF and stirred for 5 min. PPh_3 (88 mg, 0.34 mmol) and 3 mL of water is added and stirring is continued for 2 h. After the formation of amine (monitored by TLC), saturated $NaHCO_3$ is added followed by Boc anhydride (0.05 mL, 0.20 mmol) and the final product **53** is isolated as a white solid in 80% (69 mg) yield.

Mp 140-142 °C. R_f 0.48 (3:1 Hexane/ethyl acetate).

IR (neat) ν_{max}: 3362, 3322, 3055, 2980, 1734, 1710, 1534, 1484, 1437, 1384, 1194, 1119, 1070, , 750, 721, 696, 541 cm^{-1}.



53

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.11 (m, 10H), 6.38 (s, 1H), 6.13 (brs, 1H), 5.66-5.50 (m, 2H), 5.18 (brs, 1H), 5.01-4.65 (m, 1H), 4.19-4.03 (m, 2H), 4.00-3.83 (m, 2H), 1.45 (s, 9H), 1.34-1.21 (m, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 155.2, 154.9, 141.9, 138.3, 137.8, 134.3, 133.0, 132.1, 129.9, 128.6, 128.5, 127.9, 127.2, 79.3, 64.2, 62.0, 60.8, 58.3, 29.7, 28.4, 14.4.

LRMS (FAB) for $C_{29}H_{35}N_3O_6$, calcd (M^+): 521.2526; found: 544.84 $(M+Na)^+$.

2.7. References

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Chapter 3

Iodine Assisted Palladium Catalyzed Ring Opening of Bicyclic Hydrazines with Organoboronic Acids

3.1. Introduction

The carbon-carbon bond formation is the foundation of organic chemistry, and the ability to synthesize new and interesting organic molecules is inextricably linked to the discovery of novel methods that achieve this objective. In recent years, organic chemists have increasingly employed transition metal catalysts as instruments for C-C bond forming processes.[1] The prevalence of these reactions is illustrated by many transformations involving palladium that bear the names of those who discovered them. Among these, the Suzuki-Miyaura reaction which involves the coupling of organoboron compounds with various organic electrophiles is figured as one of the most important carbon-carbon bond forming process developed in the 20th century.[2] Increasingly, the application of Suzuki and related reactions is becoming a cornerstone in the efficient construction of complex organic molecules. Recently, much attention has been focused on alternative modes of reactivity of boronic acids and extending their synthetic utility. This chapter deals with a modified Suzuki type reaction of pentafulvene derived bicyclic olefins with boronic acids. As a prelude to the present work, an overview of the reactivity of boronic acids is presented in the following section.

3.2. Boronic acids: Importance and advantages

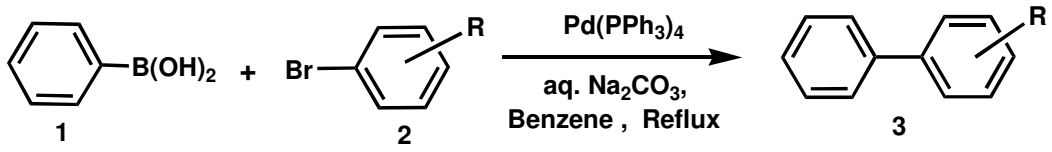
Structurally, boronic acids are trivalent boron containing organic compounds that possess one alkyl substituent (i.e., a C–B bond) and two hydroxyl groups to fill the remaining valancies on the boron atom. Boron has many similarities with carbon in terms of structural features, which makes it very useful in organic and medicinal chemistry.

Boronic acids exhibit desirable characteristics that are advantageous when compared to other organometallic and organometalloid reagents.[3] They can be synthesized from a variety of precursors and are usually stable and easily stored. A wide range of boronic acids are commercially available, that are environmentally safer than other organometallic reagents. In addition, boronic acids and boron-containing byproducts are typically non-toxic and can be easily removed from reaction media, even on large scale. Most important of all, boronic acid mediated coupling reactions proceeds with high regio- and stereoselectivity.

3.3. Suzuki-Miyaura (SM) reaction

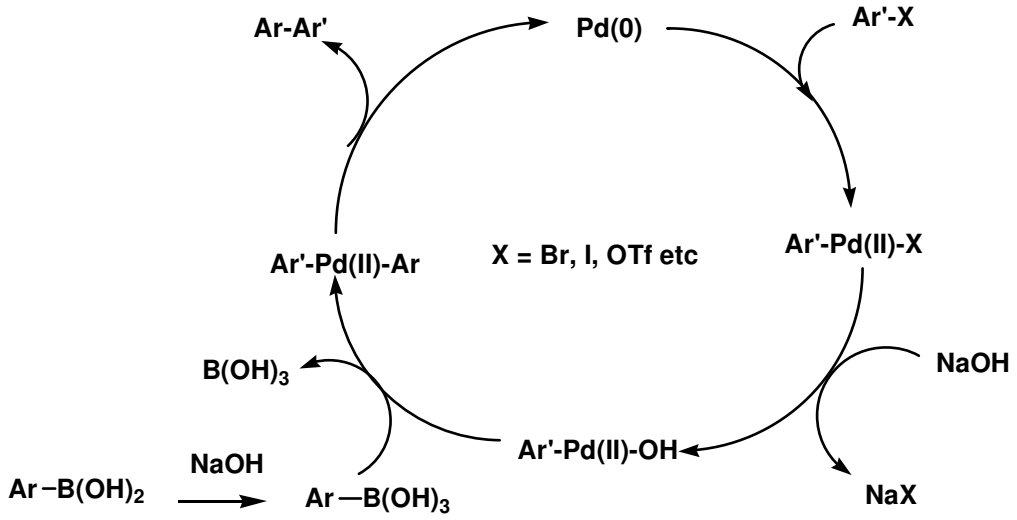
As stated, the gained prominence of boronic acids can be mainly credited to the wide spread applications of Suzuki-Miyaura (SM) reaction in organic synthesis. The discovery of this reaction has led to numerous spectacular results in synthetic organic chemistry especially in the synthesis of pharmaceutical intermediates, industrially important drug molecules and a large number of natural products.[4] The strategy has been employed in the industrial production of losartan[5] and in the synthesis of selective estrogen receptor agonists for central nervous system disorders.[6]

The first reported Suzuki reaction[7] involves the synthesis of biaryls **3** by a palladium catalyzed coupling of aryl boronic acid with aryl bromides **2** in presence of a base. The reaction was carried out in refluxing benzene under an inert atmosphere catalyzed by 3 mol% of $Pd(PPh_3)_4$ (Scheme 3.1).



Scheme 3.1

A general catalytic cycle for the reaction is illustrated in the scheme 3.2. The main difference between organoborane cross-coupling catalytic cycle and the general catalytic cycle is the displacement of halide ion from R–Pd–X to give the more reactive organopalladium alkoxide (R–Pd–OR) or organopalladium hydroxide (R–Pd–OH) depending on the base used.



Scheme 3.2 General catalytic cycle for Suzuki-Miyaura reaction

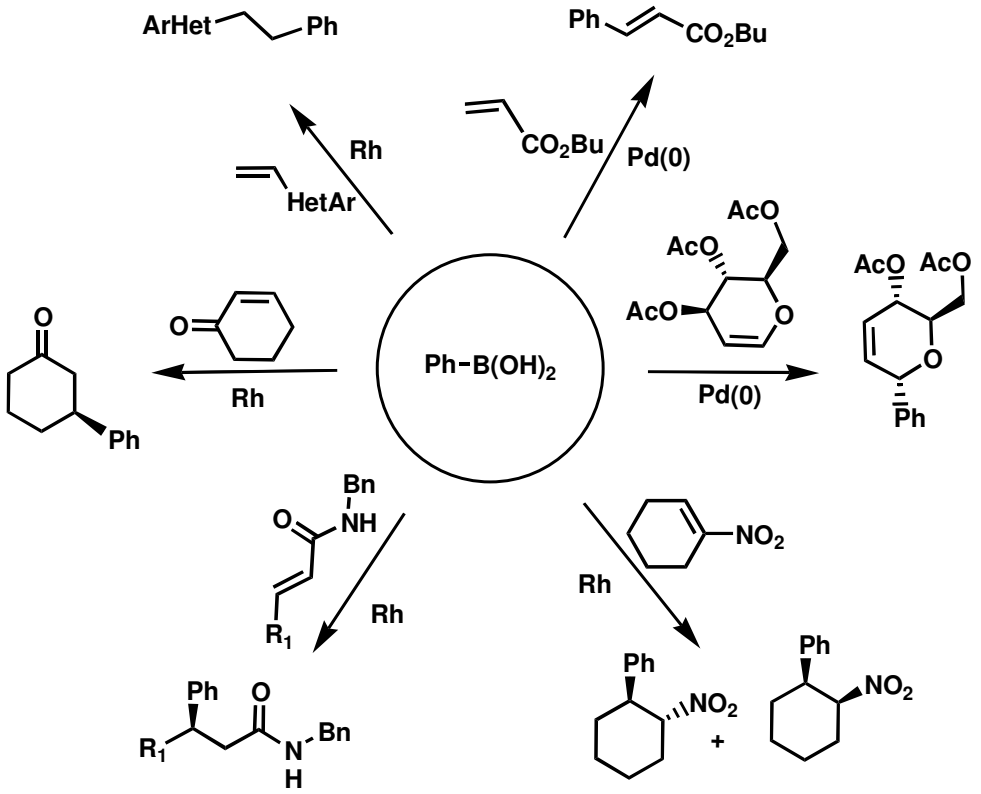
The role of base in SM reaction is to facilitate the otherwise slow transmetallation step of the catalytic cycle through a bridging hydroxyl group between the catalytic palladium center and the boron reagent. Though, Na_2CO_3 is the most commonly utilized base in SM cross-coupling reactions, bases like K_2CO_3, $Ba(OH)_2$, K_3PO_4, Cs_2CO_3 and NaOH have also been used with sterically demanding substrates.

3.4. Reactions of organoboron compounds with alkenes

After the pioneering work[7] of Suzuki and Miyaura in 1981, innumerable improvements on the original SM reaction protocol have been recorded. Important contributions include the developments in substrate scope, catalyst/ligand systems and solvents, as well as enhanced experimental conditions. These developments have broadened the possible applications enormously, so that the scope of the reaction is not restricted to the coupling of aryl halides, but extends to other substrates including alkanes, alkenes and alkynes. Among these, the cross-coupling of boronic acids with alkenes have elicited special interest and proved to be a method of great utility in synthetic organic chemistry.[8] Some of the relevant examples of the reaction of boronic acids with various olefins are described below.

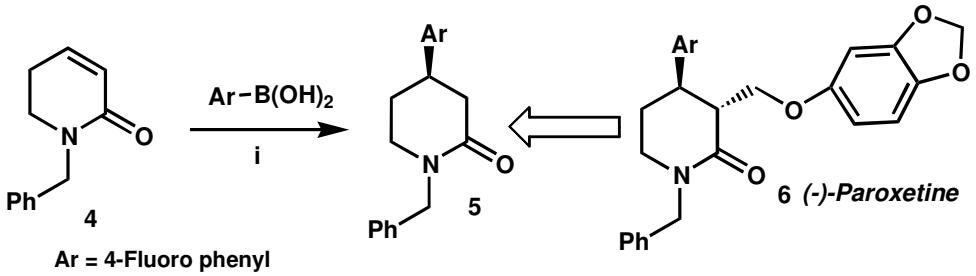
3.4.1. Reactions with activated alkenes

The transition metal catalyzed additions of organometallic reagents to activated olefins have attracted a great deal of attention in modern organic synthesis. Both palladium and rhodium catalyzed methods are known for the cross-coupling of organoboron compounds with alkenes. Significant advances have been made in the area of rhodium catalyzed additions of aryl and alkenylboronic acids to activated olefins.[9] In this regard, Hayashi and co-workers extensively worked on the enantioselective conjugate addition of boronic acids with activated alkenes.[10] A number of substrates including α,β-unsaturated ketones,[11] esters,[12] amides,[13] nitro alkenes[14] as well as alkenylphosphonates[15] undergo addition in synthetically useful yields and enantioselectivities. Palladium catalyzed Mizoroki-Heck type reactions of boronic acids with activated alkenes are also well utilized in organic synthesis.[16] Scheme 3.3 summarizes the representative reactions of boronic acids with activated olefins.



Scheme 3.3: Reactions of boronic acids with activated olefins

The interesting reactivity of boronic acids with activated alkenes has been well exploited for the construction of many natural products. For example Hayashi and co-workers reported an enantioselective 1,4-addition of 4-fluorobenzene boronic acid to lactam **4** giving **5**, a useful intermediate in the synthesis of (-)-paroxetine **6** (Scheme 3.4).[17]



Ar = 4-Fluoro phenyl

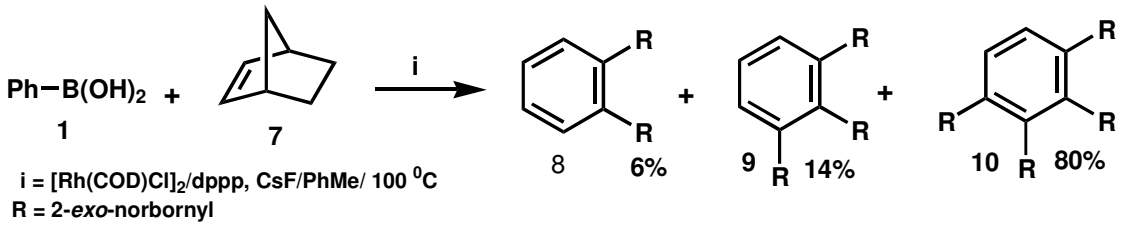
i = $Rh(acac)(C_2H_4)_2$, s-BINAP, Base, Dioxane/H_2O, 100 ^{0}C, 17%, 92% ee

Scheme 3.4

3.4.2. Reactions with norbornene system

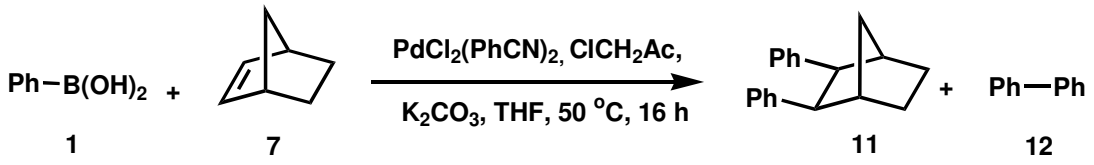
In the past few years, attempts have been devoted to the cross coupling of organoboron compounds with substrates like norbornene and norbornadiene. Unlike ordinary alkenes, these strained alkenes show remarkable reactivity difference toward boronic acids under rhodium and palladium catalysis.

Miura and co-workers reported an intriguing multiple alkylation (merry-go-round) reaction between boronic acid and norbornene under rhodium catalysis.[18] The reaction of phenyl boronic acid **1** with excess of norbornene **7** in presence of $[Rh(COD)Cl]_2$ and dppp resulted in the formation of a mixture of multiple alkylation products **8, 9** and **10**, where the tetra-alkylated arene **10** was isolated as the major product.



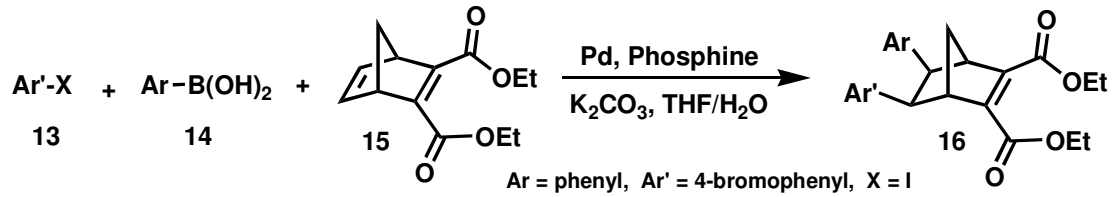
Scheme 3.5

With palladium catalyst, boronic acids undergo a Mizoroki-Heck type reaction with norbornene to give doubly arylated product **11** in 34% yield along with 59% of biphenyl.[19] The reaction is depicted in scheme 3.6.



Scheme 3.6

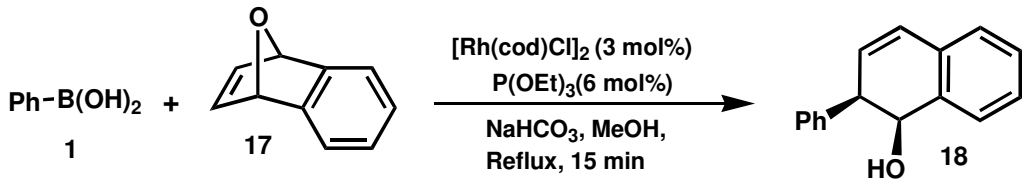
Novak *et al.* devised a bis-arylation reaction of norbornadiene **15** with boronic acid **14** and aryl halide **13** under Suzuki conditons. They have synthesized a di(*p*-bromophenyl) derivative **16** by means of a tandem Suzuki coupling-norbornadiene insertion reaction (Scheme 3.7).[20]



Scheme 3.7

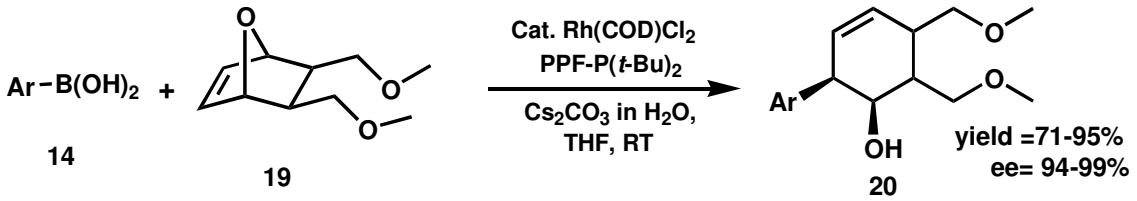
3.4.3. Ring opening reactions with heterobicyclic alkenes

Recently boronic acids have also been utilized for the ring opening of strained oxa- and azabicyclic alkenes. The use of boronic acids in the ring opening of a heterobicyclic alkene was first reported by Murakami and Igawa in 2002. They have demonstrated the ring opening of oxabenzonorbornadiene **17** with aryl and alkenyl boronic acids under rhodium catalysis, leading to *cis*-2-aryl-1,2-dihydro-1-naphthol **18** in 86% yield (Scheme 3.8).[21]



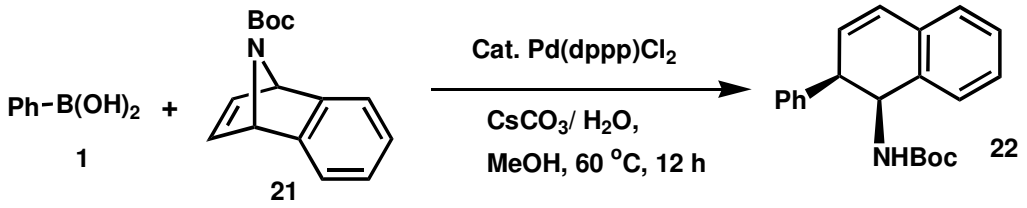
Scheme 3.8

At the same time, Lautens *et al*. have reported an asymmetric ring opening of these substrates under very mild conditions utilizing a number of boronic acids with excellent enantio- and diastereoselectivities.[22] The treatment of oxabicyclic alkene **19** with a slight excess of phenylboronic acid, $[Rh(cod)Cl]_2$ and the chiral ligand PPF-P(*t*-Bu)$_2$ in THF produced a single isomer **20** in 91% yield with 95% enantiomeric excess (Scheme 3.9).



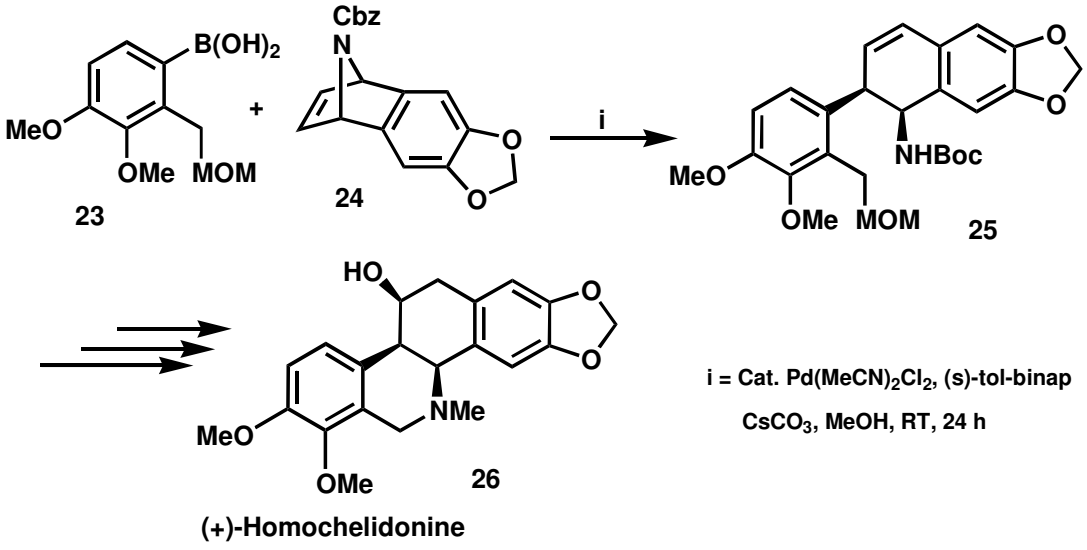
Scheme 3.9

The palladium catalyzed ring opening addition of aryl boronic acids to azabenzonorbornadiene was reported in 2003.[23] Excellent yields were obtained for the addition of an array of boronic acids to azabicyclic alkene **21**, leading to the synthesis of 1-amino-2-aryldihydronaphthalene **22.** However, rhodium catalysts were found to be unreactive or gave complex mixtures for this transformation. The reaction is represented in scheme 3.10.



Scheme 3.10

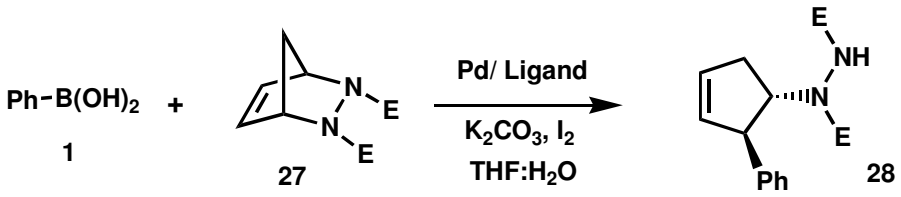
Mark Lautens and colleagues recently adopted this methodology towards the enantioselective total synthesis of (+)-Homochelidonine **26**. The strategy utilized the Pd(II) catalyzed asymmetric ring-opening reaction of a meso-azabicyclic alkene **24** with an aryl boronic acid **23** as the key step.[24]



Scheme 3.11

The pioneering report on the ring opening of bicyclic hydrazines with organoboronic acids, came from our group in 2006.[25] The reaction of boronic acid **1** with bicyclic hydrazines **27** under Suzuki reaction conditions afforded *trans*-3,4-

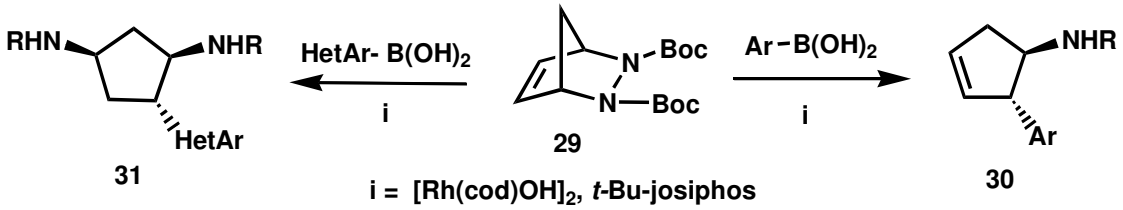
disubstituted hydrazinocyclopentenes **28** in excellent yield. The reaction protocol is outlined in scheme 3.12.



Scheme 3.12

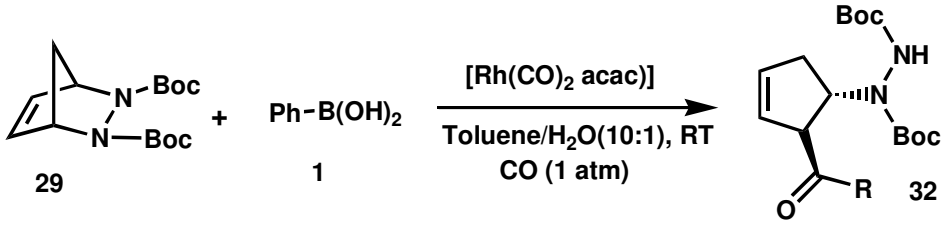
Immediately after this report an asymmetric version of the reaction was described by Pineschi *et al.* using rhodium catalysis.[26] In presence of chiral ligand, the ring opening of bicyclic hydrazine **27** with aryl boronic acids gave a regio- and diastereoselective access to **28** in an enantioenriched form.

Recently, Mark Lautens *et al.* reported some interesting aspects of the asymmetric ring opening reactions of bicyclic hydrazines with boronic acids. They observed that in presence of $[Rh(cod)OH]_2$ catalyst and ^{t}Bu-josiphos as chiral ligand, the desymmetrization of diazabicycle **29** resulted in the formation of ring-opened product **30** with aryl boronic acid and the reductive arylation product **31** with heteroaryl boronic acid (Scheme 3.13). [27]



Scheme 3.13

The acyl anion nucleophiles generated *in situ* from readily available organoboronic acids are also utilized for the desymmetrization of meso-diazabicycles.[28] The rhodium catalyzed reaction of **29** with phenylboronic acid 1 in presence of carbon monoxide resulted the stereoselective formation of densely functionalized *trans*-1,2-hydrazinoacyl cyclopentene **32** (Scheme 3.14).



Scheme 3.14

These are the available reports on the ring opening reactions of heterobicyclic alkenes with boronic acids. From the literature discussion, it is clear that the reactivity of organoboron compounds with other heterobicyclic substrates has not been studied in detail.

3.5. The present work

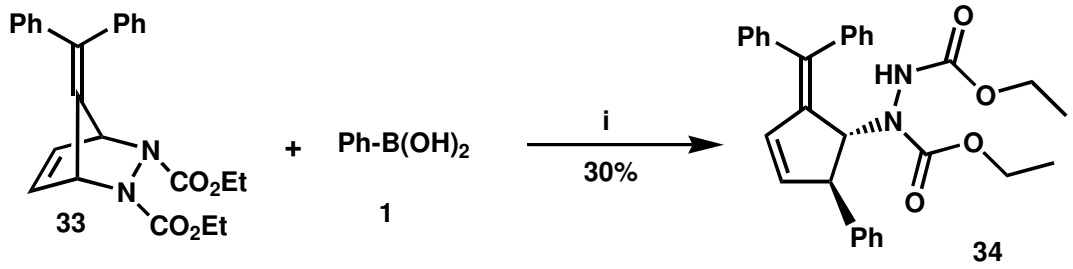
One of the most important goals in contemporary synthetic chemistry is the development of a generally applicable method to synthesize complex structures from simple precursors. The transition metal-catalyzed ring-opening reaction of heterobicyclic alkenes with suitable nucleophiles is illustrated as a powerful paradigm for the rapid construction of stereochemically complex carbocyclic compounds. Literature survey revealed that organoboronic acids have been well exploited for the ring opening of heterobicyclic alkenes toward the construction of many interesting molecular skeletons in a single step. The introduction of a new class of readily available reaction partner to this reaction protocol would significantly extend the impact of these processes. In this context, we decided to explore the reactivity of organoboronic acids with pentafulvene derived bicyclic hydrazines and the results of these studies are discussed in the following section.

3.6. Results and discussion

3.6.1. Reactions with phenyl boronic acid

Our studies commenced with the reaction of phenylboronic acid **1** with the diphenyl fulvene derived bicyclic olefin **33** in the presence of $Pd(OAc)_2/PPh_3/I_2$

catalyst system in 1:1 mixture of THF and H_2O. The reaction afforded phenyl substituted alkylidene cyclopentene **34** in 30% yield (Scheme 3.15).



i = $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O (1:1), 60 ^oC, 24 h

Scheme 3.15

Detailed optimization studies were carried out to find out the best catalyst system. Among the different catalysts (see Table 3.1) screened, $PdCl_2$/dppe/I_2 was found to be the best catalyst system and under these conditions, product **34** was obtained in 88% yield.

Table 3.1 Optimization for a suitable catalyst system

Entry	Catalyst	Ligand	Lewis acid	Yield (%)
1	$Pd(OAc)_2$	PPh_3	I_2	30
2	$PdCl_2$	PPh_3	I_2	72
3	$Pd_2(dba)_3.CHCl_3$	PPh_3	I_2	29
4	$PdCl_2(PPh_3)_2$	PPh_3	I_2	30
5	$[Pd(allyl)Cl]_2$	PPh_3	I_2	33
6	$PdCl_2$	P(*p*-tolyl)$_3$	I_2	29
7	$PdCl_2$	P(4-F-Ph)$_3$	I_2	71
8	$PdCl_2$	P(4-OMe-Ph)$_3$	I_2	56
9	$PdCl_2$	P(4-Cl-Ph)$_3$	I_2	58
10	$PdCl_2$	dppe	I_2	88
11	$PdCl_2$	dppm	I_2	82
12	$Pd(OAc)_2$	dppe	I_2	39
13	$PdCl_2$	dppe	$Cu(OTf)_2$	21
14	$PdCl_2$	dppe	$Sn(OTf)_3$	40
15	$PdCl_2$	dppe	$Yb(OTf)_3$	43

Conditions: K_2CO_3, Catalyst, Ligand, Lewis acid, THF:H_2O, 60 ^oC, 24 h

Spectral analysis was carried out to assign the structure of **34**. The IR spectrum showed the characteristic carbonyl absorptions at 1753 and 1717 cm^{-1}. A broad signal around 3332 cm^{-1} was due to the N-H stretching vibration. ^{1}H NMR spectrum of **34** (Figure 3.1) located the olefinic protons at C-1 and C-2 as a singlet and double doublet at δ 6.53 and 6.15 ppm respectively. The proton on the carbon C-3, carrying the phenyl group was appeared as a multiplet in the region δ 4.49-4.46 ppm. The methylene protons at C-9 and C-10 resonated as two multiplets in the region δ 4.20-4.15 and δ 3.85-3.68 ppm, whereas a triplet at δ 1.25 ppm and a multiplet at δ 1.00-0.88 ppm were assigned to the methyl protons of the carbo ethoxy group.

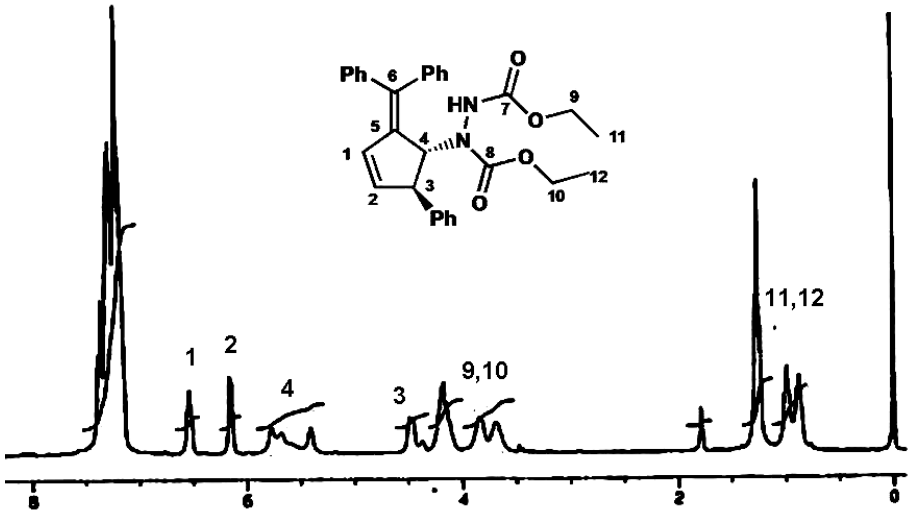


Figure 3.1 ^{1}H NMR spectrum of **34**

^{13}C NMR showed the characteristic peak of carbonyl group at δ 157.0 and 154.9 ppm. The carbons at C-3 and C-4 of the cyclopentene ring were identified at δ 55.3 and 70.0 ppm respectively. The methylene carbons at C-9 and C-10 were observed at δ 63.1 and 62.1 ppm, while the methyl carbons C-11 and C-12 showed their signals at δ 14.4 and 14.2 ppm. Mass spectrum well supported the structure with the molecular ion peak at *m/z* 482.2210.

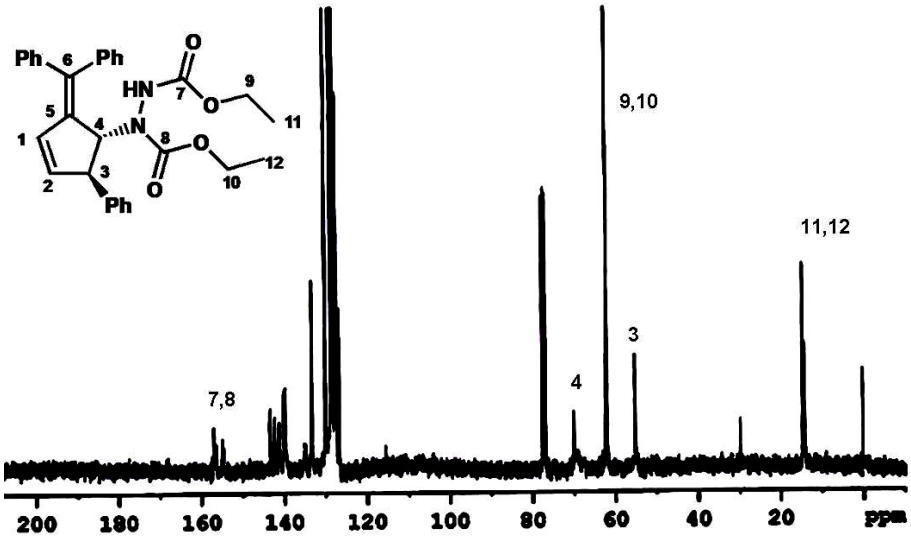


Figure 3.2 ^{13}C NMR spectrum of **34**

Unambiguous evidence for the structure and stereochemistry of the product **34** was obtained by single crystal X-ray analysis[29] (Figure 3.3).

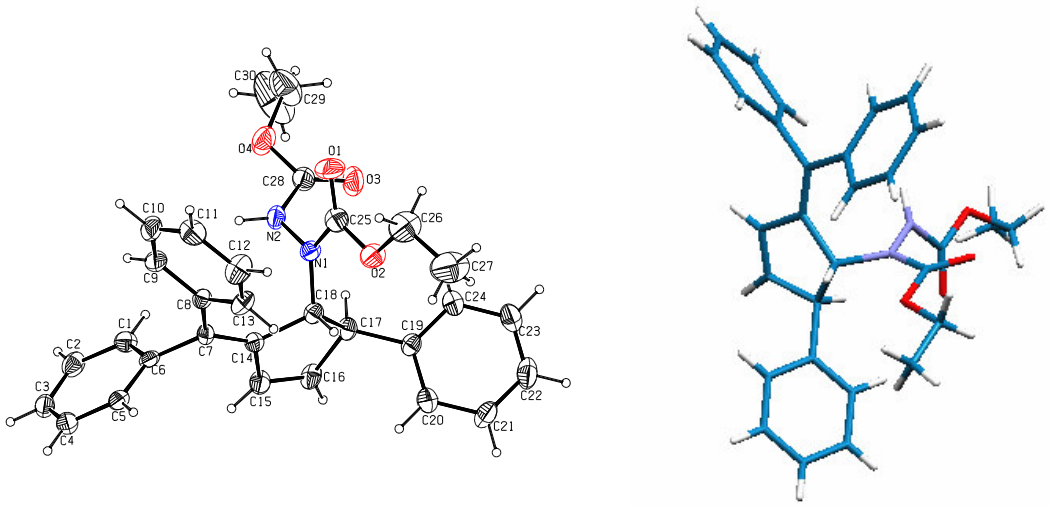
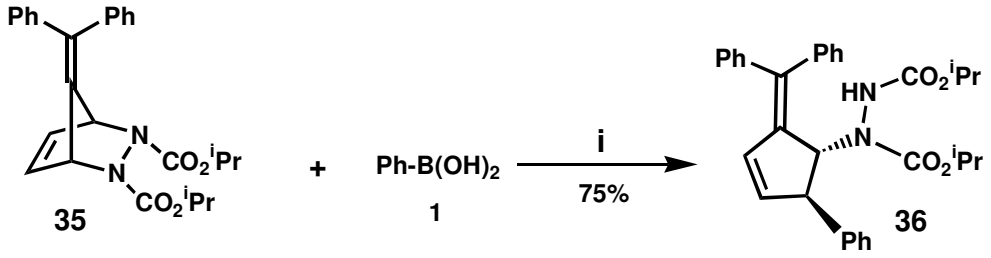


Figure 3.3 X-ray structure of compound **34**

The generality of the method was proved by the reaction of phenylboronic acid with a number of bicyclic hydrazines derived from 6,6-diphenyl fulvene and various dialkyl azodicarboxylates. The details of these investigations are described below.

When the bicyclic hydrazine **35** derived from 6,6-diphenyl fulvene and diisopropyl azodicarboxylate was subjected to palladium catalyzed ring opening with phenylboronic acid **1** in presence of iodine, alkylidene cyclopentene **36** was obtained in 75% yield (Scheme 3.16).

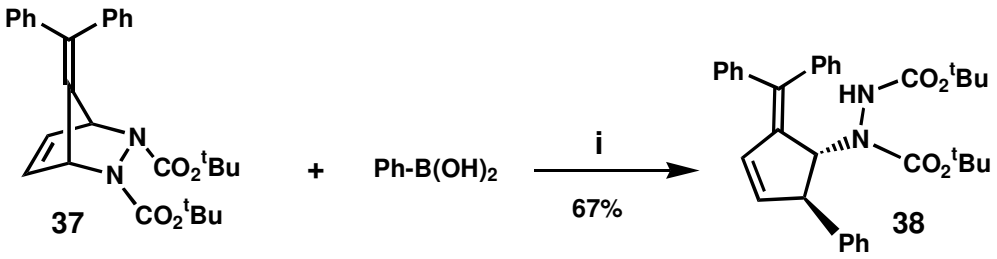


i = $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O (1:1), 60 ^oC, 24 h

Scheme 3.16

The product **36** was characterized on the basis of spectral data. IR spectrum confirmed the carbonyl absorptions in the region 1750-1721 cm^{-1}. ^1H NMR marked the multiplets observed at δ 1.30-1.25 and 1.06-0.76 ppm to the methyl protons of the isopropyl group. The characteristic aromatic protons were resonated between δ 7.41 and 7.18 ppm as multiplets. ^{13}C NMR gave the carbonyl signals at δ 157.3 and 155.3 ppm. The signals at δ 61.6 and 55.3 ppm were assigned to the carbons carrying hydrazine substituent and phenyl group, respectively. Further evidence for the structure was obtained from mass spectral analysis which showed a molecular ion peak at *m/z* 510.2497.

The bicyclic hydrazine **37** prepared from 6,6-diphenyl fulvene and di-*tert*-butyl azodicarboxylate followed similar reaction pathway under same conditions as mentioned above. The product **38** was isolated in 67% yield and the reaction is presented in scheme 3.17.

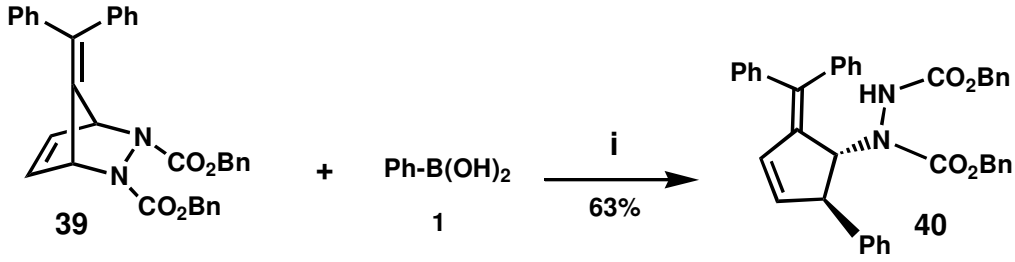


i = $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O(1:1), 60 ^oC, 24 h

Scheme 3.17

Spectral analysis was carried out for the structure elucidation. In the ^1H NMR spectrum of **38** the ring olefinic protons were presented as a doublet at δ 6.51 ppm and as a multiplet in the region δ 6.18-6.12 ppm respectively. The characteristic aromatic protons resonated in the region δ 7.46-7.16 ppm. ^{13}C NMR spectrum positioned the carbonyl groups at δ 157.0 and 154.9 ppm. The signal at δ 54.9 ppm was attributed to the carbon carrying the phenyl substituent. All other signals in ^1H, ^{13}C NMR and mass spectra well supported the structure assignment.

When bicyclic hydrazine **39** derived from dibenzyl azodicarboxylate and diphenyl fulvene was treated with phenylboronic acid **1** in presence of $PdCl_2$, dppe and molecular iodine, the corresponding alkylidene cyclopentene **40** was obtained in 63% yield (Scheme 3.18).



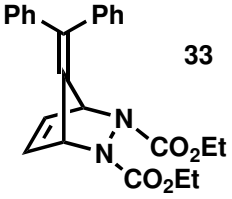
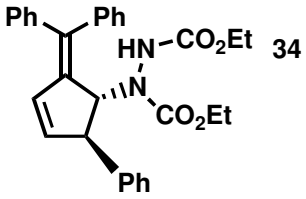
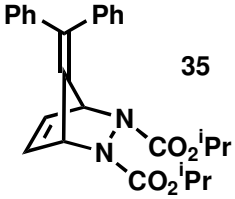
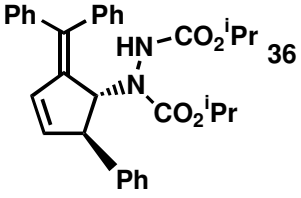
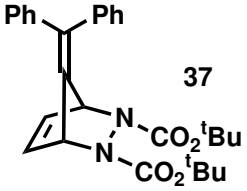
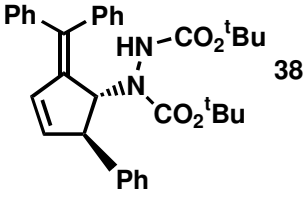
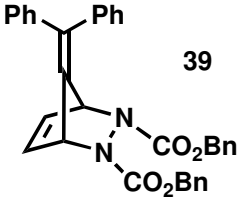
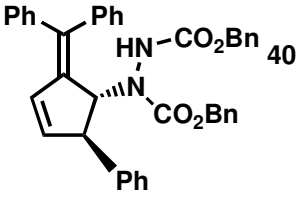
i = $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O (1:1), 60 ^oC, 24 h

Scheme 3.18

Structure of the compound **40** was assigned by spectroscopic methods. IR spectrum confirmed the carbonyl absorptions in the region 1750-1722 cm^{-1}. ^1H NMR spectrum marked the peaks corresponding to the olefinic protons as singlet at δ 6.82 ppm and multiplet centered at δ 6.10 ppm. As in other examples ^{13}C

NMR spectrum spotted the carbonyls in the region δ 157-154 ppm. The benzylic carbon was observed at δ 67.9 and 68.1 ppm. A well defined molecular ion peak observed at *m/z* 606.2532 provided another convincing evidence for the structure. These results are summarized in table 3.2.

Table 3.2. Reactions of diphenyl fulvene derived bicyclic hydrazines with phenylboronic acid

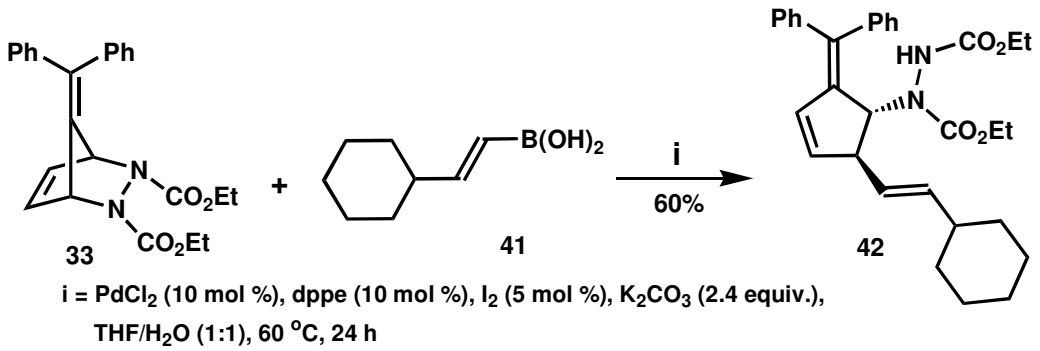
Entry	Bicyclic olefin	Product	Yield (%)
1	 33	 34	88
2	 35	 36	75
3	 37	 38	67
4	 39	 40	63

Reaction Conditions: Boronic acid (1 equiv.), bicyclic olefin (1 equiv.), $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O (1:1), 60 ^oC, 24 h

3.6.2. Reactions with alkenyl boronic acid

After the successful reactions using phenylboronic acid, we were interested in using alkenyl boronic acid for further investigation and the details of these reactions are described in the following section.

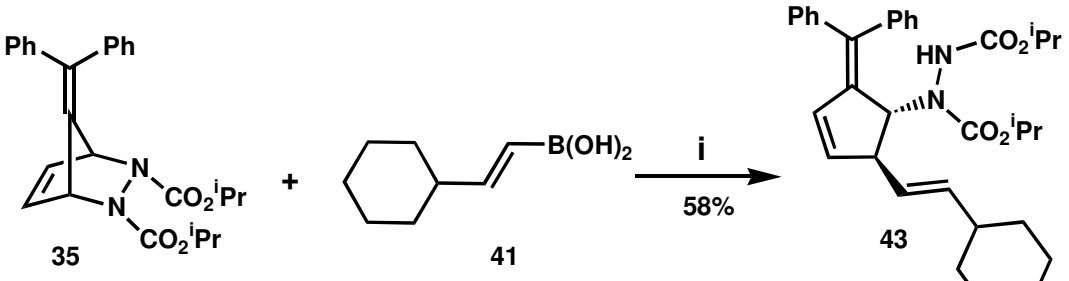
The reaction of (E)-2-cyclohexyl-vinylboronic acid **41** with bicyclic hydrazine **33** afforded the corresponding alkylidene cyclopentene **42** in 60% yield. The reaction is presented in scheme 3.19.



Scheme 3.19

As in the previous examples, the product was characterized by spectroscopic analysis. IR spectrum gave a broad absorption band at 3368 cm^{-1}, representing NH stretching. The carbonyl absorptions were detectable at 1756 and 1717 cm^{-1}. ^{1}H NMR spectrum located the cycloalkyl proton adjacent to the double bond at δ 1.94 ppm and the remaining cycloalkyl protons were resonated between δ 2.0 and 1.0 ppm. ^{13}C NMR spectrum spotted the carbonyls at δ 157.7 and 155.4 ppm, whereas the carbon bearing the cyclohexyl vinyl group showed its signal at δ 52.5 ppm. The cycloalkyl carbons resonated in the region δ 40.0-25.0 ppm. All other signals in ^{1}H and ^{13}C NMR spectra well supported the structure assignment. Mass spectrum provided additional information with molecular ion peak at *m/z* 514.2848.

Similarly the bicyclic olefin **35** with cyclohexyl vinyl boronic acid **41** under similar conditions produced **43** in 58% yield (Scheme 3.20). Structural analysis was done using spectroscopic methods.

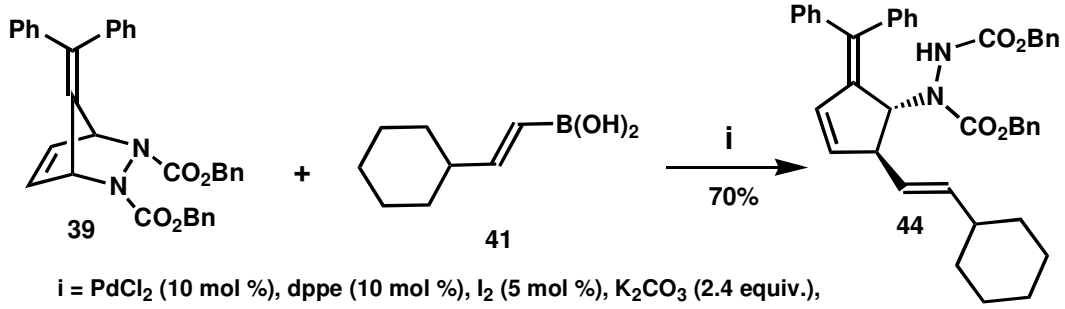


i = $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O (1:1), 60 °C, 24 h

Scheme 3.20

In the ^{1}H NMR spectrum of **43**, the cyclohexyl protons resonated in between δ 1.94 and 1.05 ppm and the characteristic aromatic protons observed in the region δ 7.35-7.10 ppm. ^{13}C NMR spectrum spotted the carbonyls at δ 157.7 and 155.5 ppm. The carbon carrying the cyclohexyl vinyl group was observed at δ 52.4 ppm, while the methine carbons of the isopropyl group were visible at δ 70.3 and 69.8 ppm. Mass spectrum provided additional information with the molecular ion peak at *m/z* 542.3154.

Under similar conditions, the palladium catalyzed ring opening of the adduct **39** with (E)-2-cyclohexyl-vinylboronic acid **41** afforded the alkylidene cyclopentene **44** in 70% yield. The reaction is depicted in scheme 3.21.



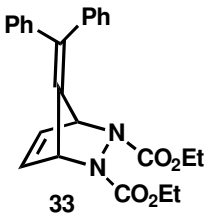
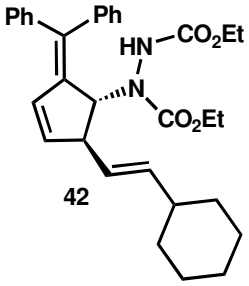
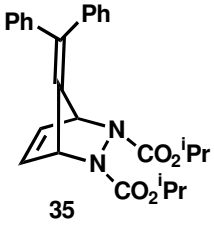
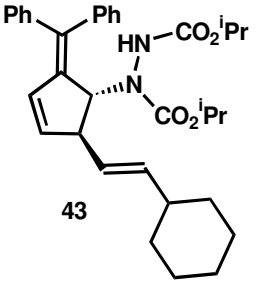
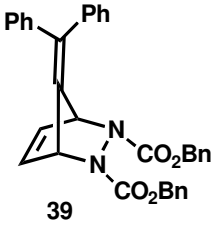
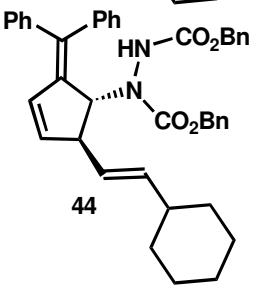
i = $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O(1:1), 60 °C, 24 h

Scheme 3.21

IR spectrum showed the carbonyl absorptions at 1753 and 1722 cm^{-1}, while NH stretching was discernible at 3363 cm^{-1}. ^{1}H NMR spectrum located the cycloalkyl protons as multiplets in the region δ 2.03-1.60 ppm and δ 1.33-0.88

ppm. The presence of carbonyl group was further confirmed by the signals at δ 156.3 and 153.2 ppm in the ^{13}C NMR spectrum. The benzylic carbons were visible at δ 68.1 and 68.0 ppm and the carbon carrying the hydrazine group was distinct at δ 68.3 ppm. The molecular ion peak at *m/z* 638.3174 observed in mass spectrum supported the proposed structure. The results are depicted in table 3.3.

Table 3.3 : Reaction of diphenyl fulvene derived bicyclic hydrazines with cyclohexylvinyl boronic acid

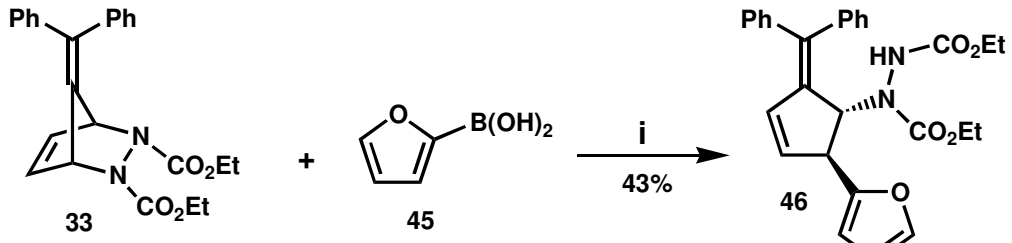
Entry	Adduct	Product	Yield (%)
1	 33	 42	60
2	 35	 43	58
3	 39	 44	70

Reaction Conditions: Boronic acid (1 equiv.), bicyclic olefin (1 equiv.), $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O (1:1), 60 ^oC, 24 h

3.6.3. Reactions with heteroaryl boronic acid

To extend the scope and generality of this reaction, we further investigated the reactivity of heteroaryl boronic acids with pentafulvene derived bicyclic hydrazines and the results are discussed in the following section.

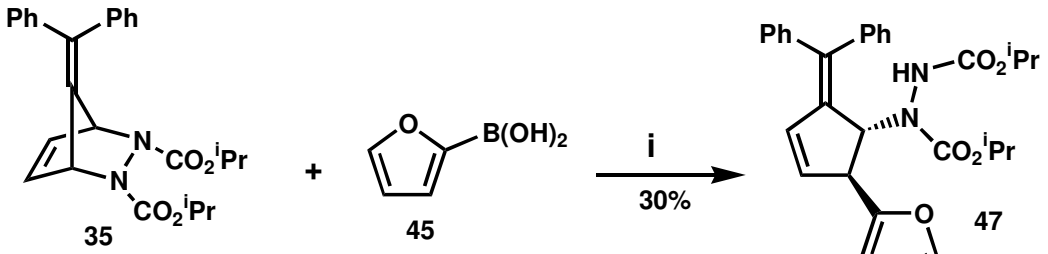
The desymmetrization of bicyclic hydrazine **33** with 2-furan boronic acid **45** under Suzuki reaction condition in presence of molecular iodine gave the product **46** in 43% yield (Scheme 3.22). The structure of the product **46** was confirmed by comparison with the spectral data of same compound **42a** in chapter 2 of this thesis.



i = $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O (1:1), 60 °C, 24 h

Scheme 3.22

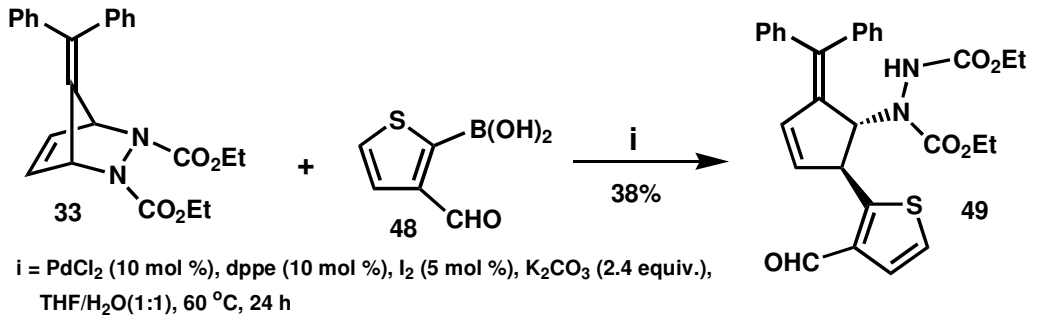
When the adduct **35** was treated with 2-furan boronic acid **45** under optimized condition, substituted alkylidene cylcopentene **47** was formed in moderate yield. The reaction is delineated in scheme 3.23. The structure of the product **47** was also confirmed by comparing with the spectral data of the compound **42b** in chapter 2.



i = $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O (1:1), 60 °C, 24 h

Scheme 3.23

Similarly, the reaction of bicyclic substrate **33** with 2-furan boronic acid **48** under palladium catalysis, resulted in the formation of furyl substituted alkylidene cyclopentene **49** in 38% yield (Scheme 3.24).

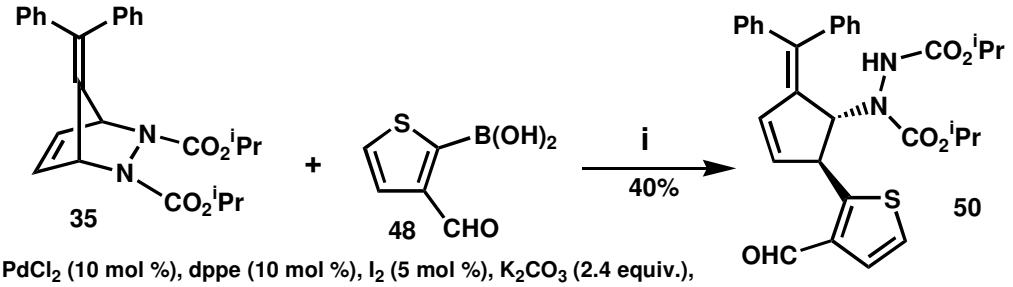


i = $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O(1:1), 60 ^oC, 24 h

Scheme 3.24

The product **49** was characterized by spectral analysis. The carbonyl absorption was confirmed by IR data. In the ^1H NMR spectrum, the aldehyde proton was identified as a sharp singlet at δ 10.28 ppm. The methyl protons of the ester functionality were appeared as multiplets in the region δ 1.29-1.25 ppm and 1.05-0.96 ppm. ^{13}C NMR spectrum marked the aldehyde carbonyl at δ 185.6 ppm, while the ester carbonyls appeared at δ 156.2 and 154.4 ppm. The hydrazine carrying carbon was discernible at δ 64.5 ppm. All other signals were in good agreement with the proposed structure. Mass spectra further confirmed the structure by giving a peak at *m/z* 539.05 $(M+Na)^+$.

In a similar way the palladium/Lewis acid mediated ring opening of the adduct **35** with boronic acid **48** produced the expected product **50** in 40% yield. The transformation is illustrated in scheme 3.25.



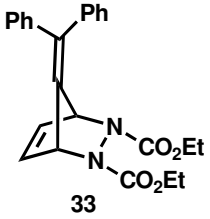
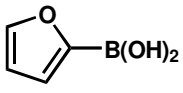
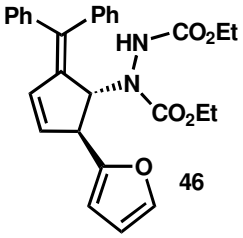
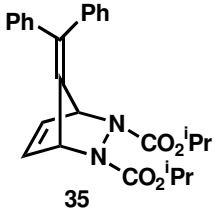
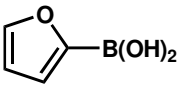
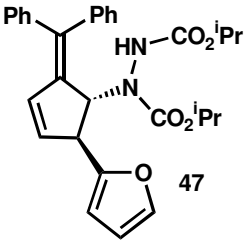
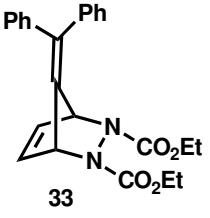
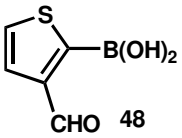
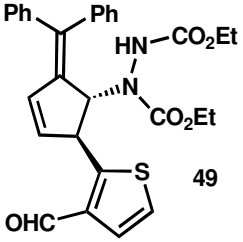
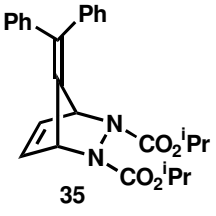
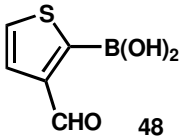
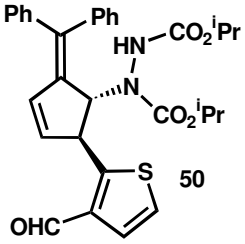
i = $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O (1:1), 60 ^oC, 24 h

Scheme 3.25

The product **50** was characterized by means of spectral data. The absorptions due to carbonyl groups were visible at 1750-1716 cm^{-1}, in the IR spectrum. In ^1H

NMR spectrum, the aldehyde proton appeared as a singlet at δ 10.29 ppm. The signals due to the methyl protons of the isopropyl group resonated as multiplets in the region δ 1.28-1.21 ppm and δ 1.06-0.91 ppm. ^{13}C NMR spectrum spotted the aldehyde group as less intense signal at δ 186.2 ppm, while the ester carbonyls were located at δ 156.1 and 154.0 ppm. The isopropyl methine carbons were discernible at δ 70.9 and 70.2 ppm. Mass spectrum also well supported the structure assignment. The results are summarized in table 3.4.

Table 3.4: Reactions of diphenyl fulvene derived bicyclic hydrazines with heteroaryl boronic acids

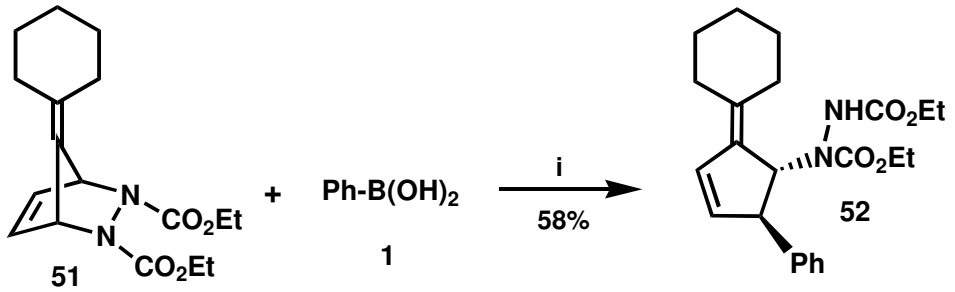
Entry	Adduct	Boronic acid	Product	Yield (%)
1	 33	 45	 46	43
2	 35	 45	 47	30
3	 33	 48	 49	38
4	 35	 48	 50	40

Reaction Conditions: Boronic acid (1 equiv.), bicyclic olefin (1 equiv.), $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O (1:1), THF/H_2O (1:1), 60 ^oC, 24 h

3.6.4. Reactions of 6,6-cycloalkyl fulvene derived bicyclic hydrazines

In the last phase of the present investigation, we have checked the reactivity of organoboronic acids with cycloalkyl 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-pentamethylene fulvene derived adduct **51** and boronic acid **1,** the substituted cyclohexylidene cyclopentene **52** was obtained in 58% yield. The reaction is presented in the following scheme.

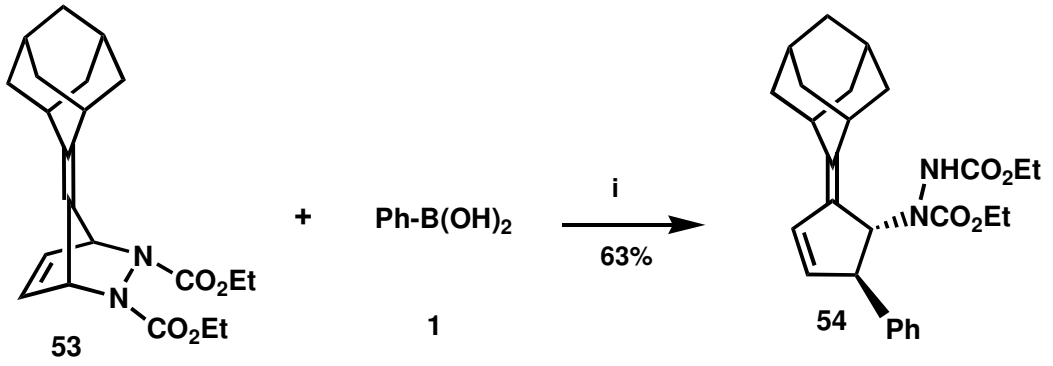


i = $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O (1:1), 60 ^oC, 24 h

Scheme 3.26

The structure of the product **52** was assigned by spectroscopic analysis. IR spectrum confirmed the carbonyl absorptions in the region 1734-1715 cm^{-1} and the N-H absorption at 3297 cm^{-1}. The characteristic cycloalkyl protons resonated as two multiplets at δ 2.32-2.06 and 1.85-1.31 ppm in the ^1H NMR spectrum. The five proton multiplet observed in the region δ 7.39-7.19 ppm was indicative of the phenyl substituent. The carbonyl groups resonated at δ 156.2 and 155.5 ppm in the ^{13}C NMR spectrum. The peaks corresponding to the cycloalkyl carbons were located in the region δ 31.9-26.4 ppm. A well defined molecular ion peak at *m/z* 421.68 $(M+Na)^+$ provided another convincing evidence for the structure.

The bicyclic hydrazine **34** prepared from 6-adamantylidene fulvene and diethyl azodicarboxylate also reacted similarly to produce the compound **54** in 63% yield. The reaction is depicted in scheme 3.27.

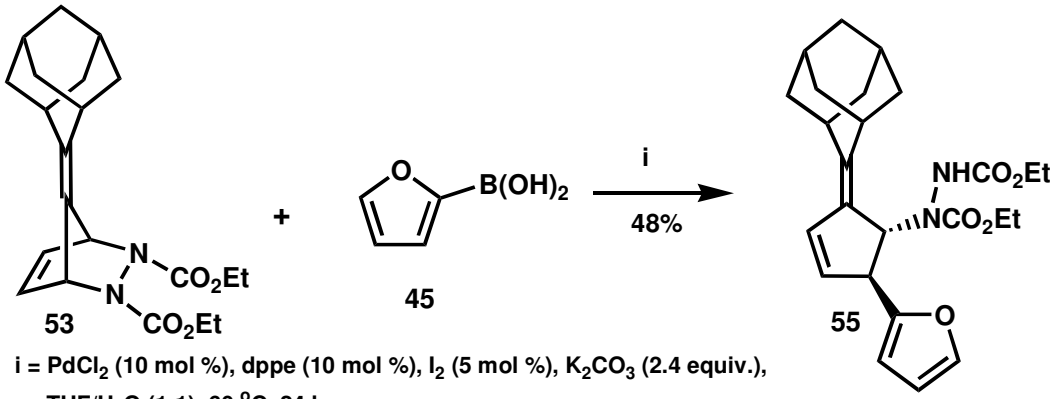


i = $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O (1:1), 60 ^oC, 24 h

Scheme 3.27

As usual, detailed spectral analysis was employed to establish the structure of the product **54**. IR spectrum presented the carbonyl and N-H signals at 1714 and 3324 cm^{-1} respectively. In ^1H NMR spectrum, the aromatic protons resonated in between δ 7.38 and 7.17 ppm and the signal referring to the carboethoxy groups were appeared as a multiplet in the region δ 4.23-4.13 ppm. ^{13}C NMR spectrum of **54** spotted the carbonyl peaks at δ 156.4 and 155.2 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* 473.88 $(M+Na)^+$.

The substrate **53** underwent smooth ring opening reaction with 2-furan boronic acid **45** under similar conditions and furnished the product **55** in moderate yield (Scheme 3.28).

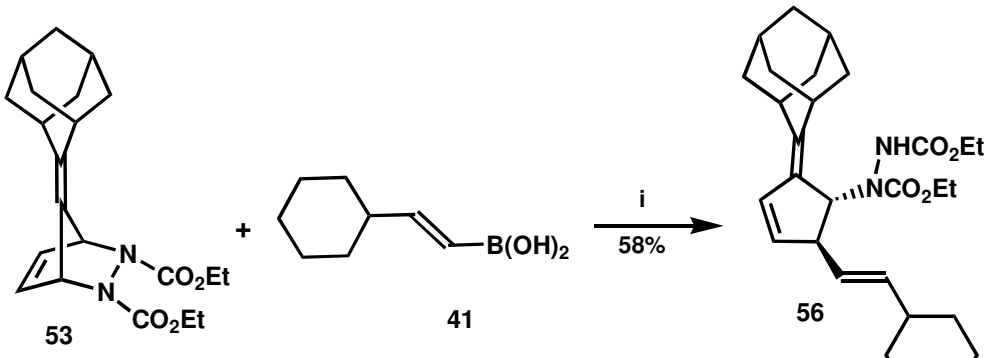


i = $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O (1:1), 60 ^oC, 24 h

Scheme 3.28

The product **55** was characterized by means of spectroscopic analysis. The signals at 1753 and 1715 cm^{-1} were diagnostic of the carbonyl groups and the N-H absorption signal was found as a broad band in the region 3300-3400 cm^{-1}. In ^{1}H NMR spectrum, furan presented its characteristic signals at δ 7.32, 6.26 and 6.03 ppm; while the adamantyl protons appeared as broad multiplet in the region δ 1.99-1.79 ppm. ^{13}C NMR spectrum produced two signals at δ 62.8 and 61.4 ppm corresponding to the methylene carbons of the ester functionality; while the carbons carrying furan and hydrazine moiety were detected at δ 47.3 and 59.1 ppm respectively. Mass spectrum gave a well defined molecular ion peak at *m/z* 463.44 $(M+Na)^{+}$.

Under similar conditions, the palladium catalyzed ring opening of the adduct **53** with (E)-2-cyclohexyl-vinylboronic acid **41** afforded the trisubstituted cyclopentene **56** in 58% yield (Scheme 3.28).



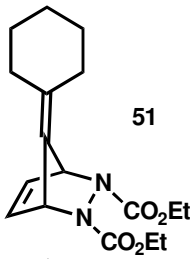
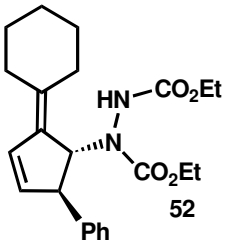
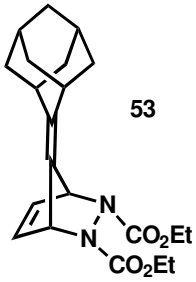
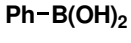
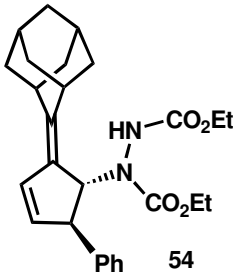
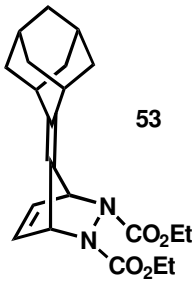
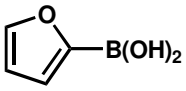
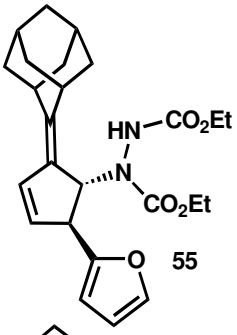
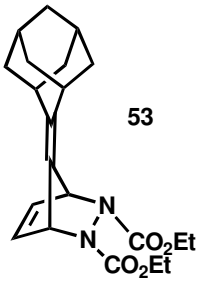
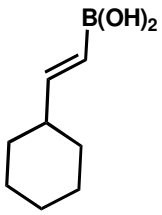
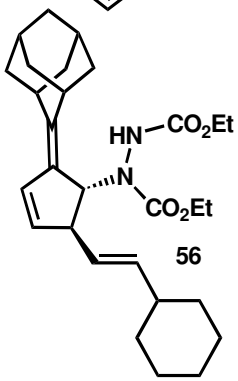
Scheme 3.29

IR spectra of **56** gave a broad absorption band at 3367 cm^{-1}, representing N-H stretching. ^{1}H NMR spectrum of **56** located the adamantyl protons adjacent to the exocyclic double bond as a singlet at δ 2.91 ppm and as a multiplet centered at δ 2.60 ppm. The remaining cycloalkyl protons resonated between δ 2.0 and 1.0 ppm as broad multiplets. ^{13}C NMR spectrum spotted the carbonyls at δ 156.7 and 156.1 ppm, whereas the carbon bearing the cyclohexylvinyl group showed its signal at δ

51.2 ppm. Mass spectrum provided additional information with the molecular ion peak at *m/z* 505.43 $(M+Na)^+$.

These results, obtained with desymmetrization of cycloalkyl fulvene derived bicyclic olefins with a number of boronic acids are summarized in table 3.5.

Table 3.5: Reactions of cycloalkyl fulvene derived bicyclic hydrazines with boronic acids

Entry	Adduct	Boronic acid	Product	Yield (%)
1	 51	 1	 52	58
2	 53	 1	 54	63
3	 53	 45	 55	48
4	 53	 41	 56	58

Reaction Conditions: Boronic acid (1 equiv.), bicyclic olefin (1 equiv.), $PdCl_2$ (10 mol %), dppe (10 mol %), I_2 (5 mol %), K_2CO_3 (2.4 equiv.), THF/H_2O (1:1), 60 ^oC, 24 h

3.7. Conclusions

We have uncovered a modified suzuki type reactivity of organoboronic acids with pentafulvene derived azabicyclic olefins leading to the stereoselective synthesis of alkylidene cyclopentenes. The generality of the method was established by the reactions of various fulvene derived bicyclic hydrazines with aryl, heteroaryl and alkenylboronic acids. The results obtained validate the methodology as a practical and rapid approach towards alkylidene cyclopentenes.

3.8. Experimental details

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

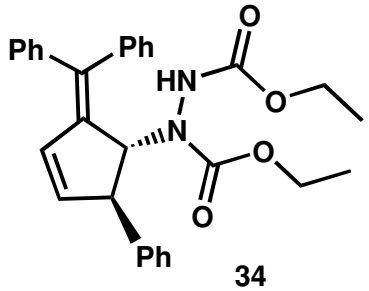
General procedure for the synthesis of alkylidene cyclopentenes

Bicyclic hydrazine (1 equiv.), boronic acid (1 equiv.), dppe (10 mol%), $PdCl_2$ (10 mol%), I_2 (5 mol%) and K_2CO_3 (2.4 equiv.) were taken in a Schlenk tube and degassed. The mixture was dissolved in 1:1 mixture of THF and H_2O (4 mL) and stirred at 60 °C for 24 h under argon atmosphere. After the completion of the reaction, the reaction mixture was diluted with dichloromethane (50 mL) and washed with water (2x25 mL) and saturated brine (25 mL) solution. The organic layer was then dried over anhydrous sodium sulfate and the solvent was evaporated *in vacuo*. The residue on silica gel (60-120 mesh) column chromatography using 20% ethyl acetate in hexane afforded the product in good yield.

Diethyl 1-(2-(diphenylmethylene)-5-phenylcyclopent-3-enyl) hydrazine -1,2-dicarboxylate 34

Following the general experimental procedure, the bicyclic hydrazine **33** (100 mg, 0.25 mmol), phenyl boronic acid **1** (30 mg, 0.25 mmol), I_2 (3 mg, 5 mol%), dppe (10 mg, 10 mol%), $PdCl_2$ (4.5 mg, 10 mol%) and K_2CO_3 (82 mg, 0.59 mmol) in 1:1 mixture of THF-H_2O (4 mL) at 60 °C under argon atmosphere for 24 h gave the product **34** as white crystalline solid (106 mg, 88%).

Mp 135-138 °C. R_f 0.40 (3:1 Hexane/ethyl acetate).



34

IR (KBr) ν_{max}: 3362, 2980, 2924, 1753, 1717, 1596, 1487, 1407, 1382, 1298, 1221, 1122, 1056, 1028, 756, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.19 (m, 15H), 6.53 (s, 1H), 6.15 (dd, J_1 = 2.0 Hz , J_2 = 5.8 Hz, 1H), 5.78-5.40 (m, 2H), 4.49-4.46 (m, 1H), 4.20-4.15 (m, 2H), 3.85-3.68 (m, 2H), 1.25 (t, J = 6.6 Hz, 3H), 1.00-0.88 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.0, 154.9, 143.5, 142.4, 141.3, 140.2, 139.9, 135.2, 134.8, 133.3, 130.0, 129.6, 128.6, 128.2, 127.8, 127.6, 127.3, 126.8, 70.0, 63.1, 62.1, 55.3, 14.4, 14.2.

HRMS (EI) for $C_{30}H_{30}N_2O_4$, cacld (M^+): 482.2206; found: 482.2210.

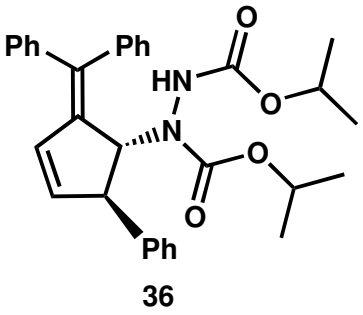
Crystal data for 34

CCDC-640116, Empirical formula, C_{30} H_{30} N_2 O_4; Formula weight- 482.56; Temperature = 293(2) K ; Wavelength, 0.71073 A; Crystal system -TRICLINIC, Space group- P-1; Unit cell dimensions = a = 8.401(2) A alpha = 95.410(4) deg., b = 10.368(3) A beta = 95.198(6) deg.; c = 15.647(4) A gamma = 102.676(5) deg., Volume = 1315.0(6) A^3; Z = 2, Density (calculated) = 1.219 Mg/m^3; Absorption coefficient = 0.081 mm^-1, F(000) ; 512 , Crystal size = 0.24 x 0.16 x 0.09 mm; Theta range for data collection = 1.32 to 22.50 deg; Index ranges = -9<=h<=8, -11<=k<=11, -16<=l<=16; Reflections collected = 7605; Independent reflections = 3428 [R(int) = 0.0828],; Absorption correction = SADABS ; Refinement method; Full-matrix least-squares on F^2, Data / restraints / parameters = 3428 / 0 / 327; Goodness-of-fit on F^2 = 1.001; Final R indices [I>2sigma(I)] = R1 = 0.0724, wR2 = 0.1485, R indices (all data) R1 = 0.1930, wR2 = 0.2136, Largest diff. peak and hole = 0.299 and -0.167 e.A^-3

Diisopropyl 1-(2-(diphenylmethylene)-5-phenylcyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 36

Following the general experimental procedure, the bicyclic hydrazine **35** (142 mg, 0.33 mmol), phenyl boronic acid **1** (40 mg, 0.33 mmol), I_2 (4 mg, 5 mol%), dppe (13 mg, 10 mol%), $PdCl_2$ (6 mg, 10 mol%) and K_2CO_3 (109 mg, 0.59 mmol) in 1:1 mixture of THF-H_2O (4 mL) at 60 °C under argon atmosphere for 24 h gave the product **36** as a colorless viscous liquid (126 mg, 75%).

R_f 0.49 (3:1 Hexane/ethyl acetate).



36

IR (neat) ν_{max}: 3362, 2981, 1750, 1721, 1599, 1471, 1401, 1300, 1247, 1177, 1108, 1029, 957, 756, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.18 (m, 15H), 6.51 (dd, J_1 = 2.2 Hz, J_2 = 6.1 Hz, 1H), 6.16-6.11 (m, 1H), 5.73-5.41 (m, 2H), 4.96-4.93 (m, 1H), 4.55-4.40 (m, 2H), 1.30-1.25 (m, 6H), 1.06-0.76 (m, 6H).

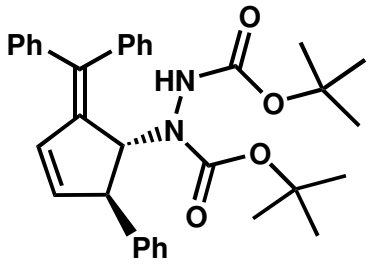
^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 155.3, 140.6, 139.0, 134.7, 134.2, 133.7, 133.2, 130.0, 128.5, 128.1, 127.9, 127.7, 127.1, 126.8, 69.8, 69.1, 61.6, 55.3, 22.1, 21.5.

HRMS (EI) for $C_{32}H_{34}N_2O_4$, calcd (M^+): 510.2519; found: 510.2537.

Di *tert*-butyl 1-(2-(diphenylmethylene)-5-phenylcyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 38

Following the general experimental procedure, the bicyclic hydrazine **37** (151 mg, 0.33 mmol), phenyl boronic acid **1** (40 mg, 0.33 mmol), I_2 (4 mg, 5 mol%), dppe (13 mg, 10 mol%), $PdCl_2$ (6 mg, 10 mol%) and K_2CO_3 (109 mg, 0.59 mmol) in 1:1 mixture of THF-H_2O (4 mL) at 60 °C under argon atmosphere for 24 h gave the product **38** as a brownish yellow viscous liquid (118 mg, 67%).

R_f 0.58 (3:1 Hexane/ethyl acetate).



38

IR (neat) ν_{max}: 3362, 2979, 1748, 1714, 1599, 1478, 1368, 1248, 1155, 944, 853, 756, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.16 (m, 15H), 6.51(d, *J* = 4.3 Hz, 1H), 6.18-6.12 (m, 1H), 5.66-5.35 (m, 2H), 4.51-4.43 (m, 1H), 1.67-1.08 (m, 18H).

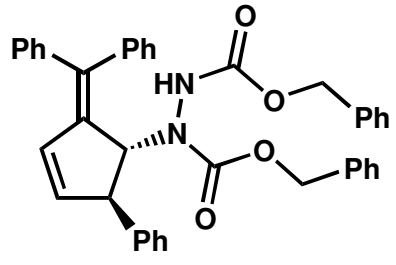
^{13}C NMR (75 MHz, $CDCl_3$): δ 157.0, 154.9, 142.4, 140.0, 138.0, 136.9, 133.4, 131.7, 130.0, 128.3, 128.0, 127.7, 127.0, 126.5, 81.7, 81.0, 64.6, 54.9, 30.7, 28.6, 28.3, 27.9.

HRMS (EI) for $C_{34}H_{38}N_2O_4$, calcd (M^+): 538.2832; found: 538.2870.

Dibenzyl 1-(2-(diphenylmethylene)-5-phenylcyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 40

Following the general experimental procedure, the bicyclic hydrazine **39** (100 mg, 0.19 mmol), phenyl boronic acid **1** (24 mg, 0.19 mmol), I_2 (2.5 mg, 5 mol%), dppe (8 mg, 10 mol%), $PdCl_2$ (3 mg, 10 mol%) and K_2CO_3 (63 mg, 0.45 mmol) in 1:1 mixture of THF-H_2O (4 mL) at 60 °C under argon atmosphere for 24 h gave the product **40** as a colorless viscous liquid (72 mg, 63%).

R_f 0.49 (3:1 Hexane/ethyl acetate).



40

IR (neat) ν_{max}: 3363, 2958, 1750, 1722, 1599, 1491, 1457, 1405, 1292, 1265, 1216, 1130, 1029, 850, 739, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.16 (m, 25H), 6.82 (s, 1H), 6.53 (s, 1H), 6.17-6.01 (m, 1H), 5.52 (bs, 1H), 5.19-5.04 (m, 2H), 4.90-4.84 (m, 1H), 4.70-4.62 (m, 1H), 4.51 (s, 1H).

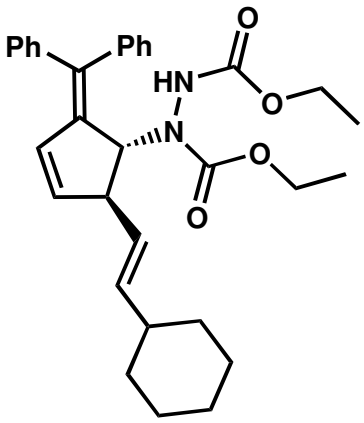
^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2, 154.1, 140.5, 137.8, 135.8, 132.2, 130.2, 129.9, 128.8, 128.5, 128.2, 128.1, 127.6, 127.4, 124.2, 70.3, 68.1, 67.9, 53.7.

HRMS (EI) for $C_{40}H_{34}N_2O_4$, calcd (M^+): 606.2519; found: 606.2532.

Diethyl 1-(2-cyclohexylvinyl-5-(diphenylmethylene)-cyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 42

Following the general experimental procedure, the bicyclic hydrazine **33** (100 mg, 0.25 mmol), cyclohexylvinyl boronic acid **41** (39 mg, 0.25 mmol), I_2 (3 mg, 5 mol%), dppe (10 mg, 10 mol%), $PdCl_2$ (4.5 mg, 10 mol%) and K_2CO_3 (82 mg, 0.59 mmol) in 1:1 mixture of THF-H_2O (4 mL) at 60 °C under argon atmosphere for 24 h gave the product **42** as light brown viscous liquid (64 mg, 60%).

R_f 0.49 (3:1 Hexane/ethyl acetate).



42

IR (neat) ν_{max}: 3368, 2924, 2851, 1756, 1717, 1597, 1487, 1409, 1380, 1300, 1218, 1125, 1059, 968, 756, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.13 (m, 10H), 6.33 (s, 1H), 6.00 (s, 1H), 5.66-5.47 (m, 3H), 4.23-4.03 (m, 3H), 3.89-3.76 (m, 3H), 1.94 (m, 1H), 1.72-1.62 (m, 6H), 1.27-1.02 (m, 10H).

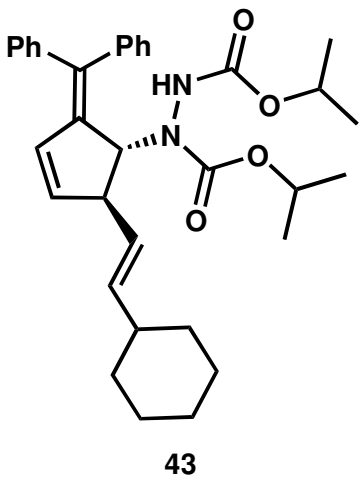
^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7, 155.4, 141.6, 140.6, 137.7, 132.2, 130.2, 128.7, 128.2, 128.0, 127.2, 126.8, 124.3, 124.0, 121.8, 65.1, 62.8, 62.1, 52.5, 40.8, 33.2, 32.4, 26.4, 26.1, 21.9, 14.7.

HRMS (EI) for $C_{32}H_{38}N_2O_4$, calcd (M^+): 514.2832; found: 514.2848.

Diisopropyl 1-(2-cyclohexylvinyl-5-(diphenylmethylene)-cyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 43

Following the general experimental procedure, the bicyclic hydrazine **35** (112mg, 0.26 mmol), cyclohexylvinyl boronic acid **41** (40 mg, 0.26 mmol), I_2 (3 mg, 5 mol%), dppe (11 mg, 10 mol%), $PdCl_2$ (5 mg, 10 mol%) and K_2CO_3 (82 mg, 0.59 mmol) in 1:1 mixture of THF-H_2O (4 mL) at 60 °C for 24 h gave the product **43** as a light yellow viscous liquid (82 mg, 58%).

R_f 0.58 (3:1 Hexane/ethyl acetate).



43

IR (neat) ν_{max}: 3362, 2924, 2852, 1747, 1716, 1597, 1469, 1385, 1300, 1181, 1110, 1028, 966, 756, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.10 (m, 10H), 6.31 (d, J = 5.5 Hz, 1H), 6.02-6.01 (m, 1H), 5.53-5.41 (m, 3H), 4.95-4.85 (m, 1H), 4.74-4.57 (m, 1H), 4.50 (bs, 1H), 3.79-3.71(m, 1H), 1.94 (bs, 1H), 1.73-1.69 (m, 6H), 1.33-1.05 (m, 11H), 0.96-0.88 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7, 155.5, 141.5, 140.3, 137.3, 132.2, 130.0, 129.8, 129.7, 129.0, 128.4, 127.9, 127.3, 126.9, 124.4, 124.0, 70.3, 69.8, 66.5, 52.4, 40.8, 33.0, 31.9, 30.3, 26.5, 26.3, 22.7, 22.1.

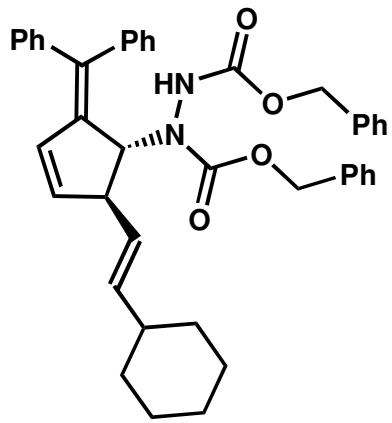
HRMS (EI) for $C_{34}H_{42}N_2O_4$, calcd (M^+): 542.3145; found: 542.3154.

Dibenzyl 1-(2-(cyclohexylvinyl)-5-(diphenylmethylene)-cyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 44

Following the general experimental procedure, the bicyclic hydrazine **39** (100 mg, 0.19 mmol), cyclohexylvinyl boronic acid **41** (30 mg, 0.19 mmol), I_2 (2.5 mg, 5 mol%), dppe (8 mg, 10 mol%), $PdCl_2$ (3 mg, 10 mol%) and K_2CO_3 (63 mg, 0.45

mmol) in 1:1 mixture of THF-H_2O (4 mL) at 60 °C under argon atmosphere for 24 h gave the product **44** as a light brown viscous liquid (85 mg, 70%).

R_f 0.55 (3:1 Hexane/ethyl acetate).



44

IR (neat) ν_{max}: 3363, 3060, 2924, 2851, 1753,1722, 1597, 1490, 1446, 1406, 1298, 1259, 1215, 1128, 1043, 971, 922, 754, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.16 (m, 20H), 6.32 (s, 1H), 6.04-5.89 (m, 2H), 5.72 (brs, 1H), 5.57 (m, 2H), 5.13-5.04 (m, 3H), 4.92-4.72 (m, 2H), 2.03-1.60 (m, 5H), 1.33-0.88 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 153.2, 140.5, 137.8, 135.9, 132.2, 130.1, 129.9, 128.7, 128.6, 128.2, 128.1, 127.9, 127.3, 124.9, 68.3, 68.1, 68.0, 52.6, 40.8, 32.1, 31.0, 30.5, 26.6, 26.3.

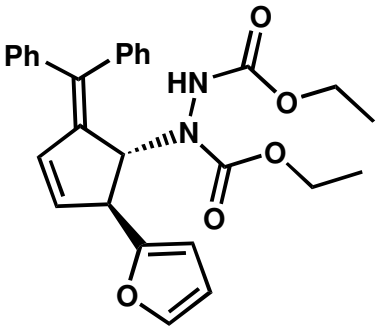
HRMS (EI) for $C_{42}H_{42}N_2O_4$, calcd (M^+): 638.3145; found: 638.3174.

Diethyl 1-(2-(diphenylmethylene)-5-(furan-2-yl) cyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 46

Following the general experimental procedure, the bicyclic hydrazine **33** (100 mg, 0.25 mmol), 2-furan boronic acid **45** (28mg, 0.25 mmol), I_2 (3 mg, 5 mol%), dppe (10 mg, 10 mol%), $PdCl_2$ (4.5 mg, 10 mol%) and K_2CO_3 (82 mg, 0.59 mmol) in 1:1 mixture of THF-H_2O (4 mL) at 60 °C under argon atmosphere for 24 h gave the product **46** as a light brown viscous liquid (50mg, 43%).

R_f 0.36 (3:1 Hexane/ethyl acetate).

IR (neat) ν_{max}: 3362, 2925, 2852, 1753, 1716, 1597, 1487, 1409, 1380, 1284, 1222, 1124, 1060, 919, 757, 702 cm^{-1}.



46

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.16 (m, 11H), 6.49-6.46 (m, 1H), 6.29 (s, 1H), 6.26-6.11 (m, 2H), 5.78-5.67 (m, 1H), 5.63-5.50 (m, 1H), 4.53-4.50 (m, 1H), 4.17-4.13 (m, 2H), 3.96-3.78 (m, 2H), 1.28-1.24 (m, 3H), 1.09-0.98 (m, 3H).

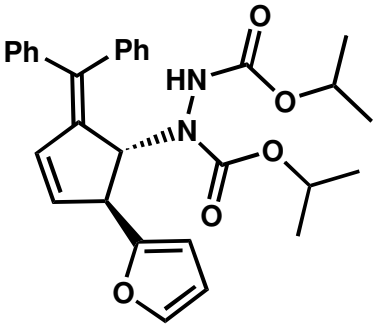
^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 154.1, 141.8, 141.7, 137.2, 136.7, 136.5, 135.7, 135.6, 133.7, 133.1, 129.8, 129.6, 128.7, 128.5, 128.2, 128.1, 127.7, 110.3, 105.7, 64.8, 63.2, 56.2, 49.2, 14.3.

HRMS (EI) for $C_{28}H_{28}N_2O_5$, calcd (M^+): 472.1998; found: 472.1926.

Diisopropyl 1-(2-(diphenylmethylene)-5-(furan-2-yl) cyclopent-3-enyl) hydrazine -1, 2-dicarboxylate 47

Following the general experimental procedure, the bicyclic hydrazine **35** (132 mg, 0.30 mmol), 2-furan boronic acid **41** (34 mg, 0.30 mmol), I_2 (4 mg, 5 mol%), dppe (12 mg, 10 mol%), $PdCl_2$ (5 mg, 10 mol%) and K_2CO_3 (101 mg, 0.73 mmol) in 1:1 mixture of THF-H_2O (4 mL) at 60 °C under argon atmosphere for 24 h gave the product **47** as brownish yellow viscous liquid (46 mg, 30%).

R_f 0.47 (3:1 Hexane/ethyl acetate).



47

IR (neat) ν_{max}: 3368, 2981, 2934, 1750, 1715, 1597, 1443, 1385, 1298, 1227, 1178, 1108, 1031, 957, 756, 701, 598 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.19 (m, 11H), 6.46-6.44 (m, 1H), 6.30-6.21 (m, 2H), 6.13-6.00 (m, 1H), 5.77-5.53 (m, 2H), 4.90-4.86 (m, 1H), 4.61-4.56 (m, 2H), 1.24-0.86 (m, 12H).

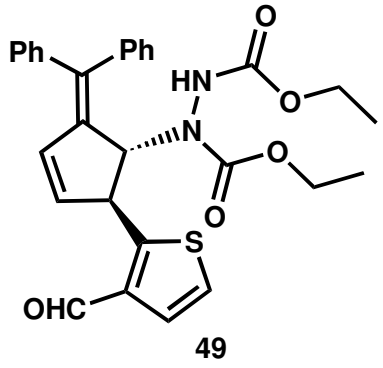
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1, 155.3, 141.5, 140.8, 137.2, 136.9, 136.5, 135.2, 132.9, 132.1, 130.2, 129.9, 128.2, 127.9, 127.7, 127.5, 127.3, 127.1, 126.8, 110.2, 105.3, 70.1, 69.8, 64.4, 49.5, 22.6, 21.9.

LRMS (FAB) for $C_{30}H_{32}N_2O_5$, calcd (M^+): 500.2311; found: 523.35 $(M+Na)^+$.

Diethyl 1-(2-(diphenylmethylene)-5-(3-formylthiophen-2-yl)cyclopent-3-enyl) hydrazine -1, 2-dicarboxylate 49

Following the general experimental procedure, the bicyclic hydrazine **33** (100 mg, 0.25 mmol), 3-formyl-2-thiophene boronic acid **41** (39 mg, 0.25 mmol), I_2 (3 mg, 5 mol%), dppe (10 mg, 10 mol%), $PdCl_2$ (4.5 mg, 10 mol%) and K_2CO_3 (82 mg, 0.59 mmol) in 1:1 mixture of THF-H_2O (4 mL) at 60 °C under argon atmosphere for 24 h gave the product **49** as light brown viscous liquid (49 mg, 38%).

R_f 0.24 (3:1 Hexane/ethyl acetate).



49

IR (neat) ν_{max}: 3368, 3291, 2982, 1716, 1671, 1596, 1487, 1405, 1383, 1298, 1233, 1124, 1057, 754, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.28 (s, 1H), 7.38-7.16 (m, 12H), 6.61 (dd, J_1 = 4.6 Hz, J_2 = 17.7 Hz, 1H), 6.15 (s, 1H), 5.91-5.71 (m, 2H), 5.50-5.42 (m, 1H), 4.21-4.18 (m, 2H), 3.86-3.71 (m, 2H), 1.29-1.25 (m, 3H), 1.05-0.96 (m, 3H).

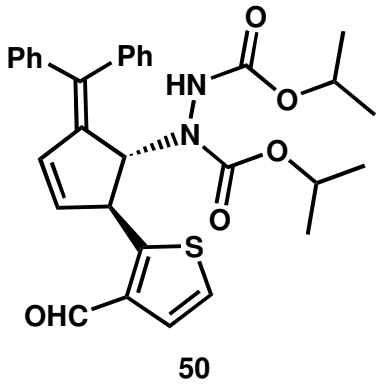
^{13}C NMR (75 MHz, $CDCl_3$): δ 185.6, 156.2, 154.4, 141.3, 140.7, 139.5, 137.6, 137.2, 134.3, 129.8, 129.7, 128.7, 128.2, 127.6, 126.7, 123.8, 64.5, 62.0, 61.6, 49.0, 14.3.

LRMS (FAB) for $C_{29}H_{28}N_2O_5S$, calcd (M^+): 516.1719; found: 539.05 $(M+Na)^+$.

Diisopropyl 1-(2-(diphenylmethylene)-5-(3-formylthiophen-2-yl)cyclopent-3-enyl) hydrazine -1, 2-dicarboxylate 50

Following the general experimental procedure, the bicyclic hydrazine **35** (111 mg, 0.26mmol), 3-formyl-2-thiophene boronic acid **41** (40 mg, 0.26 mmol), I_2 (3 mg, 5 mol%), dppe (10 mg, 10 mol%), $PdCl_2$ (5 mg, 10 mol%) and K_2CO_3 (85 mg, 0.62 mmol) in 1:1 mixture of THF-H_2O (4 mL) at 60 °C under argon atmosphere for 24 h gave the product **50** as a yellow viscous liquid (56 mg, 40%).

R_f 0.33 (3:1 Hexane/ethyl acetate).



50

IR (neat) ν_{max}: 3368, 2978, 1750, 1716, 1682, 1597, 1468, 1386, 1314, 1234, 1179, 1105, 1028, 754, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.29 (s, 1H), 7.47-7.16 (m, 12H), 6.62 (d, J = 5.0 Hz, 1H), 6.15-6.13 (m, 1H), 5.75 (m, 1H), 5.62-5.42 (m, 2H), 4.93 (m, 1H), 4.54 (m, 1H), 1.28-1.21 (m, 6H), 1.06-0.91 (m, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 186.2, 156.1, 154.0, 141.6, 140.8, 136.2, 135.7, 133.6, 133.0, 129.8, 129.6, 128.9, 128.7, 128.5, 128.4, 128.2, 128.0, 127.6, 127.5, 127.4, 127.0, 70.9, 70.2, 66.3, 48.6, 22.2, 21.7.

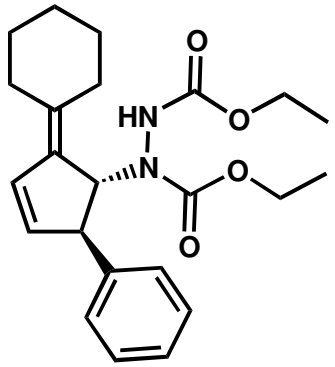
LRMS (FAB) for $C_{31}H_{32}N_2O_5S$, calcd (M^+): 544.2032; found: 567.47 ($M+Na^+$).

Diethyl 1-(2-(cyclohexylidene)-5-phenylcyclopent-3-enyl) hydrazine-1,2-dicarboxylate 52

Following the general experimental procedure, the bicyclic hydrazine **51**(118 mg, 0.37 mmol), phenyl boronic acid **1** (30 mg, 0.25 mmol), I_2 (3 mg, 5 mol%), dppe (10 mg, 10 mol%), $PdCl_2$ (4.5 mg, 10 mol%) and K_2CO_3 (82 mg, 0.59 mmol)

in 1:1 mixture of THF-H_2O (4 mL) at 60 °C under argon atmosphere for 24 h gave the product **52** as light brown viscous liquid (53 mg, 58%).

R_f 0.41 (3:1 Hexane/ethyl acetate).



52

IR (neat) ν_{max}: 3297, 2928, 2855, 1734, 1715, 1465, 1410, 1380, 1230, 1062, 853, 760, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.19 (m, 5H), 6.52 (d, *J* = 5.6 Hz, 1H), 6.17-6.13 (m, 1H), 6.00-5.95 (m, 2H), 5.27-4.90 (m, 1H), 4.27-4.07 (m, 4H), 2.32-2.06 (m, 4H), 1.85-1.31 (m, 6H), 1.30-1.23 (m, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 155.5, 142.5, 139.4, 136.5, 132.8, 130.5, 128.4, 124.8, 124.1, 62.8, 62.3, 61.4, 53.7, 31.9, 30.5, 29.6, 28.4, 26.4, 14.6.

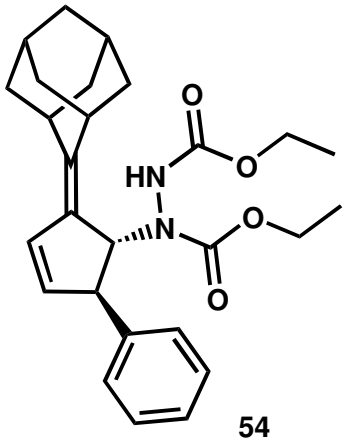
LRMS (FAB) for $C_{23}H_{30}N_2O_4$, calcd (M^+): 398.2206; found: 421.68 ($M+Na^+$).

Diethyl 1-(2-(adamantylidene)-5-phenyl cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 54

Following the general experimental procedure, the bicyclic hydrazine **53** (138 mg, 0.36 mmol), phenyl boronic acid **1** (30 mg, 0.25 mmol), I_2 (3 mg, 5 mol%), dppe (10 mg, 10 mol%), $PdCl_2$ (4.5 mg, 10 mol%) and K_2CO_3 (82 mg, 0.59 mmol) in 1:1 mixture of THF-H_2O (4 mL) at 60 °C under argon atmosphere for 24 h gave the product **54** as light brown viscous liquid (70 mg, 63%).

R_f 0.34(3:1 Hexane/ethyl acetate).

IR (neat) ν_{max}: 3324, 2922, 2852, 1714, 1599, 1446, 1416, 1377, 1303, 1256, 1222, 1169, 1062, 757, 699 cm^{-1}



54

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.17 (m, 5H), 6.54 (d, *J* = 5.7 Hz, 1H), 6.23-6.17 (m, 1H), 5.98-5.90 (m, 1H), 5.06-5.04 (m, 1H), 4.45-4.40 (m, 1H), 4.23-4.13 (m, 4H), 2.92 (s, 1H), 2.48-2.41 (m, 1H), 2.03-1.76 (m, 12H)1.29-1.23 (m, 6H)

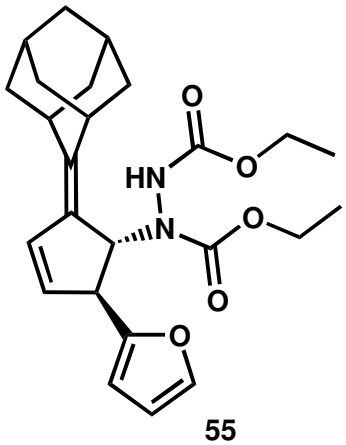
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.4, 155.2, 141.9, 138.7, 135.8, 132.4, 129.2, 128.9, 128.7, 124.4, 62.6, 62.0, 61.3, 54.4, 39.7, 38.0, 36.4, 34.8, 34.1, 28.4, 27.4, 14.5, 14.1

LRMS (FAB) for $C_{27}H_{34}N_2O_4$, calcd (M^+): 450.2519; found: 473.88 ($M+Na^+$).

Diethyl 1-(2-(adamantylidene)- 5-(furan-2-yl) cyclopent-3-enyl) hydrazine-1,2-dicarboxylate 55

Following the general experimental procedure, the bicyclic hydrazine **53** (200 mg, 0.54 mmol), 2-furan boronic acid **45** (40 mg, 0.36 mmol), I_2 (4 mg, 5 mol%), dppe (15 mg, 10 mol%), $PdCl_2$ (6.6 mg, 10 mol%) and K_2CO_3 (118 mg, 0.86 mmol) in 1:1 mixture of THF-H_2O (4 mL) at 60 °C under argon atmosphere for 24 h gave the product **55** as viscous liquid (76 mg, 48%).

R_f 0.37 (3:1 Hexane/ethyl acetate).



55

IR (neat) ν_{max}: 3307, 2923, 2850, 1753, 1715, 1591, 1449, 1409, 1374, 1315, 1219, 1062, 759, 724 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (s, 1H), 6.49 (d, *J* = 5.3 Hz, 1H), 6.26 (s, 1H), 6.15 (s, 1H), 6.03 (s, 1H), 5.93-5.91 (m, 1H), 5.40-5.11 (m, 1H), 4.41-4.35 (m, 1H), 4.24-4.16 (m, 4H), 2.95 (s, 1H), 2.58(s, 1H), 1.99-1.92 (m, 5H), 1.88-1.79 (m, 7H), 1.30-1.19 (m, 6H).

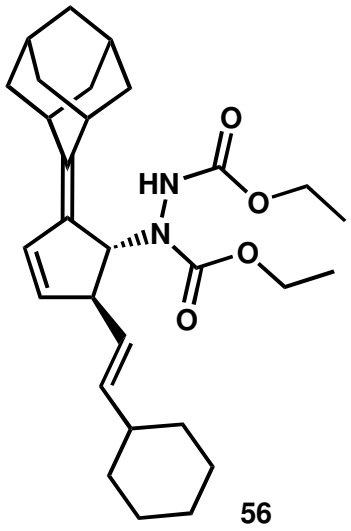
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 155.8, 142.4, 141.3, 135.5, 130.1, 128.6, 110.2, 105.8, 62.8, 61.4, 59.1, 47.3, 39.6, 37.4, 36.7, 34.8, 33.3, 28.9, 28.0, 14.8, 14.5.

LRMS (FAB) for $C_{25}H_{32}N_2O_5$, calcd (M^+): 440.2311; found: 463.44 ($M+Na^+$).

Diethyl 1-(2-cyclohexylvinyl)-5-(adamantylidene)-cyclopent-3-enyl) hydrazine - 1, 2-dicarboxylate 56

Following the general experimental procedure, the bicyclic hydrazine **53** (200 mg, 0.54 mmol), cyclohexylvinyl boronic acid **41** (55 mg, 0.36 mmol), I_2 (4 mg, 5 mol%), dppe (15 mg, 10 mol%), $PdCl_2$ (6.6 mg, 10 mol%) and K_2CO_3 (118 mg, 0.86 mmol) in 1:1 mixture of THF-H_2O (4 mL) at 60 °C under argon atmosphere for 24 h gave the product **56** as as light brown viscous liquid (99 mg, 58%).

R_f 0.57 (3:1 Hexane/ethyl acetate).



56

IR (neat) ν_{max}: 3367, 2923, 2851, 1711, 1616, 1449, 1410, 1377, 1303, 1224, 1097, 1062, 966, 761 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19-7.14 (m, 1H), 6.34 (d, J = 4.7 Hz, 1H), 6.11 (brs, 1H), 5.78 (s, 1H), 5.54-5.30 (m, 2H), 5.10-4.95 (m, 1H), 4.37-4.04 (m, 4H), 2.91 (s, 1H), 2.65-2.55 (m, 1H), 2.00-1.53 (m, 19H), 1.27-1.04 (m, 10H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 156.1, 140.2, 137.5, 137.2, 132.4, 128.4, 68.2, 62.6, 61.9, 51.2, 40.7, 39.4, 38.8, 37.2, 37.0, 34.8, 33.3, 32.9, 29.7, 28.1, 26.2, 14.7, 14.0

LRMS (FAB) for $C_{29}H_{42}N_2O_4$, calcd (M^+): 482.3145; found: 505.43 ($M+Na^+$).

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Interplay of Dual Reactivity in the Reaction of Pentafulvenes with 1,2,4-Triazolinediones: Experimental and Theoretical Investigations

4.1. Introduction

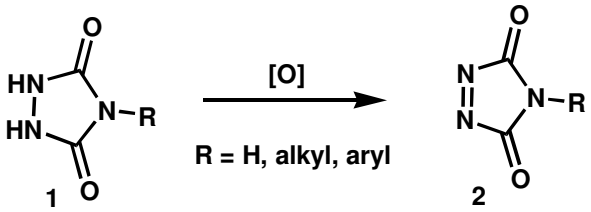
The evolution of organic synthesis relies on the design and discovery of new reactions that generate complex molecular architectures from simple starting materials with atom economy.[1] In recent years, the need for efficient generation of azapolycyclic systems has increased dramatically, due to the abundance of these molecular skeletons in nature and their growing use as scaffolds for molecular recognition.[2] In this respect, cycloaddition reactions hold a prominent place in the arsenal of currently available synthetic methods towards diverse and complex polycyclic molecules.[3]

The present chapter deals with the detailed investigation on the unusual cycloaddition reaction between pentafulvenes and 1,2,4-triazoline-3,5-diones, leading to the synthesis of novel azapolycycles. The diverse modes of reactivity exhibited by pentafulvenes as well as its synthetic potential towards various polycyclic systems have been discussed in chapter 1. In this context, a brief overview of the chemistry of 1,2,4-triazoline-3,5-dione (TAD) is provided in the following sections.

4.2. 1,2,4-Triazoline-3,5-dione (TAD)

N-substituted-1,2,4-triazoline-3,5-diones (RTADs) are molecules of special interest and versatility. TADs are red or pink crystalline solids and were first synthesized in 1894 by the oxidation of urazoles (Scheme 4.1).[4] Recently several

heterogeneous systems have been developed for the oxidation of urazoles into corresponding TADs.[5]

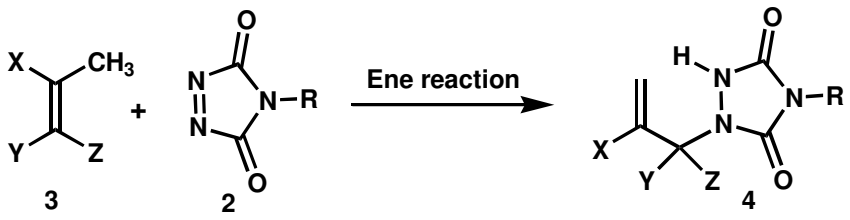


Scheme 4.1

Since its discovery, the fascinating reactions of N-substituted-1,2,4-triazoline-3,5-dione have attracted considerable mechanistic and theoretical attention in organic chemistry. TADs are highly reactive neutral electrophiles, commonly used to detect unsaturation and to introduce nitrogen functionality.[6] Similar to singlet oxygen ($^1O_2$) in reactivity, TADs undergo Diels-Alder (DA) reactions with conjugated dienes, and afford [2+2] adducts or ene products with alkenes.

4.2.1. Ene reactions of TAD

Ene reactions of RTADs have attracted considerable attention due to their synthetic applications and unusual mechanistic features.[7] An ene reaction is defined as the addition of an electrophilic double or triple bond to an unsaturated substrate bearing allylic hydrogen(s), by concomitant transfer of an allylic hydrogen atom to the electrophilic multiple bond. TADs react smoothly with a great variety of unsaturated substrates to form ene products namely N-allyl urazoles **4** (Scheme 4.2).



Scheme 4.2

After the discovery of RTAD-ene reaction by Pirkle and Stickler in 1967, the mechanism of the reaction has attracted considerable attention and still remains as a controversial issue. Different mechanisms have been proposed for this reaction and are, (a) a concerted reaction through a cyclic transition state; (b) formation of a zwitterionic or biradical intermediate and (c) formation of an aziridinium imide (AI) intermediate (Figure 4.1).[8]

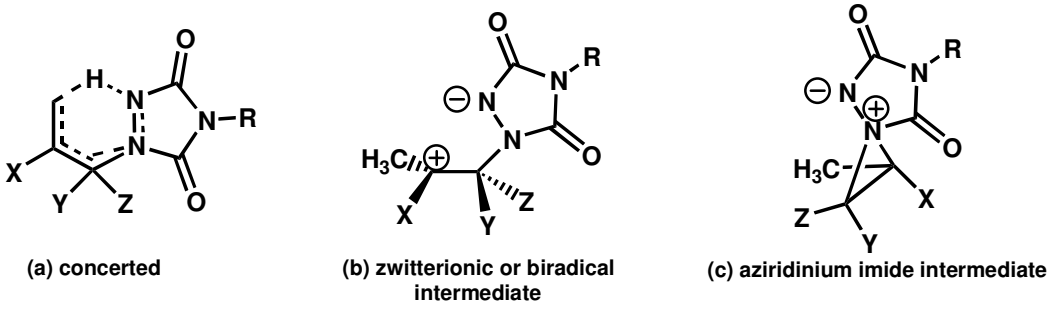
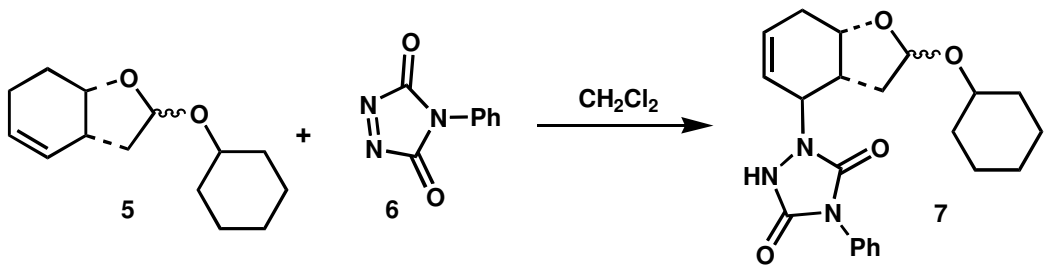


Figure 4.1 Possible mechanisms for TAD-ene reaction

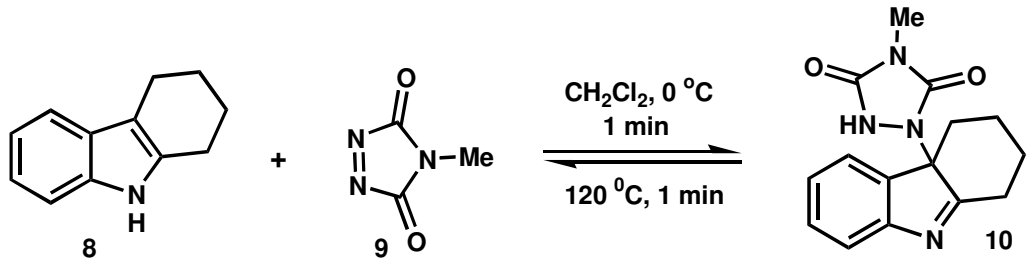
Most of the experimental as well as spectroscopic studies and to a lesser extent, computational analysis support the formation of an AI intermediate in the rate determining step.[9] Pioneering marks in this account was attributed to Orfanopoulos and co-workers for their intensive works on the mechanical aspects of TAD-ene reactions.[10]

Apart from considerable mechanistic attention, this reaction delivered substantial synthetic applications. For example, the ene reaction of N-Phenyl-1,2,4-triazoline-3,5-dione (PTAD) **6** with acetal **5** regioselectively gave the corresponding allylic derivative **7** (Scheme 4.3), which serves as a highly attractive precursor to prostaglandins $PGF_{2\alpha}$ and PGE_2.[11]



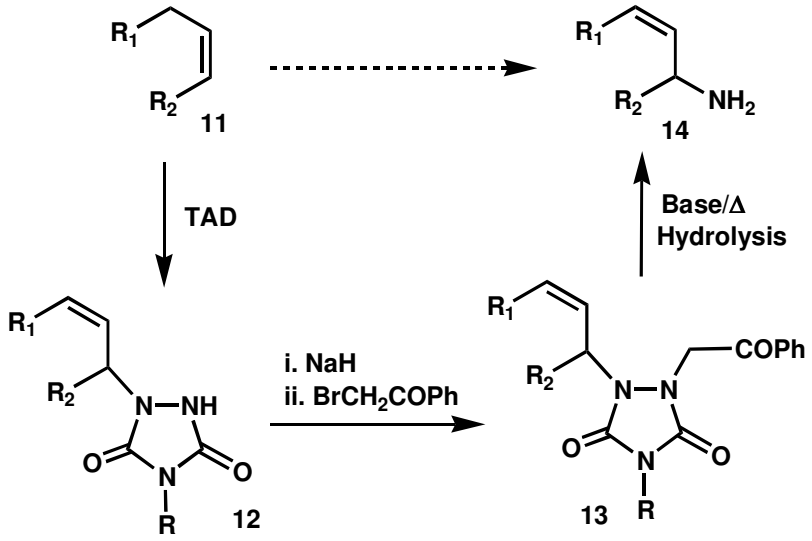
Scheme 4.3

Corey and colleagues reported a new reaction of indoles with N-Methyl-1,2,4-triazoline-3,5-dione (MTAD) **9** and the application of this method to the enantioselective synthesis of Okaramine N.[12] Later on, by extending this methodology, the same group developed a novel method for the protection of the indole 2,3-double bond. The protected molecule **10** could be converted to the starting indole **8** by a retro-ene reaction (Scheme 4.4).[13]



Scheme 4.4

Recently, Adam and co-workers reported the direct allylic amination of olefins by utilizing the diastereoselective RTAD-ene reaction.[14] The synthetic strategy is represented in scheme 4.5, which involves the base catalyzed hydrolysis of N-allylic urazoles **12** that have been prepared by the ene reaction of RTAD with olefin **11**.

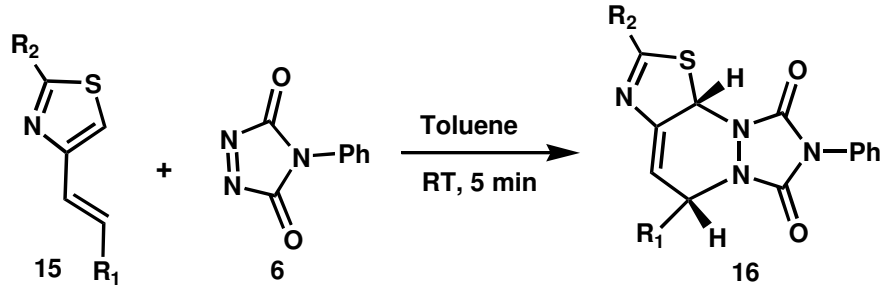


Scheme 4.5

4.2.2. Diels-Alder reactions of triazolinediones

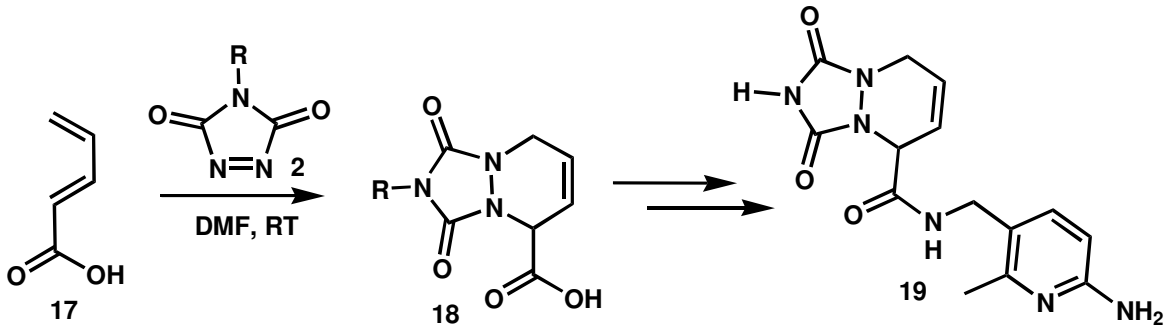
1,2,4-Triazoline-3,5-diones are among the most reactive dienophiles and their Diels-Alder reactions are exceptionally useful in trapping unstable intermediates,[15a] characterizing dienes,[15b] simplifying the isolation of dienes from complex product mixtures[15c] and temporarily protecting diene moieties from reacting with chemical agents.[15d] TADs are known to react with both electron rich and electron deficient dienes to afford Diels-Alder adducts in high yields.[16] These studies revealed that both concerted and stepwise mechanisms may occur, depending upon the structure of the diene.[17]

A more recent example for a Diels-Alder reaction of TAD is shown in scheme 4.6. Alajarin and co-workers reported an efficient hetero Diels-Alder reaction of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) with 4-alkenylthiazoles **15** leading to novel heteropolycyclic systems **16** in excellent yields and high levels of stereocontrol.[18]



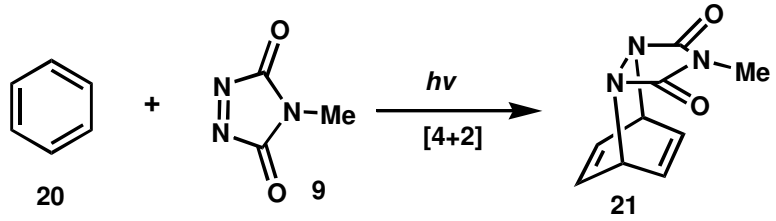
Scheme 4.6

The synthetic potential of TADs as a reactive dienophile, have also been utilized by many groups, for biological and therapeutic applications. M. Kahn *et al.* have exploited this reactivity for the synthesis of libraries of compounds that mimic the β-strand secondary structure of proteins in peptidomimetic applications.[19] They have achieved the synthesis of a potent and selective thrombin inhibitor **19** by utilizing the Diels-Alder reaction between propiolates **17** and TADs (Scheme 4.7).



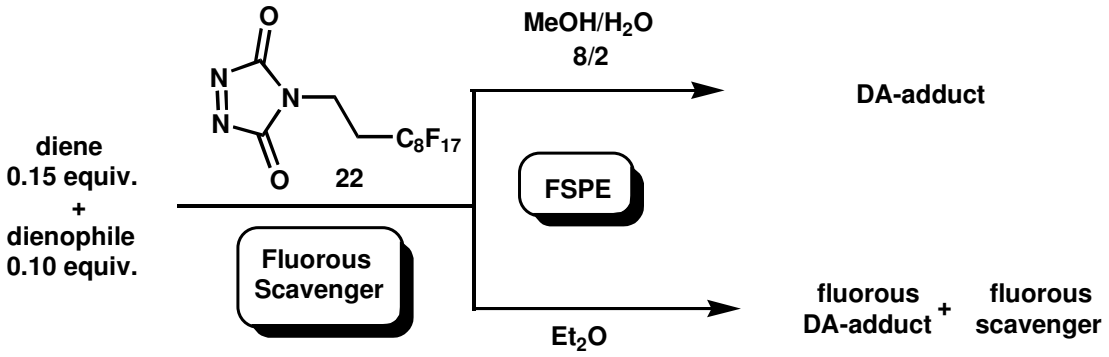
Scheme 4.7

Further more, these compounds exhibit unique photochemical properties. Sheridian *et al.* described the photochemical [4+2] cycloaddition reaction of MTAD with a number of aromatic compounds including benzene and naphthalene, and the corresponding [4+2] adducts formed have served as precursors to several theoretically interesting molecules.[20] An example is illustrated in scheme 4.8.



Scheme 4.8

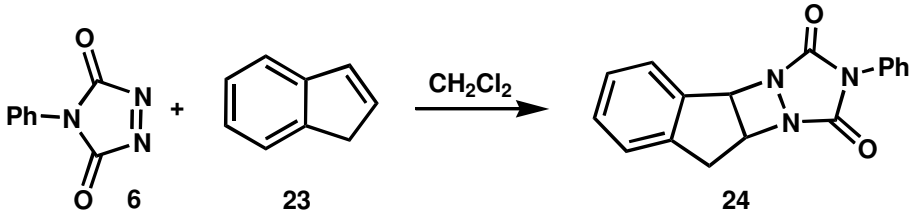
Recently, Curran and co-workers have highlighted another important application of fluorous TAD as powerful diene scavengers in Diels-Alder reactions. The fluorous 1,2,4-triazoline-3,5-dione **22** reacted with most dienes within seconds. The resulting fluorous derivatives were separated by solid-phase extraction on silicagel (FSPE).[21]



Scheme 4.9

4.2.3. [2+2] reactions of TAD: 1,2-Diazetidine formation

TADs react with some alkenes in a [2+2] manner to produce cycloadducts called 1,2-diazetidines rather than ene products.[22] The first example of the [2+2] cycloaddition of RTAD to olefins was reported by Gustorf, who found that PTAD reacts with indene **23** to give 1,2-diazetidines (Scheme 4.10).[23]



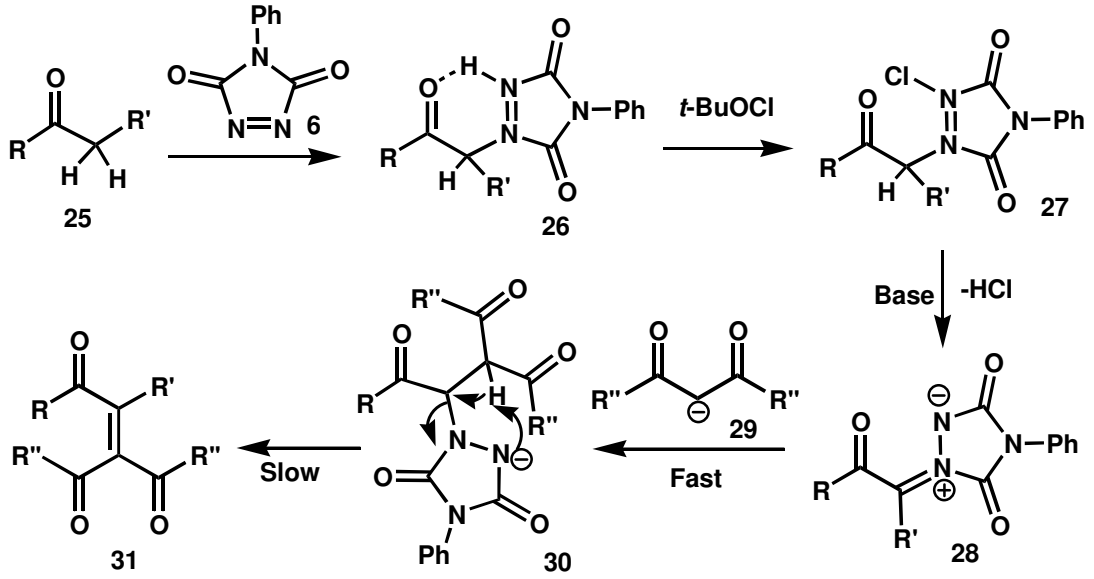
Scheme 4.10

Diazetidine formation was also observed with divinyl ether, vinylcarbamates, methoxy allenes and even with C_{60} fullerenes.[24] More recently, Eric Doris and colleagues have investigated the reactivity of TADs in the [2+2] reaction with carbon nanotubes and observed an unexpected conversion of TAD into deaza dimer through an electron transfer from the nanotubes.[25]

4.2.4. Triazolinedione ylides

TAD ylides constitute a relatively obscure class of reactive intermediates which have recently been shown to undergo extremely facile condensations with a variety of nucleophiles. Triazolinedione ylides are usually generaterd *in situ* by the simple oxidation of appropriately substituted urazoles. For example, Marshal

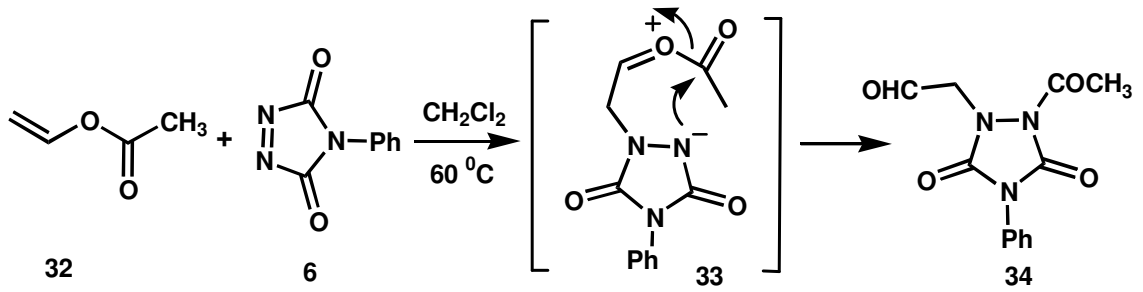
Wilson *et al.* generated an acylated PTAD ylide **28** from *α*-urazolylcarbonyl compound **26**, and studied the condensation chemistry of these ylides with a variety of enolate species (Scheme 4.11).[26]



Scheme 4.11

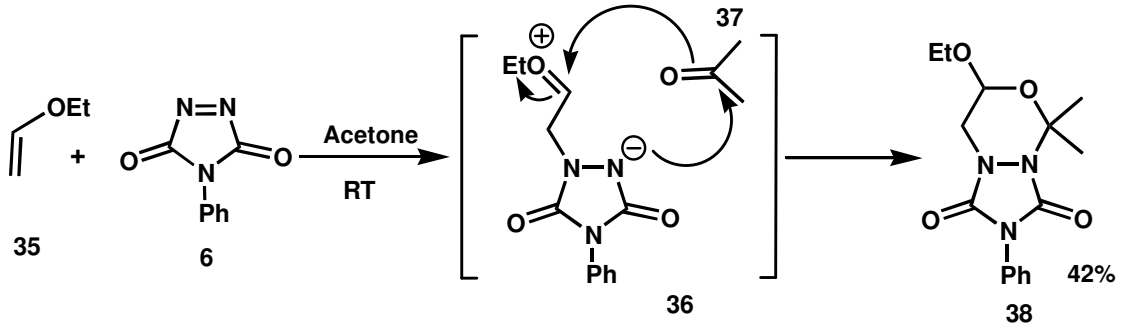
4.2.5. Triazolinedione based zwitterions

Zwitterions are a class of potentially useful dipolar species, which are transient intermediates, resulting from the addition of nucleophiles to activated π-systems.[27] TADs are capable of generating such dipolar intermediates by the addition of a variety of nucleophiles such as vinyl ether, vinyl acetate etc. The existence and the reactivity of various 1,4-dipolar species generated from PTAD was studied by Butler and co-workers.[28] For example the reaction between PTAD **6** and vinyl aceate **32** in methylenechloride at 60 ^{0}C resulted in the formation of a 1,4-dipolar intermediate **33**, which in turn get converted in to 1-formyl-2-acetyl-4-phenyl-1,2,4-triazoline-3,5-dione **34**, through an intramolecular nucleophilic attack (Scheme 4.12).[29]



Scheme 4.12

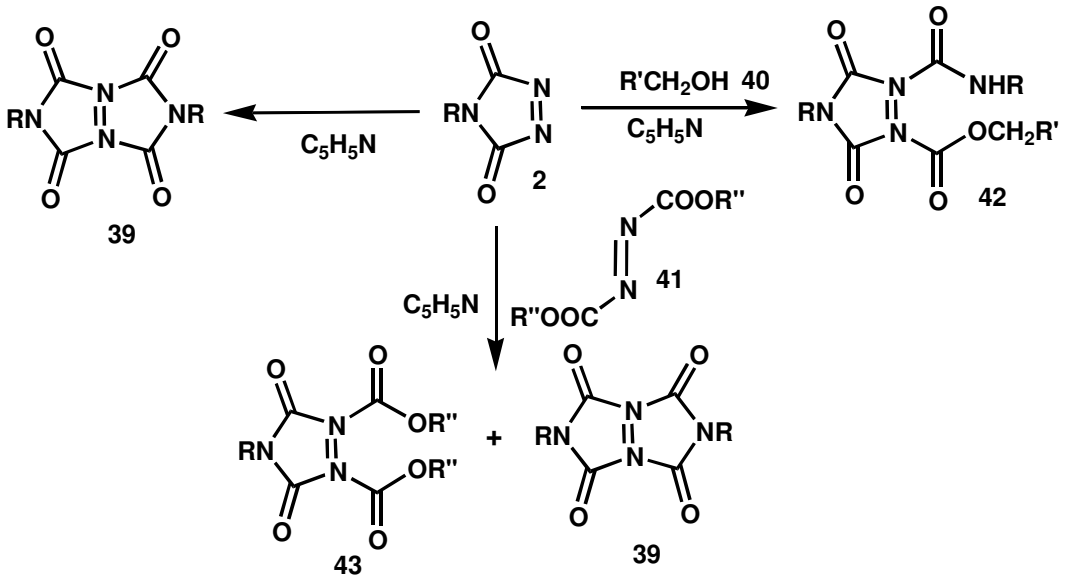
It has been shown that a stabilized 1,4-dipole such as **36** could be trapped even with the weakly dipolarophilic carbonyl group of acetone to form tetrahydro-oxadiazine **38** (Scheme 4.13).[30]



Scheme 4.13

4.2.6. Miscellaneous reactions

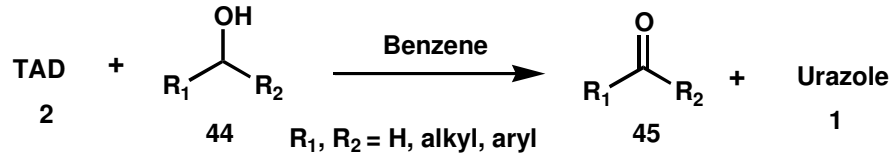
In addition to the aforementioned reactions, RTAD exhibit a wide range of reactivity including self reactions such as polymerization by light[31] and dimerization with loss of dinitrogen by a variety of agents.[32] The conversion of RTAD to deaza dimer **39** was observed on heating and it was more rapid in the presence of urazole or pyridine. The inclusion of an alcohol **40** or large excess of dialkyl azodicarboxylates **41**, in the pyridine promoted conversion of PTAD resulted in the formation of substituted urazoles **42** and **43** respectively (Scheme 4.14).[33]



Scheme 4.14

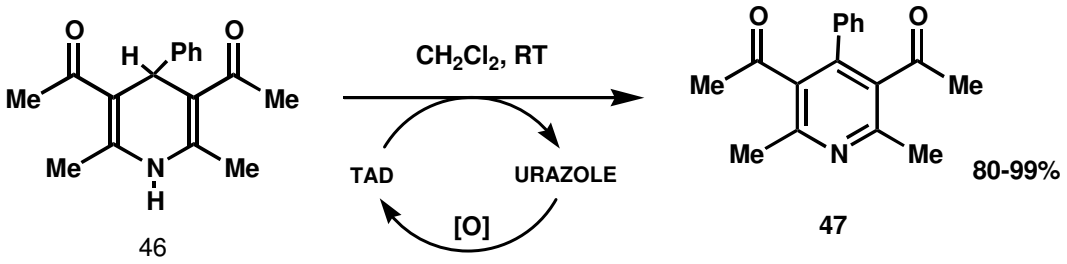
4.2.7. TADs as oxidizing agents

Triazolinediones are also found application as an efficient oxidizing agents in certain reactions. TADs are capable of oxidizing certain alcohols to aldehydes or ketones under mild reaction conditions (Scheme 4.15).[34] For such reactions benzene was used as a convenient solvent for the easy separation of the byproduct urazole from the reaction mixture.



Scheme 4.15

1,2,4-Triazoline-3,5-diones were also been used as recyclable oxidizing agents for the conversion of 1,4-dihydropyridines and 1,3,5-trisubstituted-pyrazolines to corresponding pyridines and pyrazoles, respectively.[35] A typical example is outlined in scheme 4.16.



Scheme 4.16

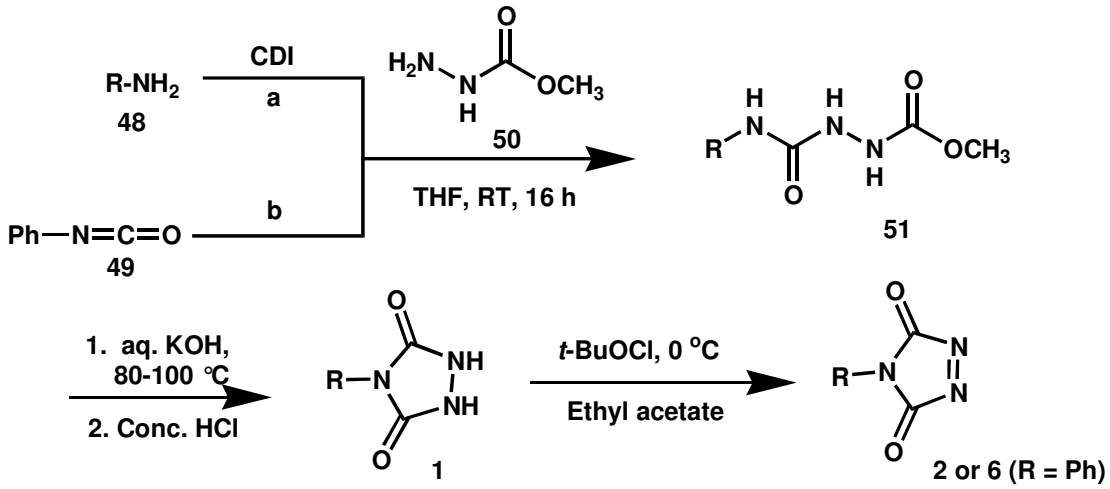
4.3. The present work

The abundance of nitrogen containing polycycles in nature and their diverse roles in biological systems make them attractive subject for innovative research in organic synthesis.[36] Despite the availability of different methods, there still exists a need for developing more efficient procedures which allow the ready synthesis of complex azapolycyclic systems. In this respect, cycloadditions of azadienophiles proved very useful for the synthesis of various nitrogen-containing compounds.

4-Substituted-1,2,4-triazole-3,5-diones are reactive dienophiles, known to undergo Diels-Alder reaction with conjugated dienes.[37] On the other hand, pentafulvenes can undergo [4+2] cycloaddition with heterodienophiles like azodicarboxylates, leading to the synthesis of bicyclic hydrazines.[38] A survey of literature revealed that there is only scant information[39] available on the reaction of 1,2,4-triazoline-3,5-dione with fulvenes. To the best of our knowledge, there are no reports on the theoretical interpretation of the observed reactivity of fulvenes with 1,2,4-triazoline-3,5-diones. Therefore we undertook a detailed experimental and theoretical investigation on the reaction of various pentafulvenes with N-substituted-1,2,4-triazoline-3,5-diones. The results of these studies are discussed in the following section.

4.4. Results and discussions

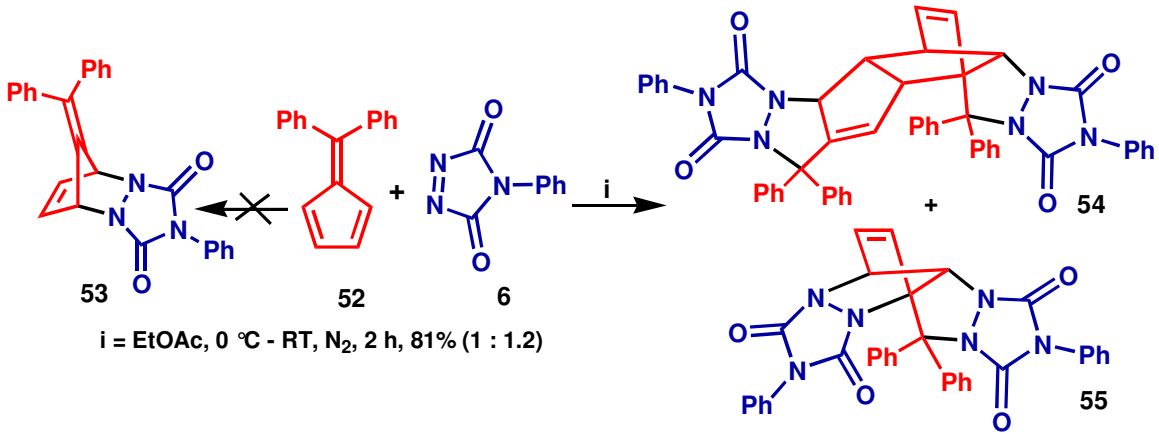
The starting materials desired for our investigations were prepared according to the literature procedures. 4-Substituted-1,2,4-triazoline-3,5-diones were prepared from the corresponding primary amines or phenyl isocyanate as shown in scheme 4.17. The amine **48** on treatment with methylcarbazate **50** and carbonyl diimidazole (CDI) in dry THF at room temperature afforded the corresponding hydrazide **51**. The hydrazide was then cyclized under basic conditions, followed by oxidation to afford the the corresponding 1,2,4-triazoline-3,5-dione **2** (path **a**). 4-Phenyl-1,2,4-triazoline-3,5-dione **6** was prepared from phenyl isocyanate **49** and methylcarbazate **50**, following the similar procedure (path **b**).



Scheme 4.17

4.4.1 Reactions of pentafulvenes with triazolinediones

In order to synthesize triazatricyclic olefin from fulvenes and 1,2,4-triazolinedione, we have carried out the cycloaddition reaction of 6,6-diphenyl fulvene **52** with N-phenyl-1,2,4-triazoline-3,5-dione (PTAD). Interestingly, instead of the expected [4+2] adduct, the reaction of one equivalent of fulvene with two equivalents of 1,2,4-triazoline-3,5-dione at 0 °C afforded a separable mixture (1:1.2) of five membered and seven membered azapolycycles **54** and **55** in 81% yield (Scheme 4.18).



Scheme 4.18

The structures of **54** and **55** were assigned based on spectral analysis and by comparison to the literature report.[39] IR spectrum of **54** showed a strong absorption due to the urazole carbonyls at 1769 cm^{-1} and 1718 cm^{-1}. In ^1H NMR spectrum of **54** (Figure 4.2), the olefinic protons at C-13 and C-14 resonated as a double doublet at δ 6.26 ppm and as a doublet at δ 5.87 ppm. The doublet at δ 5.04 ppm was assigned to the olefinic proton at C-8, while the protons of the ring junction at C-9 and C-10, appeared at δ 3.94 and 3.65 ppm respectively. The aromatic protons were observed in the region δ 7.53-7.14 ppm and the signal due to the proton at C-16 was found at δ 4.36 ppm as a singlet.

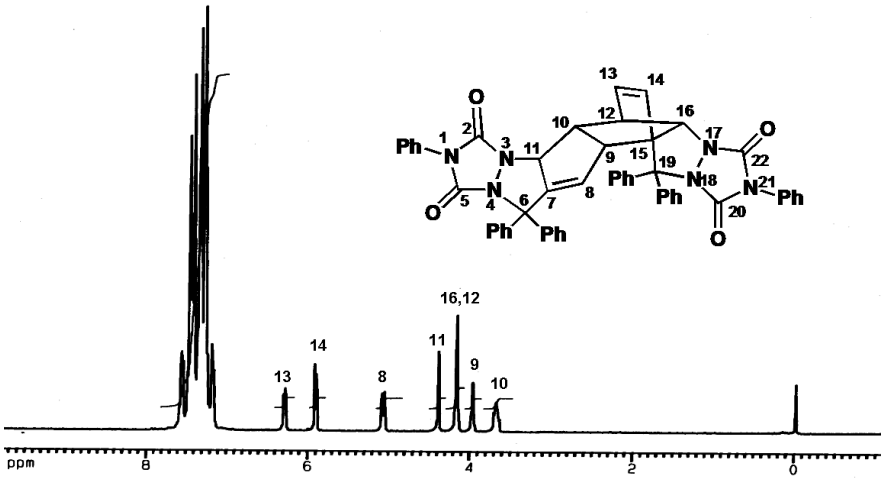


Figure 4.2 ^1H NMR spectrum of **54**

The ^{13}C NMR spectrum (Figure 4.3) of **54** positioned the characteristic carbonyl absorptions at δ 152.9, 150.7, 150.2 and 149.0 ppm. The carbons C-11 and C-16 attached to nitrogens resonated at δ 67.8 and 64.0 ppm, whereas the less intense signals at δ 75.2 and 74.0 ppm, were attributed to the tetrasubstituted carbons C-6 and C-19. High resolution mass spectral analysis also supported the structure assignment with the molecular ion peak at *m/z* 811.24 (M+2).

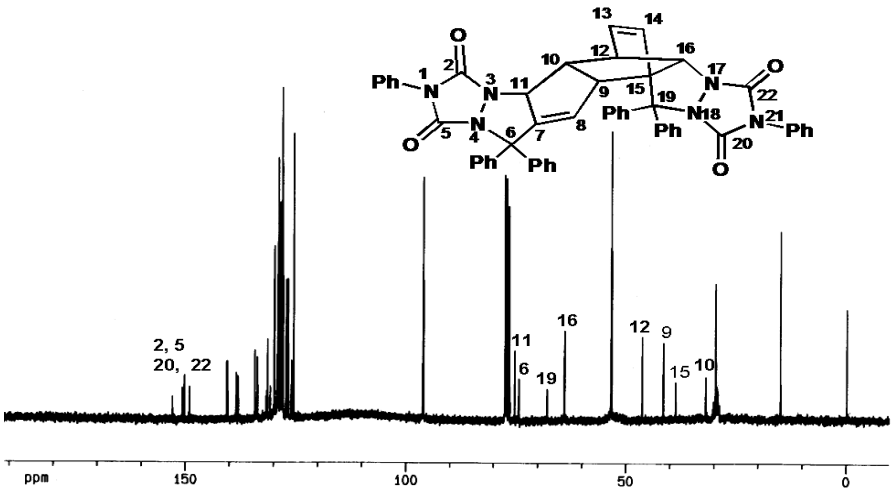


Figure 4.3. ^{13}C NMR spectrum of **54**

Finally, the structure of **54** was unambiguously confirmed by single crystal X-ray analysis (Figure. 4.4).

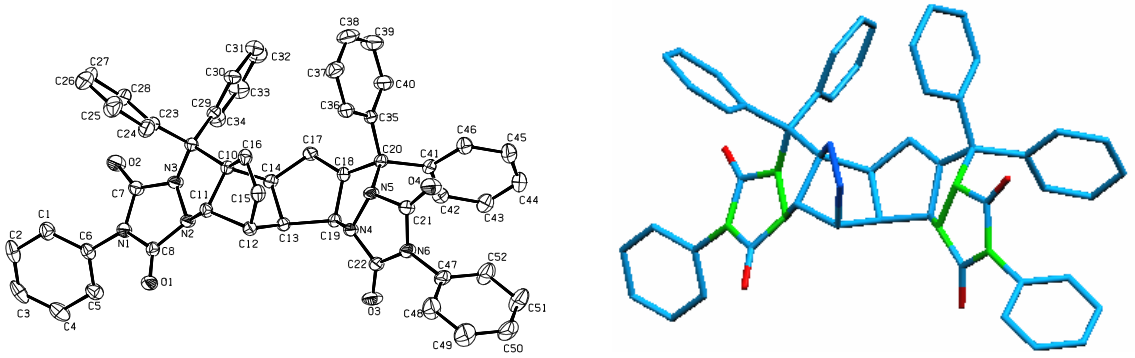


Figure 4.4: Single crystal X-ray structure of **54**

The product **55** furnished the carbonyl stretching absoptions as a broad signal at 1768-1734 cm^{-1} in the IR spectrum. The proton NMR spectrum (Figure 4.5) of

55 identified the protons at C-6 and C-10 as singlets at δ 5.56 and 4.73 ppm. The olefinic proton at C-8 was discernible as a doublet at δ 7.03 ppm, while the olefinic proton at C-7 produced a quartet at δ 6.46 ppm. The complex multiplet observed in the region δ 7.55-7.16 ppm was assigned to the aromatic protons.

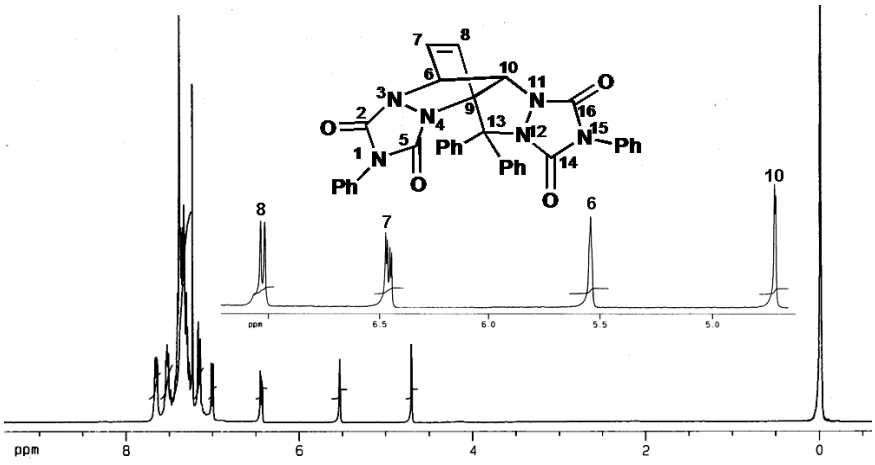


Figure 4.5: ^{1}H NMR spectrum of **55**

In the ^{13}C NMR spectrum of **55**, the four carbonyl carbons resonated at δ 157.4, 155.7, 150.2 and 149.5 ppm, whereas the C-9 carbon appeared at δ 92.3 ppm. All other signals in ^{1}H and ^{13}C NMR spectra agreed with the structure assignment. The molecular ion peak at *m/z* 581.38 in high resolution mass spectra provided additional evidence for the structure.

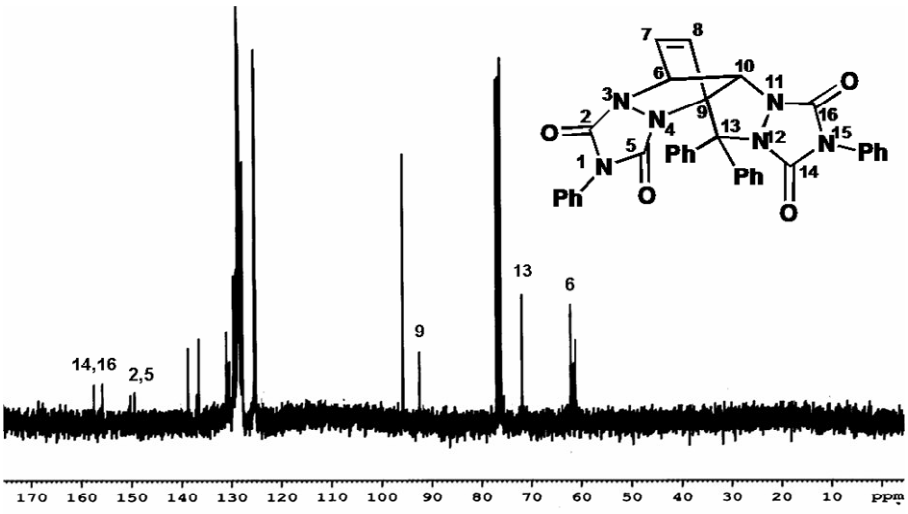


Figure 4.6: ^{13}C NMR spectrum of **55**

The reaction was repeated using various pentafulvenes and N-substituted-1,2,4-triazoline-3,5-diones and the results are summarized in table 4.1.

Table 4.1 Reaction of 1,2,4-triazoline-3,5-diones with Pentafulvenes.

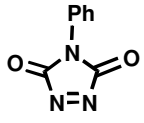
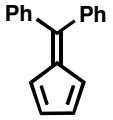
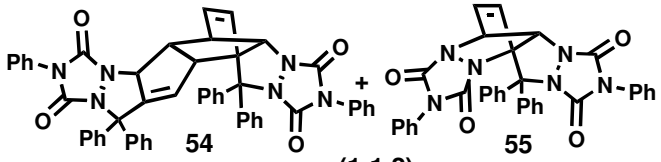
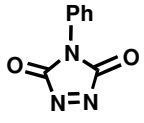
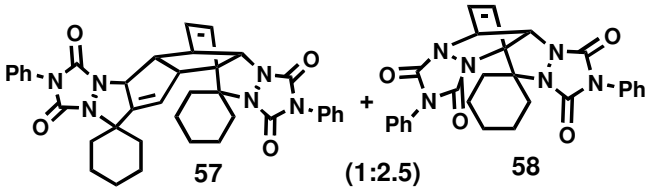
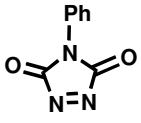
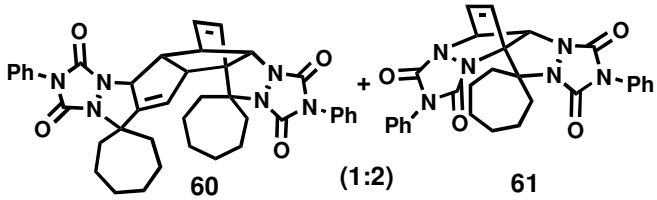
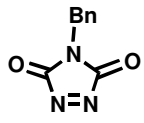
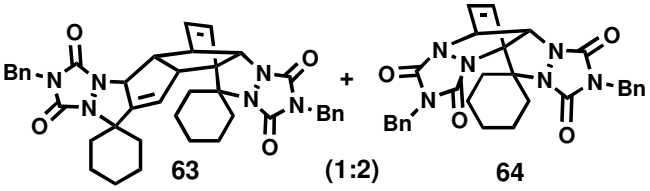
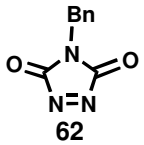
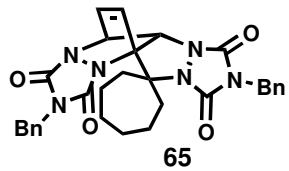
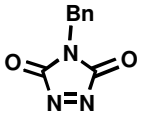
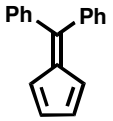
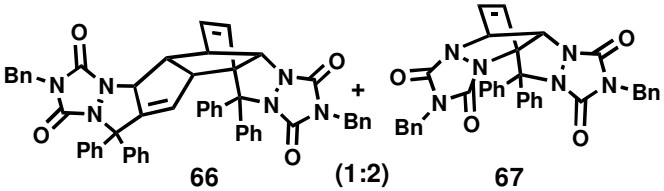
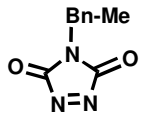
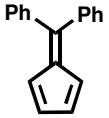
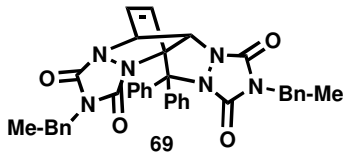
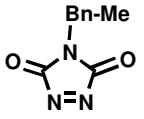
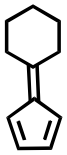
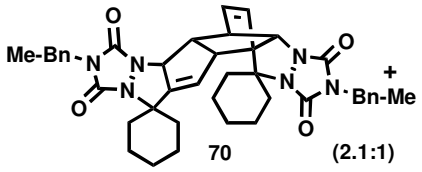
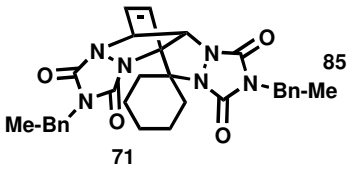
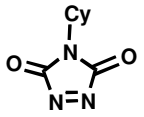
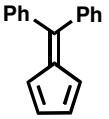
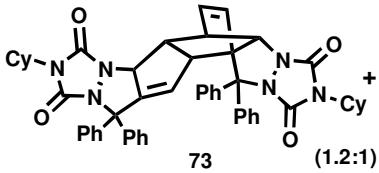
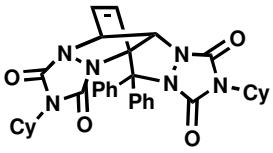
Entry	TAD	Fulvene	Products (Ratio)	Yield (%)
1	 6	 52	 54 + 55 (1:1.2)	81
2	 6	 56	 57 + 58 (1:2.5)	85
3	 6	 59	 60 + 61 (1:2)	62
4	 62	 56	 63 + 64 (1:2)	86
5	 62	 59	 65	77
6	 62	 52	 66 + 67 (1:2)	92

Table 4.1. Continues....

Entry	TAD	Fulvene	Products (Ratio)	Yield (%)
7	 68	 52	 69	78
8	 68	 56	 70 (2.1:1)  71	85
9	 72	 52	 73 (1.2:1)  74	61

Reaction conditions: EtOAc, 0 °C - RT, 2 h

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 1770-1725 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 ^{1}H NMR spectrum of **57**, the olefinic protons were found to resonate as a singlet at δ 6.08 and as a multiplet at around δ 5.92 ppm, while in the case of **58**, olefinic protons marked its signals as doublet and double doublet at δ 6.77 and 6.45 ppm, respectively. The complex multiplet observed in the region δ 2.17-1.50 ppm, could be attributed the cycloalkyl protons both in **57** and **58**. In ^{13}C NMR spectra, the cyclohexyl carbons were observed in the region δ 22.0-34.0 ppm for both the products. ^{1}H NMR spectrum of **60** located two olefinic protons as doublets at δ 6.63 and 6.47 ppm and as a multiplet in the region δ 5.95-5.91 ppm. The complex multiplet observed in the region δ 2.30-0.80 ppm was assigned to methylene protons of cycloheptyl rings. The ^{13}C NMR spectrum gave the peaks

corresponding to the cycloheptyl carbons in the range δ 37-24 ppm. In the ^{1}H NMR spectrum of **61**, the olefinic protons were identified as a doublet at δ 6.72 ppm and a double doublet at δ 6.43 ppm. The methylene protons of cycloheptyl group resonated as multiplets in the regions δ 3.04-2.81 ppm and 2.22-0.88 ppm. ^{13}C NMR spectrum of **61** positioned the cycloalkyl carbons in the region δ 37.6-23.6 ppm.

In the case of compound **63**, ^{1}H NMR spectrum identified the benzylic protons as singlets at δ 4.60 and 4.57 ppm and the cyclohexyl protons as multiplets in the region δ 1.78-1.23 ppm. The benzylic carbons were visible at δ 43.4 and 41.9 ppm in the ^{13}C NMR spectrum. In the ^{1}H NMR spectrum of **64**, the olefinic protons were observed as a doublet at δ 6.44 and as a double doublet at δ 6.15 ppm, while the singlets resonated at δ 4.58 and 4.47 ppm were assigned to the benzylic protons. ^{13}C NMR located the benzylic carbon at δ 43.8 and 43.1 ppm. ^{1}H NMR spectrum of **65** recognized the olefinic protons as a doublet at δ 6.44 ppm and as a double doublet at δ 6.16 ppm; while the benzylic protons gave two independent singlets at δ 4.59 and δ 4.50 ppm. In ^{13}C NMR spectrum, the benzylic and cycloheptyl carbons were resonated within the expected region.

A double doublet at δ 6.00 ppm and the doublets at δ 5.69 ppm and δ 4.82 ppm, observed in ^{1}H NMR spectrum of **66**, were assigned to the olefinic protons. The characteristic signals due to aromatic protons appeared in the region δ 7.34 - 7.00 ppm. ^{13}C NMR spotted the characteristic benzylic carbons at δ 44.4 and 44.1 ppm. ^{1}H NMR spectrum of **67** identified the olefinic protons as doublet and double doublet at δ 6.77 and 6.11 ppm, respectively. The complex multiplet observed between δ 7.51 and 7.15 ppm is the characteristic of aromatic protons. ^{13}C NMR spectrum located the tetra substituted carbon carrying the phenyl groups as a less intense signal at δ 72.4 ppm. In ^{1}H NMR spectrum of **69**, the aromatic protons appeared as distinct multiplets in the permissible regions and the methyl protons

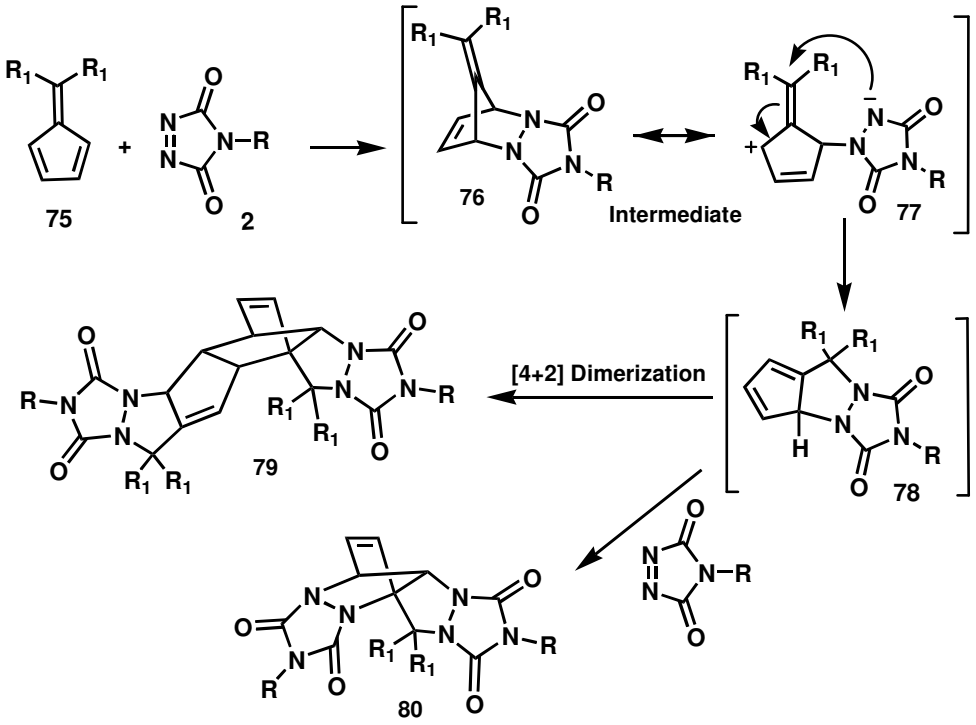
attached to the phenyl ring as a sharp singlet at δ 2.30 ppm. ^{13}C NMR spectrum provided sufficient information to support the structure assignment.

For **70**, ^{1}H NMR spectrum showed two doublets at δ 7.28 and 7.11 ppm matching with the aromatic protons. The benzylic protons resonated in the region δ 4.99-4.58 ppm, whereas methyl groups were observed as a singlet at δ 2.26 ppm. In the ^{13}C NMR spectrum, the benzylic carbons were spotted at δ 45.6 and 42.8 ppm, while the methyl carbons were discernible at δ 42.7 and 41.8 ppm. In the case of **71**, ^{1}H NMR spectrum presented the benzylic and methyl protons at around δ 4.54 and 2.35 ppm, respectively. ^{13}C NMR located the methyl carbons at δ 43.0 and 41.9 ppm. Cyclohexyl carbons were found to resonate in the region δ 32.6-21.3 ppm. ^{1}H NMR spectrum of **73**, located the olefinic protons as a double doublet at δ 6.10 ppm and two doublets at δ 5.77 and 4.88 ppm. ^{13}C NMR spectrum showed the alkyl carbons in the region δ 29.5-24.9 ppm. In the ^{1}H NMR spectrum of **74**, the aromatic protons were discernible in the region δ 7.48-7.25 ppm as a broad multiplet. A well defined doublet at δ 6.70 ppm and a multiplet centered at δ 6.36 ppm were assigned to the olefinic protons. ^{13}C NMR positioned the cyclohexyl carbons in between δ 33.0 and 24.0 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.

The reaction was carried out in different stoichiometric ratios of the substrates, but poor results were obtained. For example, when we repeated the reaction between 6,6'-diphenyl fulvene and 4-benzyl-1,2,4-triazoline-3,5-dione (with highest yield, table 4.1, entry 6) in 1:1 ratio under the same reaction conditions, afforded 10% of **66** and 16% of **67**. The reaction of two equivalents of fulvene with one equivalent of triazolinedione afforded only dimerized product **66** (15%) along with 40% of unreacted fulvene. The monoadduct was not isolated in any of the experiments.

4.4.1.1 Mechanism of the reaction

The first step of the reaction is the [4+2] cycloaddition between pentafulvene and triazolinedione leading to highly unstable adduct **76**, which in turn gets converted to highly reactive tricyclic diene **78** through an intermediate zwitterion **77**. The diene then undergoes either a [4+2] self dimerization and/or [4+2] cycloaddition with another molecule of triazolinedione leading to the formation of interesting azapolycycles **79** and **80** respectively. The mechanism is outlined in the scheme 4.19.



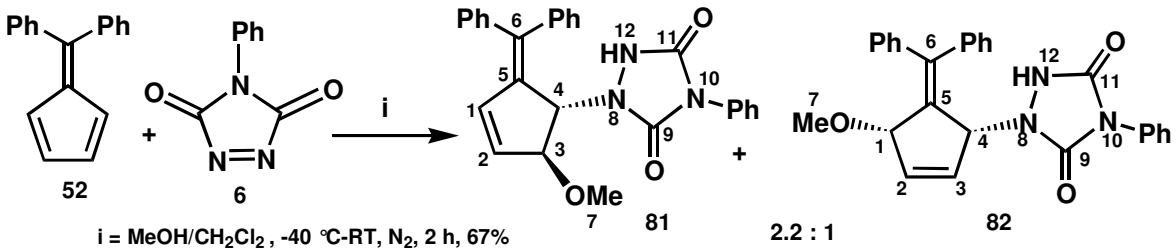
Scheme 4.19

The interesting reactivity pattern of pentafulvene with triazolinedione *via* formation of the zwitterion, prompted us to undertake studies to explore the intermediate zwitterion.

4.4.2. Trapping of the zwitterion intermediate

It was clear from the mechanism that, the reaction proceeds through an intermediate zwitterion **77**. Intrigued by the possibility of converting this

intermediate into alkylidene cyclepentenes and also to provide additional evidence to the proposed mechanism, we have decided to trap the zwitterion with suitable nucleophiles. Our investigation involved the trapping of the zwitterion intermediate with methanol. In an initial experiment we performed the cycloaddition between 6,6-diphenyl fulvene **52** and N-phenyl-1,2,4-triazoline-3,5-dione **6** in dichloromethane-methanol (1:5) mixture at -40 °C. The reaction afforded a separable mixture of alkylidenecyclopentenes **81** (46%) and **82** (21%), and the reaction is illustrated in scheme 4.20.



Scheme 4.20

Structures of the products can be well distinguished by means of spectroscopic analysis and comparison with literature data. IR spectrum of **81** and **82** marked the carbonyl absorptions as a broad band in the region 1770-1695 cm^{-1}. ^{1}H NMR spectrum of **81**, identified the protons of C-1 and C-2 as a doublet and double doublet at δ 6.66 and 6.29 ppm respectively. The doublet observed at δ 5.78 ppm was assigned to the proton on carbon C-4, while the methoxy group presented its signal as a singlet at δ 3.41 ppm. ^{13}C NMR spectrum showed the carbonyl signals at δ 153.3 and 150.4 ppm, while the methoxy carbon was observed at δ 56.2 ppm. Mass spectrum provided additional information with molecular ion peak at *m/z* 460.23 $(M+Na)^{+}$.

In the ^{1}H NMR spectrum of **82**, olefinic protons at C-2 and C-3 were observed as double doublet and doublet at δ 6.17 and 6.50 ppm, respectively. The proton adjacent to the methoxy group resonated as a doublet at δ 4.55 ppm. The three proton singlet observed at δ 3.33 ppm was attributed to the methoxy group. In the ^{13}C NMR spectrum, carbonyl signals were visible at δ 153.4 and 151.0 ppm.

The C-1 and C-4 carbons were discernible at δ 57.7 and 78.3 ppm, while the methoxy group located its carbon at δ 56.2 ppm. Mass spectrum gave the molecular ion peak at 460.50 $(M+Na)^+$ and provided the backing information for the structure.

In addition to the trapping experiments, we also undertook a detailed theoretical investigation on the reaction of pentafulvenes with N-substituted-1,2,4-triazoline-3,5-diones. These investigations well supported the observed reactivity between pentafulvenes and triazolinediones and provided additional insight into the mechanism of the reaction. The details of these studies are presented in the following sections.

4.4.3. Theoretical calculations

All the molecular geometries were optimized at the DFT level by using the Becke's three-parameter exchange functional (B3)[40] in conjunction with the Lee-Yang-Parr correlation functional (LYP)[41] as implemented in the Gaussian 03 suite of programs.[42] For H, C, and O, 6-31G(d) basis functions were selected.[43] Normal coordinate analysis has been performed for all stationary points to characterize the transition states and energy minimum structures.

4.4.3.1. Geometric and electronic features of pentafulvene and triazolinedione

The six-π electron system of pentafulvene is isoelectronic to benzene. The later one is famous for its aromatic stabilization of around 30 kcal/mol arising from six-π electron cyclic delocalization.[44] On the other hand, pentafulvene is susceptible for addition reactions and it is found to be 27 kcal/mol unstable than benzene at B3LYP/6-31G* level of theory. The optimized geometry of pentafulvene is depicted in figure 4.7, which shows the two localized double bonds of length 1.353 Å each in the ring and another one of 1.344 Å in the exo position. The exo double bond is more localized than the ring double bonds, which is consistent with the experimental geometry.[45] Though this bond length distribution implies that the exo bond is more reactive for addition reaction than

the ring double bonds, we would see that the MESP distribution of this molecule is supportive of more reactivity to the ring double bonds.

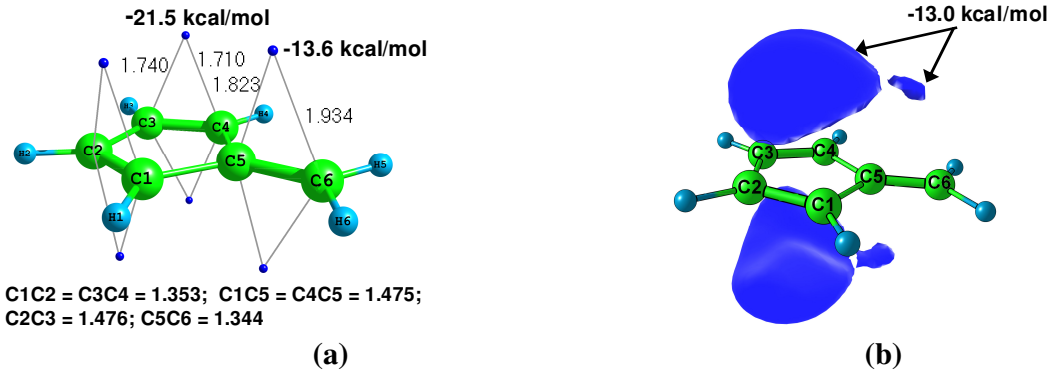


Figure 4.7 (a) MESP minima (V_{min}) over the mid point region of double bonds (Distances in Å). (b) The electronic features of fulvene visualized *via* the MESP isosurface of value -13.0 kcal/mol.

In Figure 4.7a and 4.7b, the electronic feature of fulvene is depicted via its MESP. The more localized bonds on the C1C2, C3C4 and C5C6 can be seen *via* MESP as it shows minima over the mid-point region of those bonds. The MESP minima over the ring double bonds are 58% more negative than the MESP minimum over the exo double bond. This feature is contradictory to their bond lengths because the exo bond C5C6 is the shortest and one would expect more electron rich character to this bond. This significant difference in the electron distribution can be attributed to the tendency of the four π-electron conjugation over C1, C2, C3 and C4 to acquire more electron density from the C5C6 π-bond, in order to decrease the 4n electron antiaromatic destabilization within the ring. This suggests electron deficient character to C6, and this atom is 1.973 Å away from the nearest MESP minimum (V_{min}). The V_{min} with value -21.5 kcal/mol is closer to C1 and C4 atoms, suggesting more reactivity to these atoms. Therefore, in cycloaddition reactions, the electron rich C1C2C3C4 unit would act as the diene part with probable cycloadduct connectivity at C1 and C4 atoms. On the other hand, the substantial reduction in the electron density over the exo bond suggests that this carbon is also susceptible for a nucleophilic attack.

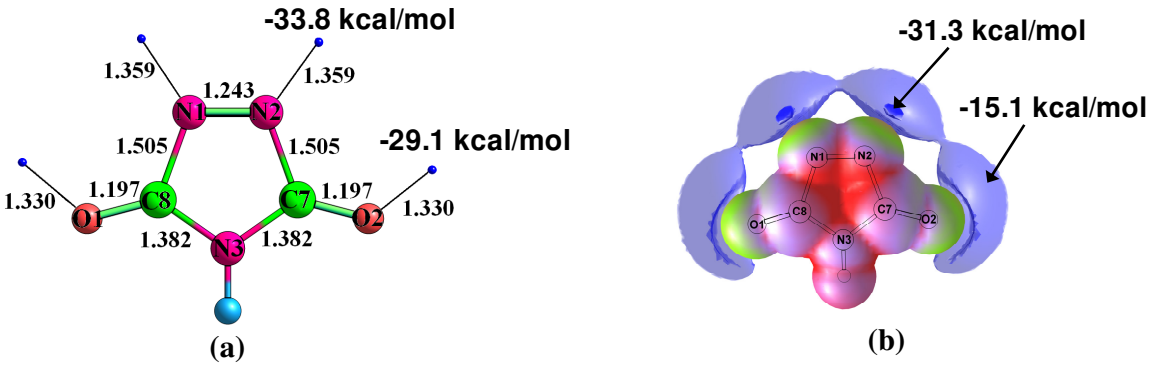


Figure 4.8 (a) Geometry of Triazolinedione (bond lengths are in Å) along with its V_{min} values (blue dots). (**b**) MESP isosurfaces and MESP mapped on atom spheres. Red region has positive MESP.

In the case of triazolinedione, a short N1N2 bond (1.243 Å) is connected to two long bonds N1C8 (1.505 Å) and N2C7 (1.505 Å) and that suggests a highly localized N-N bond (Fig. 4.8a). On the other hand, the O1C8N3C7O2 π-region is more delocalized due to a six π-electron linear conjugation through the planar N3 atom. Therefore, N1 and N2 atoms appeared to be more electron rich in comparison with the more electronegative oxygen atoms.

This feature is easily seen through the (V_{min}) as it shows a value of -33.8 kcal/mol for the lone pair region of N1 and N2 as compared to a value of -29.1 kcal/mol for oxygen atoms. The MESP distribution shown in Fig. 4.8b suggests that the peripheral region of the molecule in the molecular plane, particularly in the lone pair direction of N1 and N2, except that along the N3H bond is electron rich as compared to the π-faces of the molecule. So triazolinedione might show strong nucleophilic character for N1 and N2 atoms. On the other hand, considering the localized nature of N1N2 bond and electron deficient nature of the π-faces, it might also show π-bond reactivity of N1N2 bond for a cycloaddition by acting as a dienophile.

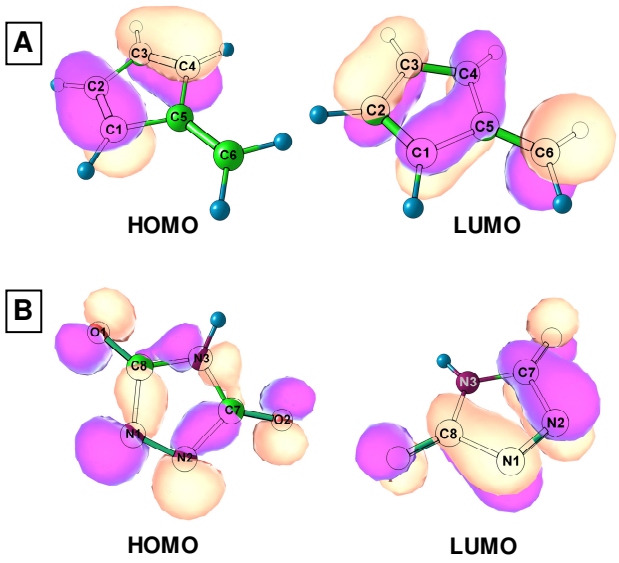


Figure 4.9 (a) Frontier molecular orbitals of (A) Fulvene and (B) Triazolinedione.

Thus the MESP analysis of both pentafulvene and triazolinedione support dual reactivity to them, *viz.* the reactivity for a cycloaddition and reactivity for a nucleophilic reaction. The frontier molecular orbitals (FMO) of these molecules depicted in figue 4.9 are also in support of their dual reactivity. For instance, the HOMO of fulvene and LUMO of triazolinedione are in perfect agreement for a [4+2] cycloaddition leading to C1N1 and C4N2 bond formation. Similarly, the vacant p orbital on the exocyclic C6 atom (LUMO) is susceptible for a nucleophilic attack by the N1 or N2 lone pair orbital (HOMO of triazolinedione).

To sum up, the electronic and geometric features of pentafulvenes and triazolinediones revealed that the electron rich diene like reactivity of ring double bonds of pentafulvenes and the dienophilic π-bond reactivity of NN double bond of TAD make them suitable candidates for cycloaddition reaction. At the same time the electron deficient exocyclic carbon of the pentafulvene and electron rich N-atoms of the TAD also probe them for nucleophilic reaction. Therefore both the cycloaddition and nucleophilic reaction profiles are taken into account for further studies.

4.4.3.2. Energetics of [4 +2] cycloaddition and nucleophilic neaction

As expected from the MESP analysis, the more reactive carbon atoms C1 and C4 interacts with the NN double bond of the triazolinedione in the transition state (TS) for a [4 + 2] cycloaddtion (Figure 4.10). The **TS1** thus formed is found to be unsymmetric as it showed a C1N1 = 1.877 Å and C4N2 = 2.631 Å distances. The activation energy based on only the total electronic energy (E_{act}) was found to be 5.9 kcal/mol.

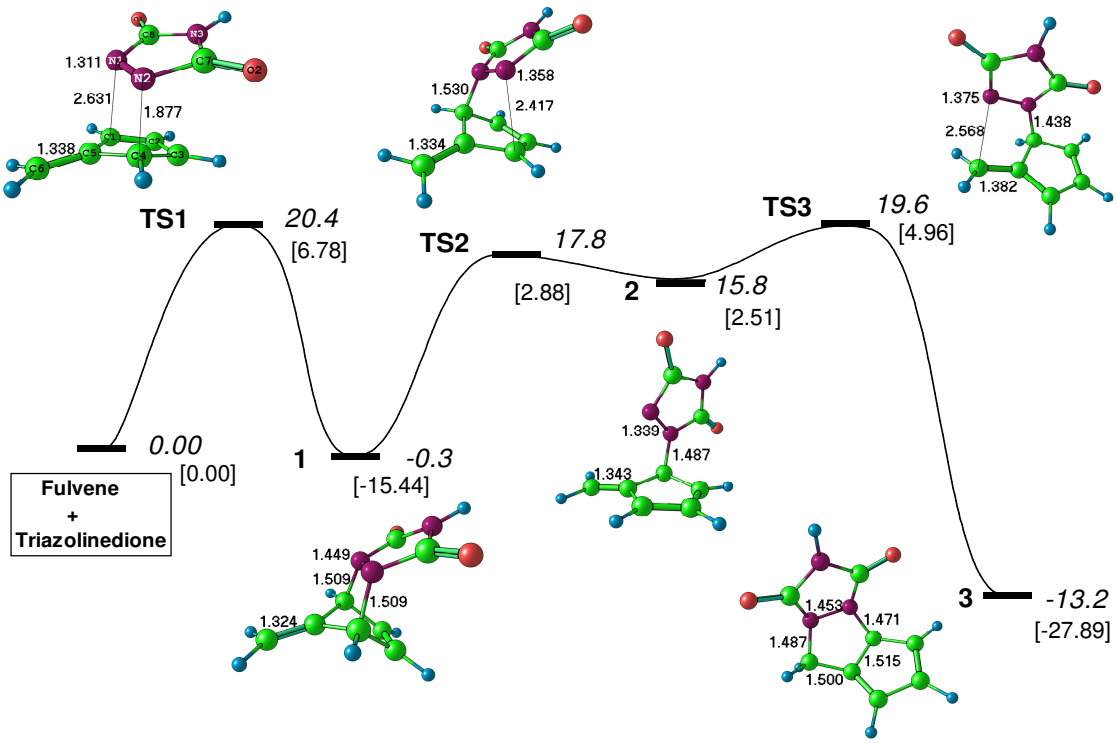


Figure 4.10 (a) Free energy profile for the cycloaddition reaction between pentafulvene and triazolinedione, and subsequent migratory insertion reaction. Values in square brackets are the corresponding enthalpy changes. Distances in Å and energies in kcal/mol.

However, entropy factor is important in intermolecular cycloaddition reactions and after including the entropy correction, the free energy of activation (G_{act}) is turned out to be 20.4 kcal/mol. The product **1** formed in this step of the reaction is nearly at the same free energy level as that of the reactant systems.

1 is not the most stable structure, and in the next step with G_{act} of 18.1 kcal/mol, the C4N2 bond breaks as it passes through **TS2** yielding the

intermediate zwitterion **2**. In the subsequent step, the N2 atom of the zwitterion migrates to the C6 atom of the exocyclic π-bond *via* **TS3** giving the most stable product **3** at the relative free energy of -13.2 kcal/mol (relative with respect to the sum of the free energies of pentafulvene and triazolinedione). Since during the conversion of **1** to **3**, the C4N2 bond and exocyclic C5C6 π-bond are broken and new C6N2 bond is formed, this part of the reaction can be considered as the migratory insertion of the CN bond to the exocyclic π-bond. It may be noted that when **TS1** is formed, the π-face of the triazolinedione is away from the exocyclic π-bond. Triazolinedione can also approach the fulvene so that the π-face of it can be at the same side of the exocyclic π-bond. For such an orientation, a TS located for the cycloaddition product similar to **1** was 6.5 kcal/mol higher in energy than **TS1**. So the reaction pathway depicted in Fig. 4.10 is the preferred one.

We have also probed for a nucleophilic reaction mechanism. According to the mechanism shown in figure. 4.11, at first the lone pair on the NN double bond interacts with the electron defficient exocyclic carbon. The G_{act} of 22.5 kcal/mol obtained from **TS4** is comparable to the rate determining step of the cycloaddition mechanism (20.4 kcal/mol). The zwitterionic intermediate **4** thus formed will be quickly converted to the product **3** *via* **TS5** because this second step required only a G_{act} of 8.8 kcal/mol.

When we compare the [4+2] cycloaddition and the nucleophilic reaction mechanism, we would like to choose the former mechanism as the dominant one because of its slightly lower G_{act} as compared to the later one. However, the two step process of the nucleophilic mechanism is also attractive. Moreover, the G_{act} of 22.5 kcal/mol obtained for the first step of nucleophilic mechanism and its overall G_{act} of 23.6 kcal/mol is within the achievable limit of a feasible reaction. Therefore, it is felt that both cycloaddition and nucleophilic reaction mechanisms are operative in the reaction.

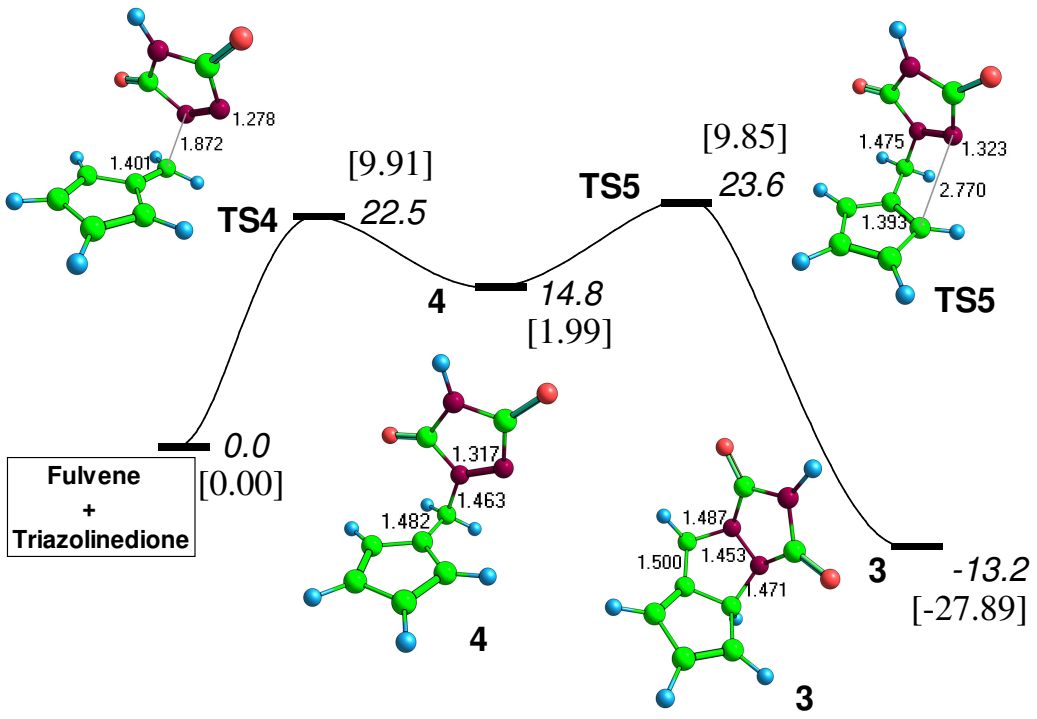


Figure 4.11 (a) Free energy profile for the nucleophilic reaction between pentafulvene and triazolinedione. Values in square brackets are the corresponding enthalpy change. Distances in Å and energies in kcal/mol.

Once, **3** is formed, the formation of products **54** and **55** given in scheme 4.19 is easy to explain. **55** is the result of the [4+2] cycloaddtion between the cyclopentadiene unit in **3** and the NN double bond of another triazolinedione molecule. Similarly, **54** is formed when C-C coupling *via* [4+2] cycloaddition occurs between two molecules of **3** at their cyclopentadiene unit.

To conclude, the observed reactivity is explained based on the electronic and frontier molecular orbital features of pentafulvene and triazolinedione, which suggested that the latter molecule can add to the former one *via* a [4+2] cycloaddition or it can undergo a nucleophilic reaction at the exo carbon atom of pentafulvene. These reactions would ultimately give the same product and the energetics of them suggested that both mechanisms are operative in the reaction conditions.

After these investigations, we focused our attention towards the interesting crystal structure of azapolycycle **54**, which forms an organic host-guest complex

with ethyl acetate.[46] The efforts to understand and explain various interactions in this host-guest complexation are discussed in the following section.

4.4.4. Molecular recognition in an organic host-guest complexation of azapolycycle 54 with ethyl acetate

Molecular recognition is considered to be one of the most challenging and fashionable area of contemporary research arising as an offshoot of the mainline synthetic organic chemistry. Several chemical and biochemical processes are initiated when a molecule is recognized by another molecule *via* specific intermolecular interactions.[47] Among these, hydrogen bonding is considered as one of the most important interaction types.[48] Several categories of hydrogen bonding are observed in nature which range from the very strong (168 kJ/mol) to very weak (1.05 kJ/mol).[49] Weak interactions, such as CH...O and CH…π, which are in the range from 21 to 4.2 kJ/mol are becoming increasingly important in crystal engineering, protein folding studies, enzyme action in biology and in host-guest chemistry.[50] The CH…O type interaction has been suggested to be a prototype of a X-H…A hydrogen bond, where X and A have moderate to low electronegativity. The attraction between the CH bond and a π system is generally termed as the CH…π interaction. Several recent findings on CH…π interactions show their importance in understanding a variety of molecular phenomena.

In this context, the azapolycycles synthesized are structurally and electronically very interesting because it consists of a network of seven connected five-membered rings containing six saturated nitrogen atoms with lone pair electrons, four C=O bonds, and six phenyl rings. Therefore, interesting intermolecular interactions are expected in this system. Moreover, a close look at the X-ray crystal structure of azapolycycle **54** revealed that a guest molecule ethyl acetate is trapped inside the crystal to form an interesting organic host-guest system. In an attempt to understand various interactions presented in this system, we analyzed the detailed packing mode and hydrogen bonding interactions of

compound **54**. The analysis showed the formation of a well-defined dimeric unit in the crystal of **54** (Figure 4.12).

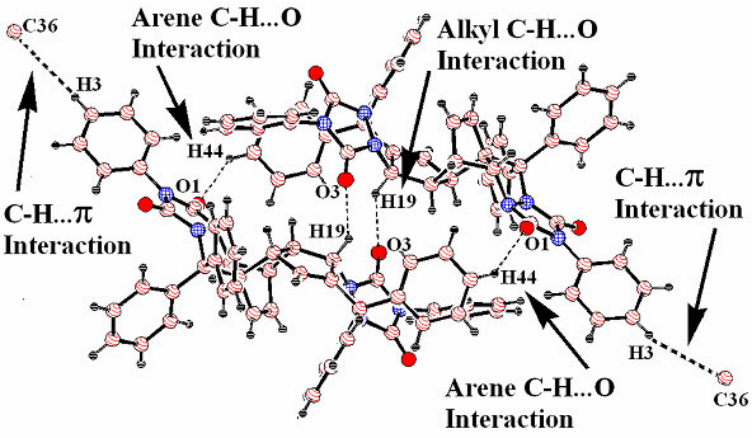


Figure 4.12 The dimeric molecular association between the azapolycyclic ligand **54** *via* CH…O interactions (Hydrogen bonding interactions are shown as dotted lines).

As we can see from figure 4.12, two azapolycyclic ligands aligned in such a way that hydrogen bonded dimers formed through CH…O interactions from one oxygen atom of each triazolinedione moiety present in the molecule. Hydrogen bonding in the dimer essentially involves the phenyl hydrogen atom with the dione oxygen, and alkyl hydrogen atom from the central five membered ring with the dione oxygens. These hydrogen bonded dimers were further arranged as bilayers *via* CH…π interactions with the neighboring dimeric units extending along c-axis.

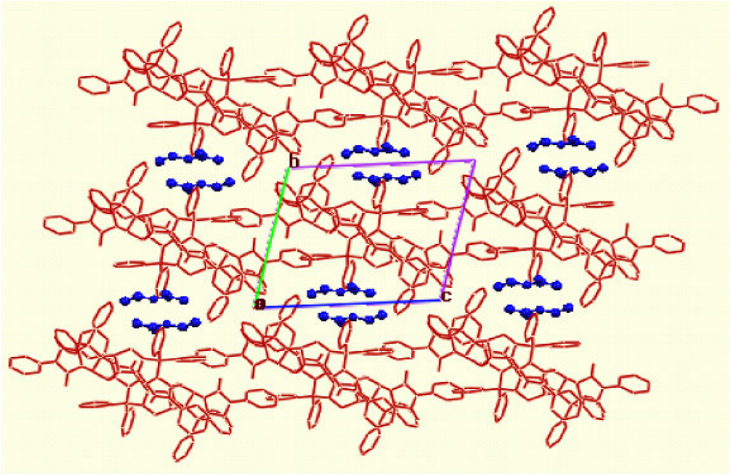


Figure 4.13 Packing diagram of the compound viewed down a-axis showing the arrangement of the organic moiety (red) with ethyl acetate molecule (blue, ball and stick model) in the crystal lattice. H-atoms are omitted for clarity.

Figure 4.13 depicts the packing diagram of the compound viewed down a-axis. Interestingly, the ethyl acetate molecules were occupied between the neighbouring bilayers of the azapolycyclic moieties creating alternate layers of the host-guest system along bc-plane. A close look at the region around ethyl acetate revealed the formation of an aromatic pocket containing four phenyl rings from four molecules of **54**. Ethyl acetate molecules are held in the aromatic pocket by three alkyl CH…π, one CH…O=C and another bifurcated CH…O interaction between the oxygen atoms from the ethyl acetate molecule with the phenyl hydrogen from the organic ligand. These interactions are depicted in Fig. 4.14 along with the corresponding interaction distances. The CH…π interaction (iv), depicted in Fig. 4.14, corresponds to the interaction between the CH bond of acetate moiety and the π-bond in the five-membered carbocycle. The other two CH…π interactions (ii and iii) correspond to arene CH…π interactions. Mainly the collective strength of the five interactions showed in Fig. 4.14 hold and stabilizes the guest molecule in the crystal lattice.

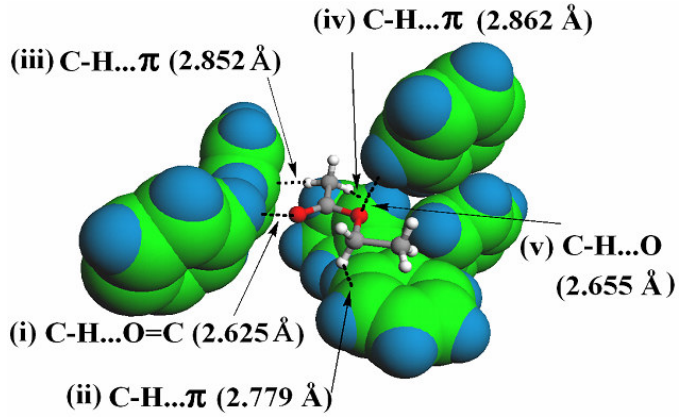


Figure 4.14 The ethyl acetate molecule and the surrounding phenyl groups. The phenyl groups in the interactions labeled as (i), (ii), (iii) and (v) belong to different molecules of **54**. Interaction (iv) corresponds to the π-bond of the five-membered carbon cycle and the alkyl CH bond.

The results presented in this study suggested that, though **54** contained six saturated nitrogen atoms capable of CH…N interactions, its crystal structure and the host-guest complexation were completely governed by CH…O and CH…π

interactions. Further, an aromatic pocket consisting of four phenyl rings from four molecules of **54** existed in the crystal structure. The guest molecule ethyl acetate trapped inside this aromatic pocket was found to interact with it *via* three CH…π and two CH…O interactions.

4.5. Conclusion

In conclusion, we have synthesized the seven and five membered novel azapolycyclic ligands by the reaction between pentafulvenes and triazolinediones. This constitutes a novel methodology for the easy synthesis of highly functionalized azapolycycles in excellent yield. The products, seven and five membered azapolycycles are versatile molecules having multiple points for functionalization and can be used as efficient scaffolds in the design of new macrocycles and can function as efficient receptors for various substrates.

In order to support the formation of intermediate zwitterion, we have effectively carried out the trapping of this intermediate using methanol under controlled conditions and synthesized the trisubstituted cyclopentenes in good yield. This method offers an alternate strategy for the synthesis of alkylidene cyclopentenes which are key intermediates in many natural product syntheses.

In addition to the trapping experiments, we have also rationalized the observed reactivity between pentafulvenes and triazolinediones using detailed theoretical calculations. These studies suggested that triazolinedione can add to the pentafulvene either *via* a [4 + 2] cycloaddition at the electron rich ring diene of the pentafulvene or by a nucleophilic reaction at the electron deficient exo carbon atom. These reactions would ultimately give the same product and the energetics of them suggests that both mechanisms are operative in the reaction conditions.

Moreover, the crystal structure analysis of the azapolycycle **54** revealed that the packing of this molecule and its host-guest complexation with ethyl acetate are completely controlled by CH…O and CH…π weak intermolecular interactions.

4.6. Experimental Details

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

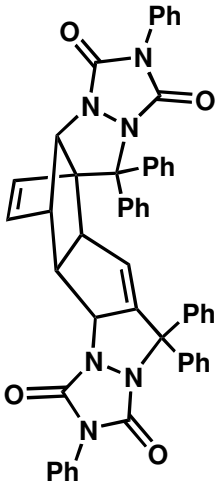
General experimental procedure: To a solution of 2,4,6-triazoline-3,5-dione (2 equiv.), in ethyl acetate (20 mL) at 0 °C, pentafulvene (1 equiv.) was added slowly under N_2 atmosphere. The reaction mixture was stirred for 2 hour at room temperature. After monitoring the reaction by TLC, the reaction mixture was diluted with water (50 mL) and extracted using ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated brine solution and dried over anhydrous sodium sulphate. The crude mixture obtained was purified by silica gel column chromatography to afford the mixture of azapolycles in good to excellent yields.

Azapolycycles 54 & 55

Following the general experimental procedure, 4-phenyl-2,4,6-triazoline-3,5-dione **6** (100 mg, 0.56 mmol) and 6,6'-diphenylfulvene **52** (65 mg, 0.28 mmol) in 20 mL of ethyl acetate for 2 h afforded the products **54** (84 mg) and **55** (72 mg) in 81% yield (1:1.2).

Azapolycycle 54

White solid, Mp 245-248 °C. R_f 0.58 (1:1 Hexane/ethyl acetate).



54

IR (KBr) ν_{max}: 3064, 2926, 2857, 1769, 1718, 1600, 1497, 1407, 1280, 1134, 913, 758, 700, 648, 505 cm^{-1}

^{1}H NMR: δ 7.53-7.14 (m, 30 H), 6.26 (dd, J_1 = 2.8 Hz, J_2 = 5.6 Hz, 1H), 5.87 (d, J = 5.8 Hz, 1H), 5.04 (d, J = 8.5 Hz, 1H), 4.36 (s, 1H), 4.13(s, 2H), 3.94 (s, 1H), 3.65 (m, 1H)

^{13}C NMR: δ 152.9, 150.7, 150.2, 149.0, 140.6, 140.4, 138.4, 138.0, 134.2, 133.6, 131.3, 130.7, 130.5, 129.8, 129.3, 129.1, 129.0, 128.9, 128.8, 128.5, 128.4, 128.0, 127.9, 127.8, 127.1, 126.8, 125.4, 75.2, 74.0, 67.8, 64.0,

63.9, 53.3, 46.3, 41.5, 31.8.

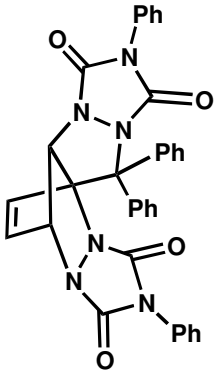
LRMS (FAB) for $C_{52}H_{38}N_6O_4$, calcd (M^+): 810.2876, found : 811.24.

Crystal data for 54

CCDC 275653; Chemical formula $C_{52}H_{38}N_6O_4$, $C_4H_8O_2$ Formula weight (Mr)-898.99; Crystal size (mm)- 0.20x0.16x0.08; Crystal system-tricilinic; Space group-P-1; a(Å)-12.2707(13); b(Å)-13.5989(15); c(Å)-15.4906(17); α(°)-71.100(2); β(°)-73.300(2); γ(°)-72.169(2); Z-2; V(Å^3)-2276.7(4); Radiation used λ(Å)-0.71073; $D_{calcd.}$(g cm^{-3})-1.311; Abs. coeff, μ(mm^{-1})- 0.087$\theta_{max.}$(deg)-28.26; No. of reflections Collected-13579; No. of Idependent reflections-9964; No. of parameters-612; R(int)=0.0285; F(000)-944; Temp(K)-100; GOF on F^2-1.025*; R1* /*w*R2([I>2σ(I)]-R1 = 0.0738/0.1924*; R1* /*w*R2(all data) 0.1444/ 0.2350.

Azapolycycle 55

Light yellow solid, Mp 149-151 °C. R_f 0.27 (1:1 Hexane/ethyl acetate).



55

IR (KBr) ν_{max}: 3065, 2957, 2855, 1768, 1734, 1597, 1498, 1396, 1283, 1142, 1014, 916, 749, 696, 642 cm^{-1}.

^{1}H NMR: δ 7.55-7.16 (m, 20H), 7.03 (d, J = 5.6 Hz, 1H), 6.46 (dd, J_1 = 2.3 Hz, J_2 = 5.7 Hz, 1H), 5.56 (s, 1H), 4.73 (d, J = 1.6 Hz, 1H)

^{13}C NMR: δ 157.4, 155.7, 150.2, 149.5, 138.6, 136.5, 130.9, 130.4, 129.5, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 127.8, 127.7, 125.3, 125.2, 125.1, 123.6, 92.3, 71.8, 62.1, 62.0.

LRMS (FAB) for $C_{34}H_{24}N_6O_4$, calcd (M^+): 580.1859, found: 581.38 (M+1).

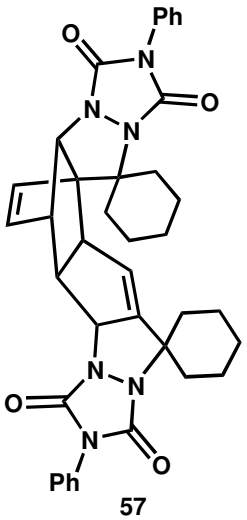
Azapolycycles 57 & 58

Following the general experimental procedure, 4-phenyl-2,4,6-triazoline-3,5-dione **6** (100 mg, 0.56 mmol) and 6,6'-pentamethylene fulvene **56** (41 mg, 0.28

mmol) in 20 mL of ethyl acetate for 2 h afforded the products **57** (43 mg) and **58** (85 mg) in 85% yield (1:2.5).

Azapolycycle 57

Yellow solid, Mp 157-159 °C. R_f 0.46 (1:1 Hexane/ethyl acetate).



57

IR (KBr) ν_{max}: 3065, 2933, 2857, 1767, 1729, 1605, 1551, 1450, 1397, 1264, 1108, 1020, 736, 711, cm^{-1}.

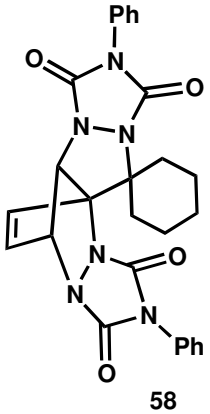
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56-7.25 (m, 10H), 6.08 (s, 1H), 5.95-5.90 (m, 1H), 5.06-4.94 (m, 2H), 4.58 (s, 1H), 3.65 (m, 2H), 3.40 (s, 1H), 1.25 (m, 9H), 2.16-2.03 (m, 11H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.8, 154.1, 153.8, 152.3, 136.5, 136.1, 135.8, 130.7, 128.8, 128.7, 128.6, 127.7, 127.1, 126.8, 125.6, 125.3, 75.6, 68.5, 65.4, 63.5, 60.1, 43.0, 42.3, 33.3, 32.2, 31.8, 30.1, 29.6, 25.3, 24.8, 23.3, 22.1.

HRMS (EI) for $C_{38}H_{38}N_6O_4$, calcd (M^+): 642.2955, found: 642.2975.

Azapolycycle 58

White solid, Mp 189-191 °C. R_f 0.21(1:1 Hexane/Ethyl Acetate).



58

IR (KBr) ν_{max}: 2930, 2860, 1779, 1725, 1499, 1411, 1364, 1233, 1141, 1016, 795, 741, 644, 515 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.35 (m, 10H), 6.77 (d, J = 5.5 Hz, 1H), 6.45 (dd, J_1 = 2.2 Hz, J_2 = 5.6 Hz, 1H), 5.52 (s, 1H), 4.21 (s, 1H), 2.17-1.50 (m, 10H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 158.4, 154.0, 153.7, 133.1, 130.8, 129.3, 129.1, 128.9, 128.3, 125.7, 125.6, 91.5, 72.6, 69.8, 61.8, 37.5, 33.7, 32.0, 29.7, 24.3.

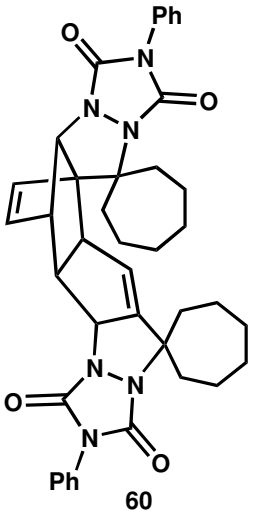
LRMS (FAB) for $C_{27}H_{24}N_6O_4$, calcd (M^+): 496.1859 found: 497.45 (M+1).

Azapolycycles 60 & 61

Following the general experimental procedure, 4-phenyl-2,4,6-triazoline-3,5-dione **6** (100 mg, 0.56 mmol) and 6,6'-hexamethylene fulvene **59** (45 mg, 0.28 mmol) in 20 mL of ethyl acetate for 2 h afforded the products **60** (39 mg) and **61** (59 mg) in 62% yield (1: 2).

Azapolycycle 60

Light yellow solid, Mp 197-199 °C. R_f 0.51 (1:1 Hexane/ethyl acetate).



60

IR (KBr) ν_{max}: 2935, 1769, 1718, 1648, 1503, 1450, 1363, 1225, 1116, 912, 770, 692, 505 cm^{-1}.

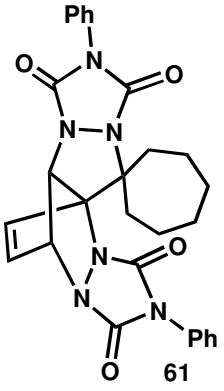
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53-7.30 (m, 10 H), 6.63 (d, *J* = 5.3 Hz, 1H), 6.47 (d, *J* = 4.2 Hz, 1H), 5.95-5.91 (m, 1H), 5.46 (s, 1H), 4.52 (s, 1H), 4.25-4.15 (m, 2H), 3.40 (s, 1H), 2.30-2.20 (m, 6H), 2.11-0.88 (m, 18H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.9, 154.3, 153.8, 151.9, 135.6, 134.7, 133.8, 132.9, 131.1, 128.6, 128.4, 128.3, 127.8, 126.5, 126.1, 125.3, 125.0, 77.5, 73.3, 72.4, 64.5, 61.1, 43.7, 43.1, 37.6, 36.5, 33.9, 33.1, 31.5, 30.4, 29.7, 24.4, 23.5.

HRMS (EI) for $C_{40}H_{42}N_6O_4$, calcd (M^+): 670.3268, found; 671.61.

Azapolycycle 61

White solid, Mp 173-175 °C. R_f 0.23 (1:1 Hexane/ethyl acetate).



61

IR (KBr) ν_{max}: 3051, 2924, 2857, 1784, 1721, 1595, 1498, 1406, 1279, 1235, 1142, 1017, 792, 739, 640, 513 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–7.35 (m, 10H), 6.72 (d, *J* = 5.6 Hz, 1H), 6.43 (dd, J_1 = 2.2 Hz, J_2 = 5.6 Hz, 1H), 5.51 (s, 1H), 4.13 (s, 1H), 3.04-2.81 (m, 2H), 2.22-0.88 (m, 10H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 156.1, 153.1, 151.5, 133.1, 130.7, 129.3, 129.1, 128.8, 128.2, 125.6, 125.5, 91.7, 73.03, 72.6, 61.9, 37.6, 34.4, 31.7, 30.5, 24.7, 23.6.

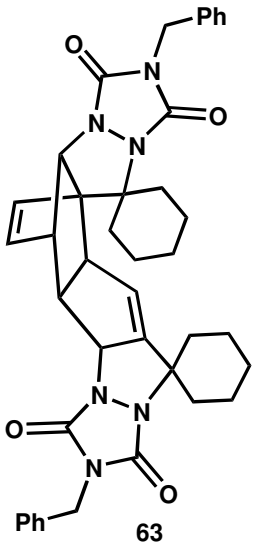
LRMS (FAB) for $C_{28}H_{26}N_6O_4$, calcd (M^+): 510.2016, found: 512.38.

Azapolycycles 63 & 64

Following the general experimental procedure, 4-benzyl-2,4,6-triazoline-3,5-dione **62** (114 mg, 0.60 mmol) and 6,6'-pentamethylene fulvene **56** (44 mg, 0.30 mmol) in 20 mL of ethyl acetate for 2 h afforded the products **63** (56 mg) and **64** (91 mg) in 86% yield (1: 2).

Azapolycycle 63

Brown viscous liquid. R_f 0.36 (1:1 Hexane/Ethyl Acetate).



63

IR (neat) ν_{max}: 3024, 2402, 1777, 1700, 1521, 1428, 1220, 1208, 1111, 929, 786, 729, 478 cm^{-1}.

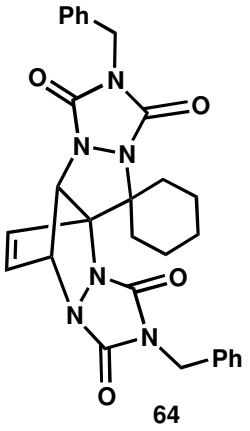
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.25 (m, 10H), 6.02-5.97 (m, 2H), 5.60 (s, 1H), 4.66 (d, *J* = 7.6 Hz, 1H), 4.60 (s, 2H), 4.57 (s, 2H), 4.17-4.07 (m, 1H), 3.59-3.55 (m, 2H), 3.47-3.41 (m, 1H), 2.27-1.93 (m, 4H), 1.78-1.23 (m, 16H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.2, 153.9, 153.0, 150.4, 136.5, 135.9, 135.8, 130.8, 128.7, 128.6, 128.5, 128.0, 127.8, 75.6, 73.8, 68.4, 65.5, 63.5, 60.5, 45.7, 43.4, 41.9, 34.8, 33.4, 31.7, 29.7, 29.3, 24.9, 24.8, 24.6, 24.1, 23.3.

LRMS (FAB) for $C_{40}H_{42}N_6O_4$, calcd (M^+): 670.3268, found: 671.83 (M+1).

Azapolycycle 64

Light brown viscous liquid. R_f 0.21 (1:1 Hexane/Ethyl Acetate).



64

IR (neat) ν_{max}: 3037, 2933, 2856, 1760, 1717, 1441, 1406, 1378, 1155, 1071, 944, 739, 697 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.16 (m, 10H), 6.44 (d, J = 5.6 Hz, 1H), 6.15 (dd, J_1 = 2.3 Hz, J_2 = 5.6 Hz, 1H), 5.30 (s, 1H), 4.58 (s, 2H), 4.47 (s, 2H), 3.97 (s, 1H), 2.57-2.53 (m, 2H), 1.76-1.24 (m, 8H).

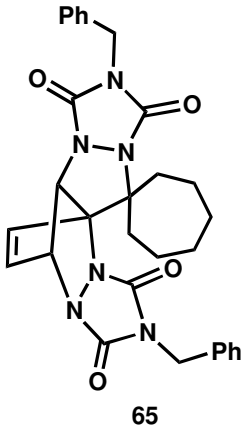
^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 158.4, 154.0, 153.7, 135.5, 134.8, 132.8, 130.0, 128.8, 128.7, 128.6, 128.5, 128.3, 127.9, 92.1, 72.5, 69.5, 61.1, 43.8, 43.1, 33.3, 32.3, 24.7, 23.2, 22.7.

LRMS (FAB) for $C_{29}H_{28}N_6O_4$, calcd (M^+): 524.2172, found: 525.55 (M+1).

Azapolycycle 65

Following the general experimental procedure, 4-benzyl-2,4,6-triazoline-3,5-dione **62** (100 mg, 0.52 mmol) and 6,6'-hexamethylene fulvene **59** (43 mg, 0.26 mmol) in 20 mL of ethyl acetate for 2 h afforded the product **65** (107 mg) in 77% yield.

White solid, Mp 141-143 °C. R_f 0.24 (1:1 Hexane/ethyl acetate).



65

IR (KBr) ν_{max}: 2928, 1763, 1719, 1442, 1411, 1353, 1163, 945, 782, 751, 703, 640 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.20 (m, 10H), 6.44 (d, J = 5.6 Hz, 1H), 6.16 (dd, J_1 = 2.1 Hz, J_2 = 5.6 Hz, 1H), 5.32 (s, 1H), 4.59 (s, 2H), 4.50 (s, 2H), 3.92 (s, 1H), 2.87-2.71 (m, 2H), 2.14-0.90 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 158.1, 153.7, 153.3, 135.4, 134.8, 132.0, 130.1, 128.9, 128.6, 128.3, 128.1, 128.0, 127.9, 127.6, 93.4, 72.7, 72.5, 62.3, 43.7, 43.1, 37.1, 33.6, 31.6, 29.1, 25.2, 23.3.

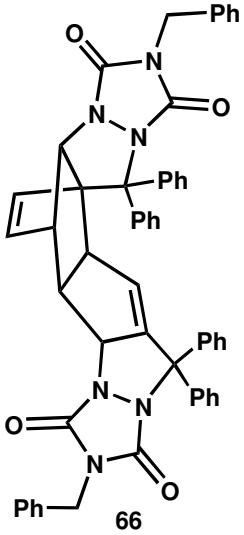
LRMS (FAB) for $C_{36}H_{30}N_6O_4$, cacld (M^+): 538.2329, found: 539.36 (M+1).

Azapolycycles 66 & 67

Following the general experimental procedure, 4-benzyl-2,4,6-triazoline-3,5-dione **62** (103 mg, 0.53 mmol) and 6,6'-diphenylfulvene **52** (60 mg, 0.26 mmol) in 20 mL of ethyl acetate for 2 h afforded the products **66** (66 mg) and **67** (95 mg) in 92% yield (1:2).

Azapolycycle 66

Light yellow viscous liquid. R_f 0.52 (1:1 Hexane/ethyl acetate).



66

IR (neat) ν_{max}: 3024, 2925, 2854, 1767, 1712, 1494, 1435, 1352, 1216, 1121, 1069, 939, 752, 698, 540 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.00 (m, 30 H), 6.00 (dd, J_1 = 3.0 Hz, J_2 = 5.7 Hz, 1H), 5.69 (d, J = 5.7 Hz, 1H), 4.82 (d, J = 8.7 Hz, 1H), 4.53 (s, 2H), 4.48 (s, 2H), 4.12 (s, 1H), 4.00 (s, 1H), 3.91 (d, J = 6.6 Hz, 1H), 3.70 (s, 1H), 3.44-3.42 (m, 1H).

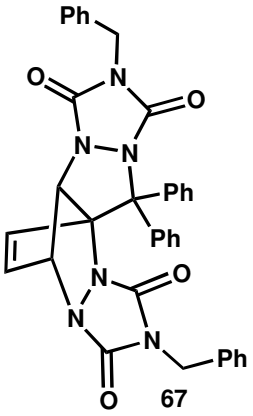
^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9, 152.9, 150.2, 149.9, 140.6, 138.4, 138.1, 134.3, 133.7, 131.4, 130.8, 130.6, 129.9, 129.7, 129.3, 129.2, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 126.0, 125.5, 93.1, 75.3, 64.0, 63.5, 53.4, 48.7, 44.4, 44.1, 38.7, 22.9.

LRMS (FAB) for $C_{54}H_{42}N_6O_4$, calcd (M^+): 838.32683, found: 839.28

Azapolycycle 67

Light brown viscous liquid. R_f 0.26 (1:1 Hexane/ethyl acetate).

IR (neat) ν_{max}: 3065, 2926, 2857, 1957, 1771, 1730, 1612, 1492, 1408, 1352, 1279, 1159, 1074, 947, 904, 753, 703, 648 cm^{-1}.



67

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.15 (m, 20H), 6.77 (d, J = 5.6.Hz, 1H), 6.11 (dd, J_1 = 2.3 Hz, J_2 = 5.6 Hz, 1H), 5.32 (s, 1H), 4.56 (s, 2H), 4.46 (s, 1H), 4.36 (s, 2H).

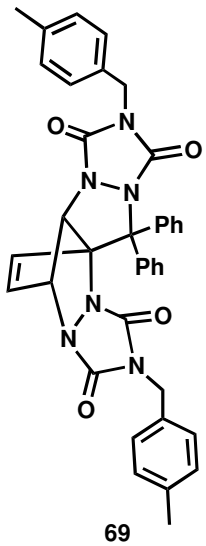
^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 157.4, 152.2, 151.6, 138.7, 136.9, 135.2, 134.9, 131.0, 130.8, 129.5, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.4, 127.3, 93.1, 72.4, 68.0, 62.0, 43.5, 43.1.

LRMS (FAB) for $C_{36}H_{28}N_6O_4$, calcd (M^+): 608.2172, found: 609.74 (M+1).

Azapolycycle 69

Following the general experimental procedure, Triazolinedione **68** (100 mg, 0.49 mmol) and 6,6'-diphenylfulvene **52** (56 mg, 0.24 mmol) in 20 mL of ethyl acetate for 2 h afforded the product **69** (119 mg) in 78% yield.

Light brown viscous liquid. R_f 0.38 (1:1 Hexane/Ethyl Acetate).



69

IR (neat) ν_{max}: 3057, 2938, 1770, 1729, 1618, 1516, 1441, 1407, 1352, 1157, 927, 796, 765, 701, 649 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.47 (m, 4H), 7.37-7.25 (m, 6H), 7.11-7.00 (m, 8H), 6.75 (d, J = 5.6 Hz, 1H), 6.10 (dd, J_1 = 2.3 Hz, J_2 = 5.7 Hz, 1H), 5.30 (s, 1H), 4.59-4.50 (m, 1H), 4.45 (s, 2H), 4.31 (s, 2H), 2.30 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 157.5, 152.2, 151.5, 138.8, 137.7, 137.5, 137.0, 132.3, 132.1, 131.0, 129.5, 129.3, 129.2, 129.1, 129.0, 128.8, 128.7, 128.5, 128.3, 128.2, 128.0, 92.4, 72.3, 62.2, 60.3, 43.3, 43.0, 21.2, 21.0.

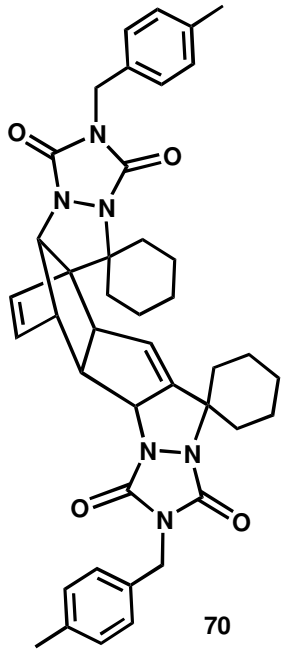
LRMS (FAB) for $C_{38}H_{32}N_6O_4$, cacld (M^+): 636.2566, found: 637.68 (M+1).

Azapolycycles 70 & 71

Following the general experimental procedure, triazolinedione **68** (100 mg, 0.49 mmol) and 6,6'-pentamethylene fulvene **56** (36mg, 0.24 mmol) in 20 mL of ethyl acetate for 2 h afforded the products **70** (97 mg) and **71** (35 mg) in 85% yield (2.1:1).

Azapolycycle 70

White solid. Mp 134-136 °C. R_f 0.53 (1:1 Hexane/ethyl acetate).



70

IR (KBr) ν_{max}: 2939, 2861, 1759, 1702, 1517, 1439, 1413, 1353, 1265, 1140, 1099, 927, 766, 737, 649, 472 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.4 Hz, 4H), 7.11 (d, *J* = 7.6 Hz, 4H), 6.03-5.96 (m, 2H), 5.60 (s, 1H), 4.66 (d, *J* = 8.4 Hz, 1H), 4.99-4.58 (m, 4H), 4.13 (d, *J* = 6.9 Hz, 1H), 3.57-3.54 (m, 2H), 3.46-3.39 (m, 1H), 2.26 (s, 6H), 2.22-1.25 (m, 20 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.2, 153.9, 153.0, 152.5, 150.2, 137.7, 137.6, 133.0, 132.9, 132.8, 130.8, 129.3, 128.7, 128.6, 127.8, 75.6, 73.7, 68.4, 65.5, 63.5, 60.4, 45.6, 42.8, 42.7, 41.8, 34.8, 33.3, 31.7, 29.9, 24.9, 24.6, 24.0, 23.4, 23.3, 21.1.

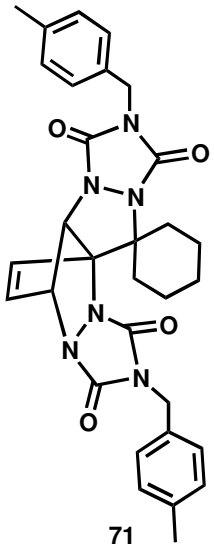
LRMS (FAB) for $C_{42}H_{46}N_6O_4$, calcd (M^+): 698.36, found, 721.26 $(M+Na)^+$.

Azapolycycle 71

Yellow solid. Mp 141-143 °C. R_f 0.38 (1:1 Hexane/ethyl acetate).

IR (KBr) ν_{max}: 2934, 2859, 1780, 1704, 1517, 1442, 1353, 1265, 1134, 928, 767, 736, 649, 472 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.5 Hz, 4H), 7.10 (d, *J* = 8.1 Hz, 4H), 6.48 (d, *J* = 5.6 Hz, 1H), 6.18 (dd, J_1 = 2.2 Hz, J_2 = 5.6 Hz, 1H), 5.31 (s, 1H),



71

4.67 (d, J = 8.5 Hz, 1H), 4.58-4.52 (m, 4H), 2.35 (s, 6H), 2.05-1.25 (m, 10H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 154.4, 153.2, 152.7, 137.9, 136.6, 133.1, 132.6, 131.0, 130.3, 129.5, 128.8, 128.7, 127.9, 92.3, 73.9, 68.6, 63.7, 43.0, 41.9, 35.0, 32.6, 30.2, 25.9, 24.8, 23.6, 23.5, 21.3.

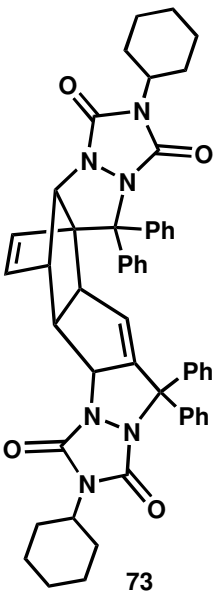
LRMS (FAB) for $C_{31}H_{32}N_6O_4$, cacld (M^+): 551.25, found, 574.72 $(M+Na)^+$.

Azapolycycles 73 & 74

Following the general experimental procedure, 4-cyclohexyl-2,4,6-triazoline-3,5-dione **72** (100 mg, 0.55 mmol) and 6,6'-diphenylfulvene **52** (64 mg, 0.28 mmol) in 20 mL of ethyl acetate for 2 h afforded the products **73** (75 mg) and **74** (45 mg) in 61% yield (1.2:1).

Azapolycycle 73

Light brown solid. Mp 235-237 °C. R_f 0.68 (1:1 Hexane/ethyl acetate).



73

IR (KBr) ν_{max}: 3060, 2933, 2856, 1760, 1705, 1494, 1448, 1416, 1381, 1220, 1164, 1002, 859, 757, 737, 699, 656, 574 cm^{-1}.

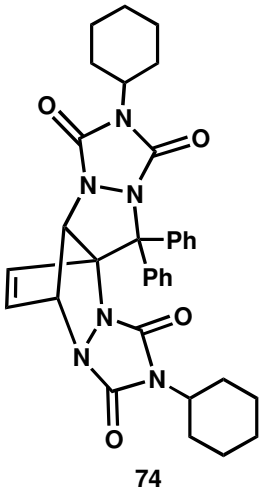
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.10 (m, 20H), 6.10 (dd, J_1 = 3.0 Hz, J_2 = 5.8Hz, 1H), 5.77 (d, J = 5.9 Hz, 1H), 4.88 (d, J = 8.4 Hz, 1H), 4.18 (s, 1H), 4.08 (s, 1H), 3.99 (d, J = 6.8 Hz, 1H), 3.77-3.67 (m, 3H), 3.54-3.48 (m, 1H), 2.03-2.00 (m, 4H), 1.79-1.58 (m, 8H), 1.28-1.20 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.8, 152.5, 151.22, 150.4, 140.8, 140.6, 138.4, 138.1, 134.4, 133.5, 131.3, 129.7, 129.1, 128.7, 128.2, 127.9, 127.8, 127.7, 127.4, 126.8, 77.2, 76.2, 75.3, 74.2, 63.8, 52.3, 52.2, 46.4, 41.8, 29.5, 29.2, 28.9, 26.9, 25.7, 25.3, 24.9.

LRMS (FAB) for $C_{52}H_{50}N_6O_4$, calcd (M^+): 822.3894, found, 823.57 (M+1).

Azapolycycle 74

Light brown viscous liquid, R_f 0.24 (1:1 Hexane/ethyl acetate).



74

IR (neat) ν_{max}: 2937, 2858, 1778, 1724, 1496, 1410, 1364, 1237, 1145, 1011, 798, 646 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.25 (m, 10H), 6.70 (d, *J* = 5.6 Hz, 1H), 6.42-6.39 (m, 1H), 5.50 (s, 1H), 4.21 (s, 1H), 3.71-3.63 (m, 1H), 3.51-3.47 (m, 1H), 2.09-2.01 (m, 4H), 1.83-1.57 (m, 8H), 1.38-1.19 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 158.1, 154.0, 153.7, 133.1, 130.8, 129.3, 129.1, 128.9, 128.3, 125.7, 125.6, 92.6, 72.6, 69.8, 61.8, 53.1, 52.4, 33.7, 32.0, 29.7, 29.1, 24.3.

LRMS (FAB) for $C_{34}H_{36}N_6O_4$, calcd (M^+): 592.2798, found, 615.26 $(M+Na)^+$.

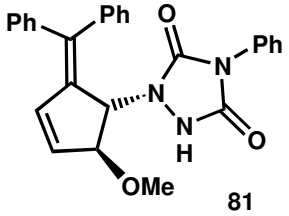
Experimental procedure for 81 & 82:

To a solution of 6,6'-diphenylfulvene **52** (65 mg, 0.28 mmol) in 20 mL methanol at -40 °C, 4-phenyl-2,4,6-triazoline-3,5-dione **6** (50 mg, 0.28 mmol) in dichloromethane (4 mL) was added slowly under N_2 atmosphere. The reaction mixture was stirred at this temperature for 1 h and then slowly brougt to RT and stirring continued for 1 more hour. After monitoring the reaction by TLC, the solvent was evaporated under reduced pressure. The crude product obtained was

purified by silica gel column chromatography to afford the products **81** (53 mg, 46%) and **82** (24 mg, 21%) in 67% yield.

Compound 81

Viscous liquid, R_f 0.35 (1:2 Hexane/ethyl acetate).



81

IR (neat) ν_{max}: 2930, 1772, 1697, 1502, 1423, 1280, 1226, 1069, 758 cm^{-1}.

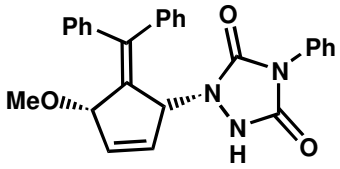
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.08 (m, 16H), 6.66 (d, J = 6.1 Hz, 1H), 6.29 (dd, J_1 = 2.4 Hz, J_2 = 6.3 Hz, 1H), 5.78 (d, J = 6.3 Hz, 1H), 4.50 (dd, J_1 = 2.4 Hz, J_2 = 6.3 Hz, 1H), 3.41 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 153.3, 150.4, 141.9, 140.3, 138.3, 135.6, 133.1, 131.6, 130.2, 129.3, 128.8, 128.4, 128.3, 127.9, 127.7, 125.4, 79.1, 57.8, 56.2.

LRMS (FAB) for $C_{27}H_{23}N_3O_3$, calcd (M^+): 436.1787, found, 460.23 $(M+Na)^+$.

Compound 82

White solid. Mp 147-149 °C, R_f 0.29 (1:2 Hexane/ethyl acetate).



82

IR (KBr) ν_{max}: 2929, 2854, 1770, 1695, 1500, 1428, 1277, 1222, 1121, 1069, 760, 645 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.08 (m, 16H), 6.50 (d, J = 6.0 Hz, 1H), 6.17 (dd, J_1 = 2.4 Hz, J_2 = 6.0 Hz, 1H), 5.71 (s, 1H), 4.55 (d, J = 2.4 Hz, 1H), 3.33 (s, 3H).

^{13}CNMR (75 MHz, $CDCl_3$): δ 153.4, 151.0, 145.3, 141.4, 140.7, 137.6, 135.8, 134.0, 131.9, 130.9, 129.2, 129.0, 128.6, 128.5, 128.1, 127.5, 127.1, 125.8, 78.3, 57.7, 56.2.

LRMS (FAB) for $C_{27}H_{23}N_3O_3$, calcd (M^+): 436.1787, found, 460.50 $(M+Na)^+$.

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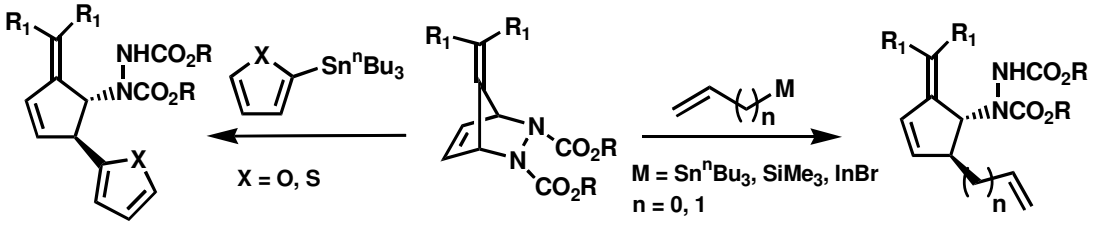
SUMMARY

The thesis entitled "**Novel Synthetic Transformations of Pentafulvenes Towards Alkylidene Cyclopentenes and Azapolycycles**" embodies the results of the investigations carried out in the area of palladium/Lewis acid mediated desymmetrization of pentafulvene derived bicyclic hydrazines.

The introductory chapter gives 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.

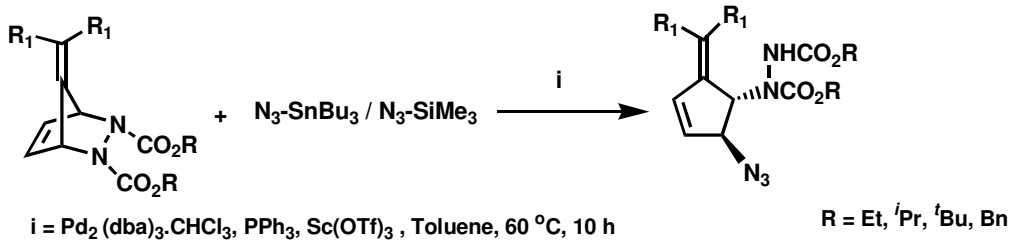
The second chapter describes a novel synthesis of *trans*-disubstituted alkylidene cyclopentenes *via* palladium catalyzed desymmetrization of pentafulvene derived azabicyclic hydrazines with various organometallic reagents. The methodology was found to be general and versatile with organostannanes, allylsilane and allylindium reagents. These reactions are presented in scheme 1.



Reaction condition: Pd catalyst , Ligand, Lewis acid, Toluene or THF, 60 ^{o}C, 10-24 h

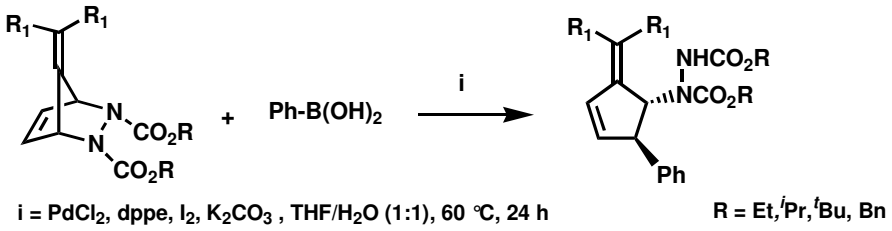
Scheme 1

Encouraged by these results, we have extended the scope of the reaction using azidostannane/silane and the corresponding *trans*-3-azido-4-hydrazino alkylidene cyclopentenes were obtained in excellent yields (Scheme 2). These products can be easily converted to synthetically and biologically important *trans*-cylopentane-1,2-diamine derivatives. The details of these investigations are also included in the second chapter.



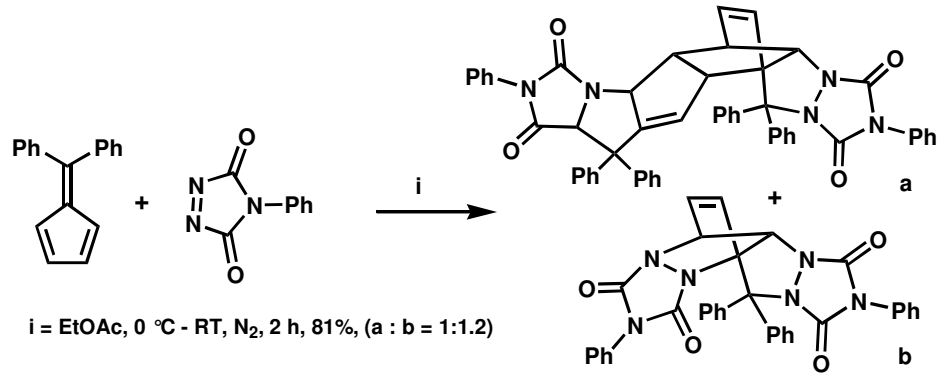
Scheme 2

We have also unraveled a novel reactivity of organoboronic acids with pentafulvene derived bicyclic hydrazines leading to the stereoselective synthesis of *trans*-vicinal disubstituted alkylidene cyclopentenes (Scheme 3). The generality of the methodology was established by the reactions of various fulvene derived bicyclic hydrazines with aryl, heteroaryl and alkenyl boronic acids and these investigations are discussed in the third chapter.



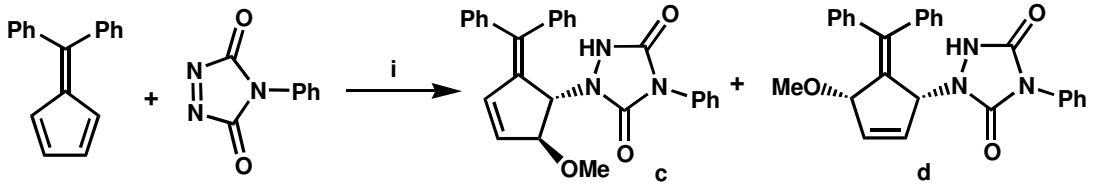
Scheme 3

The detailed investigation on the reaction between pentafulvenes and 1,2,4-triazolinediones constitutes the subject matter of the fourth chapter of the thesis. The reaction proceeded through the formation of an intermediate zwitterion and afforded a mixture of azapolycycles in good yield (Scheme 4).



Scheme 4

The formation of the intermediate zwitterion was confirmed by trapping the intermediate using methanol, under controlled reaction conditions. This method offers an alternate strategy for the synthesis of functionalized alkylidene cyclopentenes. The reaction is outlined in scheme 5.



i = MeOH/CH_2Cl_2 , -40 °C - RT, N_2, 2 hr, 67%, (c : d = 2.2:1)

Scheme 5

In addition to the trapping experiments, the observed reactivity between pentafulvene and 1,2,4-triazolinedione was rationalized using detailed theoretical investigations, which revealed that both cycloaddition and nucleophilic mechanisms are operative in the reaction conditions. The details of these investigations are embodied in the fourth chapter of the thesis.

In conclusion, we have unraveled an efficient methodology for the novel synthesis of alkylidene cyclopentenes and azapolycycles *via* synthetic modifications of pentafulvenes. It is noteworthy that alkylidene cyclopentenes are key intermediates in the synthesis of a number of biologically active molecules. The products, seven and five membered azapolycycles are versatile molecules having multiple points for functionalization and can be used as efficient scaffolds in the design of new macrocycles and can function as efficient receptors for various substrates.

List of Publications

1. Palladium-catalyzed reaction of bicyclic hydrazines with allyl- and aryl-stannanes in ionic liquid [bmim]PF_6: A facile method for the synthesis of substituted hydrazinocyclopentene derivatives. Radhakrishnan, K. V.; Sajisha, V. S.; **Anas, S.**; Krishnan, K. S. *Synlett* **2005**, 2273.

2. A facile synthesis of 3-allyl-4-hydrazinocyclopentenes by the palladium/ Lewis acid mediated ring opening of bicyclic hydrazines with allyltributyltin and allyltrimethylsilane. Sajisha, V. S.; Smitha, M.; **Anas, S.**; Radhakrishnan, K. V. *Tetrahedron* **2006**, *62*, 3997.

3. [6+3] Cycloaddition of pentafulvenes with 3-oxidopyrylium betaines: A novel methodology towards the synthesis of 5-8 fused oxabridged cyclooctanoids. Krishnan, K. S.; Sajisha, V. S.; **Anas, S.**; Suresh, C. H.; Radhakrishnan, K. V. *Tetrahedron* **2006**, *62*, 5952.

4. Palladium/Lewis acid catalyzed desymmetrization of fulvene derived bicyclic hydrazines: A facile synthesis of substituted alkylidene cyclopentenes. **Anas, S.**; Sajisha, V. S.; Smitha, M.; Radhakrishnan, K. V. *Synlett* **2006**, 2399.

5. Molecular recognition in an organic host-guest complex: C-H…O and C-H…π interactions completely control the crystal packing and the host-guest complexation. Radhakrishnan, K. V.; **Anas, S**.; Suresh, E.; Koga, N.; Suresh, C. H. *Bull. Chem. Soc. Jap.* **2007**, *80*, 484.

6. Ionic liquid [bmim]PF_6 mediated synthesis of 1,2-orthoesters of carbohydrates and the glycosidation reactions of 4-pentenyl orthoesters. **Anas, S.**; Sajisha, V. S.; Rajan, R.; Kumaran, T.; Radhakrishnan, K. V. *Bull. Chem. Soc. Jap.* **2007**, *80*, 553.

7. Interplay of dual reactivity in the reaction of pentafulvenes with 1,2,4-triazoline-3,5-diones: Experimental and theoretical investigations. **Anas, S.**; Krishnan, K. S.; Sajisha, V. S.; Anju, K. S.; Suresh, E.; Suresh, C. H. *New J. Chem.* **2007**, *31*, 237.

8. Palladium catalyzed ring opening of azabicyclic olefins with organoindium reagents: A simple, clean and efficient synthesis of functionalized cyclopentenes. John, J.; **Anas, S.**; Sajisha, V. S.; Viji, S.; Radhakrishnan, K. V. *Tetrahedron Lett.* **2007**, *48*, 7225.

9. Iodine assisted palladium catalyzed ring opening of bicyclic hydrazines with organoboronic acids: Stereoselective synthesis of functionalized cyclopentenes and alkylidene cyclopentenes. **Anas, S.**; John, J.; Sajisha, V. S.; Rajan, R.; Joshni, J.; Suresh, E.; Radhakrishnan, K. V. *Org. Biomol. Chem.* **2007**, *5,* 4010.

10. A facile synthesis of novel triazabicyclic molecules as potential bicyclic templates for pharmaceutical ligands by the ring opening metathesis-cross metathesis of triazatricyclo[3.2.1.$0^{2,6}$]dec-8-ene-3,5-diones. **Anas, S.**; Sarika, C.; Rajan, R.; Radhakrishnan, K. V. *Ind. J. Chem. B* **2008** *(*accepted).

11. Facile synthesis of substituted alkylidene cyclopentenes *via* palladium catalyzed ring opening of fulvene derived bicyclic hydrazines. **Anas, S.**; Sajisha, V. S.; John, J.; Joseph, N.; George, S. C.; Radhakrishnan, K. V. *Tetrahedron* **2008** (accepted, subject to revision).

Papers Presented at Conferences

12. Palladium catalyzed desymmetrization of fulvene derived azabicyclic olefins: Stereoselective synthesis of alkylidene cyclopentenes. **Anas, S.**; Radhakrishnan, K. V., a paper presented at 3rd J-NOST conference, Guru Nanak Dev University, Amritsar, November, **2007**, Abs-4.

13. Synthesis of novel multifunctional triazabicyclic molecules as potential bicyclic templates for pharmaceutical ligands. **Anas, S.**; Rajan, R.; Radhakrishnan, K. V., a poster presented at 3rd International Conference on Current Trends in Drug Discovery Research (CTDDR 2007), Lucknow, February, **2007**, P 171.

14. Stereoselective synthesis of functionalized cyclopentenes through palladium/iodine catalyzed ring opening of bicyclic hydrazines with boronic acids. John, J.; Sajisha, V. S.; **Anas, S.**; Radhakrishnan, K. V., a poster presented at 3rd International conference on Current Trends in Drug Discovery Research (CTDDR 2007), Lucknow, February, **2007**, P 172.

15. Facile and environmentally benign synthesis of 1,2-orthoesters of carbohydrates in ionic liquid [bmim]PF_6. **Anas**, **S.**; Sajisha, V. S.; Rajan, R.; Chacko, J. M.; Radhakrishnan, K. V., a poster presented at Joint International Conference on Building Bridges, Forging Bonds for 21st Century Organic Chemistry and Chemical Biology (ACS-CSIR OCCB 2006) , Pune, January, **2006**, P 005.

16. Palladium catalyzed reaction of bicyclic hydrazines with allyltributyltin in Ionic Liquid [bmim]PF_6: A facile method for the stereoselective synthesis of substituted hydrazinocyclopentene derivatives. Sajisha, V. S.; **Anas**, **S.**; Smitha, M.; Radhakrishnan, K. V., a poster presented at Joint International Conference on Building Bridges, Forging Bonds for 21st Century Organic Chemistry and Chemical Biology (ACS-CSIR OCCB 2006), Pune, January, **2006**, P 126.