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Preparation and utilization of organopalladium intermediates

Hanchul Song
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Iowa State University, 1988

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Preparation and utilization of organopalladium intermediates

by

Hanchul Song

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of the
Requirements for the Degree of
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Department: Chemistry
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For the Major Department

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For the Graduate College

Iowa State University
Ames, Iowa
1988

TABLE OF CONTENTS

Preparation and utilization of organopalladium intermediates

Hanchul Song

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From the Department of Chemistry
Iowa State University

π-Allylpalladium compounds have been prepared from alkenylcycloalkanes bearing 3- and 4-membered rings by reaction with organomercurials and dilithium tetrachloropalladate through a novel palladium-promoted ring-opening process. In the second part of the thesis, π-allylpalladium compounds prepared in situ from various acetoxy-substituted dienes and functionally substituted organomercurials react with base to provide a new route to dihydrobenzofurans and lactones. In the part three of the thesis, cyclic alkenes bearing vinylic halides have been shown to undergo facile, palladium catalyzed cyclization to afford a wide variety of bicyclic cycloalkenes. This methodology allows one to close a 5- or 6-membered ring onto 5-, 6-, and 7-membered ring cyclic alkenes.

GENERAL INTRODUCTION

Organopalladium compounds have been known for many years and there exist a large number of procedures available for their preparation. They possess a wide variety of characteristic features which make them suitable intermediates for many synthetic transformations.

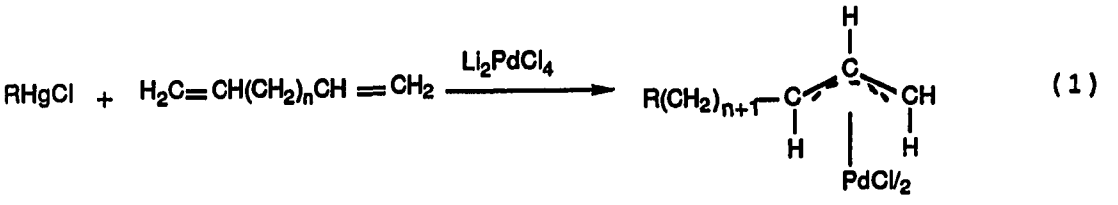
Aryl- or alkenyl-palladium intermediates usually add across a carbon-carbon double bond. The σ-bonded organopalladium intermediate generated in this manner undergoes syn-β-elimination of Pd-H, Pd-O, or Pd-C (strained C-O or C-C bond cleavage). The work that is described in this thesis involves this key reaction and is divided into three parts. The first part deals with the preparation of π-allylpalladium compounds via palladium-promoted ring-opening of alkenylcycloalkanes. The second part involves the synthesis of heterocycles via π-allylpalladium formation and subsequent intramolecular nucleophilic attack on the resulting π-allylpalladium compounds. The third part deals with the synthesis of carbocycles via palladium-catalyzed intramolecular cyclization.

PART I. π-ALLYLPALLADIUM FORMATION VIA PALLADIUM-PROMOTED RING-OPENING OF ALKENYLCYCLOALKANES

INTRODUCTION

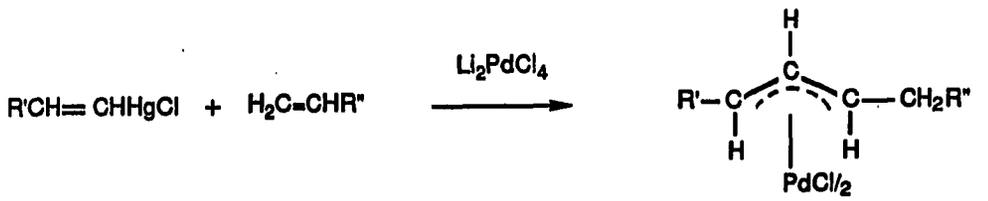
π-Allylpalladium compounds were first reported in 1957[1]. Since that time, a number of procedures have been reported for the synthesis of these compounds[2-5]. π-Allylpalladium compounds have recently become valuable intermediates in organic synthesis[6,7], particularly for the synthesis of naturally occurring organic compounds such as terpenes[8], pheromones[9], macrolide antibiotics[10], and alkaloids[11]. Two of the more useful methods of preparing these compounds involve the direct allylic hydrogen substitution of alkenes by palladium salts[12-14] and the insertion of palladium(0) reagents into the carbon-halogen or carbon-oxygen bond of allylic halides or acetates[15-18].

Besides the methods of synthesis of π-allylpalladium compounds discussed above, there are several important organomercurial routes to these compounds. Heck[19], and Stakem and Heck[20], and Larock and Mitchell[21] observed that organopalladium compounds prepared by the transmetallation of organomercurials react with conjugated or non-conjugated dienes to afford π-allylpalladium compounds (eq. 1).



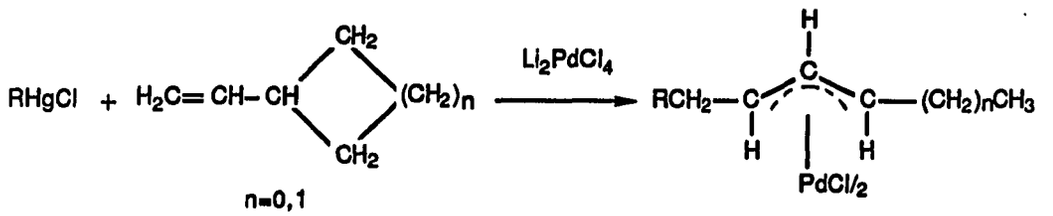
(1)

Similarly, vinylmercurials readily react with dilithium tetrachloropalladate (Li_2PdCl_4) and simple acyclic[21,22] or cyclic alkenes[23] to afford good to excellent yields of π-allylpalladium compounds via palladium hydride rearrangement (eq. 2).



(2)

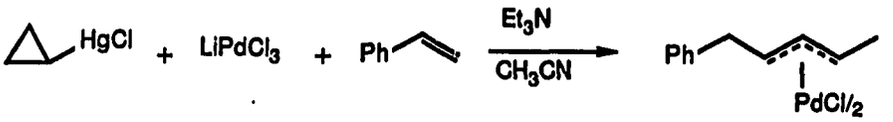
Recently, Larock and Varaprath[24] observed that π-allylpalladium compounds can also be prepared by addition of organopalladium compounds to vinylcyclopropanes and vinylcyclobutanes (eq. 3). This reaction apparently involves



(3)

a cyclopropylcarbinyl to homoallyl ring-opening and subsequent palladium hydride rearrangement. While the palladium chloride ring-opening[25-30] of methylene cyclopropanes[31-35] has been studied by several groups, those

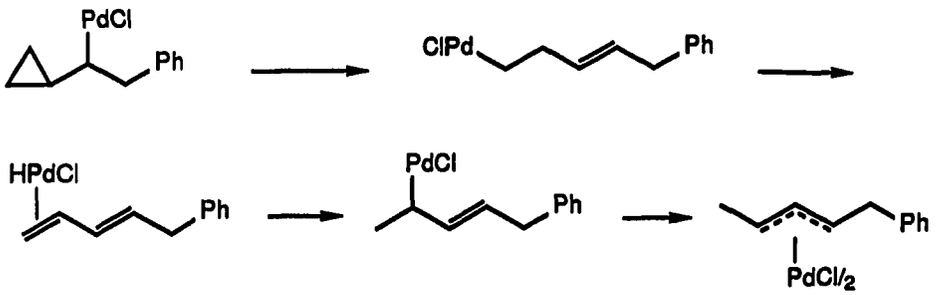
reactions apparently proceed by entirely different mechanisms from the reaction of Larock and Varaprath. More recently, Fischetti and Heck has studied extensively the mechanism of the ring opening of cyclopropylcarbinyl palladium compounds generated either by adding cyclopropylpalladium compounds to alkenes (eq. 4) or adding "phenylpalladium" to vinylcyclopropanes[36].



(4)

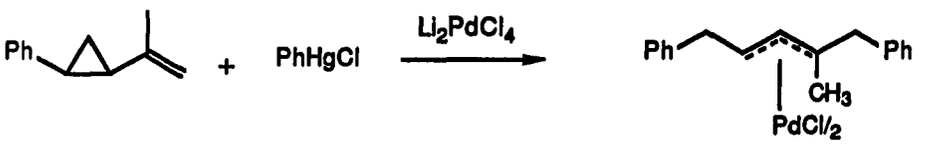
The reaction of "cyclopropylpalladium chloride" with styrene gave a π-allylpalladium compound (eq. 4). The reaction of "phenylpalladium chloride" with vinylcyclopropane gave the same π-allylpalladium compound (eq. 5). These results and the mechanism suggested (eq. 6) are consistent with those of Larock and Varaprath[24].

(5)



(6)

Prior to the initiation of our work on this reaction, little information was available on the generality of this approach to π-allylpalladium compounds and the direction of ring-opening of unsymmetrically substituted cyclopropanes and cyclobutanes. Larock and Varaprath[24] had shown that ring-opening in the reaction of 2-phenyl-1-vinylcyclopropane with Li_2PdCl_4 and phenylmercuric chloride occurs towards the phenyl substituent (eq. 7).



(7)

The work described in this chapter involves a novel synthesis of π-allylpalladium compounds using a variety of substituted vinylcyclopropanes and vinylcyclobutanes.

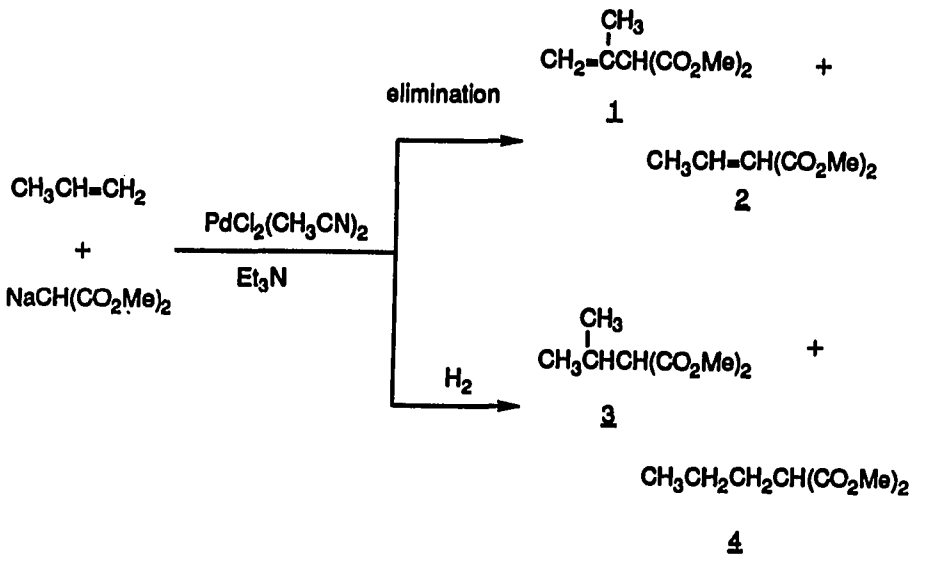
RESULTS AND DISCUSSION

Vinylcyclopropanes Chelated olefin complexes of palladium(II) salts, such as those of dicyclopentadienes[37] and other diolefins, and of allylic and homoallylic amines[38] and sulfides[38,39] readily undergo reaction with stabilized carbanions of acetylacetone, ethyl acetoacetate, and diethyl malonate to form isolable σ-alkylpalladium complexes stabilized by chelation (eq. 8).

(8)

The carbopalladation of an N,N-dimethylallylic amine was the key step in the synthesis of the prostaglandin $PGF_{2\alpha}$[40]. The alkylation of simple olefins not coordinated with a metal by chelation is a much less general process.

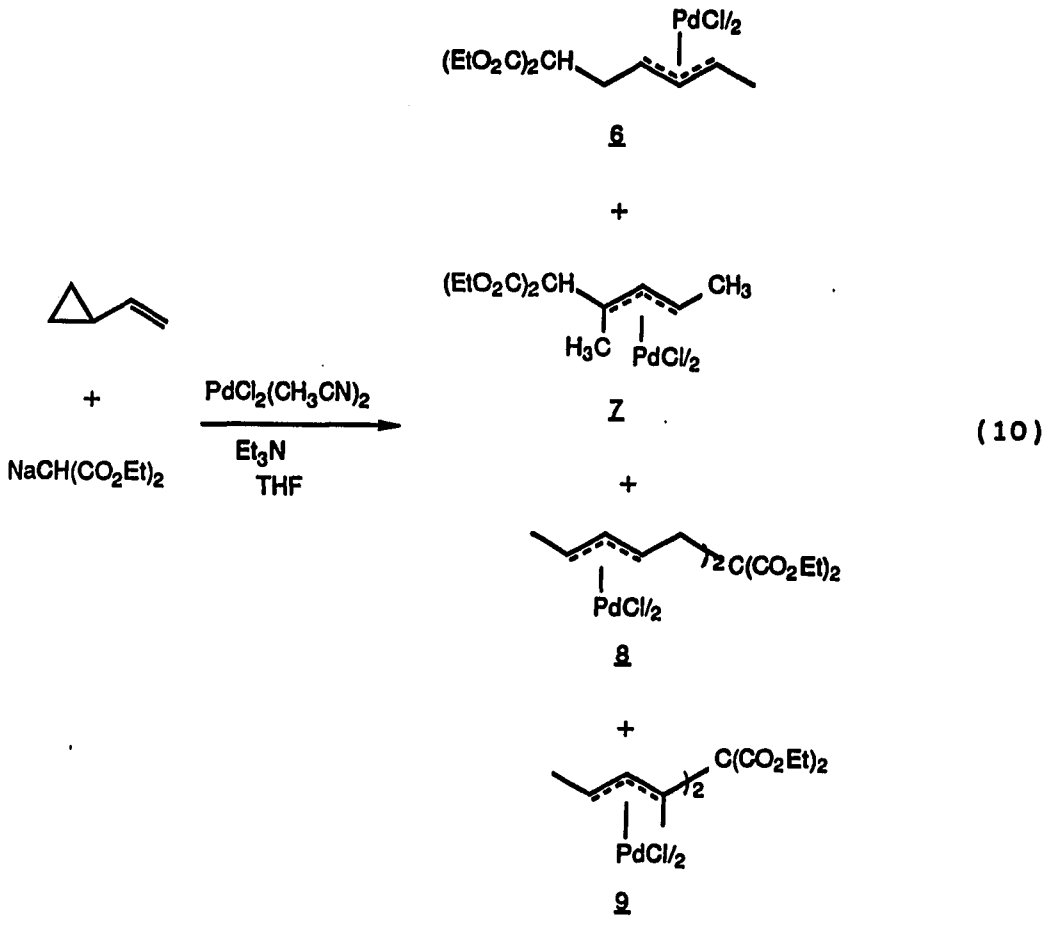
Recently, Hegedus and co-workers[41] have observed that nucleophilic attack on palladium coordinated olefins by stabilized anions such as dimethyl sodium malonate gives products rising from attack on both terminal and internal carbon atoms (eq. 9). The intermediate alkylpalladium species can decompose by β-hydride elimination to give olefins 1 and 2, or can be hydrogenated to give saturated products 3 and 4 (63 : 3 ratio).



(9)

Since it is known that stabilized nucleophiles will react with olefins in the presence of a palladium salt to produce σ-alkylpalladium complexes and that cyclopropylcarbinyl palladium complexes will ring-open, it was believed that the reaction of vinylcyclopropane with a stabilized nucleophile might be used to prepare π-allylpalladium compounds.

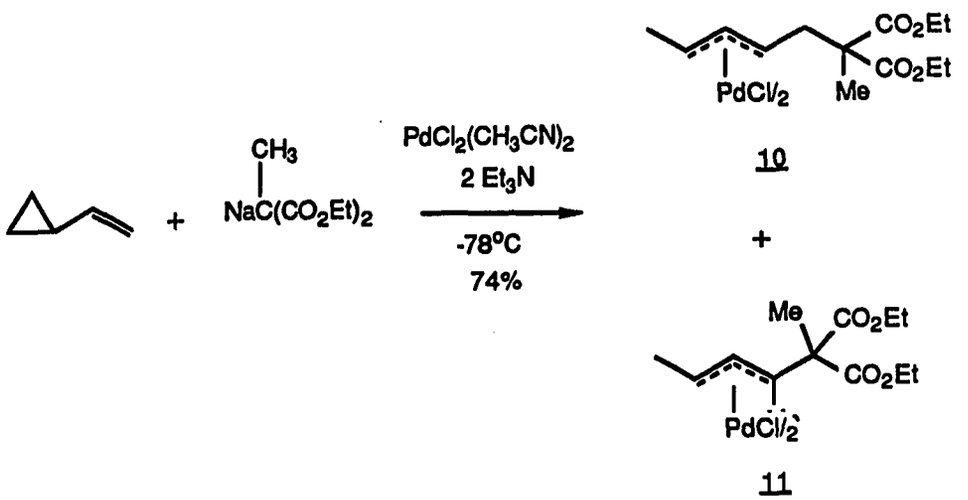
The first nucleophile examined was diethyl sodium malonate. The reaction of diethyl sodium malonate with vinylcyclopropane (5) in the presence of bis(acetonitrile)-palladium chloride and 2 equivalent of triethylamine in tetrahydrofuran produced an inseparable mixture of, possibly consisting the products 6 - 9 (eq. 10), although this mixture was not characterized further.



(10)

Compounds 8 and 9 might be formed from nucleophilic attack on the olefin by an anion formed from compounds 6 and 7, because the α-hydrogen to the carbonyl group of 6 or 7 seems to be more acidic than that of diethyl malonate. To avoid the formation of a second nucleophile, diethyl sodium methylmalonate was used as the nucleophile (eq. 11).

The reaction of this nucleophile with vinylcyclopropane in the presence of bis(acetonitrile)palladium chloride and triethylamine did produce π-allylpalladium compounds 10 and 11 in a ratio of 65 : 35 in a combined yield of 74%.



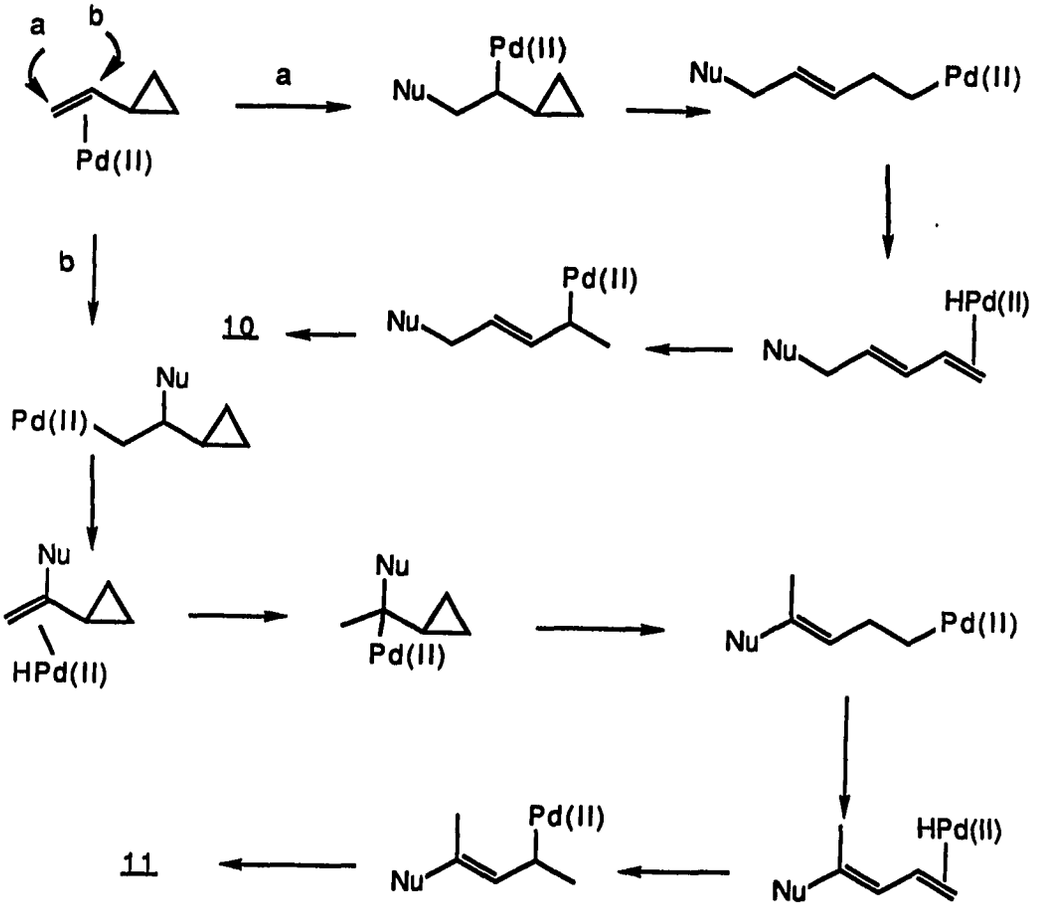
(11)

Interestingly, the isomer ratio of the products from terminal attack and internal attack was not consistent with that of Hegedus' (eq. 9). The reason for this different isomer ratio is not clear.

A likely mechanism for the formation of compound 10 involves terminal addition of the nucleophile to the palladium coordinated olefin of vinylcyclopropane to generate a cyclopropylcarbinyl palladium complex, followed by ring-opening to form a terminal alkyl palladium species from which palladium hydride elimination would occur to form the

hydridopalladium-olefin π-complex. Re-addition of the metal hydride in the reverse direction would produce π-allylpalladium compound 10 (Scheme I). A similar reaction pathway would account for the formation of compound 11. This involves initial addition of the nucleophile to the internal

Scheme I



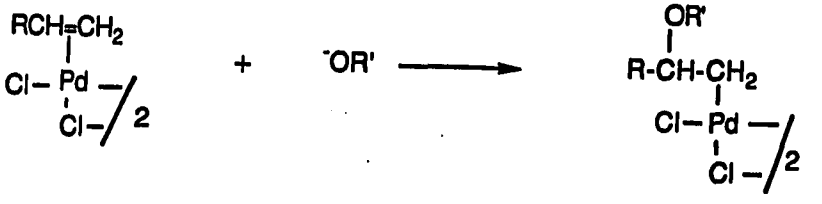
carbon of the olefin, followed by elimination of palladium hydride to form a hydridopalladium-vinylcyclopropane π-complex. Re-addition of the metal hydride in the reverse direction to produce a cyclopropylcarbinyl palladium species, followed by ring-opening, would form a terminal alkylpalladium species. A final palladium hydride elimination-readdition would produce compound 11 (Scheme I).

The use of a non-stabilized anion such as the lithium enolate of cyclopentanone was observed not to give an analogous π-allylpalladium compound under the reaction conditions used by Hegedus and co-workers[41].

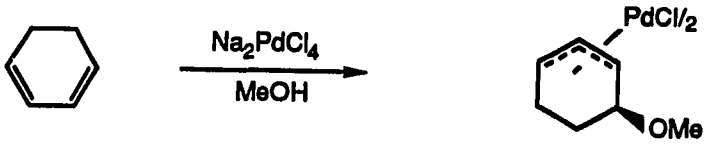
Alkoxypalladation of olefins was first discovered by Moiseev et al.[42] and Stern and Spector[43] in the reaction of ethylene with palladium chloride in alcohols in the presence of base to produce vinyl ethers and acetals (eq. 12).

$$RCH{=}CH_2 + R'OH + PdCl_2 \longrightarrow \underset{\displaystyle OR'}{\overset{\displaystyle |}{RC{=}CH_2}} + \underset{\displaystyle OR'}{\overset{\displaystyle OR'}{\overset{\displaystyle |}{R\text{-}\overset{\displaystyle |}{C}\text{-}CH_3}}} \qquad (12)$$

The first step of the reaction was oxypalladation (eq. 13). This chemistry has been extended to form π-allylpalladium compounds via alkoxypalladation of conjugated dienes[44-47] (eq. 14).



(13)



(14)

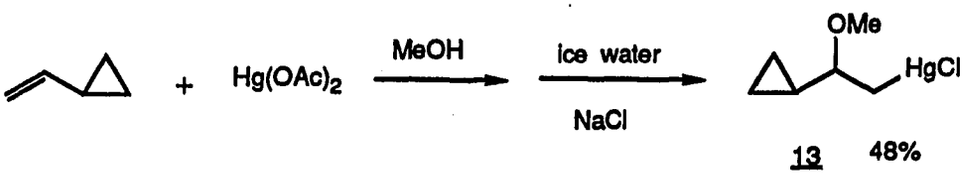
It was believed that the analogous reaction of vinylcyclopropane might produce π-allylpalladium compound 12 after methoxypalladation of the olefin, followed by palladium hydride rearrangement, ring-opening of the cyclopropane and then palladium hydride rearrangement. The methoxypalladation reaction was not successful using either palladium acetate or dilithium tetrachloropalladate (eq. 15).

(15)

12

An alternative approach to the preparation of the π-allylpalladium compound 12 would be to transmetallate 2-cyclopropyl-2-methoxyethylmercuric chloride 13, which would

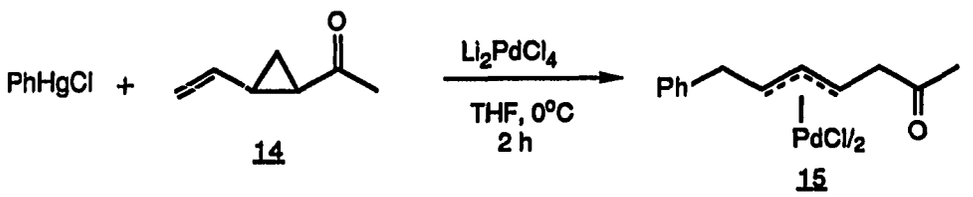
lead to the same intermediate. Compound 13 was easily prepared from the reaction of vinylcyclopropane and mercuric acetate in methanol followed by treatment with sodium chloride at 0°C (eq. 16).



13 48% (16)

Compound 13 was purified by crystallization from methanol at -78°C. The reaction of compound 13 with either dilithium tetrachloropalladate or palladium chloride in tetrahydrofuran was not successful in producing π-allylpalladium compound 12.

The palladium-promoted ring-opening of functionally substituted vinylcylopropanes and vinylcyclobutanes would be expected to provide a useful approach for the functional homologation of organopalladium compounds. The first substrate that was examined was 1-acetyl-2-vinylcyclopropane 14. Compound 14 was prepared from 1,4-dibromo-2-butene and sodium hydroxide in dry acetone in 35% yield[48]. The reaction of compound 14 with phenylmercuric chloride in the presence of dilithium tetrachloropalladate was observed to afford compound 15 (eq. 17). π-Allylpalladium compound 15 was isolated after direct crystallization of the crude



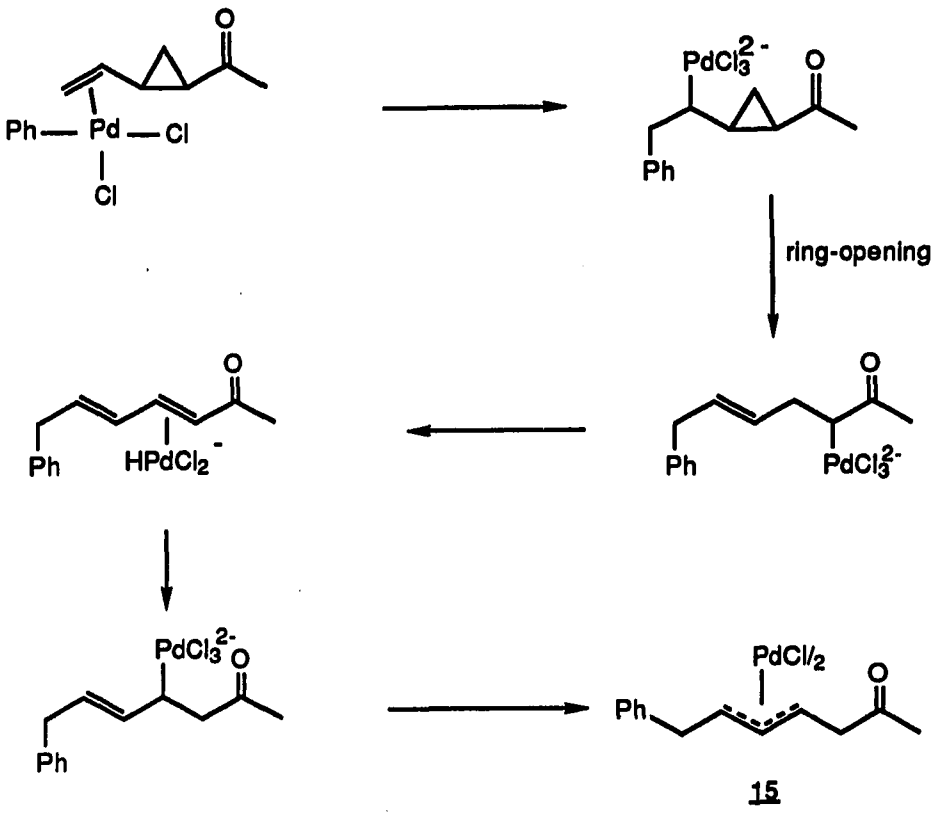
(17)

material and recrystallization using a mixed solvent system (5 : 1 hexanes/ethyl acetate). Compound 15 was found to be so unstable that it was decomposed easily by any column packing material, such as silica gel or neutral alumina, to generate diene 16 (eq. 18). An attempt to obtain an elemental analysis for compound 15 was not successful.

(18)

A likely mechanism for the formation of π-allylpalladium compound 15 involves the addition of "phenylpalladium chloride" to the olefin to generate a cyclopropylcarbinyl palladium intermediate followed by ring-opening towards the substituent. Palladium-hydride elimination-readdition would lead to formation of compound 15 (Scheme II). This mechanism is consistent with that proposed by Larock and Varaprath[24]

Scheme II

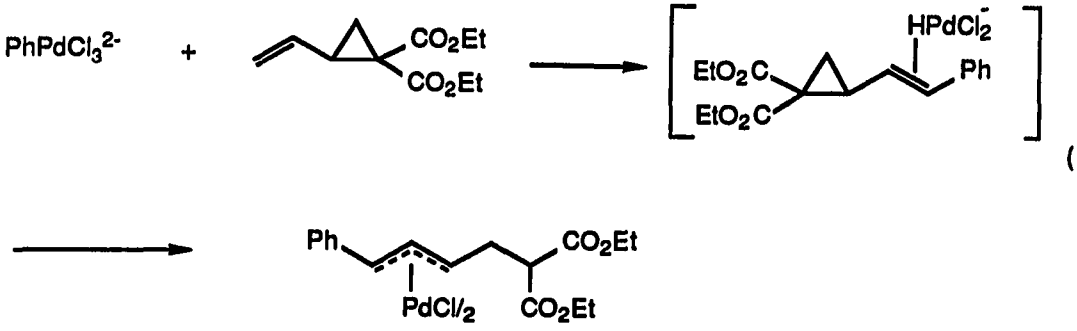


15

earlier. However, the high acidity of the α-hydrogen seems to cause easy decomposition of compound 15 to produce the rather stable diene 16.

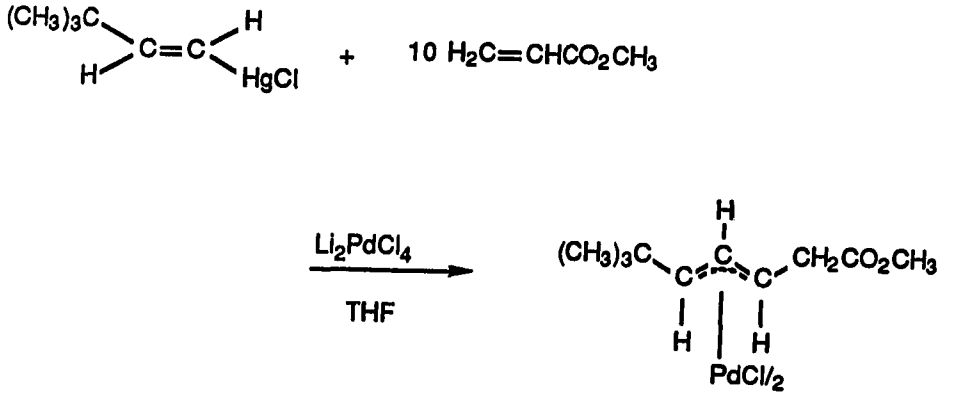
In contrast to this result, Fischetti and Heck[36] were able to isolate a π-allylpalladium compound from the reaction of 1,1-dicarboethoxy-2-vinylcyclopropane and "phenylpalladium chloride" generated from dilithium tetrachloropalladate and phenylmercuric chloride in the presence of triethylamine (eq.

19). They proposed a conceivable mechanism that involves direct formation of the π-allylic product by proton transfer from the initial palladium hydride elimination complex as shown in eq. 19.



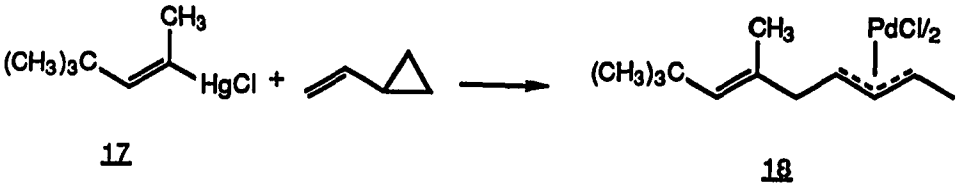
(19)

Vinylcyclobutanes The reaction of a vinylmercurial with olefins in the presence of a palladium(II) salt has been shown to produce π-allylpalladium compounds (eq. 20)[21,23].



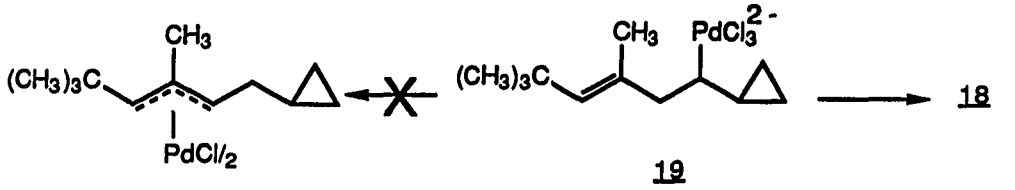
(20)

Recently, Larock and Varaprath[24] have shown that the reaction of vinylmercurial 17 with vinylcyclopropane produces the π-allylpalladium compound 18 after ring-opening (eq. 21).



17 18 (21)

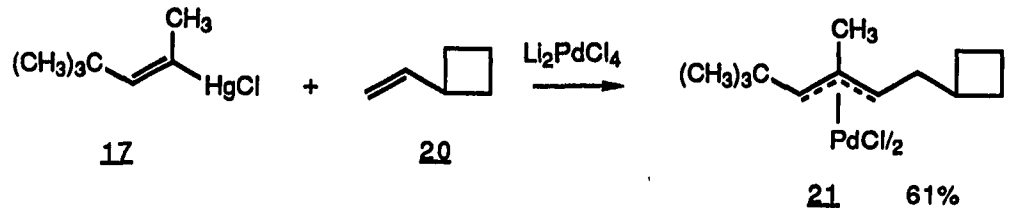
The initial addition product 19 from the above reaction contains both a homoallyl- and a cyclopropylcarbinyl palladium species, but the only π-allylpalladium product observed was the compound rising from cyclopropane ring-opening and not simple palladium migration to the original double bond (eq. 22).



19 (22)

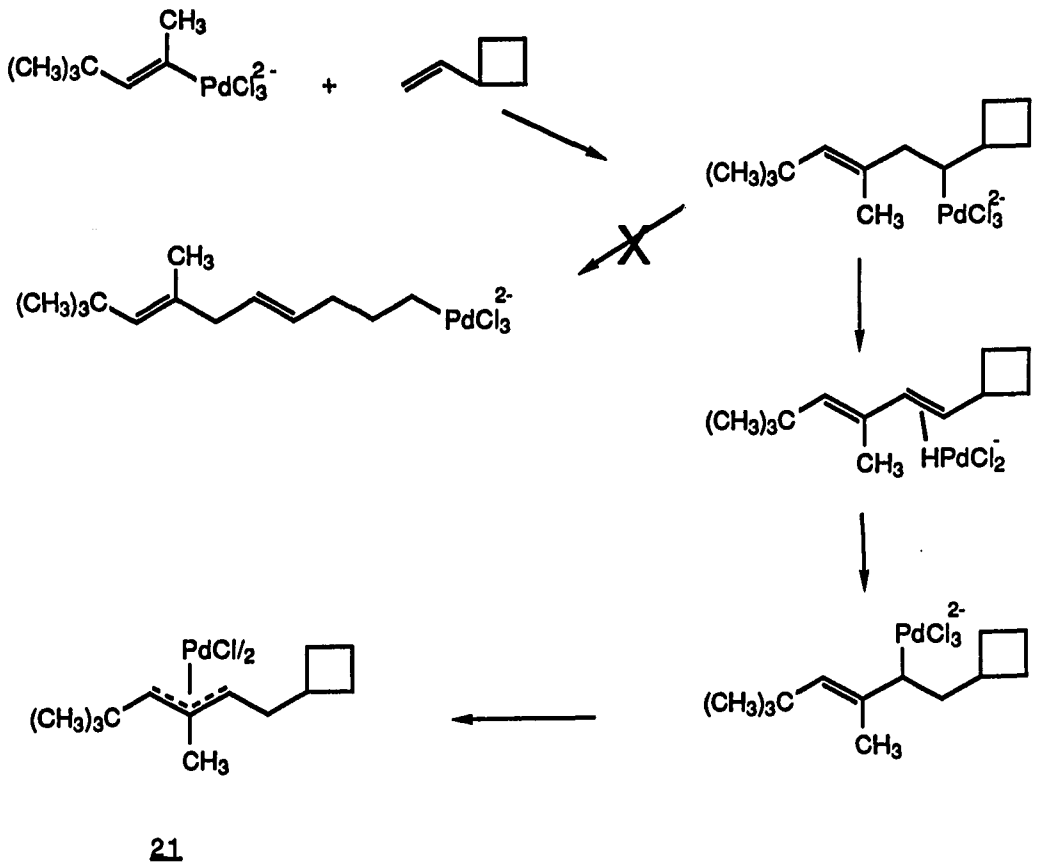
It was of interest to determine whether an analogous intermediate containing a cyclobutylcarbinyl palladium species would ring-open or undergo palladium migration to the original double bond. The reaction of vinylcyclobutane with E-2-chloromercurio-4,4-dimethyl-2-pentene (17) in the presence of dilithium tetrachloropalladate produced only π-

allylpalladium compound 21 in 61% yield (eq. 23). The structure of compound 21 was established by x-ray crystallography and is shown in Figure 1.



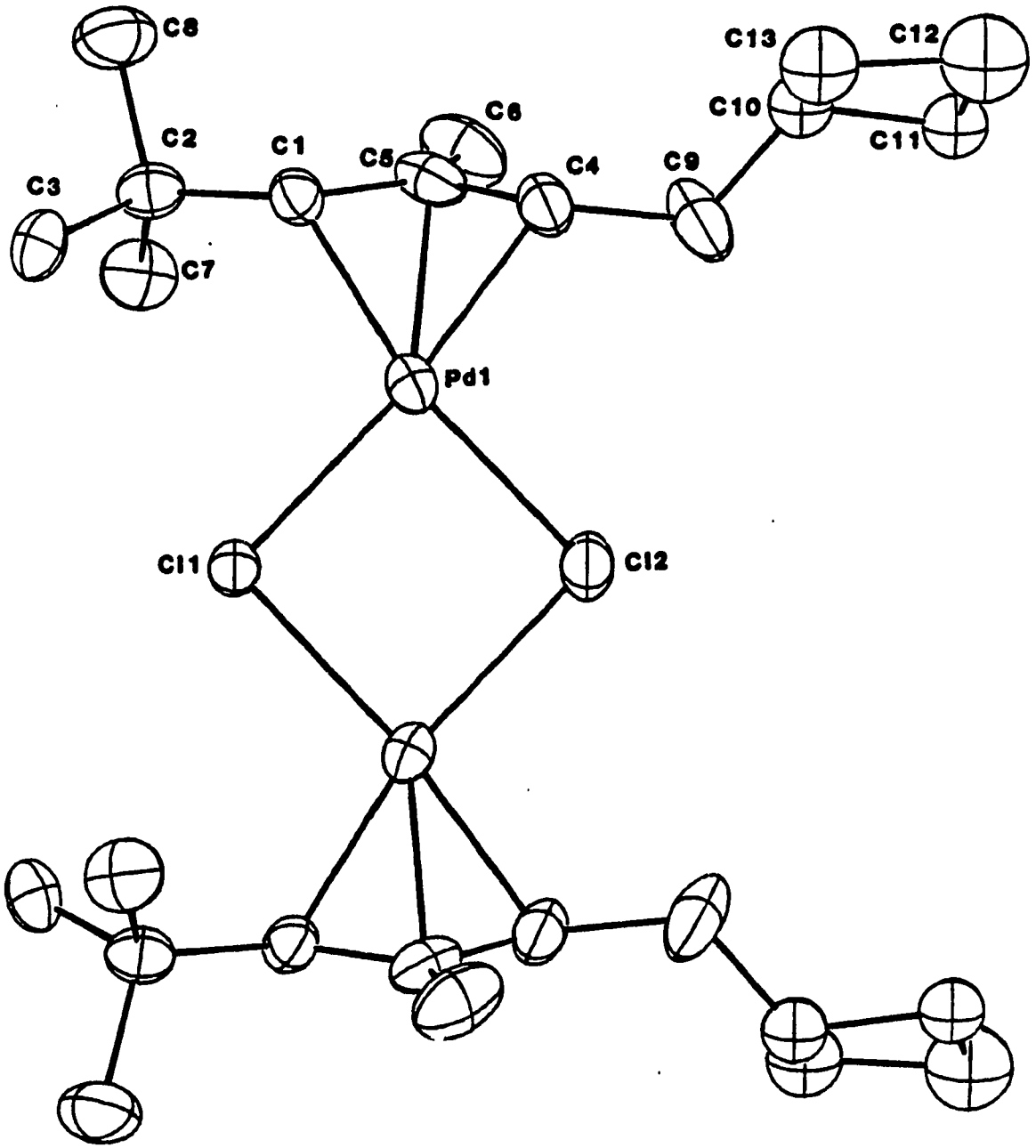
17 20 21 61% (23)

Scheme III



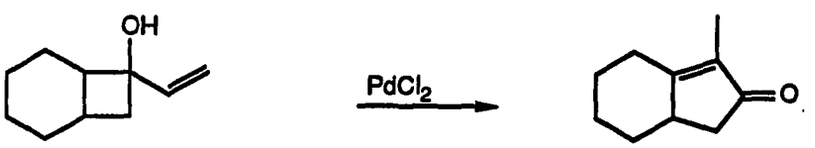
21

Figure 1. An ORTEP drawing of compound 21


C8
C2
C3
C7
C1
C5
C6
C4
C9
C10
C13
C12
C11
Pd1
Cl1
Cl2

It is interesting to note that the cyclobutane ring was not opened under the same reaction conditions in which the analogous cyclopropane-containing intermediate underwent ring opening. A likely mechanism for this reaction is shown in Scheme III.

The next substrate examined was 1-vinylcyclobutanol (22) in order to determine whether it would ring-open to afford a π-allylpalladium compound or rearrange to afford cyclopentenones. 1-Vinyl-1-cyclobutanols have recently been reported to rearrange in the presence of palladium chloride to afford cyclopentenones (eq. 24)[49]. Also, in a related reaction of a 1-alkynyl-1-cyclobutanol, Liebeskind and co-workers observed the formation of a cyclopentanone (eq. 25)[50].



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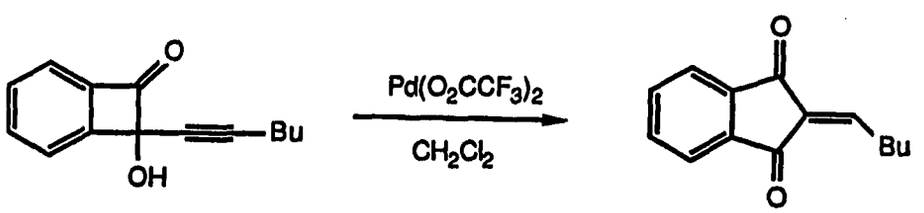
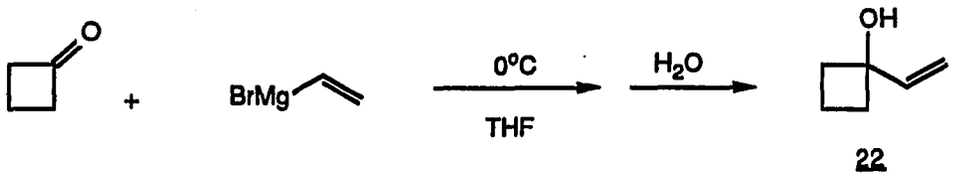


(25)

Compound 22 was prepared easily from the reaction of cyclobutanone and vinyl magnesium bromide in tetrahydrofuran at 0°C (eq. 26)[49].

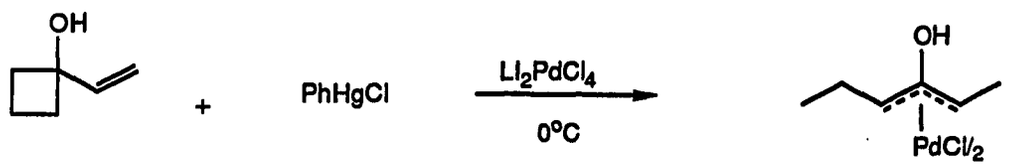


22

72%

(26)

The reaction of compound 22 with phenylmercuric chloride in the presence of dilithium tetrachloropalladate produced π-allylpalladium compound 23 in 15% yield (eq. 27).

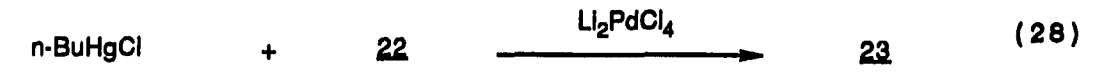


22

23

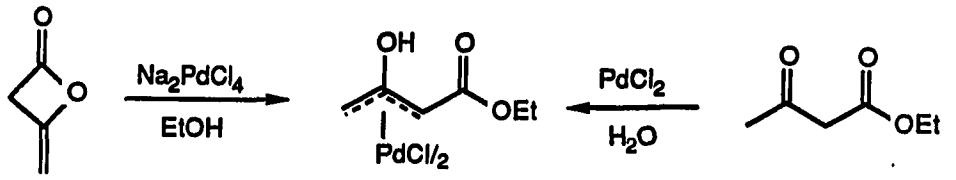
(27)

Surprisingly, product 23 was neither a pinacol-type rearrangement product nor a carbopalladation product, but a π-allylpalladium compound containing a free hydroxy group. In order to prove the structure of compound 23, a similar reaction was examined using n-butylmercuric chloride from which palladium chloride is known to generate "hydridopalladium chloride" in situ (eq. 28). The product (83% yield) from this reaction was identical to that formed



(28)

from the previous reaction as established by its ^1H NMR and infrared spectra. A π-allylpalladium complex containing a free hydroxy group has been reported earlier[51,52]. It was prepared from either diketene or ethyl acetoacetate as shown in eq. 29. Compound 24 was believed to be stable because of

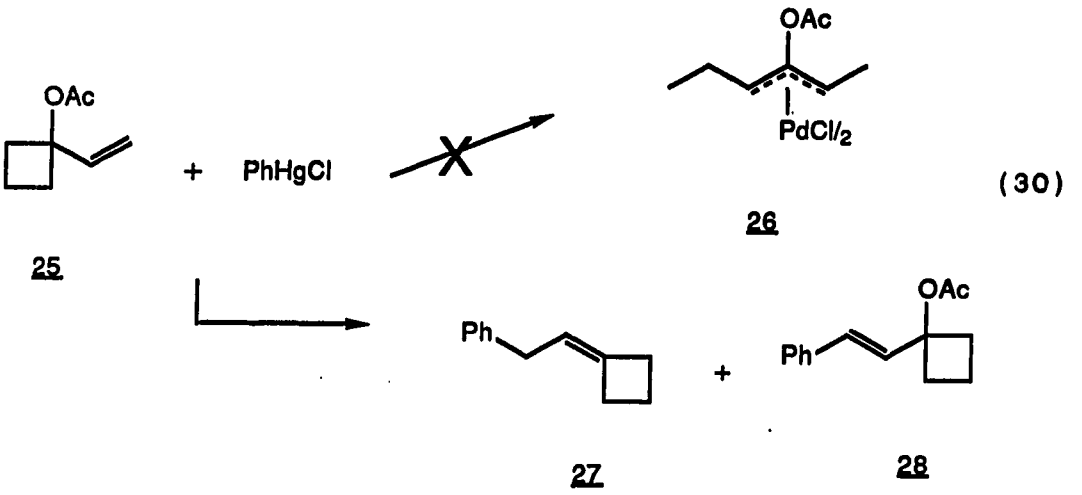


(29)

24

intramolecular hydrogen-bonding of the hydroxyl proton with the β-carbonyl group. Compound 23 does not have such a stabilizing interaction in the molecule and was not stable at room temperature and easily decomposed.

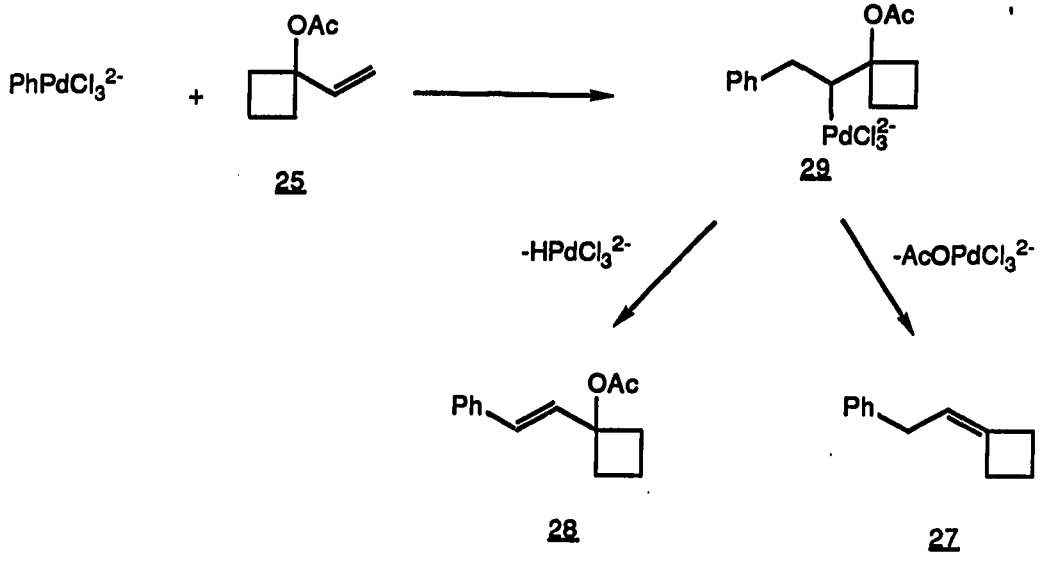
The assumption that the corresponding acetate 25 would follow the same reaction pathway and would give more stable π-allylpalladium compound 26 prompted us to study the reaction of compound 25 with phenylmercuric chloride in the presence of dilithium tetrachloropalladate. The reaction, however, produced olefins 27 (12%) and 28 (22%) (eq. 30).



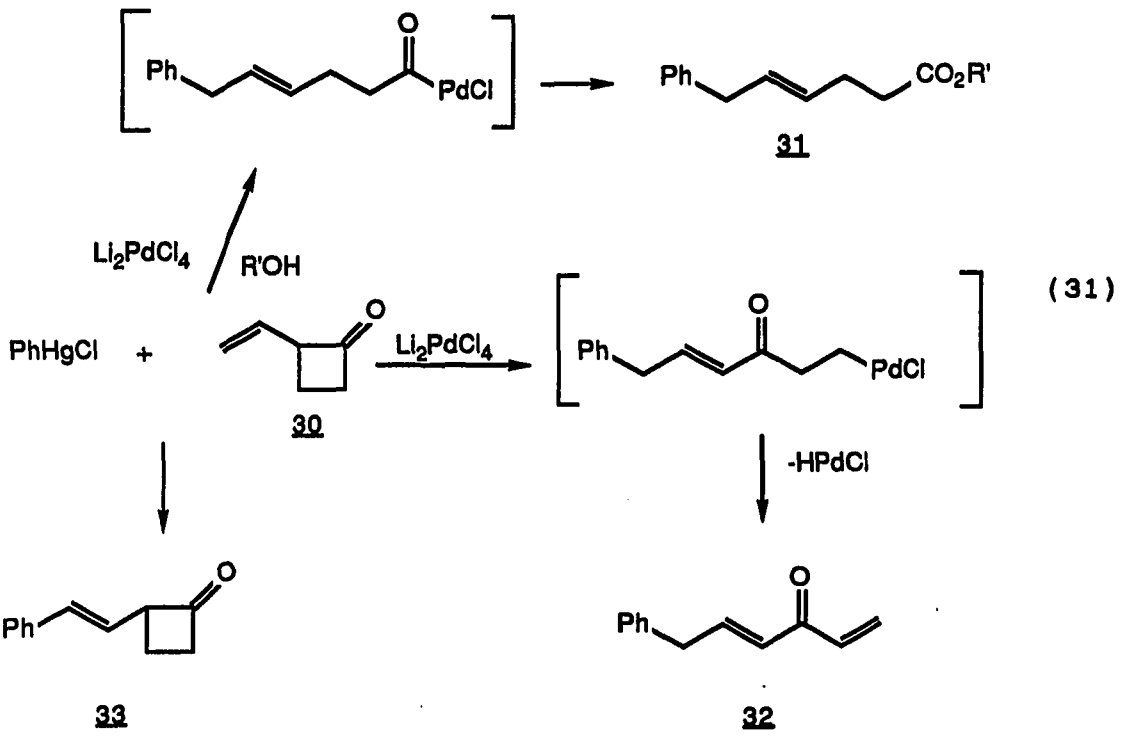
(30)

Formation of compounds 27 and 28 can be explained by a common intermediate 29. Elimination of palladium hydride or acetatopalladium from the intermediate would result in the formation of compounds 28 or 27 respectively (Scheme IV).

Scheme IV



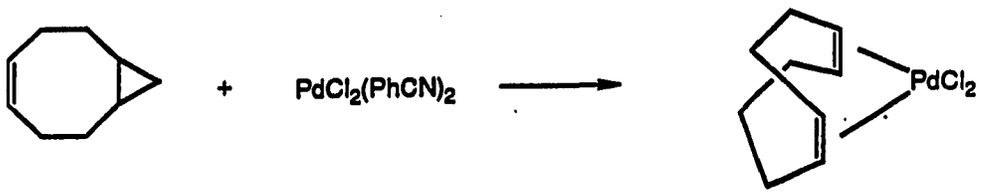
The next substrate examined was 2-vinylcyclobutanone 30 in order to determine whether ring-opening would occur away from or towards a carbonyl carbon. One might expect compound 31 if ring-opening occurs toward the carbonyl carbon, or compound 32 if ring-opening occurs away from the carbonyl carbon (eq. 31). Neither compound 31 nor compound 32 was



(31)

produced from the reaction of phenylmercuric chloride and compound 30. The only identifiable product from the reaction of phenylmercuric chloride was compound 33. 2-Vinylcyclobutanone seems extremely unreactive toward palladium-promoted ring-opening.

Allylcyclopropanes Albelo and Rettig[53] and Albelo and et al.[54] previously observed ring-opening of allylcyclopropanes in the reaction of bicyclo[6.1.0]non-4-ene (34) with bis(benzonitrile)palladium chloride in non-polar solvents to produce dichloro-cis,cis-1,5-cyclononadiene palladium(II) (35) as the final product (eq. 32). The



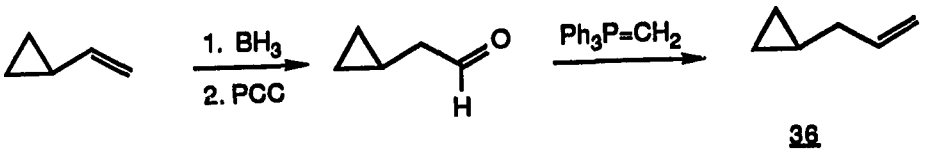
34 35 (32)

reaction proceeds by cis addition of Pd-Cl to a strained cyclopropane C-C bond, followed by 1,2-hydrogen migration and Pd-Cl elimination.

Larock and Takagi[22] have shown that π-allylpalladium compounds can be prepared by the reaction of dilithium tetrachloropalladate, organomercurials, and non-conjugated dienes such as 1,4-pentadiene or 1,5-hexadiene via palladium migration. The observed migration of palladium to form a π-allylpalladium compounds prompted us to examine whether we could extend the procedure for the formation of π-allylpalladium compounds from vinylcyclopropanes to allylcyclopropane (36).

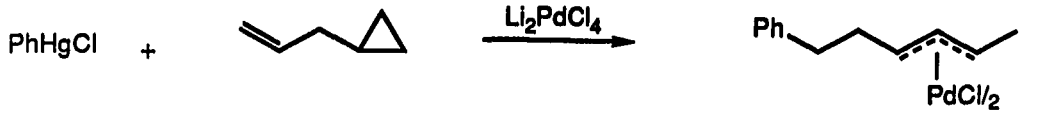
Allylcyclopropane (36) was prepared from vinylcyclopropane by hydroboration with borane and oxidation

with PCC, followed by Wittig olefination using methylenetriphenylphosphorane (eq. 33).



36 (33)

The reaction of allylcyclopropane (36) with phenylmercuric chloride in the presence of dilithium tetrachloropalladate gave the expected π-allylpalladium compound 37 in high yield (eq. 34). Compound 37 was reported previously by Larock and Takagi[22].

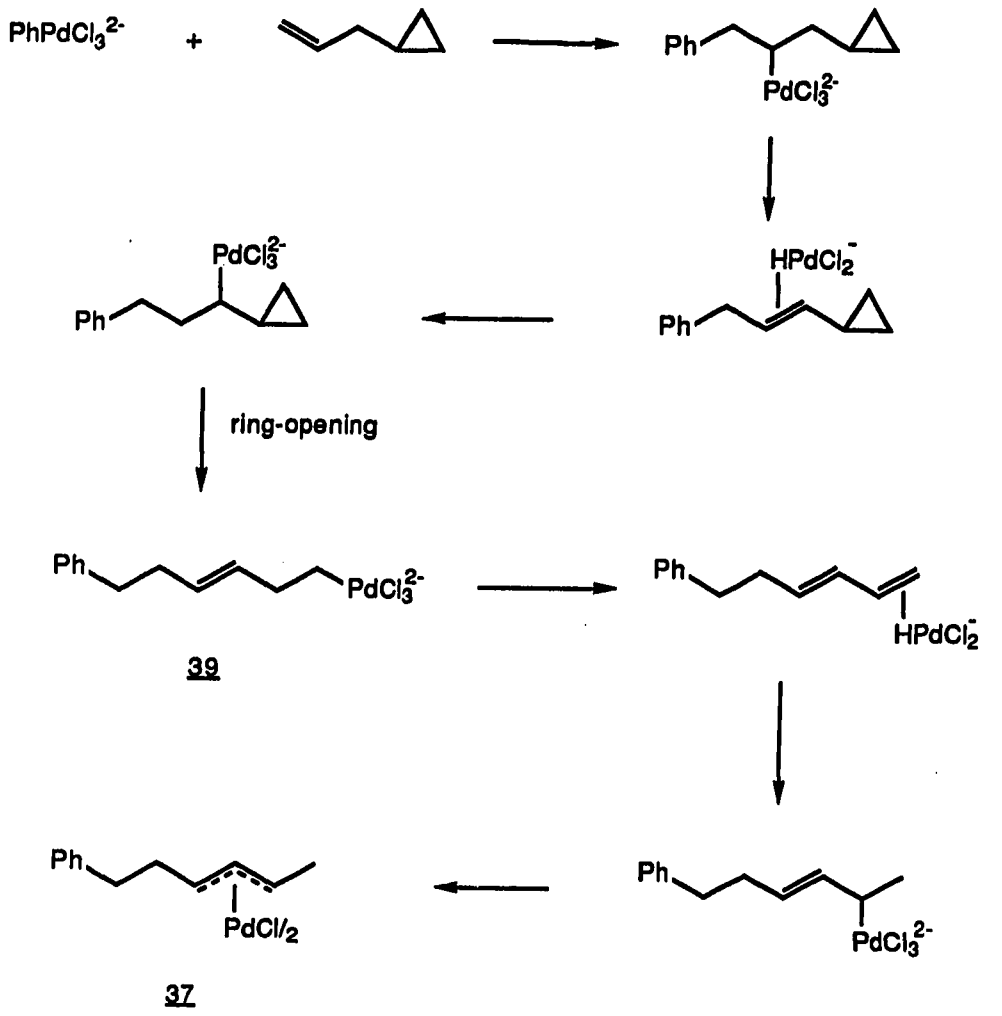


(34)

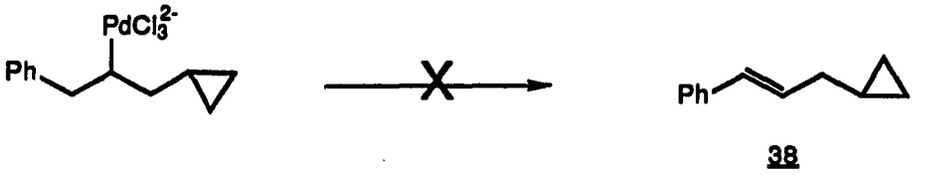
37 95%

A likely mechanism involves addition of "phenylpalladium chloride" to the carbon-carbon double bond and migration of palladium to give a cyclopropylcarbinyl palladium intermediate, followed by ring-opening to form a terminal alkylpalladium intermediate 39. Elimination of palladium hydride and re-addition in the reverse direction would generate compound 37 (Scheme V).

Scheme V

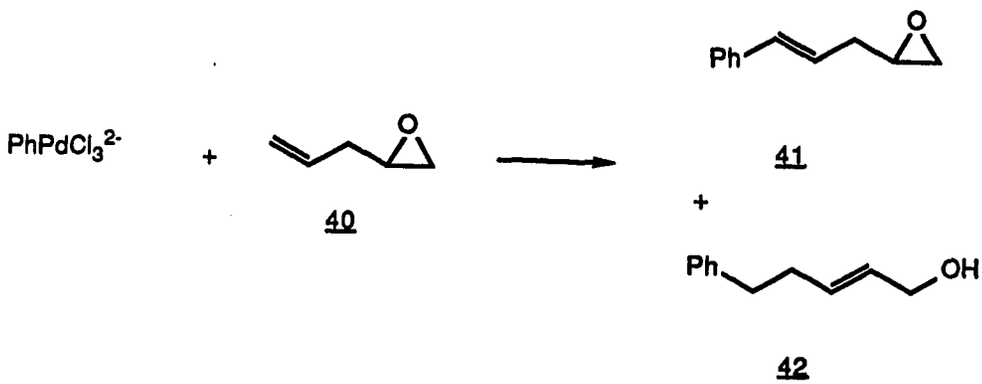


Interestingly, β-hydride elimination toward the phenyl group, which would lead to olefin 38 was not observed (eq. 35).



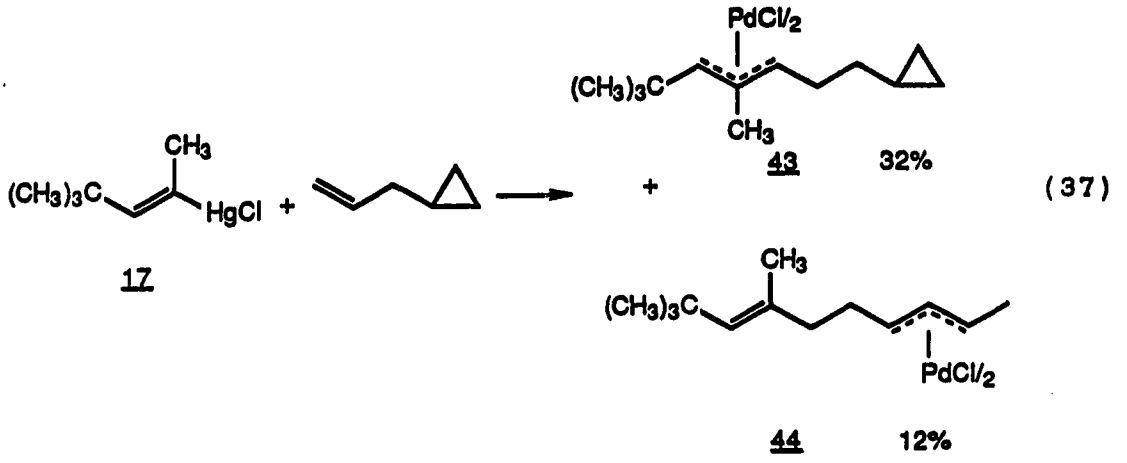
38 (35)

Recently, an analogous observation was made by Mr. Steven Ilkka with 4,5-epoxy-1-pentene (40)[55]. It is interesting to note that he observed both Heck product 41 and ring-opened product 42 (eq. 36).



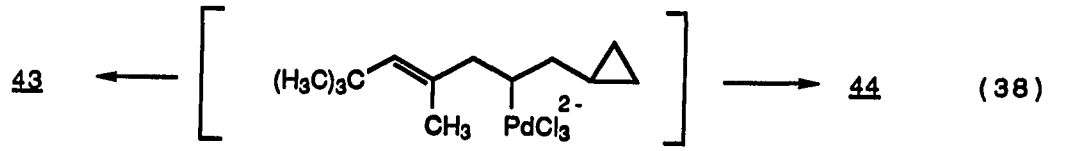
40 (36)

In an effort to determine whether palladium hydride would migrate toward the original double bond of vinylmercurial 17 or open up the cyclopropane of allylcyclopropane, the reaction of vinylmercurial 17 with allylcyclopropane was examined. The products from this reaction were π-allylpalladium compounds 43 and 44 (eq. 37).



17 (37)

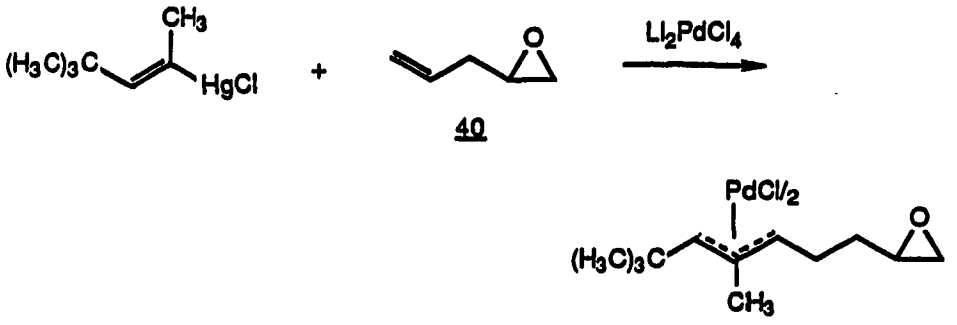
Migration in both directions is observed in this reaction (eq. 38). Compound 43 was able to be isolated and



(38)

characterized; however, compound 44 was not able to be isolated pure. Yields for each product were determined by integration of appropriate ^{1}H NMR spectral peaks.

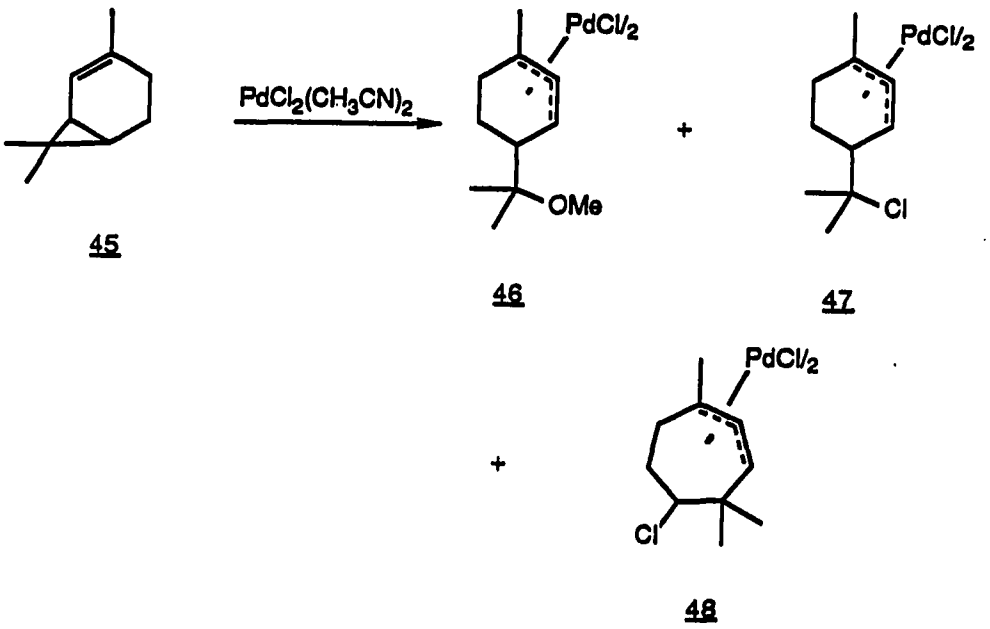
This result is not entirely consistent with the known reaction of vinylmercurials and simple alkenes[21,23] or the result from an analogous reaction with 4,5-epoxy-1-pentene (40) (eq. 39). None of the ring-opened product was observed in the reaction of compound 40[55]. It would appear that



40 (39)

migration towards and ring-opening of the cyclopropane is more favorable than the analogous reactions of an epoxide.

Bicyclic Alkenes Recently, Wilhelm and co-workers[47] prepared π-allylpalladium compounds 46, 47, and 48 from a bicyclic compound, 2-carene (45) (eq. 40). The reaction

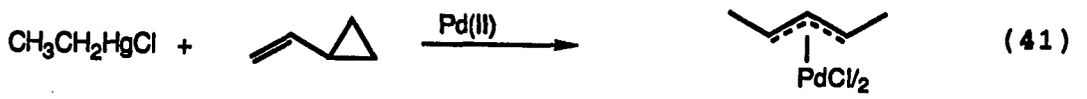


45 46 47 (40)

48

pathway requires electrophilic activation of the cyclopropane by palladium followed by a nucleophilic attack.

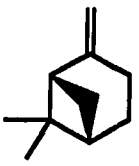
Larock and Varaprath[24] have shown that a π-allylpalladium product derived from palladium hydride addition to the olefin and subsequent rearrangement can be isolated if a vinylcyclopropane reacts with alkylmercurials bearing hydrogen beta to mercury (eq. 41).



(41)

It was of interest to determine whether a highly substituted cyclobutane ring would be opened under the same reaction conditions and to examine whether the stereochemistry of the starting material would be retained during the reaction. The first substrate examined was (1S)-(-)-β-pinene (49). The reaction of compound 49 (98% pure) with n-butylmercuric chloride in the presence of dilithium tetrachloropalladate produced π-allylpalladium compound 51 in 71% yield (eq. 42).

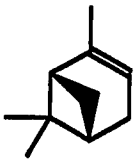
The same compound 51 was prepared from the reaction of (1S)-(-)-α-pinene (50) (99% pure) in 20% yield. Specific rotations for the compounds from both reactions were



49

(S)-(-)- β -pinene

or

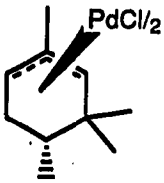


50

(S)-(-)- α -pinene

Li_2PdCl_4

n-BuHgCl



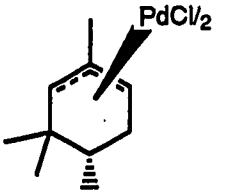
51

(42)

identical. It was believed that the reaction of (1R)-(+)-α-pinene (52) (99% pure) produced π-allylpalladium compound 53 in 20% yield (eq. 43). The specific rotation of compound 53

52

(R)-(+)- α -pinene



53

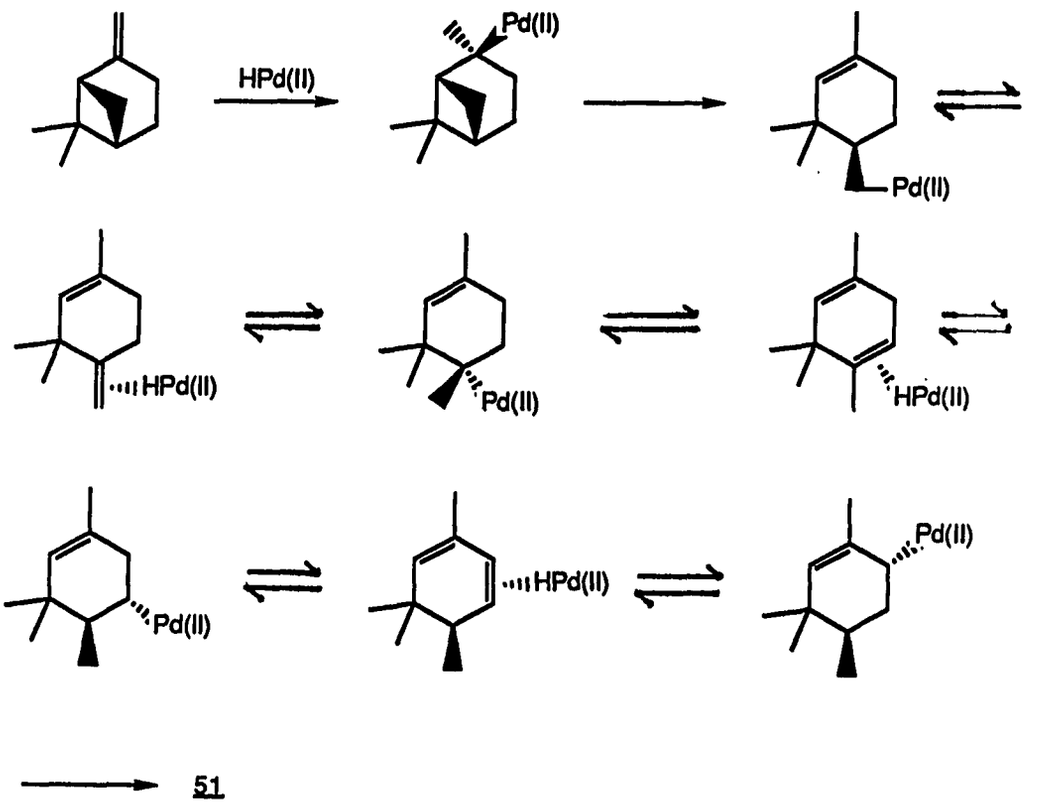
(43)

was the same as compound 51, but in the opposite direction. Compounds 51 and 53 appear to be optically pure by comparison of the specific rotations. This organopalladium methodology appears to afford one of the few good ways presently

available for the preparation of optically pure π-allylpalladium compounds[13,56-60].

While α- and β-pinenes have previously been converted into π-allylpalladium compounds[13,59], those reactions did not involve ring-opening. The formation of compounds 51 and 53 is best explained mechanistically by a sequence involving reversible palladium hydride addition and elimination reactions and cyclobutylcarbinyl palladium ring-opening (Scheme VI). The driving force for the reversible palladium hydride migration would be π-allyl formation.

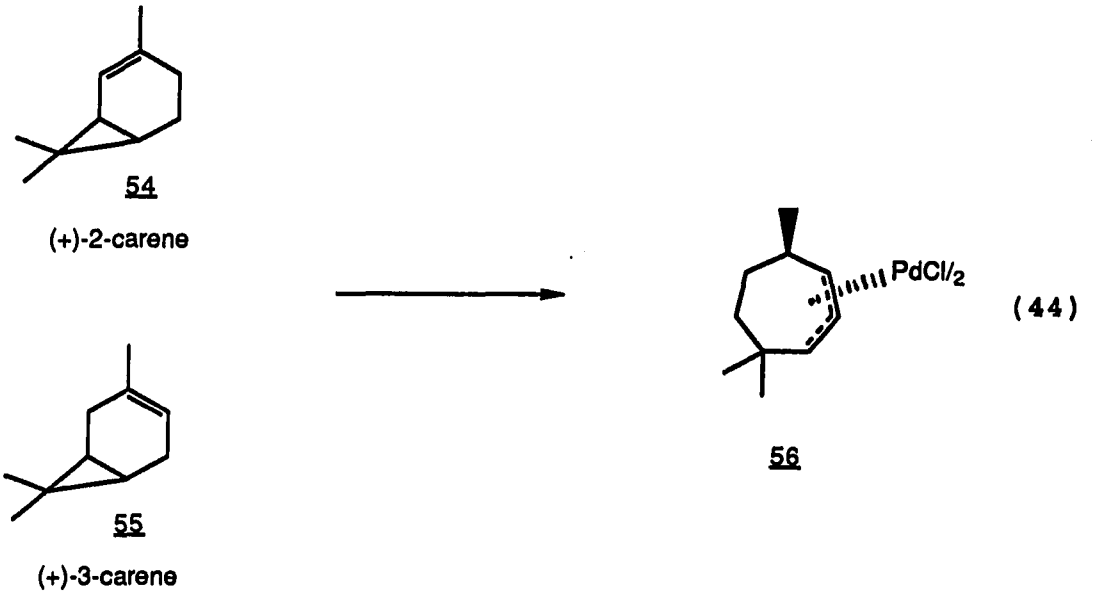
Scheme VI



→ 51

The structure of compound 51 derived from (s)-(-)-β-pinene was established by X-ray crystallography and is shown in Figure 2. The allyl groups adopt a cis arrangement and the chlorine bridge is bent, the interplanar angle between Pd(1)-Cl(1)-Cl(2) and Pd(2)-Cl(1)-Cl(2) being 130.5°. While most dimeric halogen-bridged π-allylpalladium complexes adapt a "trans-planar" arrangement[61], "cis-bent" features have been reported in a few cases[62-64], only one of which is acyclic[52].

Analogous palladium hydride reactions have been carried out on (+)-2-carene (54) (97% pure) and (+)-3-carene (55) (99% pure) (eq. 44). (+)-2-Carene afforded π-allylpalladium



54
(+)-2-carene

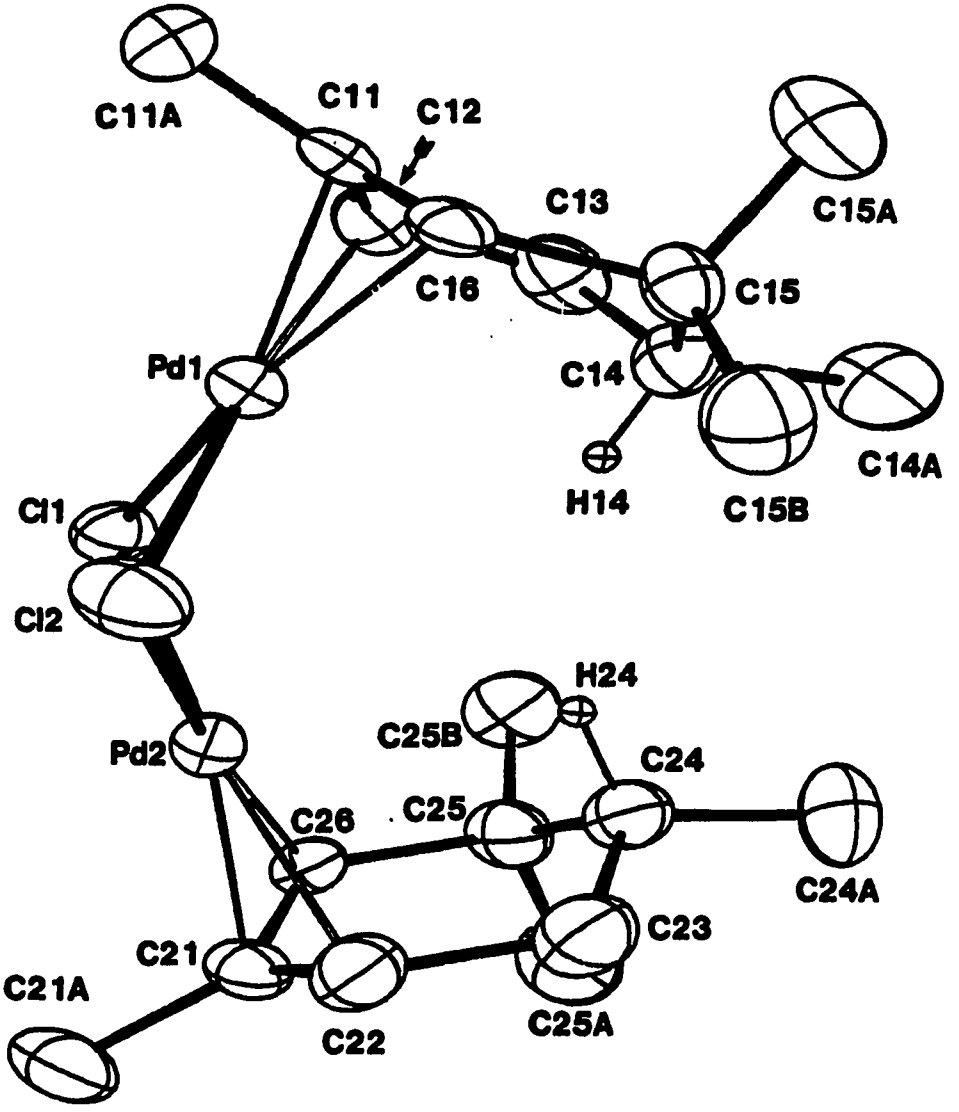
55
(+)-3-carene

56

(44)

compound 56 in 19% yield, while (+)-3-carene gave the same palladium compound in 23% yield. The structure of compound

Figure 2. An ORTEP drawing of compound 51


C11A
C11
C12
C13
C15A
C16
C15
Pd1
C14
C14A
H14
C15B
Cl1
Cl2
H24
C25B
C24
Pd2
C26
C25
C24A
C23
C21
C21A
C22
C25A

56 was established by X-ray crystallography and is shown in Figure 3. The molecule resides at a crystallographic inversion point, adopting a "trans-planar" arrangement, in contrast to compound 51. The allylic C-C-C bond angle of 123.5° is somewhat larger than that of compound 51 (114.8°).

It is noteworthy that the same π-allylpalladium compound is formed from both 2- and 3-carene. While the formation of compounds 51 and 53 can be explained by palladium hydride addition to the starting alkenes to form an alkylpalladium intermediate which can immediately undergo ring-opening, the formation of compound 60 requires a palladium migration prior to ring-opening (Scheme VII). The alkylpalladium

Scheme VII

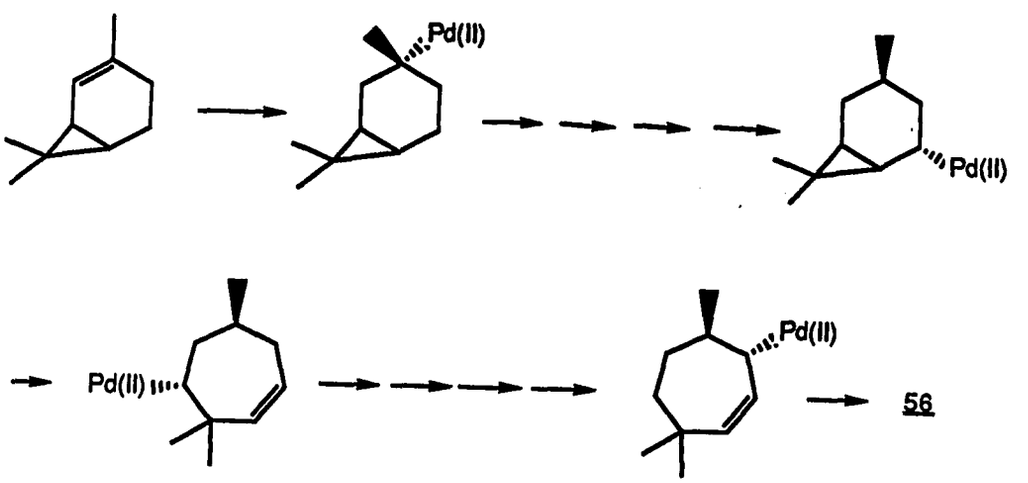
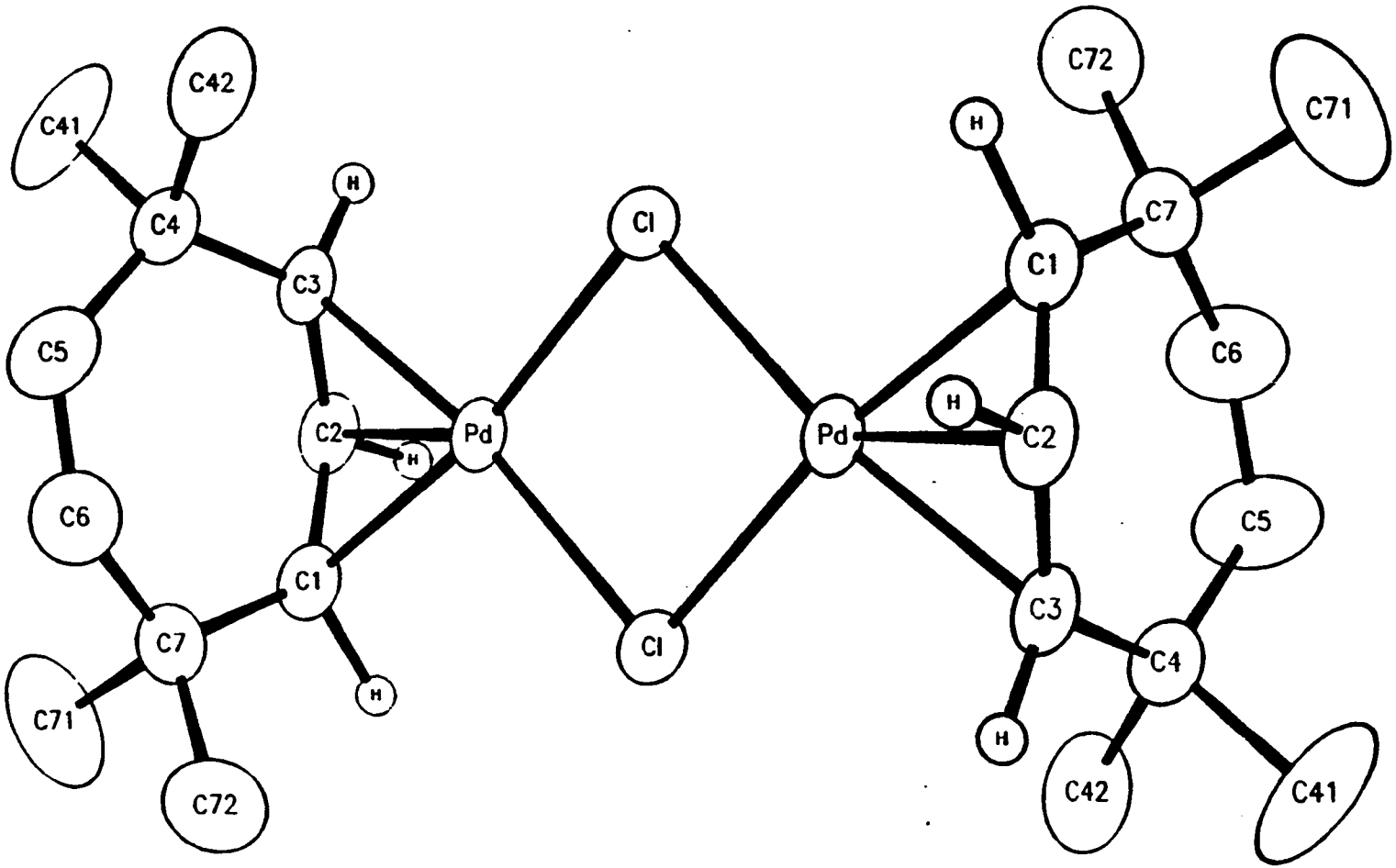
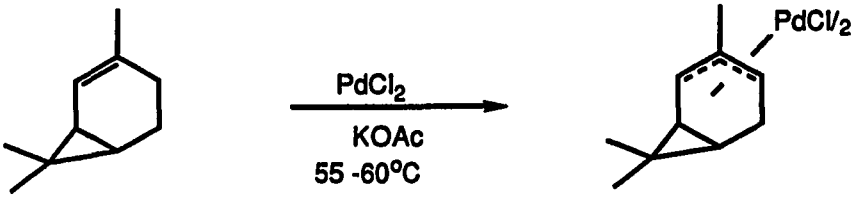


Figure 3. An ORTEP drawing of compound 60


C42
C41
C4
H
C3
C5
C2
H
Pd
Cl
C6
C1
C7
C71
H
C72
Cl
Pd
C72
C71
H
C7
C1
C6
H
C2
C5
C3
C4
H
C42
C41

intermediates which actually undergo ring-opening seem to be determined by the conformations of the alkenes or their intermediate palladium hydride adduct leading up to ring-opening.

It is interesting to note that reaction of (+)-2-carene with palladium chloride in acetic acid in the presence of potassium acetate has recently been reported to give π-allylpalladium complex 57 (eq. 45)[65].



65%

57

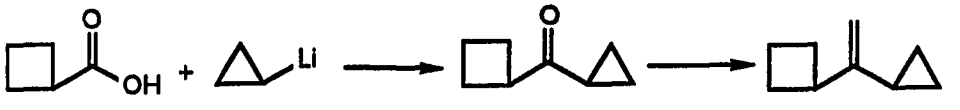
(45)

These novel stereospecific rearrangements provide a new route to optically pure π-allylpalladium compounds which should prove useful in mechanistic studies of reactions of π-allylpalladium compounds.

Comparison of Relative Reactivities Although it is apparent that a cyclopropane ring is more reactive than a cyclobutane ring toward palladium-promoted ring-opening by comparison of the two reactions shown in eqs. 21 and 23, their relative reactivity can be directly compared using a

substrate which contains both a cyclopropane and a cyclobutane ring.

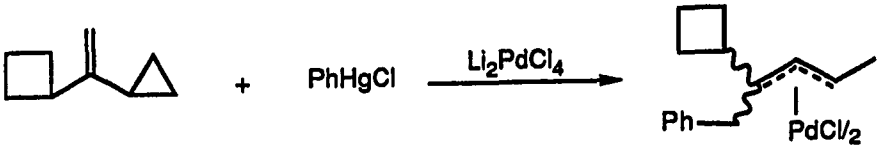
1-Cyclopropyl-1-cyclobutylethene 58 was prepared from the reaction of cyclobutane carboxylic acid and 2 equivalents of cyclopropyllithium, followed by Wittig olefination (eq. 46).



(46)

58

The reaction of compound 58 with phenylmercuric chloride in the presence of dilithium tetrachloropalladate produced only the cyclopropane ring-opened product 59 in 65% yield (eq. 47). The product was a mixture of two stereoisomers in a ratio of 1.8 : 1. The result from this reaction shows that cyclopropane ring-opening is apparently considerably more facile than cyclobutane ring-opening.

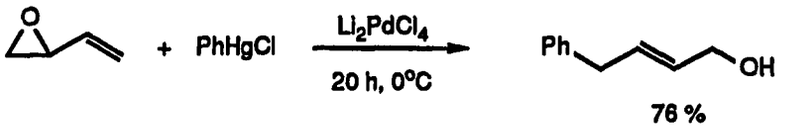


(47)

58 59

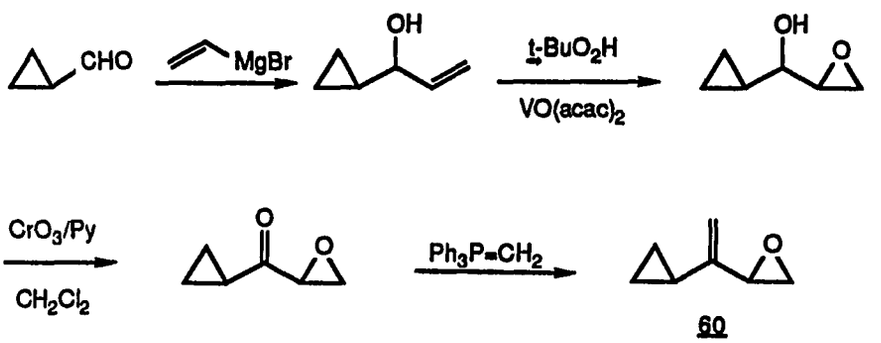
Mr. Steven Ilkka earlier examined the reactions of vinyl epoxides and organomercurials in the presence of

stoichiometric or catalytic amounts of palladium (II) salts (eq. 48)[55]. It was thought that comparison of the



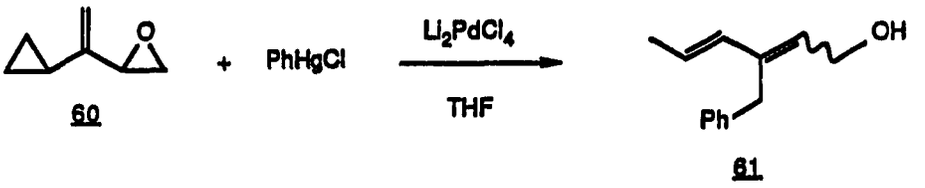
(48)

reactivities of a cyclopropane versus an epoxide towards palladium-promoted ring-opening should be interesting. Thus, 2-cyclopropyl-3,4-epoxy-1-butene (60) was prepared from cyclopropanecarboxaldehyde following the reaction scheme described in eq. 49.



(49)

Compound 60 was subjected to three different reaction conditions. The results are listed in Table 1 and the reaction is represented by eq. 50.



60 61 (50)

Table 1. Reaction of compound 60 with phenylmercuric chloride

entry	amount of compound 60	reaction time	reagent	yield[a] %	isomer ratio[b] Z,E : E,E
1	2 equiv.	2 h	none	16	2 : 1
2	2 equiv.	10 h	5% water[c]	32	3 : 1
3	1 equiv.	11 h	5% sat'd NH_4Cl[c]	51	1.4 : 1

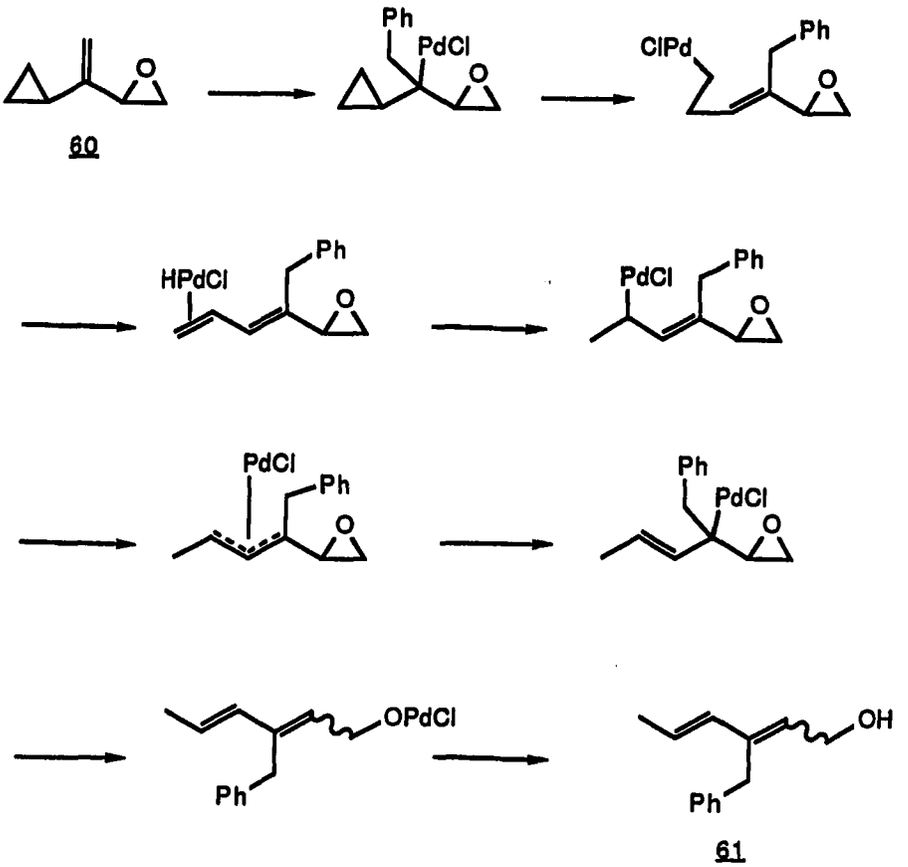
[a]Yield based on phenylmercuric chloride.

[b]Ratio determined from integration of appropriate peaks in the proton NMR spectra.

[c]Five percent by volume.

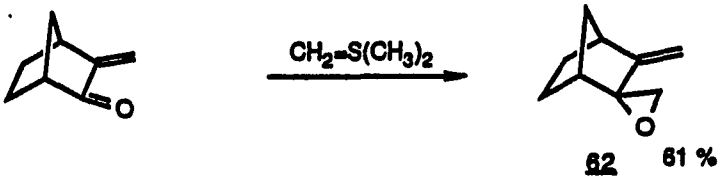
A mechanism for this transformation can be proposed as follows (Scheme VIII). The σ-palladium species formed initially opens the cyclopropane ring. This is followed by palladium hydride elimination and subsequent migration to form a π-allylpalladium species. Because the π-allylpalladium moiety is attached to an epoxide, the epoxide ring is also opened by the palladium. Similar openings of epoxide rings have been reported earlier[66,67].

Scheme VIII



The next substrate examined was endo-spiro[3-methylenebicyclo[2.2.1]heptane-2,2'-oxirane] (62). While it is known that palladium opens the carbon-oxygen bond of acyclic epoxides in a syn fashion[55], this cyclic epoxide presents a case where the initial palladium adduct should have a palladium and carbon bond syn and might be expected to

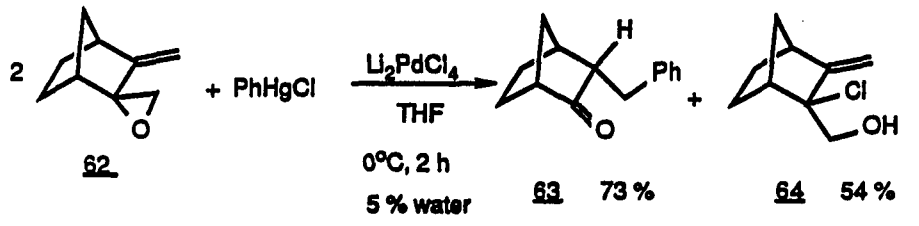
open the carbon-carbon bond of the epoxide. It was worth determining whether a carbon-carbon bond or a carbon-oxygen bond would be cleaved. Compound 62 was prepared from 3-methylene-2-norbornanone by reacting with a sulfur ylide (eq. 51)[68]. While the stereochemistry of compound 62 is not



62 61 % (51)

absolutely certain, it seems likely that the new carbon would be introduced from the exo face. Only one stereoisomer is evident by ^{13}C NMR spectroscopy.

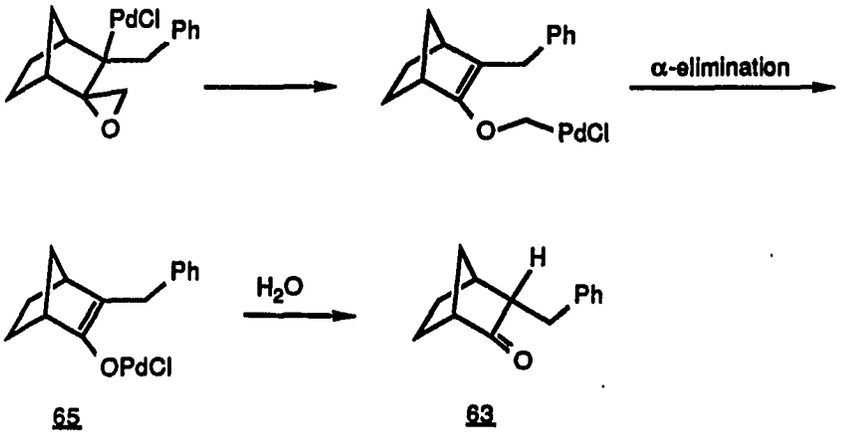
The reaction of compound 62 (2 equivalents) and phenylmercuric chloride in the presence of dilithium tetrachloropalladate produced compound 63 along with compound 64 (eq. 52). The structure of compound 63 was determined by



62 63 73 % 64 54 % (52)

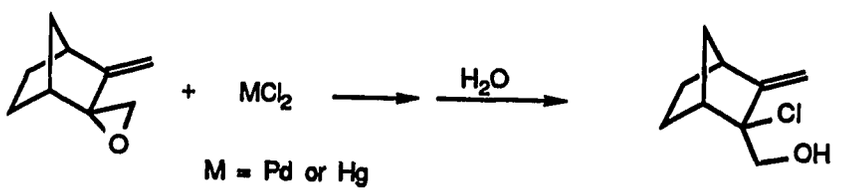
^{1}H and ^{13}C NMR, infrared, and mass spectral data. The reaction mechanism shown in Scheme IX is proposed to explain

Scheme IX



65 63

the formation of compound 63. Addition of a phenylpalladium species across the double bond from the exo-face, followed by carbon-carbon bond cleavage and α-elimination of a palladium alkoxide produces intermediate 65. Compound 63 is then formed by protonation after aqueous workup. Compound 64 is presumably produced by palladium(II) or mercury(II) salt induced ring-opening of the epoxide followed by protonolysis (eq. 53).



(53)

In the rigid cyclic epoxide 62, palladium-promoted cleavage of the carbon-carbon bond instead of the carbon-oxygen bond was observed.

CONCLUSION

A wide variety of π-allylpalladium compounds can be prepared from the reactions of organomercurials and alkenylcycloalkanes bearing 3- or 4-membered ring in the presence of palladium(II) salts. In addition, the reactivities of these strained rings have been directly compared. Cyclopropane rings are more reactive than cyclobutane rings. In the rigid cyclic epoxide 62, palladium-promoted cleavage of the cis carbon-carbon bond instead of the trans carbon-oxygen bond was observed.

EXPERIMENTAL SECTION

Equipment Proton NMR spectra were recorded on either an EM 360 or a Nicolet NT-300 spectrometer. ^{13}C NMR spectra were recorded on a Nicolet NT-300 spectrometer (operating at 75 MHz for carbon nuclei). Infrared spectra were recorded on either a Beckman Acculab 2 or an IBM IR-98 spectrometer. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. Mass spectral data were obtained on a MS-50 high resolution mass spectrometer. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc.

Reagents All compounds were used directly as obtained unless otherwise noted. All starting materials were purchased from Aldrich, except for sodium hydride (J. T. Baker), cyclobutanone (Fluka), (+)-2-carene and (+)-3-carene (Fluka), and 1,3-butadiene (Matheson Gas Products). Vinyl magnesium bromide was obtained from Alfa and titrated before used by the method of Watson and Eastham[69]. Phenylmercuric chloride was used directly as obtained from Aldrich and Fluka. n-Butylmercuric chloride and E-2-chloromercurio-4,4-dimethyl-2-pentene were prepared according to the procedure of Larock and Brown[70] and were recrystallized from 95%

ethanol before use. Methanol was distilled from magnesium methoxide; acetonitrile and methylene chloride were distilled from phosphorus pentoxide; diethyl ether and dimethyl sulfoxide were distilled from calcium hydride; tetrahydrofuran was distilled from benzophenone-sodium ketyl. Lithium chloride was purchased from J. T. Baker and was dried before use. Palladium chloride was generously supplied by Johnson Matthey, Inc.

Preparation of vinylcyclopropane (5) Vinylcyclopropane was prepared via 3-vinyl-1-pyrazoline using the procedure developed by Crawford and Cameron[71].

3-Vinyl-1-pyrazoline To a flask containing 15 ml of butadiene at -78°C was added a solution of 3 g of diazomethane prepared from 21.5 g of diazald. After the reaction mixture stood overnight, ether was distilled out at atmospheric pressure. The remaining concentrate was distilled at 62°C (25 mm Hg) (lit.[71] bp 70 - 75°C (40 mm Hg)) to provide 4.23 g (44 mmol, 61%) of 3-vinyl-1-pyrazoline: ^{1}H NMR ($CDCl_3$) δ 1.31 - 1.38 (m, 1 H, N-CH-C$\underline{H}_2$), 1.85 - 1.95 (m, 1 H, N-CH-C$\underline{H}_2$), 4.23 - 4.35 (m, 1 H, N-CH_2), 4.59 - 4.70 (m, 1 H, N-CH_2), 4.89 - 4.92 (m, 1 H, N-CH), 5.30 (dd, 1 H, J = 10.43 Hz, J = 1.2 Hz, =CH_2 trans), 5.36 (dd, 1 H, J = 17.43 Hz, J = 1.2 Hz, =CH_2 cis).

Vinylcyclopropane (5) 3-Vinyl-1-pyrazoline was placed in a flask equipped with a magnetic stirring bar and distillation apparatus and heated in an oil bath kept at 135°C. Vinylcyclopropane was trapped in a flask kept at -78°C: yield 4.36 g (64.0 mmol, 69%); bp 45°C; ^{1}H NMR ($CDCl_3$) δ 0.36 - 0.41 (m, 2 H, CH_2CH_2 trans), 0.68 - 0.74 (m, 2 H, CH_2CH_2 cis), 1.37 - 1.44 (m, 1 H, CH), 4.85 (dd, 1 H, J = 10.15 Hz, J = 1.67 Hz, $=CH_2$ trans), 5.07 (dd, 1 H, J = 17.03 Hz, J = 1.67 Hz, $=CH_2$ cis), 5.34 (ddd, 1 H, J = 9.26 Hz, J = 10 Hz, J = 17.11 Hz, =CH-).

1-Acetyl-2-vinylcyclopropane (14) To a solution of 21.3 g (100 mmol) of 1,4-dibromo-2-butene in 100 ml of dry acetone was added 30 g of powdered sodium hydroxide in 6 equal portions at intervals of 15 min. at 0°C. After stirring for 4 h at room temperature, the reaction was diluted with 50 ml of ether. The excess sodium hydroxide and sodium bromide were filtered off, and the filtrate was washed with saturated brine and dried over anhydrous magnesium sulfate. After evaporation of the solvents, the residue was vacuum distilled at 71°C (50 mm Hg) to give 3.83 g (35%) of the desired product. The product was a mixture of cis and trans isomers in a ratio of 2 : 1; cis: ^{1}H NMR ($CDCl_3$) δ 1.19 (ddd, 1 H, J = 4.5 Hz, J = 8.4 Hz, J = 7.5 Hz, CH_2 trans), 1.41 (m, 1 H, J = 4.5 Hz, J = 6.6 Hz, CH_2 cis), 1.93 - 2.09 (m, 2 H, CHCH),

2.24 (s, 3 H, CH_3), 5.01 (dd, 1 H, J = 10.2 Hz, J = 1.2 Hz, $=CH_2$ trans), 5.19 (dd, 1 H, J = 17.1 Hz, J = 1.2 Hz, $=CH_2$ cis), 5.65 (ddd, 1 H, J = 10.2 Hz, J = 17.1 Hz, J = 9.3 Hz, -CH=); trans: ^1H NMR ($CDCl_3$) δ 1.02 (ddd, 1 H, J = 4.2 Hz, J = 8.1 Hz, J = 6.3 Hz, CH_2), 1.44 (ddd, 1 H, J = 4.2 Hz, J = 5.1 Hz, J = 9.0 Hz, CH_2), 1.93 - 2.09 (m, 2 H, CHCH), 2.63 (s, 3 H, CH_3), 4.98 (dd, 1 H, J = 10.2 Hz, J = 1.8 Hz, $=CH_2$ trans), 5.15 (dd, 1 H, J = 17.1 Hz, J = 1.8 Hz, $=CH_2$ cis), 5.40 (ddd, 1 H, J = 10.2 Hz, J = 17.1 Hz, J = 8.4 Hz, =CH-); IR (neat) 3084, 3005, 2984, 1699 (C=O), 1637, 1386, 1353, 1286, 1294, 1171, 1107, 1091, 1051, 1126, 991, 943, 906, 839, 662 cm^{-1}; mass spectrum m/z 110.07335 (calcd for $C_7H_{10}O$, 110.07317).

Preparation of vinylcyclobutane (20)

Cyclobutanemethanol The alcohol was prepared by the reduction of cyclobutanecarboxylic acid using a general procedure for the preparation of alcohols from carboxylic acids[72]. To a flask containing 0.8 g of lithium aluminum hydride in 20 ml of anhydrous ether at 0°C under nitrogen was added over 10 min 2.0 g (20 mmol) of cyclobutanecarboxylic acid dissolved in 10 ml of anhydrous ether. After the addition of the acid was completed, the mixture was refluxed for 30 min. The extra lithium aluminum hydride was destroyed by careful addition of water at 0°C. The reaction mixture

was extracted with ether, washed with saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The product was distilled at 127°C to give 1.30 g (15.1 mmol, 75% yield) of cyclobutanemethanol: ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 1 H OH), 1.65 - 2.10 (m, 6 H, CH_2), 2.41 - 2.57 (h, 1 H, J = 7.3 Hz, CH), 3.57 (d, 2 H, J = 6.6 Hz, OCH_2).

Cyclobutanecarboxaldehyde The aldehyde was prepared by the oxidation of cyclobutanemethanol using a modification of the procedure reported by Corey and Suggs[73]. To a flask containing 5.0 g (22.5 mmol) of pyridinium chlorochromate in 30 ml of methylene chloride at room temperature was added 1.29 g (15.0 mmol) of cyclobutanemethanol under nitrogen. The reaction mixture was stirred at room temperature for 2 h and filtered through a Florisil column. Cyclobutanecarboxaldehyde was distilled at 114°C [lit.[74] bp 114 - 115.5°C (753 mm Hg)]: yield 0.6582 g (7.8 mmol, 52%); ^{1}H NMR ($CDCl_3$) δ 1.82 - 2.37 (m, 6 H, CH_2), 3.11 - 3.26 (p, 1 H, J = 8.1 Hz, CH), 9.76 (d, 1 H, J = 1.9 Hz, O=CH).

Vinylcyclobutane (20) This compound was prepared by olefination of cyclobutanecarboxaldehyde using the procedure employed by Greenwald and co-workers[75]. In a flame dried 50 ml 3-neck round bottom flask equipped with a magnetic stirring bar, reflux condenser, and a dropping

funnel, was placed 0.1794 g (7.8 mmol) of sodium hydride (50% dispersion in mineral oil). The sodium hydride was then washed with several portions of dry pentane to remove the mineral oil. After the remaining pentane was removed using a vacuum pump, 10 ml of freshly distilled dimethyl sulfoxide was introduced via syringe, and the mixture was heated at 75 - 80°C until the evolution of hydrogen ceased. The resulting solution of methylsulfinyl carbanion was cooled in an ice bath, and 2.7865 g (7.8 mmol) of methyltriphenylphosphonium bromide in 10 ml of dimethyl sulfoxide was added. After the resulting dark solution of the ylide was stirred at room temperature for 10 min, 0.6582 g (7.8 mmol) of cyclobutanecarboxaldehyde was added. The reaction mixture was stirred at room temperature for 30 min, followed immediately by distillation under reduced pressure, to give 0.3013 g (3.7 mmol, 47%) of vinylcyclobutane which was collected in a dry ice/acetone trap at -78°C: ^{1}H NMR ($CDCl_3$) δ 1.33 - 1.60 (m, 4 H, CH_2), 1.67 - 1.84 (m, 2 H, CH_2), 2.47 - 2.68 (m, 1 H, CH), 4.52 (d, 1 H, J = 10 Hz, $=CH_2$ trans), 4.56 (d, 1 H, J = 17 Hz, $=CH_2$ cis), 5.47 - 5.67 (ddd, 1 H, J = 17.06 Hz, J = 10.4 Hz, J = 6.7 Hz, =CH-); IR ($CDCl_3$) 3160, 3080, 2960, 2870, 2250, 1820, 1795, 1635, 1470, 1380, 1100, 910, 700 cm^{-1}; mass spectrum m/z 82.07828 (calcd for C_6H_{10}, 82.07825).

1-Vinyl-1-cyclobutanol (22) The alcohol was prepared using a modification of the procedure used by Sieja[76]. To a solution of 11 ml (1.64 M, 18 mmol) of vinylmagnesium bromide in THF at 0°C was added 1 g (14.3 mmol) of cyclobutanone in 6 ml of THF over a 40 min period. The mixture was stirred at 25°C for 1 h, cooled to 0°C, and acidified with 20 ml of 5% HCl. The organic material was extracted with 30 ml of ether in three portions. The ether solutions were combined, washed with 10 ml of saturated aqueous sodium bicarbonate and 10 ml of saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The solvent was removed by distillation, and the residue was distilled under reduced pressure to give 1.0021 g (10.21 mmol, 72%) of 1-vinyl-1-cyclobutanol: ^{1}H NMR ($CDCl_3$) δ 1.61 (p, 2 H, J = 8.7 Hz, CH_2), 1.74 - 1.88 (m, 2 H, CH_2), 2.10 - 2.26 (m, 2 H, CH_2), 2.17 (s, 1 H, OH), 5.08 (dd, 1 H, J = 10.8 Hz, J = 0.9 Hz, $=CH_2$ trans), 5.27 (dd, 1 H, J = 17.4 Hz, J = 0.9 Hz, $=CH_2$ cis), 6.14 (dd, 1 H, J = 10.8 Hz, J = 17.1 Hz, =CH-); IR (neat) 3340 (OH), 3080, 2980, 2935, 2870, 1640, 1415, 1240, 1180, 1145, 1060, 1020, 990, 960, 915 cm^{-1}; mass spectrum m/z 97.06514 (calcd for C_6H_9O, 97.06534).

1-Acetoxy-1-vinylcyclobutane (25) To a solution of 11 ml (1.64 M, 18 mmol) of vinylmagnesium bromide in THF at 0°C was added 1.0 g (14.3 mmol) of cyclobutanone in 6 ml of THF

over a 40 min period. The mixture was stirred at 25°C for 1 h, cooled to 0°C and quenched with 1.413 g (18 mmol) of acetyl chloride. The reaction mixture was stirred at room temperature for 1 h, and poured into ice-water. The organic material was extracted with 30 ml of ether in 3 portions. The ether extracts were combined, washed with 10 ml of saturated aqueous sodium bicarbonate and 10 ml of saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The solvent and low boiling material were removed by distillation and the residue was distilled at 43°C (5 mm Hg) to give 1.60 g (80%) of 1-acetoxy-1-vinylcyclobutane: ^{1}H NMR ($CDCl_3$) δ 1.54 - 1.92 (m, 2 H, CH_2), 2.02 (s, 3 H, CH_3), 2.08 - 2.26 (m, 1 H, CH_2), 2.31 - 2.42 (m, 3 H, CH_2), 5.18 (dd, 1 H, J = 0.6 Hz, J = 10.8 Hz, $=CH_2$ cis), 5.26 (dd, 1 H,J = 0.9 Hz, J = 17.4 Hz, $=CH_2$ trans), 6.15 (dd, 1 H, J = 10.8 Hz, J = 17.1 Hz, =CH-); IR (neat) 3080, 2982, 2945, 2872, 1735 (C=O), 1640, 1425, 1410, 1367, 1255, 1230, 1129, 1086, 1013, 985, 947, 919, 610 cm^{-1}; mass spectrum m/z 140.08372 (calcd for $C_8H_{12}O_2$, 140.08373).

2-Vinylcyclobutanone (30) 2-Vinylcyclobutanone was prepared using the procedure reported by Trost and co-workers[77,78]: ^{1}H NMR ($CDCl_3$) δ 1.90 - 2.05 (m, 1 H, O=C-$CH_2C\underline{H}_2$), 2.20 - 2.35 (m, 1 H, $O=CCH_2C\underline{H}_2$), 2.90 - 3.17 (m, 2 H, $O=CCH_2$), 3.97 - 4.30 (m, 1 H, CH), 5.12 - 5.20 (m, 2 H,

$=CH_2$), 5.80 - 5.95 (m, 1 H, =CH-); mass spectrum m/z 96.05752 (calcd for C_6H_8O, 96.05757).

Preparation of allylcyclopropane (36)

2-Cyclopropylethanol This compound was prepared from vinylcyclopropane (5) using the hydroboration-oxidation procedure developed by Brown[79]. To a solution of 3.405 g (50 mmol) of vinylcyclopropane (5) in 25 ml of THF at 0°C under nitrogen was added 20 ml (0.88 M, 17.6 mmol) of borane-THF solution. The reaction mixture was stirred for 12 h while slowly warming to room temperature. Unreacted borane was destroyed by adding 12.5 ml of water. After 25 ml of 3 N NaOH was added in one portion, 14 ml of 30% hydrogen peroxide was added dropwise to maintain the temperature at about 40°C. The reaction mixture was stirred at 40°C for an additional 1 h, saturated with sodium chloride, poured into a separatory funnel, and extracted with 150 ml of ether in 3 portions. The ether extracts were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. After the low boiling materials were distilled off, the residue was distilled at 140°C (lit.[80] bp 135°C) to give 3.7476 g (43.5 mmol, 87%) of 2-cyclopropylethanol: ^1H NMR ($CDCl_3$) δ 0.03 - 0.10 (m, 2 H, CH_2 ring), 0.40 - 0.48 (m, 2 H, CH_2 ring), 0.71 (m, 1 H, CH), 2.45 (q, 2 H, J = 6.6 Hz, O-

$CH_2C\underline{H}_2$), 2.48 (s, 1 H, OH), 3.69 (t, 2 H, J = 6.5 Hz, OCH_2); IR (neat) 3380 (OH), 3090, 3020, 2945, 1055, 1013 cm^{-1}.

Cyclopropylacetaldehyde The aldehyde was prepared from the alcohol prepared above using the procedure used for the preparation of cyclobutanecarboxaldehyde. To a suspension of 16.7 g (77.25 mmol) of pyridinium chlorochromate in 100 ml of methylene chloride at room temperature under nitrogen was added 4.435 g (51.5 mmol) of cyclopropylethanol in 40 ml of methylene chloride. The reaction mixture was stirred at room temperature for 2 h, diluted with 100 ml of ether, filtered through a Florisil column, and concentrated by distillation. The residue was distilled at 116°C (lit.[81] bp 112°C) to give 1.77 g (21.0 mmol, 42%) of cyclopropylacetaldehyde: ^1H NMR ($CDCl_3$) δ 0.17 (m, 2 H, CH_2CH_2 ring), 0.61 (m, 2 H, CH_2CH_2 ring), 0.97 (m, 1 H, CH), 2.90 (dd, 2 H, J = 2.0 Hz, J = 7.1 Hz, CH_2), 9.80 (t, 1 H, J = 2.0 Hz, O=CH); IR (neat) 3090, 3020, 1725 (C=O), 1020, 825 cm^{-1}.

Allylcyclopropane (36) This compound was prepared from the above aldehyde using the procedure for the preparation of vinylcyclobutane. In a flame dried 100 ml 3-neck round bottom flask equipped with a magnetic stirring bar, reflux condenser, and a dropping funnel, was placed 0.504 g (21.0 mmol) of sodium hydride (50% dispersion in mineral oil). The sodium hydride was washed with several

portions of dry pentane to remove the mineral oil. After the remaining pentane was removed using a vacuum pump, 15 ml of freshly distilled dimethyl sulfoxide was introduced via syringe, and the mixture was heated at 75 - 80°C until the evolution of hydrogen ceased. The resulting solution of methylsulfinyl carbanion was cooled in an ice bath, and 7.5 g (21.0 mmol) of methyltriphenylphosphonium bromide in 40 ml of dimethyl sulfoxide was added. After the resulting dark solution of the ylide was stirred at room temperature for 10 min, 1.77 g (21.0 mmol) of cyclopropylacetaldehyde was added. The reaction mixture was stirred at room temperature for 30 min followed immediately by distillation under reduced pressure to give 0.81 g (9.9 mmol, 47%) of allylcyclopropane which was collected in a dry ice/acetone trap at -78°C: ^{1}H NMR ($CDCl_3$) δ 0.04 - 0.09 (m, 2 H, CH_2CH_2 ring), 0.41 - 0.47 (m, 2 H, CH_2CH_2 ring), 0.68 -0.82 (m, 1 H, CH), 1.96 (dd, 2 H, J = 6.50 Hz, J = 6.50 Hz, CH_2), 4.96 (dd, 1 H, J = 10.0 Hz, J = 1.7 Hz, $=CH_2$ trans), 5.07 (dd, 1 H, J = 17.0 Hz, J = 1.7 Hz, $=CH_2$ cis), 5.88 (ddt, 1 H, J = 17.0 Hz, J = 10.34 Hz, J = 6.35 Hz, =CH-); IR (neat) 3090, 3018, 2920, 1642, 1018, 997 cm^{-1}; mass spectrum m/z 82.07838 (calcd for C_6H_{10}, 82.07825).

1-Cyclobutyl-1-cyclopropylethene (58) This compound was prepared from cyclobutanecarboxylic acid by treating it with cyclopropyllithium followed by Wittig olefination. Thus, cyclopropyllithium was prepared in 50 ml of ether by slowly adding 16.94 g (140 mmol) of bromocyclopropane to 2.0 g of lithium wire. To a stirred solution of 3.36 g of sodium hydride in 100 ml of ether was added 13.4 g (136 mmol) of cyclobutanecarboxylic acid. After addition of the acid was completed, the cyclopropyllithium was added by a cannula at room temperature under nitrogen and the reaction was stirred for 2 h at room temperature. The reaction was quenched by slowly adding water at 0°C. The solution was then extracted with ether. The ether extracts were combined, washed with saturated aqueous sodium chloride, sodium bicarbonate, and dried over anhydrous magnesium sulfate. The solvents were distilled off and the residue was distilled at 73°C (17 mm Hg) to give 2.4 g (19.3 mmol, 14%) of cyclobutyl cyclopropyl ketone: ^{1}H NMR ($CDCl_3$) δ 0.80 (m, 2 H, CH_2CH_2 cyclopropane ring), 1.00 (m, 2 H, CH_2CH_2 cyclopropane ring), 1.80 (m, 2 H, CH_2 cyclobutane ring), 1.90 (m, 1 H, CH cyclopropane ring), 2.25 (m, 4H, CH_2 cyclobutane ring), 3.3 (m, 1H, CH cyclobutane ring).

In a flame dried 100 ml 3-neck round bottom flask equipped with a magnetic stirring bar, reflux condenser, and a dropping funnel, was placed 0.463 g (19.3 mmol) of sodium

hydride (50% dispersion in mineral oil). The sodium hydride was washed with several portions of dry pentane to remove the mineral oil. After the remaining pentane was evacuated using a vacuum pump, 15 ml of freshly distilled dimethyl sulfoxide was introduced via syringe, and the mixture was heated at 75 - 80°C until the evolution of hydrogen ceased. The resulting solution of methylsulfinyl carbanion was cooled in an ice water bath, and 6.89 g (19.3 mmol) of methyltriphenylphosphonium bromide in 40 ml of dimethyl sulfoxide was added. After the resulting dark solution of the ylide was stirred at room temperature for 10 min, 2.4 g (19.3 mmol) of the ketone was added neat at room temperature. The color of the solution changed from yellow to orange and heat was generated. After stirring for 30 min, the reaction mixture was extracted with pentane. The pentane extracts were combined, washed with water, and dried over anhydrous magnesium sulfate. Pentane was removed by fractional distillation using a 30 cm Vigreux column. Short path distillation of the remaining oil at 140°C gave 0.413 g (18% yield) of the desired product: ^{1}H NMR ($CDCl_3$) δ 0.33 - 0.41 (m, 2 H, CH_2CH_2 cyclopropane ring), 0.52 - 0.61 (m, 2 H, CH_2CH_2 cyclopropane ring), 1.16 - 1.27 (m, 1 H, CH cyclopropane ring), 1.60 - 2.12 (m, 6 H, CH_2 cyclobutane

ring), 2.81 - 2.97 (m, 1 H, CH cyclobutane ring), 4.55 (s, 2 H, $=CH_2$); mass spectrum m/z 122.1093 (calcd for C_9H_{14}, 122.1095).

Preparation of 2-cyclopropyl-3,4-epoxy-1-butene (60)

This compound was prepared from cyclopropanecarboxaldehyde by reacting with vinylmagnesium bromide followed by epoxidation, oxidation and then Wittig olefination. Thus, in a flask containing 65 ml (1.05 M in THF) of vinylmagnesium bromide at 0°C under nitrogen was added a solution of 3.09 g (44 mmol) of cyclopropanecarboxaldehyde in 20 ml of THF. The reaction mixture was warmed to room temperature by removing the cold bath and then stirred for 1 h. The reaction was quenched with 60 ml of 5% HCl and then extracted with ether. The ether extracts were combined, washed with saturated sodium chloride and sodium bicarbonate, and dried over anhydrous magnesium sulfate. After the solvent was removed by distillation, the residue was distilled at 75°C (60 mm Hg) to give 3.507 g (81% yield) of the allylic alcohol: ^1H NMR ($CDCl_3$) δ 0.21 - 0.30 (m, 1 H, CH_2 cyclopropane), 0.31 - 0.39(m, 1 H, CH_2 cyclopropane), 0.47 - 0.60 (m, 2 H, CH_2 cyclopropane), 0.69 (s, 1 H, OH), 0.92 - 1.08 (m, 1 H, CH), 3.46 (dd, 1 H, J = 6.9 Hz, J = 6.9 Hz, CH-O), 5.10 (ddd, 1 H, J = 2.1 Hz, J = 2.1 Hz, J = 10.2 Hz, $=CH_2$ trans), 5.25 (ddd, 1 H, J = 2.1 Hz, J = 2.1 Hz, J = 17.4 Hz, $=CH_2$ cis), 5.94

(ddd, 1 H, J = 5.7 Hz, J = 10.5 Hz, J - 17.4 Hz, -CH=); ^{13}C NMR ($CDCl_3$) δ 2.03, 3.06, 17.39 (cyclopropyl), 77.19 (C-O), 114.63, 139.64 (olefinic); IR (neat) 3371, 3082, 3009, 2874, 1431, 1123, 1026, 991, 922, 656 cm^{-1}.

The allylic alcohol was epoxidized using t-butyl hydroperoxide in the presence of catalytic amounts of vanadyl acetylacetonate following a literature procedure[82]. To a flask containing 3.6322 g (41.2 mmol) of the allylic alcohol and 0.3194 g of vanadyl acetylacetonate in benzene at reflux under nitrogen was added 27 ml of t-butyl hydroperoxide (3.15 M solution in benzene) dropwise over 1 h. After the addition was complete, the reaction mixture was quenched with ether, washed with saturated sodium sulfite, dried over anhydrous magnesium sulfate, and concentrated. The resulting residue was purified by column chromatography (R_f = 0.37, 1 : 2 hexanes/ethyl acetate) to give 1.6564 g (35% yield) of a diastereomeric mixture (2.3 : 1) of the desired epoxy alcohol:

Diastereomer A: ^1H NMR ($CDCl_3$) δ 0.21 - 0.48 (m, 2 H, CH_2 cyclopropane), 0.50 - 0.65 (m, 2 H, CH_2 cyclopropane), 0.92 (m, 1 H, CH cyclopropane), 1.90 (s, 1 H, OH), 2.78 (dd, 1 H, J = 4.8 Hz, J = 3.0 Hz, CH_2-O), 2.83 (dd, 1 H, J = 4.8 Hz, J = 4.5 Hz, CH_2-O), 3.09 - 3.19 (m, 2 H, HO-CH-CH-O).

Diastereomer B: ^{1}H NMR ($CDCl_3$) δ same except 1.05 (m, 1 H, CH), 1.68 (s, 1 H, OH), 2.74 (dd, 1 H, J = 4.8 Hz, J = 4.0 Hz, CH_2-O), 2.89 (dd, 1 H, J = 4.8 Hz, J = 2.4 Hz, CH_2-O).

The following spectral data were obtained from the mixture: IR (neat) 3420 (OH), 3090, 3010, 2880, 1258, 1028, 990, 922, 850, 858 cm^{-1}; mass spectrum m/z 114.06762 (calcd for $C_6H_{10}O_2$, 114.06808).

The epoxy alcohol was oxidized following a literature procedure[83]. To a solution of 34 g of pyridine in 1800 ml of methylene chloride at 0°C under nitrogen 21.45 g (215 mmol) of dry chromic acid (CrO_3) in small portions. The resulting burgundy solution was stirred at room temperature for 30 min and then cooled to 0°C. A solution of 2.4485 g (21.45 mmol) of the epoxy alcohol in 100 ml of methylene chloride was added dropwise to the oxidizing mixture. The mixture was stirred at room temperature for 3 h. The solution was then decanted from the gummy residue, washed with ice-cold 5% HCl, saturated sodium carbonate, and saturated sodium chloride, and finally dried over anhydrous magnesium sulfate. After the solvent was removed by distillation, the residue was distilled at 60°C (30 mm Hg) to dive 1.8519 g (77% yield) of the desired epoxy ketone: ^{1}H NMR ($CDCl_3$) δ 0.92 - 0.99 (m, 2 H, CH_2CH_2), 1.01 - 1.16 (m,2 H, CH_2CH_2), 2.05 (tt, 1 H, J = 7.5 Hz, J = 4.5 Hz, CH), 2.99 (dd, 1 H, J = 2.4 Hz, J = 6.0 Hz, CH_2-O), 3.05 (dd, 1 H, J = 4.8 Hz, J = 6.0 Hz, CH_2-O),

3.50 (dd, 1 H, J = 2.4 Hz, J = 4.8 Hz, CH-O); IR (neat) 3013, 1701, 1445, 1398, 1358, 1234, 1196, 1088, 1067, 991, 957, 901, 854, 733 cm^{-1}; mass spectrum m/z 112.05235 (calcd for $C_6H_8O_2$, 112.05243).

The epoxy ketone was converted to 2-cyclopropyl-3,4-epoxy-1-butene following a literature procedure[84]. To a solution of 3.3 ml of diisopropylamime in dry THF at 0°C under nitrogen was added 9.4 ml (2.5 M in hexane) of n-butyllithium. After the mixture was stirred at room temperature for 20 min, the solution was transferred by a cannula to a suspension of 8.4 g (15.7 mmol) of methyltriphenylphosphonium bromide in 45 ml of THF at 0°C. The resulting reaction mixture was stirred at 0°C for 2 h and then treated with 1.85 g (15.7 mmol) of the epoxy ketone dissolved in 20 ml of THF. The reaction mixture was stirred at room temperature for 4 h, and quenched with cold saturated ammonium chloride. The mixture was diluted with ether, washed with 5% HCl, saturated sodium chloride, and sodium bicarbonate, and then dried over anhydrous magnesium sulfate. After the solvent was removed by distillation, the residue was distilled at 85°C (100 mm Hg) to give 0.9616 g (56%) of the desired product: ^1H NMR ($CDCl_3$) δ 0.39 (m, 1 H, CH_2 cyclopropane), 0.57 (m, 1 H, CH_2 cyclopropane), 0.68 (m, 2 H, CH_2CH_2), 1.28 (m, 1 H, CH), 2.82 (dd, 1 H, J = 2.7 Hz, J = 5.7 Hz, CH_2-O), 3.40 (dd, 1 H, J = 2.7 Hz, J = 4.5 Hz, CH-O),

4.80 (s, 1 H, $=CH_2$), 5.04 (s, 1 H, $=CH_2$); ^{13}C NMR ($CDCl_3$) δ 5.24, 7.15, 11.3 (cyclopropyl), 47.72, 53.81 (epoxy), 119.59, 147,18 (olefinic); IR (neat) 3088, 3057, 3000, 2255, 1643, 1474, 1429, 1024, 947, 908, 733, 650 cm^{-1}; mass spectrum m/z 110.07336 (calcd for $C_7H_{10}O$, 110.07317).

Preparation of endo-spiro[3-methylenebicyclo[2. 2. 1]heptane-2,2'-oxirane] (62) This compound was prepared following the procedure of Corey and Chaykovsky[68]. In a 100 ml 3-neck flask were placed 0.43 g of oil free sodium hydride, 3.67 g of trimethylsulfonium iodide, and 15 ml of dry dimethyl sulfoxide (DMSO). The mixture was stirred at 80°C for 1 h. To this solution, 2.0 g (16.3 mmol) of 3-methylene-2-norbornanone dissolved in 20 ml of DMSO was added using a dropping funnel. The reaction mixture was stirred at 80°C for 2 h and poured onto 100 g of ice. The mixture was extracted with ether. The ether extracts were combined, washed with saturated sodium chloride and sodium bicarbonate, dried over anhydrous magnesium sulfate, and concentrated. The resulting liquid was purified by column chromatography (R_f = 0.52, 5 : 1 hexanes/ethyl acetate) to give 1.355 g (61% yield) of compound 62: ^1H NMR ($CDCl_3$) δ 1.43 - 1.87 (m, 6 H, 3 CH_2's), 2.06 (m, 1 H, CH-C-O), 2.89 (m, 1 H, CH-C=), 2.90 (d, 1 H, J = 5.7 Hz, CH_2-O), 3.03 (d, 1 H, J = 5.7 Hz, CH_2-O), 4.60 (s, 1 H, $=CH_2$), 4.86 (s, 1 H, $=CH_2$); ^{13}C NMR ($CDCl_3$)

δ 29.20, 29.86, 36.93 (CH_2), 41.61, 45.36 (bridgehead), 56.45, 65.93 (C-O-C), 101.71, 153.43 (olefinic); IR (neat) 3120, 3080, 2990, 2900, 1730, 1683, 1495, 1460, 1400, 1250, 1120, 1085, 1028, 930, 884 cm^{-1}; mass spectrum m/z 136.08847 (calcd for $C_9H_{12}O$, 136.08882).

Reaction of vinylcyclopropane with diethyl sodium methylmalonate Diethyl sodium methylmalonate was prepared as follows. In a flame dried 10 ml round bottom flask was placed 0.014 g (0.58 mmol) of sodium hydride (50% dispersion in mineral oil). The sodium hydride was then washed with dry pentane under nitrogen. Most of the pentane was removed by a syringe and the remaining pentane was removed by evacuating the flask on a vacuum line. The flask was flushed with argon and 1 ml of THF was added. Diethyl methylmalonate was added to the sodium hydride suspension at 0°C at a rate sufficient to promote gentle evolution of hydrogen gas. The flask was allowed to warm to room temperature and stirred until the solution became homogeneous. The resulting solution was cooled to -78°C before use.

To a flask containing 0.1315 g (0.53 mmol) of bis(acetonitrile)palladium chloride in 10 ml of THF at room temperature under nitrogen was added 0.072 g (1.06 mmol) of vinylcyclopropane (5) and the mixture was stirred for 10 min at room temperature. After the solution turned to a reddish

brown homogeneous solution, the temperature of the mixture was lowered to -78°C, 0.1073 g (1.06 mmol) of freshly distilled triethylamine was added, and the reaction mixture was stirred for 30 min. The temperature was raised to -60°C and pre-cooled diethyl sodium methylmalonate was added using a canula. After stirring for 30 min at -60°C, the reaction was diluted with 100 ml of ether, washed with saturated aqueous ammonium chloride (30 ml x 3), dried over anhydrous magnesium sulfate, and concentrated. The concentrate was purified by flash column chromatography (R_f = 0.34, 2 : 1 hexanes/ethyl acetate) to give 0.1498 g (74%) of product which was a mixture of π-allylpalladium compounds 10 and 11 (ratio 65 : 35). The ratio was calculated from integration of appropriate peaks in the ^1H NMR spectrum. The mixture was partially separated using column chromatography to give pure π-allylpalladium compound 10.

Compound 10: mp 107 - 108°C; ^1H NMR ($CDCl_3$) δ 1.25 (t, 6 H, J = 7.2 Hz, CH_2-C$\underline{H}_3$), 1.27 (d, 3 H, J = 6.3 Hz, CH-C$\underline{H}_3$), 1.45 (s, 3 H, C-CH_3), 2.15 (dd, 1 H, J = 11.1 Hz, J = 14.1 Hz, CH-C$\underline{H}_2$-C), 2.35 (dd, 1 H, J = 2.9 Hz, J = 14.3 Hz, CH-C$\underline{H}_2$-C), 3.52 (ddd, 1 H, J = 2.6 Hz, J = 10.73 Hz, J = 10.73 Hz, CH-CH-C$\underline{H}$-CH_2), 3.74 (dq, 1 H, J = 6.16 Hz, J = 10.94 Hz, CH_3-C$\underline{H}$-CH-CH), 4.18 (q, 4 H, J = 7.03 Hz, O-C$\underline{H}_2$-CH_3), 5.15 (dd, 1 H, J = 10.87 Hz, J = 10.87 Hz, CH-C$\underline{H}$-CH); ^{13}C NMR ($CDCl_3$) δ 14.12, 17.79, 20.34, 38.39, 53.18, 61.48, 74.24,

77.64, 113.33, 171.40. Anal. Calcd for $C_{13}H_{21}O_4PdCl$: C, 40.75; H, 5.52. Found: C, 40.70; H, 5.71.

Compound 11: ^1H NMR ($CDCl_3$) δ 1.15 (s, 3 H, C-CH_3), 1.28 (m, 9 H, CH-C$\underline{H}_3$ and CH_2-C$\underline{H}_3$), 1.56 (s, 3 H, CH-CH-C-C$\underline{H}_3$), 4.19 (m, 4 H, O-CH_2)4.35 (m, 1 H, CH_3-C$\underline{H}$=), 5.25 (d, 1 H, J = 12.9 Hz, CH-C$\underline{H}$-C).

Reaction of 1-acetyl-2-vinylcyclopropane (14) with phenylmercuric chloride Dilithium tetrachloropalladate was prepared as follows. Into a 50 ml round bottom flask equipped with a magnetic stirring bar was weighed 0.0466 g (1.1 mmol) of lithium chloride. The flask was heated by a heat-gun under vacuum to dry the lithium chloride. After the flask was cooled to room temperature, 0.0887 g (0.5 mmol) of palladium chloride and 20 ml of THF were added successively under nitrogen at room temperature. Stirring overnight gave a reddish brown homogeneous solution.

To a flask containing 0.5 mmol of dilithium tetrachloropalladate in 20 ml of THF at 0°C under nitrogen were added 0.1102 g (1.0 mmol) of 1-acetyl-2-vinylcyclopropane (14) and 0.1566 g (0.5 mmol) of phenylmercuric chloride successively. After stirred at 0°C for 2 h, the reaction was quenched with 20 ml of ether. The resulting yellow solution was washed with saturated ammonium chloride, dried over anhydrous magnesium sulfate, and filtered through Celite. After

removal of the solvent, the yield of compound 15 was 1.069 g (0.37 mmol, 74%). The product was crystallized using 5 : 1 hexanes/ethyl acetate: 0.753 g, 52% yield; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3 H, O=C-CH_3), 2.65 (dd, 1 H, J = 18.3 Hz, J = 8.7 Hz, CH_2-C=O), 2.96 (dd, 1 H, J = 4.5 Hz, J = 18.3 Hz, CH_2-C=O), 3.00 (d, 2 H, J = 6 Hz, PhCH_2), 3.78 (ddd, 1 H, J = 8.7 Hz, J = 4.5 Hz, J = 10.8 Hz, C<u>H</u>-CH_2-CO-), 4.04 (dt, 1 H, J = 11.1 Hz, J = 5.7 Hz, Ph-CH_2-C<u>H</u>), 5.07 (dd, 1 H, J = 10.8 Hz, J = 10.8 Hz, CH-C<u>H</u>-CH), 7.22 - 7.43 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) δ 29.30, 37.08, 44.95, 71.39, 81.44, 110.20, 125.91, 128.20, 136.92, 220.93; IR (film) 3751, 3065, 3030, 1718, 1601, 1558, 1541, 1518, 1494, 1454, 1429, 1359, 1161, 725 cm^{-1}.

The π-allylpalladium compound was easily decomposed by silica gel or neutral alumina to give 7-phenyl-3,5-heptadien-2-one (16): ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3 H, CO-CH_3), 3.47 (d, 2 H, J = 6.3 Hz, PhCH_2), 6.04 (d, 1 H, J = 15.7 Hz, CH=C<u>H</u>-CO-), 6.1 - 6.33 (m, 3 H, -CH_2-C<u>H</u>=C<u>H</u>-C<u>H</u>=CH-CO-), 7.03 - 7.30 (m, 5 H, Ar).

<u>Reaction of vinylcyclobutane (20) and E-2-chloromercurio-4,4-dimethyl-2-pentene (17)</u> To a solution of 0.5 mmol of dilithium tetrachloropalladate in 20 ml of THF were added 0.082 g (1.0 mmol) of vinylcyclobutane 20 and 0.1687 g (0.5 mmol) of E-2-chloromercurio-4,4-dimethyl-2-

pentene (17) successively at 0°C under nitrogen. The reaction was stirred for 2 h at 0°C and quenched with 20 ml of ether. The reaction mixture was worked up as described above. After removal of the solvents, the resulting yellow oil was purified by column chromatography on a silica gel column using 6 : 1 hexanes/ethyl acetate as the eluent to give 0.097 g (61% yield) of pure π-allylpalladium complex 21: decomposed at 181 - 182°C; R_f = 0.61, 6 : 1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 9 H, $-C(CH_3)_3$), 1.60 - 1.92 (m, 6 H, CH_2 cyclobutane ring), 1.98 - 2.13 (m, 2 H, CH-$C\underline{H}_2$-CH), 2.12 (s, 3 H, $C-CH_3$), 2.50 (p, 1 H, J = 7.70 Hz, CH cyclobutane ring), 3.25 (s, 1 H, $C-C\underline{H}-C(CH_3)_3$), 3.26 (t, 1 H, J = 6 Hz, $-CH_2-C\underline{H}-C-CH_3$); ^{13}C NMR ($CDCl_3$) δ 14.75, 18.64, 28.14, 28.55, 29.83, 33.58, 34.60, 35.83, 80.76, 92,57, 120.17. Anal. Calcd for $C_{13}H_{23}PdCl$: C, 48.61; H, 7.22. Found: C, 48.71; H, 6.94.

The structure of the compound was established by x-ray crystallography.

All subsequent π-allylpalladium compounds were prepared using the basic general procedure.

Reaction of 1-vinyl-1-cyclobutanol (22) and phenylmercuric chloride

Compound 23: R_f = 0.11, 3 : 1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.23 (d, 3 H, H = 6.6 Hz, CH-C<u>H</u>$_3$), 1.26 (t, 3 H, J = 6.9 Hz, CH_2-C<u>H</u>$_3$), 1.71 (dq, 2 H, J = 6.9 Hz, J = 6.9 Hz, CH-C<u>H</u>$_2$-CH_3) 3.12 (t, 1 H, J = 6.9 Hz, CH_2-C<u>H</u>), 3.24 (q, 1 H, J = 6.6 Hz, CH_3-C<u>H</u>), 5.35 (s, 1 H, OH).

Reaction of 1-acetoxy-1-vinylcyclobutane (25) and phenylmercuric chloride

Compound 27: R_f = 0.67, 5 : 1 hexanes/ethyl acetate; 0.0091 g, 12% yield; ^1H NMR ($CDCl_3$) δ 1.92 - 2.00 (m, 2 H, CH_2 cyclobutane ring), 2.61 - 2.78 (m, 4 H, CH_2 cyclobutane ring), 3.21 (d, 2 H, J = 7.2 Hz, $PhCH_2$), 5.18 - 5.31 (m, 1 H, =CH-), 7.16 - 7.35 (m, 5 H, Ar).

Compound 28: R_f = 0.44; 0.0216 g, 22% yield; ^1H NMR ($CDCl_3$) δ 1.56 - 1.82 (m, 1 H, CH_2 cyclobutane ring), 1.82 - 1.94 (m, 1 H, CH_2 cyclobutane ring), 2.03 (s, 3 H, CO-CH_3), 2.33 - 2.52 (m, 4 H, CH_2 cyclobutane ring), 6.54 (d, 1 H, J = 16 Hz, =CH-C-O), 6.63 (d, 1 H, J = 16 Hz, Ph-CH=), 7.18 - 7.43 (m, 5 H, Ar).

Reaction of Allylcyclopropane (36) and Phenylmercuric Chloride

Compound 37: The crude material was purified by a column chromatography using 4 : 1 hexanes/ethyl acetate to give 0.1425 g (95% yield) of yellow solid which was crystallized from methylene chloride, ethyl ether, and hexanes to give 0.0702 g (47% yield) of π-allylpalladium compound 37: mp 152 - 153°C (lit.[22] mp 153 - 154°C); R_f = 0.38, 3 : 1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.21 - 1.30 (d, 3 H, J = 6.3 Hz, CH-C<u>H</u>$_3$), 1.79 - 2.11 (m, 2 H, CH-C<u>H</u>$_2$-CH$_2$-Ph), 3.54 - 3.76 (m, 2 H, C<u>H</u>-CH-C<u>H</u>-CH$_3$), 5.00 - 5.14 (dd, 1 H, J = 10.8 Hz, J = 10.8 Hz, CH-C<u>H</u>-CH-CH$_3$), 7.11 - 7.34 (m, 5 H, Ar).

Reaction of allylcyclopropane (36) and E-2-chloromercuri-4,4-dimethyl-2-pentene (17)

Compound 43: 0.0496 g, 32% yield; mp 156 - 157°C; R_f = 0.45, 10 : 1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 0.00 - 0.07 (m, 2 H, CH_2CH_2 cyclopropane ring), 0.32 - 0.44 (m, 2 H, CH_2CH_2 cyclopropane ring), 0.60 - 0.74 (m, 1 H, CH cyclopropane ring), 1.23 (s, 9 H, C(CH$_3$)$_3$), 1.30 - 1.52 (m, 2 H, CH-C<u>H</u>$_2$-CH$_2$-CH=), 1.57 - 1.82 (m, 2 H, CH-CH$_2$-C<u>H</u>$_2$-CH=), 2.11 (s, 3 H, C-CH$_3$), 3.22 (s, 1 H, (CH$_3$)$_3$C-C<u>H</u>-C), 3.26 - 3.35 (t, 1 H, J = 5.7 Hz, C-C<u>H</u>-CH$_2$); ^{13}C NMR ($CDCl_3$) δ 4.66, 4.80, 10.88, 14.58, 29.39, 29.78, 33.35, 33.56, 82.48, 92.54,

120.14. Anal. Calcd for $C_{13}H_{23}PdCl$: C, 48.61; H, 7.22. Found: C, 48.13; H, 7.52.

Compound 44: the yield of compound 44 was 12% based on the integration of appropriate ^1H NMR spectral peaks.

Reaction of pinenes with n-butylmercuric chloride

The reaction was run at room temperature for 2 days. After the usual workup, the residue was a yellow crystalline material. Recrystallization from methylene chloride and pentane gave yellow crystals (prism) which decomposed at 142°C.

Compound 51 from (S)-(-)-β-pinene (49): 71% yield; $[\alpha]_D^{20}$ = +73.33° ($CHCl_3$, 11.66 mg/ml); ^1H NMR ($CDCl_3$) δ 0.67 (d, 1 H, J = 14.9 Hz, =CH-C$\underline{H}_2$), 0.75 (s, 3 H, C(CH_3)$_2$), 0.78 (d, 3 H, J = 8.3 Hz, CH-C$\underline{H}_3$), 1.20 (s, 3 H, C(CH_3)$_2$), 1.98 (m, 1 H, =CH-C$\underline{H}_2$), 2.01 (s, 3 H, C-CH_3), 2.80 (m, 1 H, C$\underline{H}$-CH_3), 4.50 (s, 1 H, =C$\underline{H}$-CH_2), 4.74 (s, 1 H, (CH_3)$_2$C-C$\underline{H}$); ^{13}C NMR ($CDCl_3$) δ 15.3, 22.5, 22.9, 27.7, 34.4, 39.0, 41.4, 79.3, 90.9, 113.7; IR (neat) 2960, 2930, 2870, 2830, 1480, 1465, 1445, 1390, 1380, 1370, 1360, 1210, 900 cm^{-1}. Anal. Calcd for $C_{10}H_{17}PdCl$: C, 43.03; H, 6.14. Found: C, 43.36; 6.16.

The structure of compound 51 was established by x-ray crystallography.

Compound 51 from (S)-(-)-α-pinene (50): 20% yield; $[\alpha]_D^{20}$ = +73.28° ($CHCl_3$, 6.7 mg/ml).

Compound 53 from (R)-(+)-α-pinene (52): 20% yield; $[\alpha]_D^{20}$ = -73.18° ($CHCl_3$, 6.6 mg/ml).

Reaction of Carenes with n-butylmercuric chloride

Compound 56 from (+)-2-carene (54): 19% yield; $[\alpha]_D^{20}$ = -70.6° ($CHCl_3$, 7.24 mg/ml); ^1H NMR ($CDCl_3$) δ 1.05 (s, 3 H, $C(CH_3)_2$), 1.10 (d, 3 H, J = 7.1 Hz, CH-$C\underline{H}_3$), 1.32 (s, 3 H, $C(CH_3)_2$), 1.38 - 1.48 (m, 1 H, H_3C-CH-$C\underline{H}_2$), 1.56 - 1.69 (m, 1 H, H_3C-CH-$C\underline{H}_2$), 1.82 - 1.97 (m, 1 H, $(H_3C)_2C$-$C\underline{H}_2$), 2.09 - 2.28 (m, 1 H, $(H_3C)_2C$-$C\underline{H}_2$), 4.59 - 4.78 (m, 3 H, $C\underline{H}$-$C\underline{H}$-$C\underline{H}$); ^{13}C NMR ($CDCl_3$) δ 23.6, 29.7, 30.0, 31.5, 38.9, 39.4, 39.6, 90.1, 95.0, 97.2; IR (film) 2951, 2914, 2866, 1458, 754 cm^{-1}. Anal. Calcd for $C_{20}H_{34}Pd_2Cl_2$: C, 43.03; H, 6.14. Found: C, 42.88; H, 6.13.

Compound 56 from (+)-3-carene (55): 23% yield; $[\alpha]_D^{20}$ = -71.7° ($CHCl_3$, 7.14 mg/ml).

The structure of compound 56 was established by x-ray crystallography.

Reaction of 1-cyclobutyl-1-cyclopropylethene (58) and phenylmercuric chloride The product was a mixture of 2 stereoisomers 59a and 59b (R_f = 0.44, 4 : 1 hexanes/ethyl acetate; isomer ratio, 1 : 1.8) in 65% yield.

Isomer 59a: ^1H NMR ($CDCl_3$) δ 1.57 (d, 3 H, J = 6.7 Hz, CH-$C\underline{H}_3$), 1.60 - 2.06 (m, 6 H, CH_2 cyclobutane ring), 2.30 - 2.43

(m, 1 H, CH cyclobutane ring), 2.89 (d, 1 H, J = 17.0 Hz, $PhCH_2$), 2.99 (d, 1 H, J = 17.0 Hz, $PhCH_2$), 4.44 (dq, 1 H, J = 6 Hz, J = 12.0 Hz, H_3C-CH), 5.06 (d, 1 H, J = 12.0 Hz, H_3C-CH-CH-C), 5.05 - 7.28 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) δ 17.65, 18.45, 26.44, 29.70, 39.88, 41.66, 75.48, 104.58, 126.54, 128.422, 128.65, 129.90, 137.83.

Isomer 59b: ^1H NMR ($CDCl_3$) δ 1.33 (d, 3 H, J = 6 Hz, CH-CH_3), 1.60 - 2.06 (m, 6 H, CH_2 cyclobutane ring), 2.30 - 2.43 (m, 1 H, CH cyclobutane ring), 2.99 (d, 1 H, J = 17.0 Hz, $PhCH_2$), 3.10 (d, 1 H, J = 17.0 Hz, $PhCH_2$), 4.23 (dq, 1 H, J = 6 Hz, J = 12.0 Hz, H_3C-CH), 4.65 (d, 1 H, J = 12.0 Hz, H_3C-CH-CH-C), 7.05 - 7.28 (m, 5 H, Ar).

Reaction of 2-cyclopropyl-3,4-epoxy-1-butene (60) and phenylmercuric chloride The reaction was run at 0°C. The reaction time and reagents are listed in Table 1.

Z,E-3-Benzyl-2,4-hexadien-1-ol (61): ^1H NMR ($CDCl_3$) δ 1.33 (br s, 1 H, OH), 1.75 (dd, 3 H, J = 1.5 Hz, J = 6.6 Hz, CH_3), 3.53 (s, 2 H, $ArCH_2$), 4.32 (d, 2 H, J = 6.9 Hz, CH_2-O), 5.40 (t, 1 H, J = 6.9 Hz, CH_2-CH=), 5.81 (dq, 1 H, J = 15.3 Hz, J = 6.9 Hz, CH=CH-CH_3), 6.35 (dd, 1 H, J = 15.6 Hz, J = 0.9 Hz, CH=CH-CH_3), 7.13 - 7.21 (m, 3 H, Ar), 7.23 - 7.30 (m, 2 H, Ar).

E,E-3-Benzyl-2,4-hexadien-1-ol (61): ^1H NMR ($CDCl_3$) same except 1.61 (br s, 1 H, OH), 1.70 (dd, 3 H, J = 6.6 Hz, J =

0.9 Hz, CH_3), 3.62 (s, 2 H, $ArCH_2$), 4.27 (d, 2 H, CH_2-O), 5.69 (dq, 1 H, J = 15.9 Hz, J = 6.3 Hz, =C<u>H</u>-CH_3), 5.76 (t, 1 H, J = 6.9 Hz, =C<u>H</u>-CH_2), 6.08 (dd, 1 H, J = 15.3 Hz, J = 1.2 Hz, C<u>H</u>=CH-CH_3).

The following spectral data were obtained from the mixture: ^{13}C NMR ($CDCl_3$) δ 13.36, 18.18 (CH_3), 33.02, 40.46 (benzylic), 58.80, 59.58 (CH_2-O), 126.03, 126.23, 126.84, 127.91, 128.33, 128.50, 128.75, 129.21, 133.97, 138.43, 139.88 (aromatic and olefinic); IR (neat) 3342, 3084, 3061, 2912, 1603, 1495, 1452, 1070, 1011, 960, 733, 698 cm^{-1}; mass spectrum m/z 188.12048 (calcd for $C_{13}H_{16}O$, 188.12012).

<u>Reaction of endo-spiro[3-methylenebicyclo[2. 2. 1]heptane-2,2'oxirane] (62) and phenylmercuric chloride</u> The reaction was run at 0°C for 10 h with 5% water. The product was isolated by column chromatography.

<u>Compound 63</u>: R_f = 0.41, 5 : 1 hexanes/ethyl acetate; 73% yield; ^1H NMR ($CDCl_3$) δ 1.42 - 1.54 (m, 1 H, CH_2), 1.57 (s, 1 H, CH_2), 1.59 - 1.69 (m, 2 H, CH_2), 1.75 - 1.92 (m, 2 H, CH_2), 2.33 (dt, 1 H, J = 11.4 Hz, J = 3.3 Hz, OC-C<u>H</u>-CH_2-Ar), 2.44 (dd, 1 H, J = 11.4 Hz, J = 11.1 Hz, CH_2-Ar), 2.47 (s, 1 H, CH bridgehead), 2.67 (d, 1 H, J = 4.7 Hz, CH bridgehead), 3.12 (dd, 1 H, J = 13.9 Hz, J = 3.4 Hz, $ArCH_2$), 7.16 - 7.32 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.29, 25.43, 32.10, 36.95, 37.98, 50.50, 55.94 (aliphatic), 126.08, 128.48, 140.30,

218.48; IR (neat) 3028, 2964, 2878, 1742, 1495, 1454, 1080, 943, 750, 702 cm^{-1}; mass spectrum m/z 200.12043 (calcd for $C_{14}H_{16}O$, 200.12012).

Compound 64: R_f = 0.27, 5 : 1 hexanes/ethyl acetate; 54% yield; ^1H NMR ($CDCl_3$) δ 1.16 - 1.26 (m, 1 H, CH_2), 1.41 (d, 1 H, J = 9.9 Hz, CH_2), 1.59 (m, 2 H, CH_2), 1.63 - 1.77 (m, 1 H, CH_2), 2.02 (s, 1 H, OH), 2.04 (d, 1 H, J = 11.4 Hz, CH_2), 2.71 (s, 1 H, CH bridgehead), 2.85 (s, 1 H, CH bridgehead), 3.73 (d, 1 H, J = 12.3 Hz, CH_2-O), 3.91 (d, 1 H, J = 12.3 Hz, CH_2-O), 5.05 (s, 1 H, $=CH_2$), 5.11 (s, 1 H, $=CH_2$).

The peak at 2.02 disappeared upon addition of D_2O.

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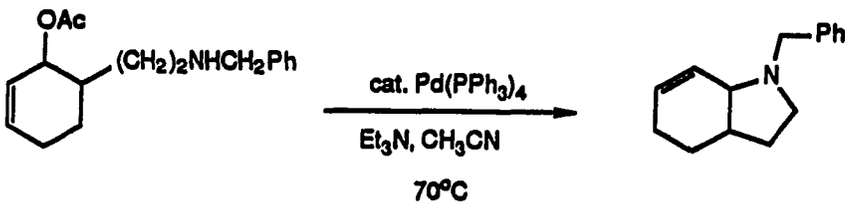
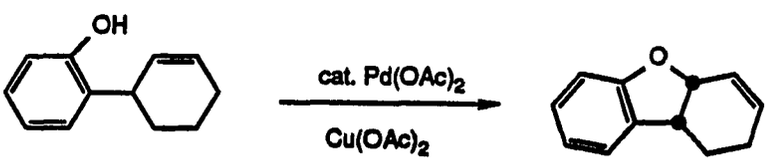
PART II. PREPARATION OF HETEROCYCLES VIA π-ALLYLPALLADIUM FORMATION AND INTRAMOLECULAR NUCLEOPHILIC ATTACK ON π-ALLYLPALLADIUM COMPOUNDS

INTRODUCTION

There are many examples of palladium-assisted preparations of heterocyclic compounds. The majority of these reactions involve the synthesis of a carbon-heteroatom bond via either π-allylpalladium formation followed by intramolecular nucleophilic displacement of the palladium moiety[1-3] (eq. 1) or intramolecular oxy-[4-6] or amino-palladation[7-10] followed by elimination of a palladium-hydride species (eqs. 2 and 3). Palladium-assisted carbon-carbon bond formation has also been used to prepared heterocyclic compounds. Trost and Verhoeven have reported a



(1)[2]



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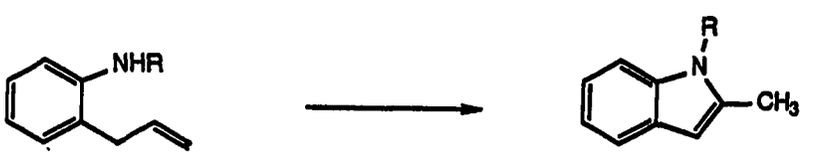
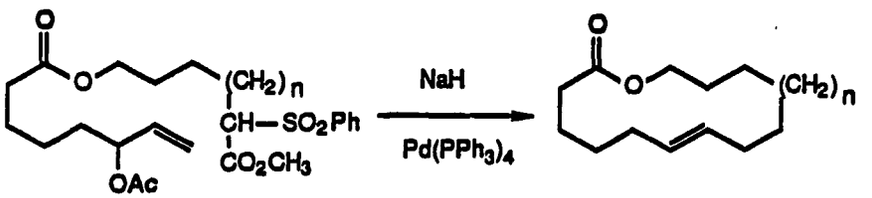


(3)[7]

novel method for the preparation of large ring lactones by carbon-carbon bond formation via intramolecular nucleophilic attack on a π-allylpalladium species (eq. 4)[11]. The intermediate π-allylpalladium species was formed from an allylic acetate and palladium(0) catalyst. Reactions involving oxidative addition to carbon-halogen bonds to form an arylpalladium species followed by addition to an olefin and elimination of a palladium hydride species have also been used in the synthesis of heterocyclic compounds (eq. 5)[12-17].



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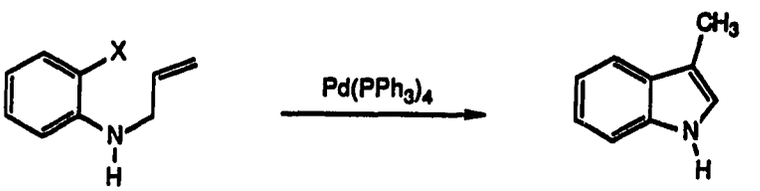


(5)

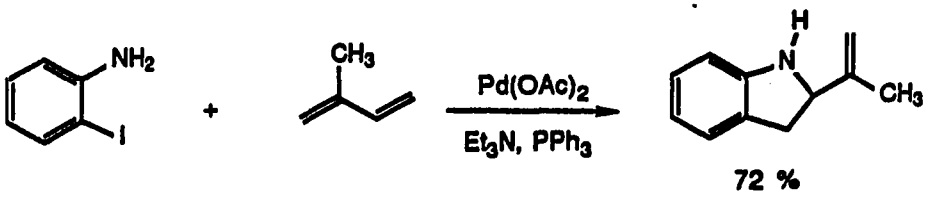
X = Br

X = I

X = Br 60 %

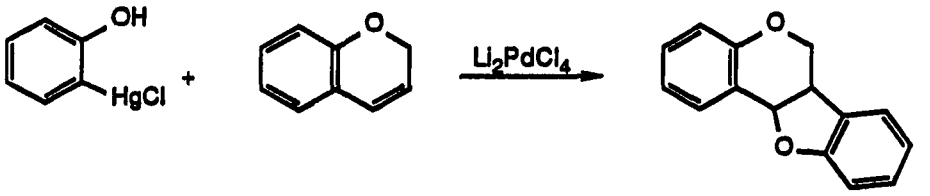
X = I 87 %

A couple of approaches to annulations forming both a carbon-carbon and a carbon-heteroatom bonds have appeared in the literature. O'Connor et al.[18] reported the preparation of a heterocyclic compound from o-iodoaniline and isoprene in the presence of a palladium(0) catalyst and a base (triethylamine) (eq. 6). In this reaction, an arylpalladium



(6)

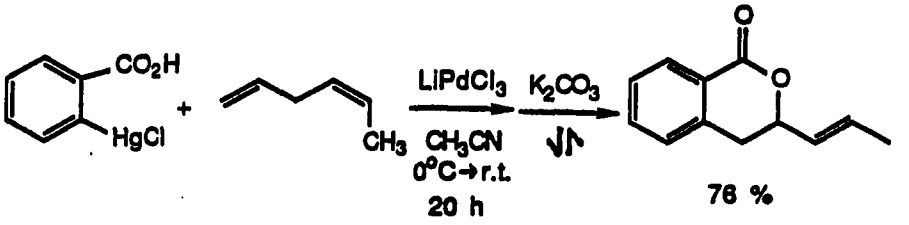
species was generated by oxidative addition of the carbon-iodide bond to a palladium(0) species. The reaction involves addition of the arylpalladium species across the less hindered carbon-carbon double bond to form a π-allylpalladium intermediate, followed by intramolecular nucleophilic attack of the amine nucleophile on the π-allyl ligand. Horino and Inoue[19] reported a similar approach to heterocyclic compounds (eq. 7). Their approach involved



(7)

formation of an arylpalladium species via transmetallation of o-(chloromercurio)phenol with a palladium(II) salt. Addition of the arylpalladium intermediate across the double bond to form a σ-palladium intermediate, followed by intramolecular nucleophilic displacement of the σ-palladium moiety, resulted in the product.

Recently, a convenient one-pot approach to a wide variety of heterocycles starting with dienes or vinylcyclopropanes and functionally substituted organomercurials was reported by Larock and co-workers[20]. These reactions involve initial π-allylpalladium formation and subsequent intramolecular π-allylpalladium displacement by a variety of oxygen and nitrogen nucleophiles (eqs. 8 and 9).



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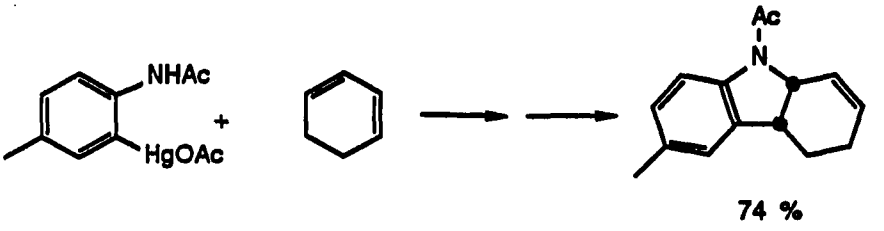
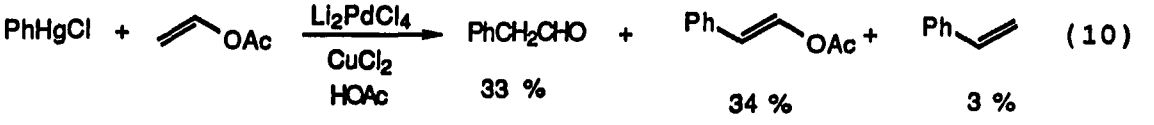
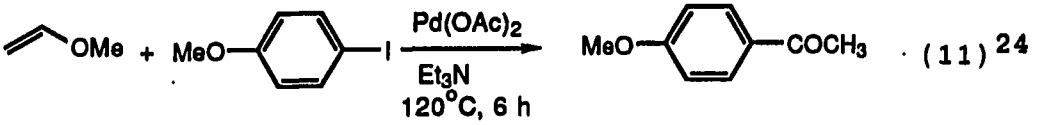


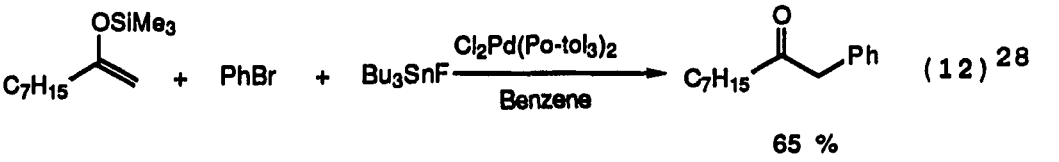
(9)

Although palladium-assisted cyclizations using conjugated or non-conjugated dienes and vinylcyclopropanes were explored[20], no information is available on cyclizations using hetero-substituted dienes. Heck[21] reported reactions of phenylmercuric chloride with vinyl acetate or methyl vinyl ether in the presence of catalytic amounts of dilithium tetrachloropalladate and stoichiometric amounts of cupric chloride (eq. 10). Since Heck's initial report, a number



of studies of palladium-assisted carbon-carbon bond formation using vinyl acetate[22], vinyl ethers[23-28] (eq. 11), and enol silyl ethers[29,30] (eq. 12) have been reported.

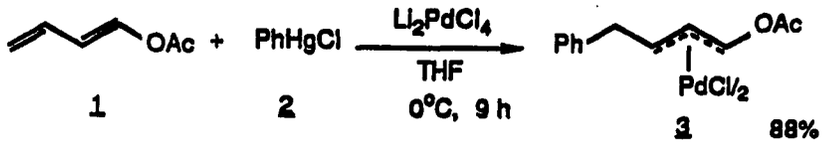




Because no information is available for cyclizations using hetero-substituted dienes, we decided to examine reactions of acetoxy-substituted butadienes and functionally substituted organomercurials in the presence of a palladium(II) salt.

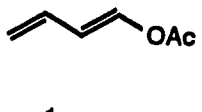
RESULTS AND DISCUSSION

Initially, the reaction of 1-acetoxy-1,3-butadiene (1) and phenylmercuric chloride (2) in the presence of dilithium tetrachloropalladate was run to determine if π-allylpalladium compounds substituted by a hetero atom can be formed (eq. 13). Surprisingly, the reaction gave π-allylpalladium compound 3 in high yield.



1 2 3 88% (13)

The above results indicated that acetoxy-substituted dienes should be applicable to palladium-catalyzed annulations. The following dienes (1, 4 - 8) and organomercurials (9, 10) were considered for our study of these palladium-promoted hetero-annulation reactions. Compounds 4 - 6 and 8 were prepared from the corresponding α,β-unsaturated ketone or aldehyde and isopropenyl acetate in the presence of catalytic amount of sulfuric acid following the procedure of Bohlmann and co-workers[31] (eq. 14). The preparation of compound 7 involved rearrangement of a propargylic acetate to an allenic acetate in the presence of silver acetate. The allenic acetate was then treated with sodium chloride to yield compound 7 (eq. 15)[32].



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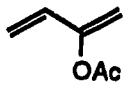

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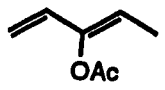

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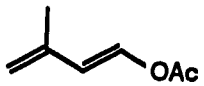

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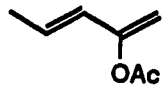

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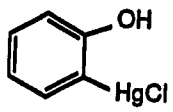

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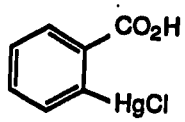

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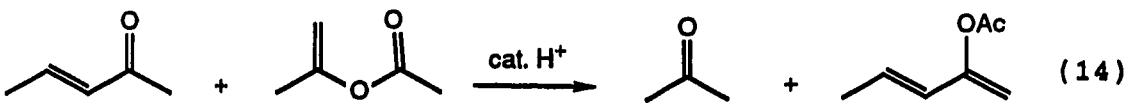
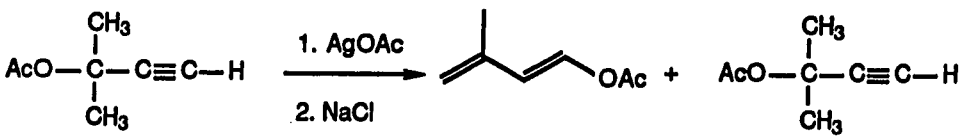


(14)

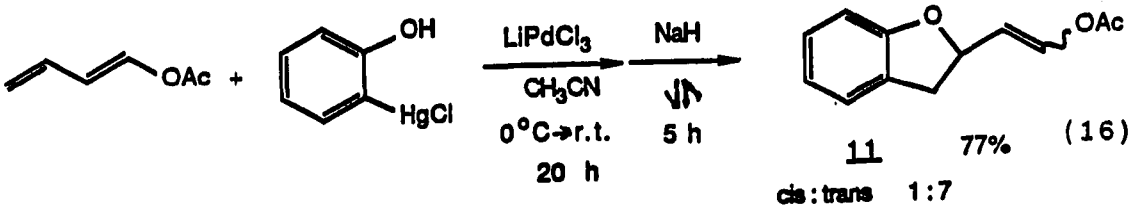
8 74 %



(15)

7 12 %

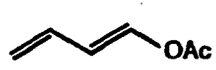
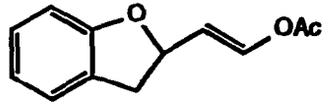
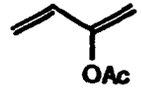
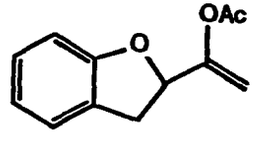
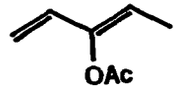
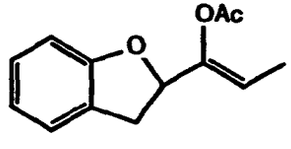
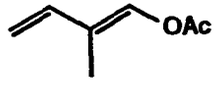
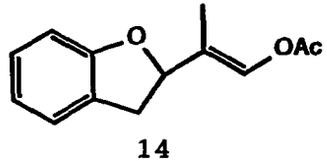
o-(Chloromercurio)phenol was initially subjected to the hetero-annulation reaction conditions listed in Table 1. A typical reaction is represented by eq. 16. The yields of the

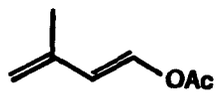
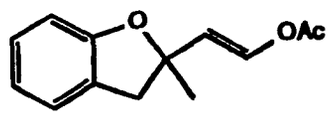
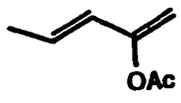
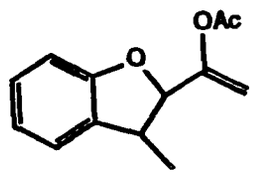
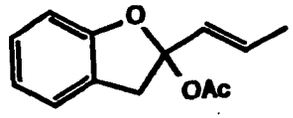


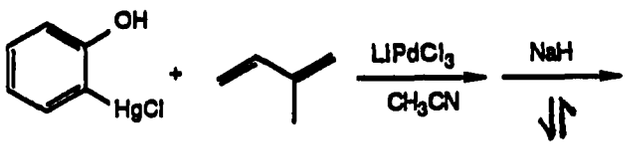
(16)

reactions in THF in the presence of dilithium tetrachloropalladate were lower than the yields in acetonitrile in the presence of lithium trichloropalladite (entries 1 - 3 and 5). It is not clear whether it is the polarity of the solvents which affects the reaction or some other factor. Terminal double bonds appear to be more reactive than internal double bonds, entries 1, 4, and 5 vs entries 2, 3, and 6. It is worth noting that the reaction of compound 4 produced only compound 12. In contrast, a similar reaction of isoprene was observed to give a mixture of compounds 18 and 19 in a ratio of 4 : 1 (eq. 17)[20]. An electronic effect in the starting dienes might be the best explanation for the reduced reactivity of the enol acetate double bond and the regioselectivity observed in entry 2. When the arylpalladium intermediate is given a choice between an internal double bond and a terminal double

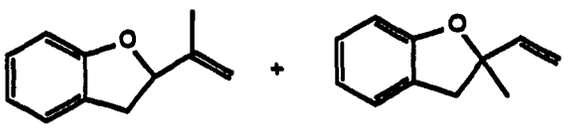
Table 1. The reactions of organomercurial 9 with dienes 1, 4 - 8

entry	diene	product	$LiPdCl_3/CH_3CN$ % yield	Li_2PdCl_4/THF % yield
1	 1	 11	77	54
2	 4	 12	53	6
3	 5	 13	28	0
4	 6	 14	51	---

5	 	65	64
	7 15		
6	  	13	---
	8 16 17		



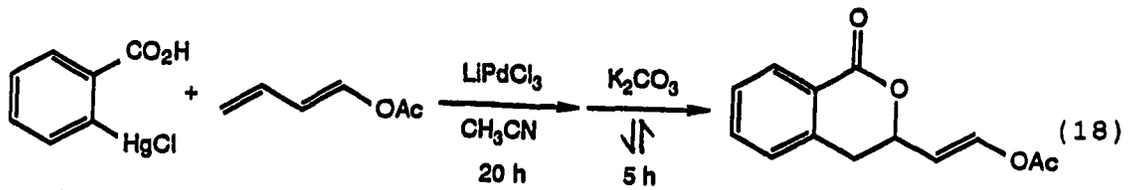
(17)



18 4 : 1 19

bond bearing an acetoxy group as in entry 6, the reaction product is a mixture of compounds 16 and 17 with compound 17 present as the major isomer (1 : 2.5 ratio). In this case, a steric effect seemed to affect the direction of arylpalladium addition to the double bond. The structures of compounds 16 and 17 were determined by analysis of the ^1H NMR spectrum of compound 16 and from the molecular ion peaks in the GC-MS of compounds 16 and 17.

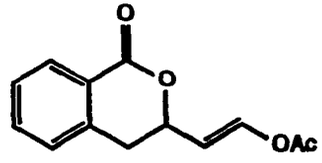
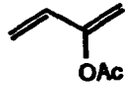
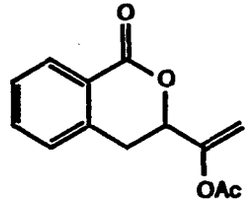
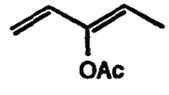
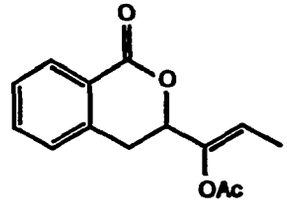
o-(Chloromercurio)benzoic acid 10 was also used in palladium-promoted annulation onto dienes 1 and 4 - 6. The reaction is represented by eq. 18 and the results are summarized in Table 2.

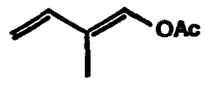
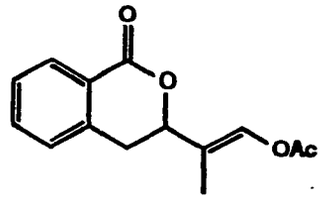
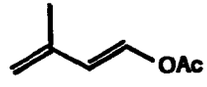
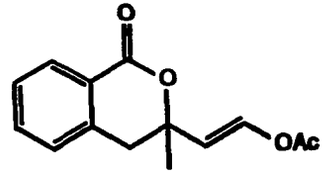


(18)

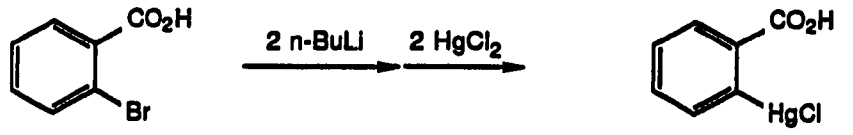
10 1 20

Table 2. The reactions of organomercurial 10 with dienes 1 and 4 - 7

entry	diene	product	$LiPdCl_3/CH_3CN$ % yield	Li_2PdCl_4/THF % yield
1	 1	 20	84	99
2	 4	 21	53	33
3	 5	 22	54	84

4			72	59
	6	23		
5			61	44
	7	24		

Mercurial 10 was prepared from o-bromobenzoic acid in 14% yield (eq. 19)[33]. In contrast to the reaction of mercurial 9, the reactions of mercurial 10 with dienes 1, 4 - 7 have neither a consistent solvent effect nor an electronic



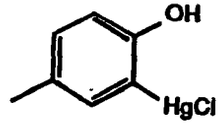
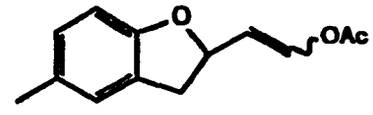
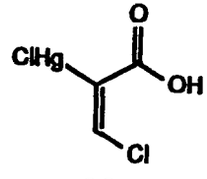
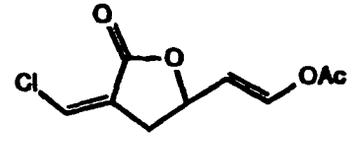
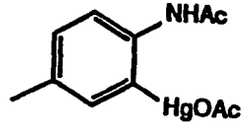
(19)

10 14 %

effect. Reactions run in THF using dienes 1 and 5 provide higher yields than those run in CH_3CN (entries 1 and 3). The reactions of terminal acetates provided products in higher yields (entries 1, 4, and 5) in both acetonitrile and THF as compared to internal acetates (entries 2 and 3). An exception was compound 5 which gave a higher yield of product in THF (entry 3).

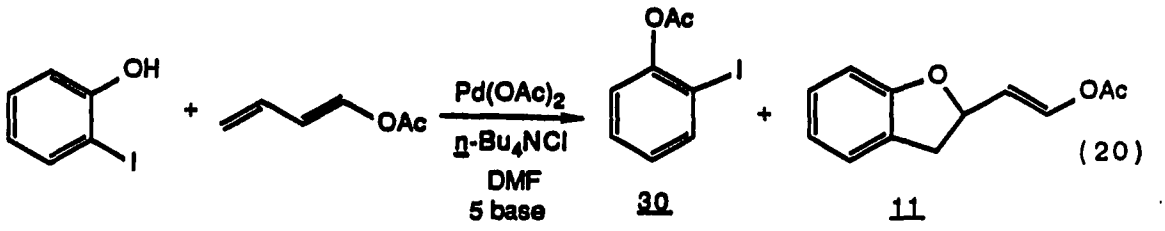
Organomercurials 25 - 27 were also used in the reaction. The results are summarized in Table 3. The reactions of diene 1 with organomercurials 25 or 26 gave products 28 (41% yield) and 29 (24% yield) respectively. On the other hand, reaction using the amine nucleophile 27 did not give any identifiable product.

Table 3. The reactions of organomercurials 25 - 27 with diene 1

entry	organomercurial	conditions[a]	product	yield %
1	 25	A	 28	41
2	 26	B	 29	24
3	 27	A	---	---

[a]Procedure A: The reaction was run in THF using Li_2PdCl_4 starting 0°C and slowly warming to room temperature over 20 h. The reaction was treated with sodium hydride and then refluxed for 5 h.
Procedure B: same as Procedure A except treating with K_2CO_3.

The reaction of diene 1 and o-iodophenol with 2.5 mol % palladium acetate, was explored to determine if a catalytic version of the annulation was possible (eq. 20).



(20)

30 11

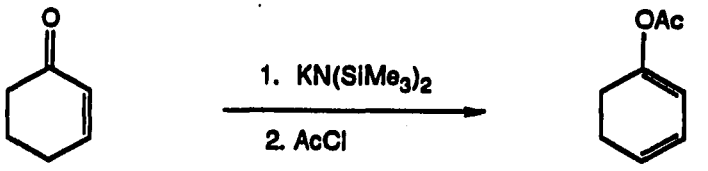
base		
KOAc	20 %	11 %
NaOAc	27 %	19 %

An inseparable mixture of compounds 30 and 11 was isolated. The yield of each compound was estimated from integration of the appropriate peaks in the proton NMR spectra of the purified mixture. The formation of compound 30 may be due to base-catalyzed trans esterification of o-iodophenol by the diene 1. Further attempts to optimize this catalytic reaction were not made.

The success of the annulation reactions using acyclic acetoxy-dienes prompted us to extend the chemistry to cyclic acetoxy-dienes. Compound 31, 1-acetoxy-1,3-cyclohexadiene, was chosen as a model.

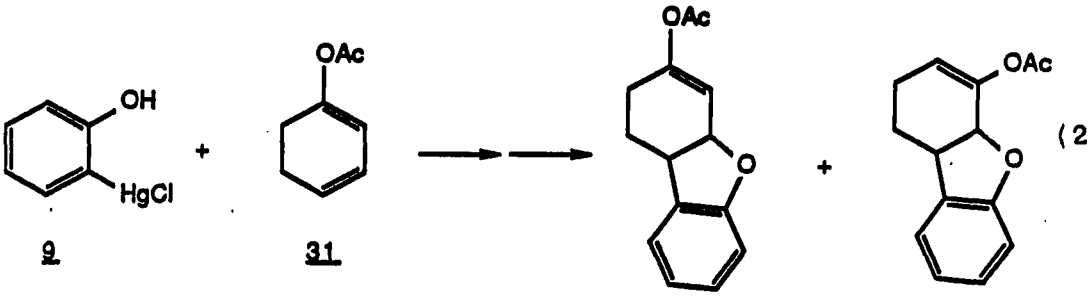
Compound 31 was prepared using the procedure of Kawasaki et al.[34] (eq. 21). Interestingly, the reaction of compound 31 and mercurial 9 produced the desired compound 32 along with an unexpected compound 33 in 50% combined yield in a 1 :

1 ratio (eq. 22). Similarly, the reaction of compound 31 with mercurial 26 gave a mixture of two isomers 34 and 35 in a 1.7 : 1 ratio (eq. 23). It is believed that isomers 33 and



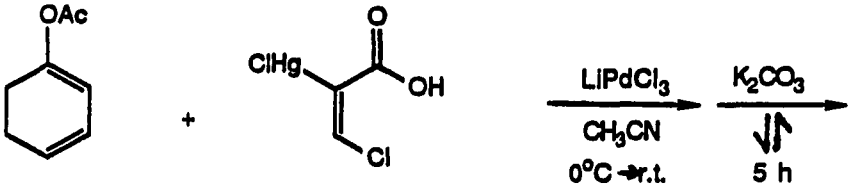
(21)

31 41 %

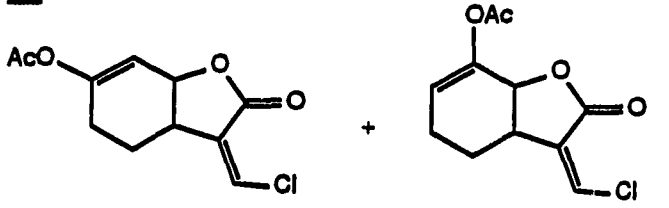


(22)

9 31 32 33



31 26

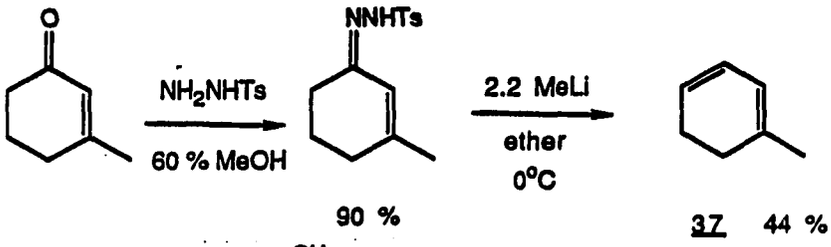


(23)

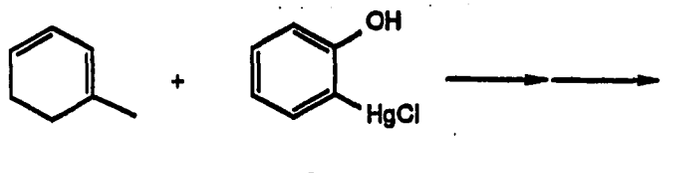
34 35

35 arise from addition of the initial organopalladium species to the less substituted carbon-carbon double bond with the organic group going to the internal carbon of the diene system (Scheme I, route b). Subsequent palladium migration results in a π-allylpalladium intermediate isomeric to the expected on formed by path a. Intramolecular displacement results in the isomers 33 and 35.

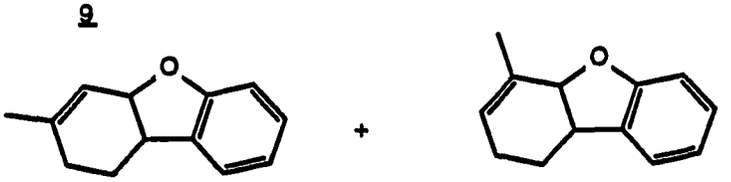
To explore the proposed mechanism, 1-methyl-1,3-cyclohexadiene (37) was used in the annulation reaction. The preparation of compound 37 was achieved by the method of Dauben et al. (eq. 24)[35]. The reaction of compound 37 and organomercurial 9 in the presence of lithium trichloropalladite produced the expected mixture of compounds 38 and 39, in a 47% yield (1 : 1.1) (eq. 25).



(24)



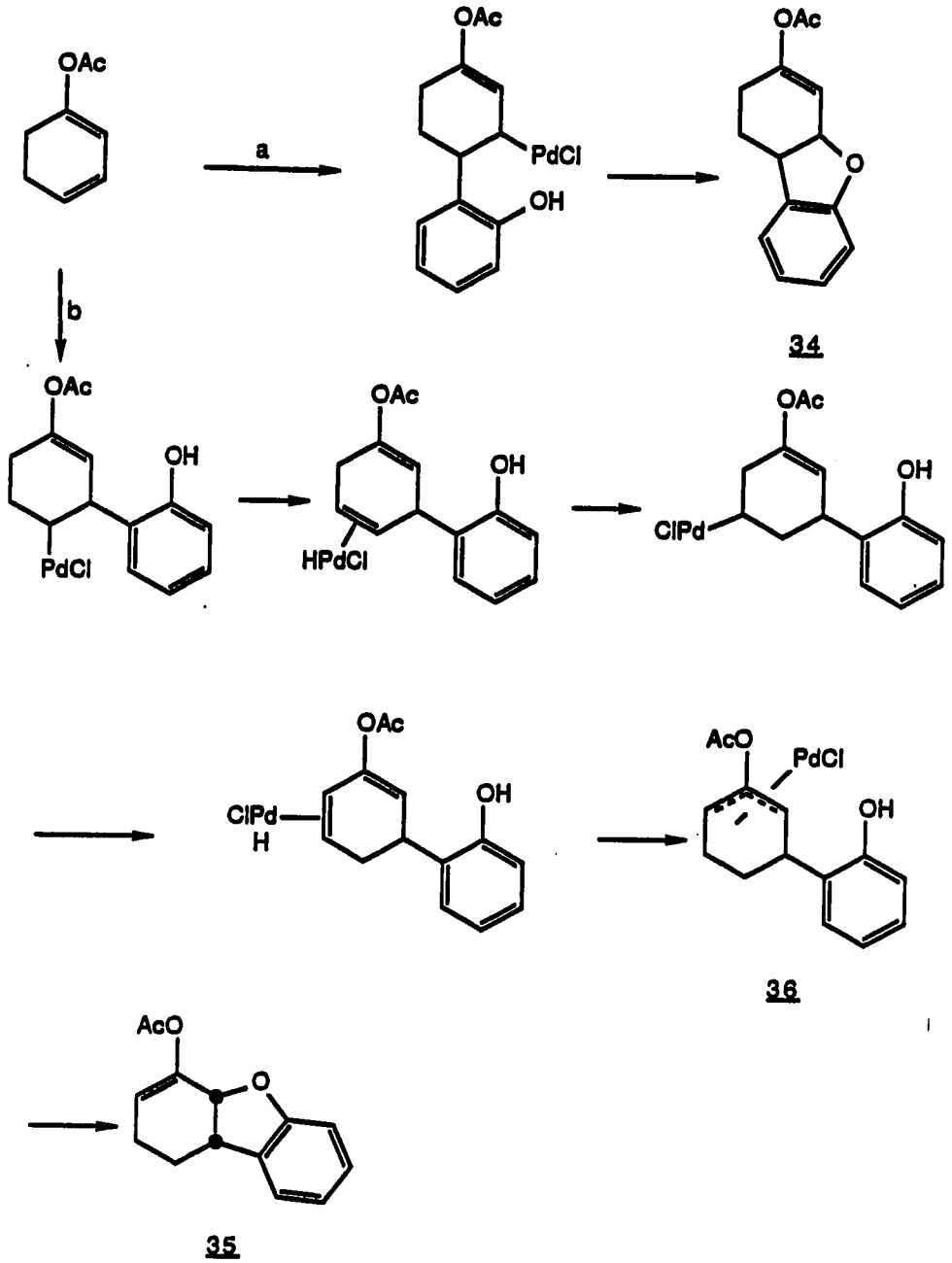
37 9



38 1 : 1.1 39

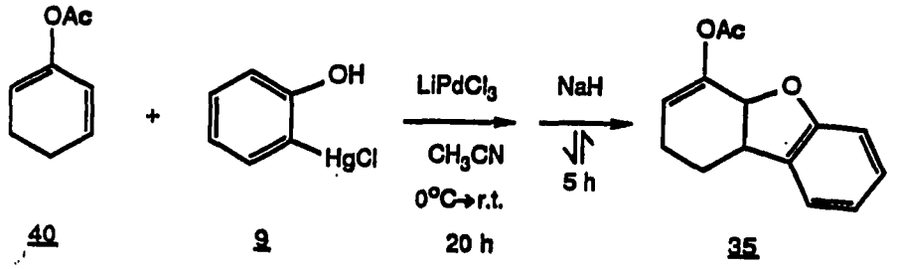
(25)

Scheme I



An alternative explanation for the formation of the products (33, 35, and 39) might be prior isomerization of the dienes catalyzed by either a palladium species or acid under the reaction condition. Addition of the initial organopalladium species to the isomerized diene in a similar fashion could lead to the intermediate 36.

To determine whether such isomerization is actually occurring, compound 31 was reacted with bis(acetonitrile)palladium chloride in acetonitrile at room temperature for 7 h. The product from the reaction was a mixture of cyclohexenone and phenol (2 : 1 ratio). No isomerized 2-acetoxy-1,3-cyclohexadiene (40) was observed, thus ruling out isomerization by palladium chloride. Another experiment was conducted using compound 40. Compound 35 was isolated from the reaction of compound 40 and organomercurial 9 (eq. 26). None of the other isomer 34 was isolated. The



40 9 35 (26)

result from these two reactions seems to exclude isomerization of the dienes prior to reaction.

CONCLUSION

Conjugated dienes substituted by an acetoxy group and various functionally substituted organomercurials were reacted in the presence of palladium salts. The intermediate π-allylpalladium species were cyclized to form derivatives of benzofuran and lactone. An effort to develop a catalytic version of this reaction was not successful. Reactions employing cyclic dienes produced a mixture of regio-isomers arising from separate addition pathways.

EXPERIMENTAL SECTION

Equipment Proton and ^{13}C NMR spectra were recorded on a Nicolet NT-300 spectrometer (^{1}H NMR: 300 MHz, ^{13}C NMR: 75 MHz). Infrared spectra were recorded on either a Beckman Acculab 2 or IBM IR-98 spectrometer. Mass spectral data were obtained on a Kratos MS-50 high resolution spectrometer.

Reagents All compounds were used directly as obtained unless otherwise noted. The starting materials were purchased from Aldrich, except for sodium hydride (J. T. Baker) and potassium carbonate (J. T. Baker). o-Iodophenol was purchased from Alfa. Phenylmercuric chloride was purchased from Fluka. 1-Acetoxy-1,3-butadiene (1) was purchased from Aldrich and distilled before use. 2-Acetoxy-1,3-butadiene (4), 3-acetoxy-1,3-pentadiene (5), 1-acetoxy-2-methyl-1,3-butadiene (6), 2-acetoxy-1,3-pentadiene (8) were prepared from the corresponding aldehyde or ketone and isopropenyl acetate in the presence of catalytic amounts of sulfuric acid according to the procedure of Bohlmann and co-workers[31]. 1-Acetoxy-2-methyl-1,3-butadiene (7) was prepare according to the procedure of Banks et al.[32]. 1-Acetoxy-1,3-cyclohexadiene (31) was prepared using the procedure of Kawasaki et al.[34]. 1-Methyl-1,3-cyclohexadiene (37) was prepared from the p-toluene sulfonyl hydrazone of 3-methyl-2-

cyclohexen-1-one and methyllithium[35].

o-(Chloromercurio)phenol (9) was prepared following a literature procedure[36]. o-(Chloromercurio)-p-cresol was generously supplied by Mr. Norman Berrios-Pêna. o-(Chloromercurio)benzoic acid (10) was prepared by quenching o-lithiated benzoic acid[33] with mercuric chloride. E-β-Chloro-α-(chloromecurio)acrylic acid (26) was prepared using the method of Nesmeyanov et al.[37]. Palladium chloride was generously supplied by Johnson Matthey Inc.

Compound 3 π-Allylpalladium compound 3 was prepared from 1-acetoxy-1,3-butadiene (1.0 mmol) and phenylmercuric chloride (0.5 mmol) following the procedure described in part I: R_f = 0.28, 2 : 1 hexanes/ethyl acetate; 88% yield; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3 H, CH_3), 3.02 (dd, 2 H, J = 4.2 Hz, J = 6.0 Hz, $ArCH_2$), 3.95 (dt, 1 H, J = 11.7 Hz, J = 6.0 Hz, CH_2-C<u>H</u>), 5.32 (dd, 1 H, J = 11.7 Hz, J = 8.4 Hz, CH_2-C<u>H</u>), 6.54 (d, 1 H, J = 8.4 Hz, CH-O), 7.25 - 7.33 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) δ 20.7, 37.39 (aliphatic), 95.74, 98.20, 126.83, 128.78, 129.11, 137.41, 167.71 (olefinic); IR (neat) 3040, 1767, 1600, 1520, 1500, 1456, 1430, 1372, 1260, 1200, 1106, 1076, 1045, 1015, 880, 730 cm^{-1}.

No Elemental Analysis was obtained because the compound decomposed readily.

Benzofurans 11 - 17 were prepared in a similar manner. The preparation of benzofuran 11 is representative.

Benzofuran 11 To a solution of 0.5 mmol of dilithium tetrachloropalladate in THF or 0.5 mmol of lithium trichloropalladite in acetonitrile were added 0.1121 g (1.0 mmol) of diene 1 and 0.1645 g (0.5 mmol) of o-(chloromercurio)phenol (9) at 0°C under nitrogen. The reaction mixture turned yellow very slowly. The reaction was stirred for 20 h while warming to room temperature. The mixture was treated with 0.024 g (0.5 mmol) of sodium hydride (50% suspension in mineral oil) and then refluxed for 5 h. The reaction was diluted with ether, washed with saturated ammonium chloride, dried over anhydrous magnesium sulfate, and concentrated. The resulting yellow crude material was purified by column chromatography (R_f = 0.35, 5 : 1 hexanes/ethyl acetate) to give 0.0547 g (77% yield) of a mixture of cis and trans isomers (1 : 7).

Trans isomer: ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3 H, CH_3), 2.99 (dd, 1 H, J = 15 Hz, J = 8.1 Hz, $ArCH_2$), 3.37 (dd, 1 H, H = 15.3 Hz, J = 9.0 Hz, $ArCH_2$), 5.20 (ddd, 1 H, J = 8.4 Hz, J = 8.4 Hz, J = 8.1 Hz, CH-O), 5.63 (dd, 1 H, J = 8.4 Hz, J = 12.3 Hz, C<u>H</u>=CH-O), 6.75 - 6.86 (m, 2 H, Ar), 7.08 - 7.16 (m, 2 H, Ar), 7.46 (d, 1 H, J = 12.3 Hz, CH=C<u>H</u>-O); ^{13}C NMR ($CDCl_3$) δ 20.52, 36.51, 76.29, 109.47, 113.42, 113.87, 120.58, 124.78, 126.30, 128.15, 135.85, 138.43, 159.16, 167.59.

Cis isomer: ^{1}H NMR ($CDCl_3$) same except 7.48 (d, 1 H, J = 10.3 Hz, O-CH=).

The following spectral data were obtained from the mixture: IR (neat) 3080, 3045, 3030, 2920, 2855, 1760, 1676, 98, 1480, 1460, 1370, 1327, 1210, 1103, 1043, 1015, 960, 932, 870, 790, 750, 710 cm^{-1}; mass spectrum m/z 204.07831 (calcd for $C_{12}H_{12}O_3$, 204.07865). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 68.83; H, 5.86.

Benzofuran 12: R_f = 0.63, 2 : 1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3 H, CH_3), 3.19 (dd, 1 H, J = 7.2 Hz, J = 15.6 Hz, $ArCH_2$), 3.36 (dd, 1 H, J = 9.6 Hz, J = 15.6 Hz, $ArCH_2$), 5.00 (d, 1 H, J = 1.8 Hz, $=CH_2$), 5.19 (d, 1 H, J = 1.8 Hz, $=CH_2$), 5.21 (dd, 1 H, J = 7.5 Hz, J = 10.2 Hz, CH-O), 6.81 (d, 1 H, J = 7.8 Hz, Ar), 6.85 (t, 1 H, J = 7.5 Hz, Ar), 7.11 (t, 1 H, J = 7.5 Hz, Ar), 7.15 (d, 1 H, J = 7.5 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 20.90, 34.02, 80.78, 102.98, 109.45, 120.85, 124.79, 125.78, 128.11, 153.11, 129.23, 168.63; IR (neat) 1780, 1610, 1490, 1470, 1379, 1238, 1190, 1025, 750 cm^{-1}; mass spectrum m/z 204.07851 (calcd for $C_{12}H_{12}O_3$, 204.07865). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.96; H, 5.95.

Benzofuran 13: R_f = 0.36, 4 : 1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.55 (d, 3 H, J = 6.9 Hz, =CH-C<u>H</u>$_3$), 2.08 (s, 3 H, CH_3), 3.17 (dd, 1 H, J = 7.2 Hz, J = 15.6 Hz, $ArCH_2$), 3.30 (dd, 1 H, J = 9.3 Hz, J = 15.6 Hz, $ArCH_2$), 5.20 (t, 1 H, J = 8.1 Hz, CH-O), 5.58 (q, 1 H, J = 7.0 Hz, =CH-), 6.79 (d, 1 H, J = 8.1 Hz, Ar), 6.84 (t, 1 H, J = 7.5 Hz, Ar), 7.10 (t, 1 H, J = 8.4 Hz, Ar), 7.14 (d, 1 H, J = 7.8 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 10.96, 20.34, 33.55, 81.95, 109.41, 114.74, 120.64, 124.68, 128.05, 146.28, 159.33, 168.20; IR (neat) 2960, 1770, 1610, 1485, 1470, 1240, 1220, 1190, 1028, 930, 750 cm^{-1}; mass spectrum m/z 218.09430 (calcd for $C_{13}H_{14}O_3$, 218.09428). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: 71.03; H, 6.46.

Benzofuran 14: R_f = 0.50, 4 : 1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.71 (d, 3 H, J = 1.2 Hz, =C-CH_3), 2.16 (s, 3 H, CH_3), 3.08 (dd, 1 H, J = 8.1 Hz, J = 15.6 Hz, $ArCH_2$), 3.29 (dd, 1 H, J = 9.6 Hz, J = 15.9 Hz, $ArCH_2$), 5.16 (t, 1 H, J = 7.5 Hz, CH-O), 6.77 (d, 1 H, J = 8.1 Hz, Ar), 7.10 (t, 1 H, J = 7.5 Hz, Ar), 7.14 (d, 1 H, J = 7.8 Hz, Ar), 7.30 (s, 1 H, =CH-O); ^{13}C NMR ($CDCl_3$) δ 9.00, 25.57, 34.36, 83.49, 109.25, 120.44, 124.69, 126.52, 131.57, 132.83, 159.71, 167.64; IR (neat) 3051, 2923, 1757, 1597, 1481, 1462, 1371, 1231, 1113, 962, 922, 752 cm^{-1}. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.08; H, 6.72.

Benzofuran 15: R_f = 0.42, 7 : 1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.58 (s, 3 H, O-C-CH_3), 2.09 (s, 3 H, CH_3), 3.07 (d, 1 H, J = 15.3 Hz, $ArCH_2$), 3.17 (d, 1 H, J = 15.3 Hz, $ArCH_2$), 5.67 (d, 1 H, J = 12.3 Hz, C<u>H</u>=CH-O), 6.74 - 6.86 (m, 2 H, Ar), 7.06 - 7.15 (m, 2 H, Ar), 7.42 (d, 1 H, J = 12.6 Hz, =CH-O); ^{13}C NMR ($CDCl_3$) δ 20.56, 26.69, 42.73, 85.46, 109.67, 118.73, 120.41, 124.98, 126.14, 128.15, 136.07, 158.49, 167.72; IR (neat) 2976, 1759, 1501, 1481, 1462, 1371, 1296, 1217, 1111, 750 cm^{-1}; mass spectrum m/z 218.09390 (calcd for $C_{13}H_{14}O_3$, 218.09430). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.20; H, 6.53.

Benzofuran 16: R_f = 0.44, 6 : 1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.37 (d, 3 H, J = 6.9 Hz, CH-C<u>H</u>$_3$), 2.12 (s, 3 H, CH_3), 3.47 (dq, 1 H, J = 6.9 Hz, J = 6.9 Hz, CH_3-C<u>H</u>), 4.67 (d, 1 H, J = 1.8 Hz, $=CH_2$), 5.21 (d, 1 H, J = 1.8 Hz, $=CH_2$), 6.75 - 6.91 (m, 2 H, Ar), 7.12 (m, 2 H, Ar); GC-MS m/z (relative intensity) 218 (m+, 22), 176 (19), 133 (84), 43 (100).

Benzofuran 17 was identified by its GC-MS: m/z (relative intensity) 218 (m+, 9), 176 (29), 161 (31), 133 (10), 43 (100).

Lactones 20 - 24 were prepared in a manner similar to preparation of the benzofurans except the cyclization of the intermediate was performed by adding potassium carbonate instead of sodium hydride.

Lactone 20: R_f = 0.28, 2 : 1 hexanes/ethyl acetate; 1H NMR ($CDCl_3$) δ 2.08 (s, 3 H, CH_3), 2.93 - 3.09 (m, 2 H, $ArCH_2$) 4.94 - 5.02 (m, 1 H, CH-O), 5.63 (dd, 1 H, J = 7.8 Hz, J = 12.3 Hz, CH=CH-O), 7.19 (t, 1 H, J = 7.2 Hz, Ar), 7.32 (t, 1 H, J = 7.2 Hz, Ar), 7.43 (d, 1 H, J = 12.9 Hz, =CH-O), 7.49 (d, 1 H, J = 7.5 Hz, Ar), 7.99 (d, 1 H, J = 7.5 Hz, Ar); IR (neat) 1781, 1736, 1690, 1465, 1375, 1280, 1208, 1100, 1079, 738 cm^{-1}; mass spectrum m/z 232.07331 (calcd for $C_{13}H_{12}O_4$, 232.07356). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.51; H, 5.20.

Lactone 21: R_f = 0.34, 2 : 1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 2.16 (s, 3 H, CH_3), 3.17 (m, 2 H, $ArCH_2$), 5.08 (dd, 1 H, J = 6.0 Hz, J = 8.1 Hz, CH-O), 5.13 (d, 1 H, J = 2.1 Hz, $=CH_2$), 5.27 (d, 1 H, J = 1.8 Hz, $=CH_2$), 7.28 (d, 1 H, J = 7.5 Hz, Ar), 7.40 (t, 1 H, J = 7.8 Hz, Ar), 7.56 (t, 1 H, J = 7.5 Hz, Ar), 8.07 (d, 1 H, J = 9.3 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 20.73, 31.01, 76.34, 104.63, 124.86, 127.42, 127.58, 130.15, 133.84, 137.88, 151.03, 163.92, 168.35; IR (neat) 1775, 1738, 1615, 1467, 1372, 1275, 1175, 1115, 1080,

1025, 740 cm^{-1}; mass spectrum m/z 236.07326 (calcd for $C_{13}H_{12}O_4$, 232.07356). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 66.63; H, 5.40.

Lactone 22: R_f = 0.30, 2 : 1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.57 (d, 3 H, J = 6.9 Hz, =CH-CH_3), 2.15 (s, 3 H, CH_3), 3.13 (m, 2 H, $ArCH_2$), 5.05 (dd, 1 H, J = 4.2 Hz, J = 9.3 Hz, CH-O), 5.65 (q, 1 H, J = 6.9 Hz, =CH), 7.26 (d, 1 H, J = 7.5 Hz, Ar), 7.39 (t, 1 H, J = 7.5 Hz, Ar), 7.55 (t, 1 H, J = 7.5 Hz, Ar), 8.06 (d, 1 H, J = 7.5 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 10.82, 20.17, 30.92, 77.32, 116.37,124.93, 127.39, 127.60, 130.06, 133.69, 138.19, 144.50, 164.18, 168.00; IR (neat) 2950, 1769, 1735, 1615, 1462, 1370, 1272, 1200, 1025, 735 cm^{-1}; mass spectrum m/z 246.08895 (calcd for $C_{14}H_{14}O_4$, 246.08921). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 67.71; H, 5.57.

Lactone 23: R_f = 0.36, 2 : 1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.86 (d, 3 H, J = 1.5 Hz, =C-CH_3), 2.19 (s, 3 H, CH_3), 2.86 (dd, 1 H, J = 3.0 Hz, J = 16.2 Hz, $ArCH_2$), 3.29 (dd, 1 H, J = 12.6 Hz, J = 15.9 Hz, $ArCH_2$), 4.94 (dd, 1 H, J = 12.7 Hz, J = 12.3 Hz, CH-O), 7.27 (d, 1 H, J = 7.5 Hz, Ar), 7.34 (s, 1 H, =CH), 7.39 (t, 1 H, J = 7.5 Hz, Ar), 7.55 (t, 1 H, J = 7.5 Hz, Ar), 8.08 (d, 1 H, J = 7.8 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 9.93, 20.47, 32.09, 79.52, 118.60, 124.93, 127.31,

127.67, 130.21, 133.68, 134.25, 138.89, 164.92, 167.44; IR (neat) 2950, 1765, 1730, 1610, 1462, 1370, 1273, 1210, 1102, 1080, 990, 910, 740 cm^{-1}; mass spectrum m/z 246.08929 (calcd for $C_{14}H_{14}O_4$, 246.08921). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.18; H, 5.92.

Lactone 24: a mixture of trans and cis (12 : 1): R_f = 0.36, 2 : 1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.62 (s, 3 H, O-C-CH_3), 2.70 (s, 3 H, CH_3), 3.13 (d, 1 H, J = 16.2 Hz, $ArCH_2$), 3.20 (d, 1 H, J = 16.5 Hz, $ArCH_2$), 5.57 (d, 1 H, J = 13.5 Hz, CH=CH-O), 7.25 (d, 1 H, J = 7.5, Ar), 7.35 (d, 1 H, J = 12.6 Hz, =CH-O), 7.37 (t, 1 H, J = 7.5 Hz, Ar), 7.55 (t, 1 H, J = 7.5 Hz, Ar), 8.07 (d, 1 H, J = 7.5 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 20.32, 27.31, 38.62, 79.88, 117.18, 127.57, 127.66, 127.96, 133.81, 137.34, 137.50, 142.94, 164.23, 167.27; IR (film) 3120, 3000, 2979, 1764, 1722, 1680, 1610, 1460, 1370, 1290, 1210, 1105, 1020, 930, 900, 735, 710, 685 cm^{-1}; mass spectrum m/z 246.08949 (calcd for $C_{14}H_{14}O_4$, 246.08921). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.18; H, 5.92.

Benzofuran 28: ^1H NMR ($CDCl_3$) δ 2.13 (s, 3 H, $COCH_3$), 2.26 (s, 3 H, CH_3), 2.95 (dd, 1 H, J = 8.1 Hz, J = 15.6 Hz, $ArCH_2$), 3.32 (dd, J = 9.0 Hz, J = 15.3 Hz, $ArCH_2$), 5.17 (ddd, 1 H, J = 8.4 Hz, J = 8.4 Hz, J = 8.4 Hz, CH-O), 5.62 (dd, 1

H, J = 8.4 Hz, J = 12.3 Hz, CH-C<u>H</u>=CH), 6.66 (d, 1 H, J = 8.1 Hz, Ar), 6.96 (s, 1 H, Ar), 7.44 (d, 1 H, J = 12.0 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 20.63, 20.80, 36.60. 79.94, 109.02, 113.94, 125.43, 126.37, 128.47, 129.92, 138.38, 154.04, 167.75; IR (neat) 2940, 1770, 1685, 1490, 1372, 1200, 1110, 1095, 930, 805 cm^{-1}. Anal. Calcd for $C_{13}H_{14}O_4$: C, 71.54; H, 6.47. Found: C, 70.59; H, 6.64.

<u>Lactone 29</u>: a mixture of cis and trans (1 : 1.3).

<u>Cis isomer</u>: ^1H NMR ($CDCl_3$) δ 2.19 (s, 3 H, CH_3), 2.75 (ddd, 1 H, J = 2.4 Hz, H = 4.8 Hz, J = 7.2 Hz, CH_2), 3.28 (ddd, 1 H, J = 2.4 Hz, J = 7.5 Hz, J = 9.9 Hz, CH_2), 5.04 (dd, 1 H, J = 8.4 Hz, J = 6.6 Hz, CH-O), 5.45 (dd, 1 H, J = 8.4 Hz, J = 12.6 Hz, C<u>H</u>=CH-O), 6.69 (t, 1 H, J = 2.4 Hz, =CHCl), 7.26 (d, 1 H, J = 6.6 Hz, CH=C<u>H</u>-O).

<u>Trans isomer</u>: ^1H NMR ($CDCl_3$) δ 2.17 (s, 3 H, CH_3), 2.81 (ddd, 1 H, J = 2.7 Hz, J = 5.1 Hz, J = 7.2 Hz, CH_2), 3.21 (ddd, 1 H, J = 2.1 Hz, J = 7.8 Hz, J = 9.9 Hz, CH_2), 4.98 (ddd, 1 H, J = 7.5 Hz, J = 7.5 Hz, J = 15 Hz, CH-O), 5.48 (dd, 1 H, J = 8.4 Hz, J = 12.6 Hz, C<u>H</u>=CH-O), 6.69 (t, 1 H, J = 2.4 Hz, =CHCl), 7.45 (d, 1 H, J = 12.3 Hz, CH=C<u>H</u>-O).

The following spectral data were obtained from the mixture: ^{13}C NMR ($CDCl_3$) δ 20.44, 35.63, 35.68, 70.60, 77.00, 110.94, 111.94, 126.10, 126.36, 126.55, 137.46, 139.67, 165.70, 165.93, 166.79, 167.34; IR (neat) 3070, 2930,

1760, 1680, 1640, 1440, 1370, 1325, 1215, 1175, 1100, 1020, 975, 910, 890, 850, 740, 660 cm^{-1}; mass spectrum m/z 216.01906 (calcd for $C_9H_9O_4Cl$, 216.01894). Anal. Calcd for $C_9H_9O_4Cl$: C, 49.90; H, 4.19. Found: C, 50.07; H, 4.12.

Benzofuran 32: R_f = 0.66, 1 : 1 hexanes/ethyl acetate; ^1H NMR ($CDCl_3$) δ 1.78 - 1.90 (m, 1 H, CH-C<u>H</u>$_2$-CH_2-CH=), 2.0 - 2.10 (m, 1 H, CH-C<u>H</u>$_2$-CH_2-C=), 2.11 - 2.22 (m, 2 H, =C-CH_2), 2.13 (s, 3 H, CO-CH_3), 3.40 (dt, 1 H, J = 8.4 Hz, J = 5.1 Hz, Ar-CH-), 5.20 (dd, 1 H, J = 7.5 Hz, J = 3.9 Hz, O-CH), 5.67 (d, 1 H, J = 3.9 Hz, =CH), 6.79 - 6.89 (m, 2 H, Ar), 7.08 - 7.16 (m, 2 H, Ar). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.46; H, 6.38.

Benzofuran 33: ^1H NMR ($CDCl_3$) δ 1.65 - 1.78 (m, 1 H, CH-C<u>H</u>$_2$-CH_2-C=), 1.92 - 2.00 (m, 1H, CH-C<u>H</u>$_2$-CH_2-C=), 2.11 - 2.22 (m, 2 H, C<u>H</u>$_2$-C=), 2.21 (s, 3 H, CH_3), 3.59 (dt, 1 H, J = 8.4 Hz, J = 5.1 Hz, ArCH), 5.07 (d, 1 H, J = 8.1 Hz, CH-O), 5.76 (t, 1 H, J = 4.2 Hz, =CH-), 6.79 - 6.89 (m, 2 H, Ar), 7.08 - 7.16 (m, 2 H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.13, 21.97, 25.00, 41.39, 78.43, 110.30, 120.80, 123.74, 128.39, 130.18, 145.06, 158.88, 164.20, 169.49; IR (neat) 3080, 2950, 1760, 1600, 1480, 1465, 1370, 1210, 1130 cm^{-1}. Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.71; H, 6.24.

Compound 34: ^{1}H NMR ($CDCl_3$) δ 1.51 - 2.00 (m, 2 H, $C\underline{H}_2$-CH_2-C=), 2.16 (s, 3 H, CH_3), 2.20 - 2.40 (m, 2 H, CH_2-C=), 3.12 - 3.31 (m, 1 H, C<u>H</u>-CH-O), 5.00 (dd, 1 H, J = 5.1 Hz, J = 5.1 Hz, CH-O), 5.64 (d, 1 H, J = 3.6 Hz, =CH), 6.68 (s, 1 H, =CHCl).

Compound 35: ^{1}H NMR ($CDCl_3$) δ 1.51 - 2.00 (m, 2 H, $C\underline{H}_2$-CH_2-CH=), 2.19 (s, 3 H, CH_3), 2.20 - 2.24 (m, 2 H, $C\underline{H}_2$-CH=), 3.34 - 3.47 (m, 1 H, ArCH), 4.94 (d, 1 H, J = 6.9 Hz, CH-O), 5.81 (t, 1 H, J = 3.9 Hz, CH=), 6.68 (s, 1 H, =CHCl).

Compound 38: ^{1}H NMR ($CDCl_3$) δ 1.45 - 1.6 (m, 1 H, =C-CH_2-C<u>H</u>$_2$), 1.77 (s, 3 H, CH_3), 1.80 - 2.05 (m, 3 H, =C-C<u>H</u>$_2$-C<u>H</u>$_2$), 3.30 (m, 1 H, ArCH), 5.00 (m, 1 H, O-CH), 5.70 (m, 1 H, CH=), 6.75 - 6.88 (m, 2 H, Ar), 7.07 - 7.18 (m, 2 H, Ar).

Compound 39: ^{1}H NMR ($CDCl_3$) same except 1.9 (s, 3 H, CH_3), 4.79 (d, 1 H, J = 8.1 Hz, O-CH), 5.78 (m, 1 H, =CH).

The following spectral data were obtained from a mixture of compounds 37 and 38: IR (neat) 3060, 2930, 2865, 1613, 1600, 1480, 1465, 1230, 935, 910, 750 cm^{-1}; mass spectrum m/z 186.10457 (calcd for $C_{13}H_{14}O$, 186.10447).

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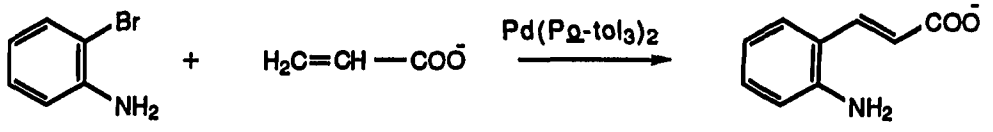
PART III. PREPARATION OF CARBOCYCLES VIA PALLADIUM-PROMOTED INTRAMOLECULAR CYCLIZATION

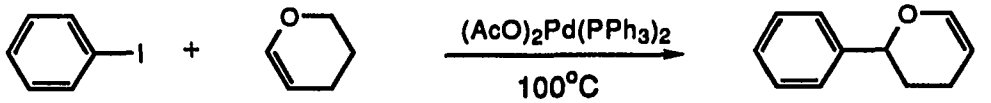
INTRODUCTION

The palladium-catalyzed arylation of alkenes has proven to be a valuable method for carbon-carbon bond formation in the appropriate synthetic context[1,2]. The majority of these reactions involve intermolecular carbopalladation of an acyclic alkene followed by palladium-hydride elimination to form a Heck product (eq. 1)[3]. Palladium-catalyzed allylic-



(1)

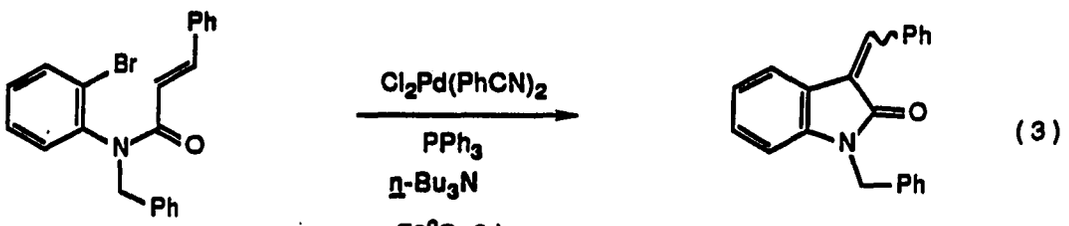
cross coupling with alkenes has received some attention. Arai and Daves[4] have found that the product from the reaction of iodobenzene and dihydropyran in the presence of a palladium catalyst was 5-phenyl-4,5-dihydropyran which is presumably arising from palladium-hydride migration after the formation of a olefin-π-complex (eq. 2). This type of isomerization has been observed in a number of cases and the



(2)

resulting products are mixtures of double bond regioisomers[5]. Recently, Larock and Baker[6] developed a very mild, catalytic procedure for such reactions which circumvents the olefin isomerization and has proven applicable to a wide variety of cyclic alkenes and aryl halides.

Intramolecular arylation processes have been utilized to synthesize heterocyclic compounds. After Mori and Ban[7] and Terpko and Heck[8] reported the synthesis of oxindole derivatives (eq. 3) and quinoline derivatives (eq. 4), Grigg



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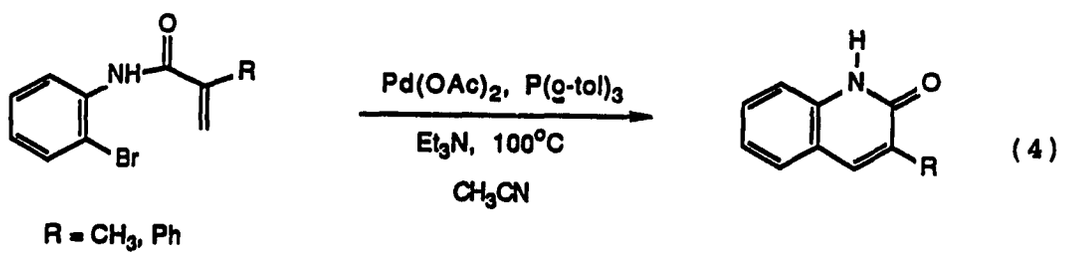
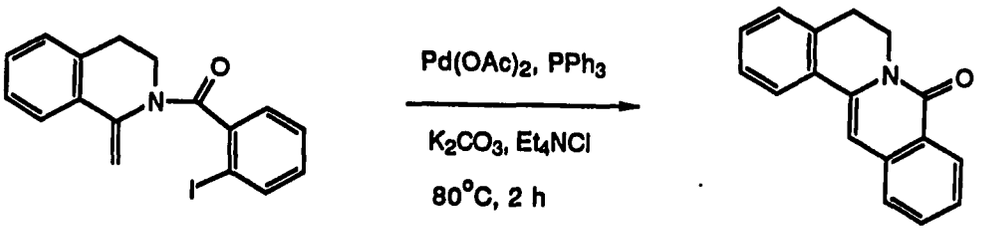


(4)

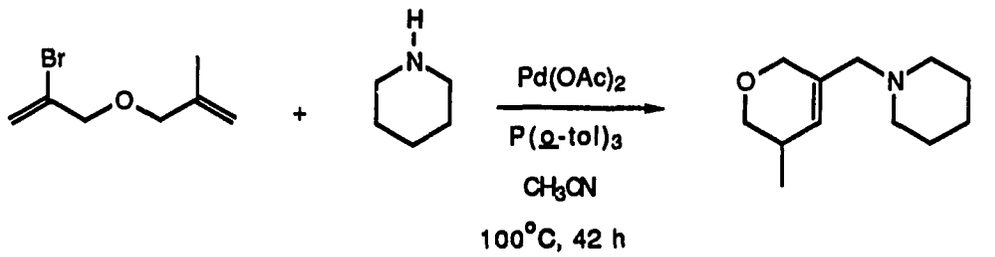
R = CH_3, Ph

et al.[9] recently reported the syntheses of various tetra-substituted carbon centers, as well as spiro- and bridged-ring compounds, from N-vinyl- and N-allyl amides of 2-iodobenzoic acids using an intramolecular cyclization reaction in the presence of tetraethylammonium chloride and a palladium catalyst (eq. 5). In contrast to the abundance of



(5)

intramolecular arylation procedures, there are fewer examples of intramolecular alkenylation reactions. Heck et al.[10] reported an intramolecular cyclization reaction of vinylic bromoalkenyl ethers and piperidine in the presence of a palladium catalyst and tri-o-tolylphosphine to produce various heterocyclic allylamines (eq. 6). Similar approaches for the formation of carbocyclic compounds were reported by Grigg et al.[11] and Narula et al.[12] (eqs. 7 and 8).



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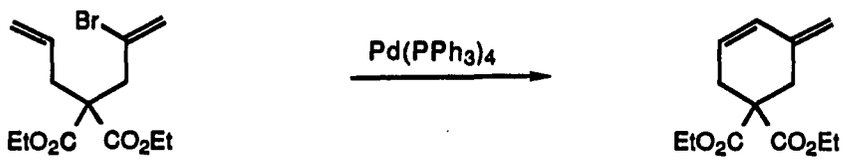

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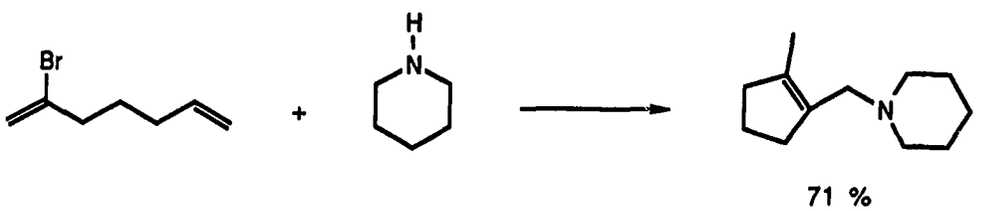
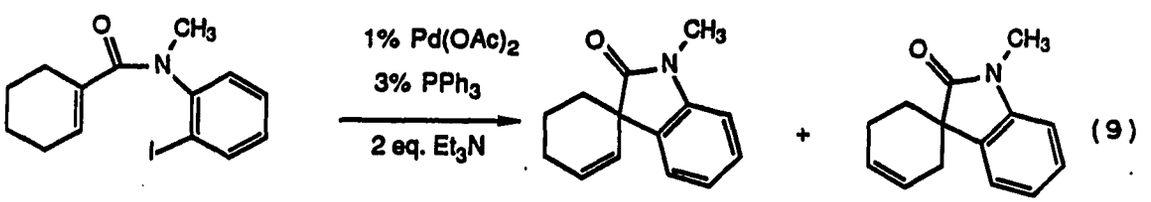


71 %

(8)

Much less information is available on the palladium-catalyzed allylic cross-coupling of alkenyl halides and cycloalkenes and intramolecular versions of these reactions. The aforementioned success in the development of mild catalytic procedures for the reactions of aryl halides and cycloalkenes prompted us to explore intramolecular cyclization reactions of haloalkenylcycloalkenes.

In addition, Abelman et al.[13] recently reported the preparation of a variety of tricyclic ring systems by palladium-catalyzed intramolecular cyclizations of unsaturated aryl halides. The reaction consists of treating a cycloalkenyl-2-halobenzamide or a N-(2-halophenyl) cycloalkenecarboxamide with catalytic amounts of palladium acetate and triphenylphosphine and equivalent amounts of triethylamine either in the presence or in the absence of a silver salt (silver nitrate or silver carbonate) in acetonitrile at room temperature or 82°C. A typical reaction done under these conditions is represented below (eq. 9). It



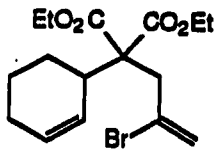
(9)

82°C, 36h	1	:	1	
1 eq. $AgNO_3$, rt, 3 h	26	:	1	76 % yield

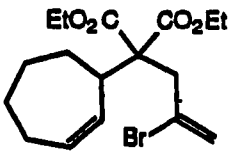
is worth noting that the addition of a silver salt reduced isomerization of the double bond in the cyclization products. The reduced double bond isomerization seen when silver salts are employed also prompted us to examine analogous reaction conditions in our intramolecular cyclization of haloalkenylcycloalkenes.

RESULTS AND DISCUSSION

The following compounds 1 - 7 were considered for cyclization. The preparation of compounds 1 and 2 involved



1



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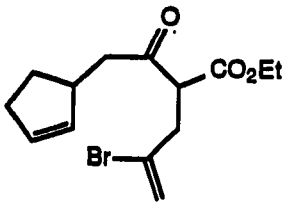

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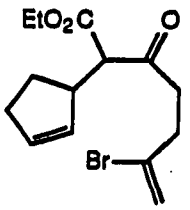

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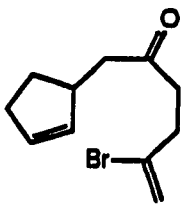

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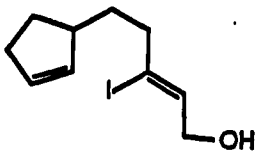

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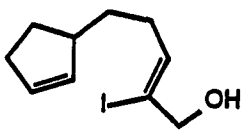

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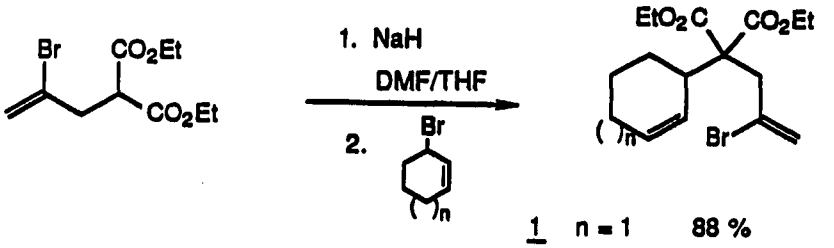
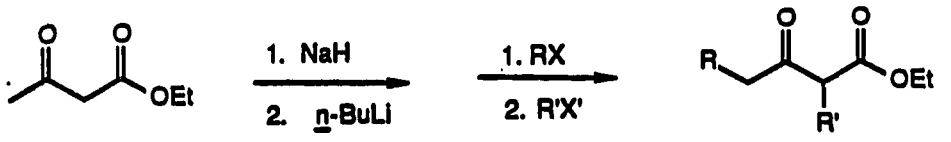


(10)

1 n = 1 88 %

2 n = 2 80 %

treatment of diethyl 2-bromo-2-propenylmalonate with sodium hydride followed by the appropriate cycloalkenyl halides (eq. 10). Compounds 3 and 4 were prepared by treating the anion of ethyl acetoacetate sequentially with the appropriate halides (eq. 11). Treatment of compound 4 with lithium

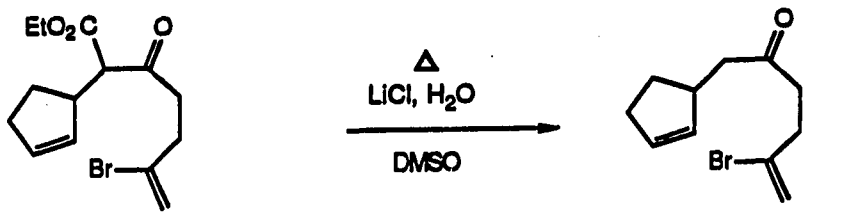


(11)

3 RX = Cl , R'X' = Br, Br 10 %

4 RX = Br, Br , R'X' = Cl 30 %

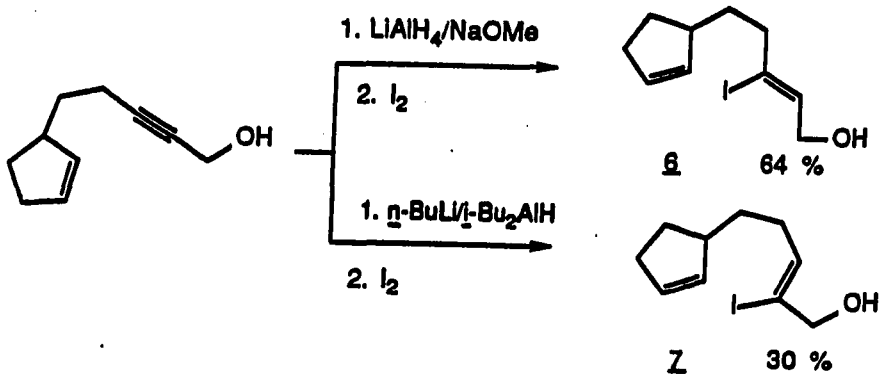
chloride in the presence of water in dimethylsulfoxide gave compound 5 (eq. 12). Compounds 6 and 7 were obtained from a common precursor 8, which was treated with either lithium



(12)

4 5 36 %

aluminum hydride in the presence of sodium methoxide or diisobutylaluminum hydride in the presence of n-butyllithium and then quenched with iodine (eq. 13). Compound 8 was prepared from cyclopentenylacetic acid following the reaction sequence described in eq. 14.



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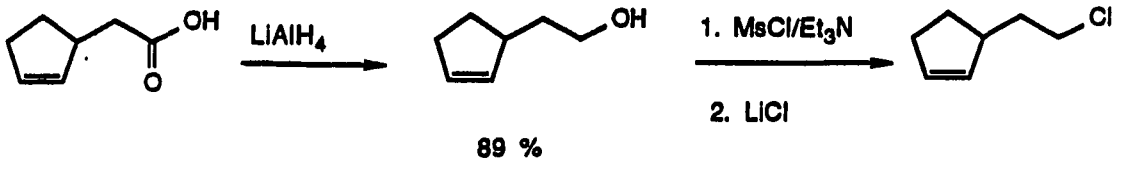

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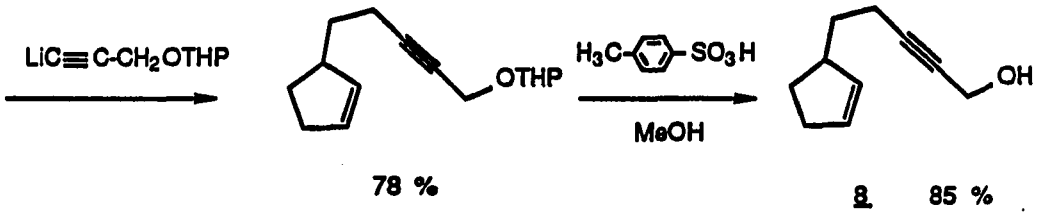


In order to obtain the best reaction conditions for the intramolecular cyclization of haloalkenylcycloalkenes leading to carbocycles, compound 1 was chosen for a model study. Compound 1 was subjected to three different types of reaction conditions (Table 1). A typical reaction is represented by eq. 15.

Table 1. Pd-catalyzed cyclization of compound 1 leading to 9

entry	Pd-catalyst %	Base equiv.	added salt	reaction temperature	reaction time	yield % (ratio[a])
1	2.5 $Pd(OAc)_2$	3 KOAc	Bu_4NCl	25°C	6 d[b]	40[c] (1 : 1.3)
2	2.5 $Pd(OAc)_2$	3 KOAc	Bu_4NCl	25°C	6 d[b]	0
3	2.5 $Pd(OAc)_2$	3 KOAc	Bu_4NCl	80°C	5 d[b]	86 (1 : 2.0)
4	2.5 $Pd(OAc)_2$	3 KOAc	Bu_4NCl	80°C	5 d[b]	82 (1 : 1.5)
5	2.5 $Pd(OAc)_2$	3 KOAc	Bu_4NCl	80°C	5 h	87 (1 : 2.0)
6	2.5 $Pd(OAc)_2$	1 KOAc	Bu_4NCl	80°C	4 d	84 (1 : 2.4)
7	2.5 $Pd(OAc)_2$	3 KOAc	Bu_4NCl LiI	80°C	4 d	0
8	2.5 $Pd(OAc)_2$	3 Na_2CO_3	Bu_4NCl	80°C	19 h	trace
9	2.5 $Pd(dba)_2$	3 KOAc	Bu_4NCl	80°C	19 h	59 (1 : 2.8)
10	2.5 $PdCl_2(PPh_3)_2$	3 KOAc	Bu_4NCl	80°C	17 h	70 (1 : 1.5)
11	2.5 $Pd(OAc)_2$ 2.5 dppe	3 KOAc	Bu_4NCl	80°C	19 h	73 (1 : 2.3)

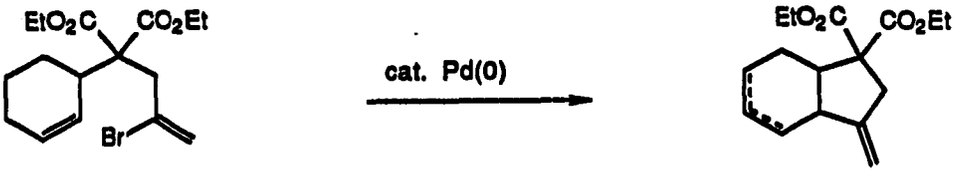
12	2.5 $Pd_2(dba)_3 \cdot CHCl_3$	3 KOAc	Bu_4NCl	80°C	17 h	61 (1 : 3.0)
13	2.5 $Pd(OAc)_2$	3 Na_2CO_3	Bu_4NCl	80°C	23 h	57 (1.6 : 1)
14	2.5 $Pd(OAc)_2$	2 Na_2CO_3	Bu_4NCl	80°C	27 h	87 (2.0 : 1)
15[d]	2.5 $Pd(OAc)_2$ 10 Ph_3P	Et_3N	$AgNO_3$	80°C	10 h	62 (5.1 : 1)
16[d]	2.0 $Pd(OAc)_2$ 6.0 Ph_3P	------	Ag_2CO_3	80°C	2 d	91 (10 : 1)

[a]Isomer ratio was obtained from integration of appropriate peaks in the proton NMR spectra. Regioisomer ratios are reported with indicated allylic isomer on the left and the predumed homoallylic isomer on the right.

[b]These reactions were not monitored by GLC analysis.

[c]The reaction was not complete. Isomer ratio and yields were calculated from integration of appropriate peaks in the proton NMR spectra.

[d]Reactions run in CH_3CN.

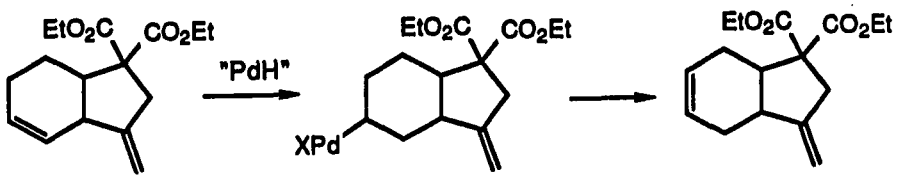


(15)

1 2

Under on set of reaction conditions (entries 1 - 12), compound 1 was treated with a palladium catalyst (2.5 mol %), tetra-n-butylammonium chloride (1 equiv.), and a base (2.5 equiv.) in N,N-dimethylformamide at either room temperature or 80°C. The reaction was usually completed within a day at 80°C and gave moderate to good yields. However, the reaction was not complete even after 6 days at room temperature (entry 1). Although potassium acetate was superior to sodium acetate at room temperature (entries 1 and 2), sodium acetate worked fairly well at 80°C (entry 4). Sodium carbonate, on the other hand, gave only a trace amount of the cyclized product even at 80°C (entry 8). Catalysts other than palladium acetate in the presence of potassium acetate produced the cyclized product in moderate yields (entries 9 - 12). Reducing the amount of base did not affect reaction time or yield (entry 6). The addition of lithium iodide prevented product formation (entry 7). The major product under these conditions (entries 1 - 12) was the compound arising from double bond isomerization caused by readdition-

elimination of a palladium-hydride species as shown in eq. 16.

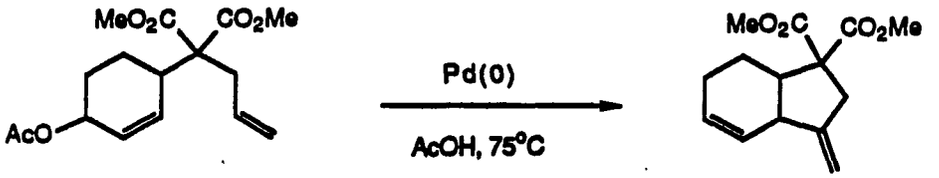


(16)

A silver salt was added in addition to the phase transfer reagent to the reaction mixture in a second set of reactions (entries 13 and 14). Abelman and co-workers[13] observed less double bond isomerization when silver salts were employed. Because silver ions produce an insoluble salt with chloride ions, 2 equiv. of silver nitrate was used when the phase transfer reagent was ammonium chloride (entry 13). These reactions produced the cyclized product in moderate to good yields. Isomer ratios were reversed from the first set of reaction conditions favoring the first formed olefin isomer.

Under a third set of reaction conditions (entries 15 and 16), a phase transfer reagent was not employed. Under both conditions, yields were moderate to excellent. Interestingly, isomer ratios were dramatically changed to give the unrearranged product in high yields (entry 15; 5.1 : 1, entry 16; 10 : 1).

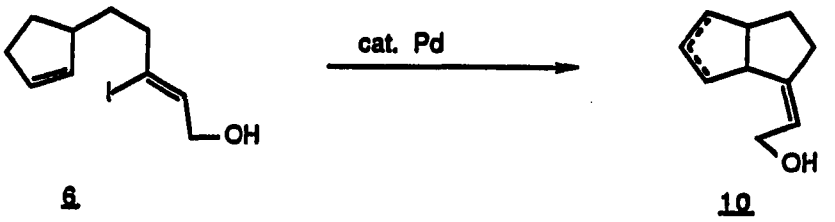
The structure of the reaction product was determined from ^{1}H NMR and ^{13}C NMR spectra. The coupling constant between the two bridgehead protons of compound 9 was 6.3 Hz, which supports the cis, stereochemistry of the compound[14]. Recently, Oppolzer and Gaudin[14] reported a synthesis of a similar compound via a palladium catalyzed intramolecular cyclization (eq. 17) which followed a different mechanism.



(17)

Of the many reaction conditions listed above, it is obvious that silver carbonate, plus catalytic amounts of palladium acetate and triphenylphosphine should be employed in the stereospecific cyclization. For a shorter reaction time, palladium acetate, potassium acetate, and tetra-n-butylammonium chloride can be employed in the cyclization reaction but isomers arise.

In another model study, compound 6 was subjected to a variety of reaction conditions listed in Table 2. The reaction is represented by eq. 18.



(18)

8 10

The results can be summarized as follows. Reaction temperature plays a great role in the reactions of vinylic iodides. The reactions examined at 80°C provided a by-product 8 which was formed from unreacted starting material via palladium promoted elimination of hydrogen iodide (entries 1, 5 and 6). Sodium acetate and sodium carbonate retarded the reactions (entries 2 and 3). The presence of a silver salt in addition to the ammonium salt required a longer reaction period (entries 5, 6, and 7). While the reactions conducted in the presence of an ammonium salt in N,N-dimethylformamide produced a mixture of double bond regioisomers (entries 1 - 4) in 2 - 3 : 1 ratio, the reactions in the presence of only a silver salt in acetonitrile produced only 0 - 5% of the double bond isomerization product (entries 8 and 9). It is obvious from the two model studies shown above that reactions employing vinylic iodides proceed readily at room temperature, but heating to 80°C is required when the starting material is a vinylic bromide.

Table 2. Pd-catalyzed cyclization of compound 6 leading to 10

entry	$Pd(OAc)_2$ %	Base equiv.	added salt	reaction temperature	reaction time	product (yield, ratio)
1	2.5	3 KOAc	Bu_4NCl	25°C	1 d	10 (49, 2.4 : 1) 6 (26)
2	5.0[a]	3 NaOAc	Bu_4NCl	25°C 80°C	10 d 1 d	10 (64, 2.2 : 1)
3	5.0[b]	3 Na_2CO_3	Bu_4NCl	25°C	10 d	10 (66, 3.0 : 1)
4	5.0	3 KOAc	Bu_4NCl	25°C	5 d	10 (61, 2.8 : 1)
5	2.5	2 Na_2CO_3	Bu_4NCl 2 $AgNO_3$	25°C 80°C	2 d 11 d	10 (17)[c] 8 (28)
6	2.5	2 NA_2CO_3	Bu_4NOAc 0.5 Ag_2CO_3	25°C 80°C	2 d 11 d	10 (trace)[c] 8 (56)
7	2.5	3 KOAc	Bu_4NCl 2 Ag_2CO_3	25°C 80°C	2 d 11 d	10 (12)[c] 8 (37)
8	3.0[d] 9.0 Ph_3P	Et_3N	$AgNO_3$	25°C	3 d	10 (48, 20 : 1)
9	3.0 9.0 Ph_3P	-------	2 Ag_2CO_3	25°C	3 d	10 (56)

10	1.0 3.0 Ph_3P	Et_3N	--------	25°C	10 d	-------

[a]The reaction was started with 2.5% of $Pd(OAc)_2$ and an additional 2.5% of catalyst was added after 2 days.

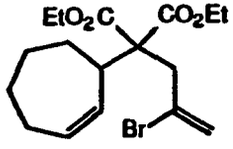
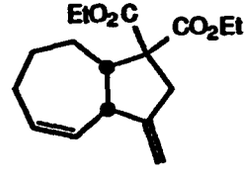
[b]The reaction was started with 2.5% of $Pd(OAc)_2$ and an additional 2.5% of catalyst was added after 1 day.

[c]Isomer ratio was not obtained.

[d]The reaction was started with 1% of $Pd(OAc)_2$ and additional 1% of $Pd(OAc)_2$ and 3% of Ph_3P were added after 30 h and 42 h respectively. The reaction was run in CH_3CN.

Intramolecular cyclizations of substrates 2 - 5 and 7 were performed under three different reaction conditions (footnote a in Table 3) and are summarized in Table 3. While reactions employing procedure A have a tendency to produce a regioisomer, the isomerization of the double bond was greatly reduced when the reactions were conducted using procedures B or C as shown in the model studies. It is worth noting that closing a 5 - or 6-membered ring onto a 5-, 6-, or 7-membered ring is easier than closing a 7-membered carbocyclic ring.

Table 3. Pd-catalyzed cyclization of compounds 2 - 5 and 7

entry	organic halide	procedure[a]	total Pd	reaction conditions	product[b] (isomer ratio)[c]	% isolated yield[d]
						
1	2	A	2.5	6 h, 80°C	11 (1.0 : 2.3)	88
2	2	B	2.0	8 d, 25°C	11 (1.5 : 1.0)	82

[a]Procedure A: 0.5 mmol organic halide, 1.0 ml DMF, 2.5 or 3.0 mol % $(Pd(OAc)_2$, 0.5 mmol n-Bu_4NCl, 1.5 mmol KOAc. Procedure B: 0.5 mmol organic halide, 6.0 ml CH_3CN, 1.0 mmol Ag_2CO_3, 1.0 mol % $Pd(OAc)_2$, 3.0 mol % PPh_3; the reaction is checked by gas chromatography at 6 and 24 h and every 24 h after that; if the reaction is incomplete and the yield of product has improved less than 10% since the previous reading, an additional 1.0 mol % $Pd(OAc)_2$ and 3.0 mol % PPh_3 is added. Procedure C: same as Procedure B except 3.0 mol % $Pd(OAc)_2$ and 9.0 mol % PPh_3 is added.

[b]All products gave appropriate proton and carbon-13 NMR, IR, and mass spectral data. Spectral assignments are based on NMR spectral data, mechanistic arguments and assignment made by others on similar reactions, and are tentative.

[c]Regioisomer ratios are reported with indicated allylic isomer on the left and the presumed homoallylic or othe isomer on the right. If no ratio is reported, the product is essentially pure.

[d]All yields refer to chromatographically purified products.

Table 3. (continued)

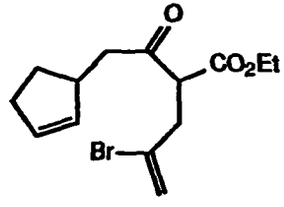
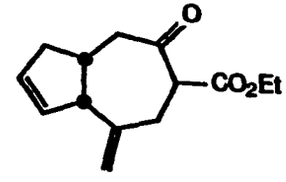
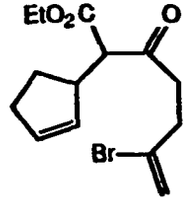
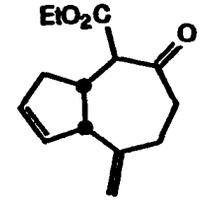
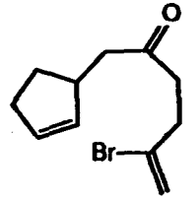
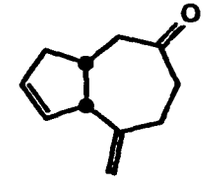
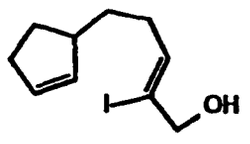
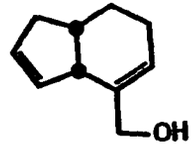
entry	organic halide	procedure[a]	total Pd	reaction conditions	product[b] (isomer ratio)[c]	% isolated yield[d]
						
3	3	A	2.5	3 d, 80°C	12	0
4	3	B	1.0	3 d, 25°C	3	75
						
5	4	A	2.5	3 d, 80°C	13	0
6	4	B	1.0	14 d, 25°C	4	85
7	4	C	3.0	3 d, 80°C	4	38
						
8	5	A	5.0	8 d, 25°C	14 (5.0 : 1.0)	22

Table 3. (continued)

entry	organic halide	procedure[a]	total Pd	reaction conditions	product[b] (isomer ratio)[c]	% isolated yield[d]
						
9	7	A	5.0	8 d, 25°C	15 (18 : 1)	43
10	7	C	4.0	3 d, 25°C	15	48

CONCLUSION

The palladium-catalyzed intramolecular cyclization of haloalkenylcycloalkenes presented in this part provides a novel synthesis of carbocyclic ring systems. One can form a 5- or 6-membered ring cyclic alkene. Reactions employing silver carbonate reduced double bond isomerization caused by palladium-hydride rearrangements. It is worth nothing that both exocyclic and endocyclic alkenes can be prepared stereospecifically from a common precursor via the intramolecular cyclization of isomeric vinylic halides.

EXPERIMENTAL SECTION

Equipment Proton and ^{13}C NMR spectra were recorded on a Nicolet NT-300 spectrometer (^{1}H NMR: 300 MHz, ^{13}C NMR: 75 MHz). Infrared spectra were recorded on either a Beckman Acculab 2 or IBM IR-98 spectrometer. Mass spectral data were obtained on a Kratos MS-50 high resolution spectrometer.

Reagents All compounds were used directly as obtained unless otherwise noted. The starting materials were purchased from Aldrich, except for sodium hydride (J. T. Baker), 3-bromocyclohexene (Fluka), and lithium chloride (J. T. Baker). Diethyl 2-bromo-2-propenylmalonate was generously supplied by Colleen Fried, and 3-chlorocyclopentene was supplied by Mr. Peter Johnson. n-Butyllithium was purchased from Aldrich and titrated with 2,5-dimethoxybenzyl alcohol[15] before use. Acetonitrile and N,N-dimethylformamide (DMF) were distilled from calcium hydride; tetrahydrofuran (THF) was distilled from benzophenone-sodium ketyl. Palladium acetate was generously supplied by Johnson Matthey, Inc.

Preparation of compounds 1 and 2 The procedure for the preparation of compound 1 is representative. To a flask containing 0.0744 g (50% dispersion in mineral oil) of sodium hydride in 3 ml of dry THF and 6 ml of dry DMF at room

temperature under nitrogen was added 0.88 g (3.15 mmol) of diethyl 2-bromo-2-propenylmalonate. The reaction mixture was stirred for 30 min, and then 0.4831 g (3.0 mmol) of freshly distilled 3-bromocyclohexene was added slowly. The reaction became cloudy. After stirring for 7 h at room temperature, the reaction was quenched with ether, washed with saturated sodium bicarbonate and sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The residual yellow liquid was purified by column chromatography using 10 : 1 hexanes/ethyl acetate (R_f = 0.4) to give 1.058 g (2.9 mmol, 98% yield) of the desired product 1: ^{1}H NMR ($CDCl_3$) δ 1.26 (q, 6 H, J = 7.2 Hz, O-CH_2-C$\underline{H}_3$), 1.46 - 1.62 (m, 2 H, =CH-CH_2-C$\underline{H}_2$), 1.74 - 2.0 (m, 4 H, =CH-C$\underline{H}_2$-CH_2-C$\underline{H}_2$-CH), 3.00 - 3.10 (m, 1 H, CH), 3.18 (s, 2 H, =CBr-CH_2), 4.20 (m, 4 H, O-C$\underline{H}_2$-CH_3), 5.56 (d, 1 H, J = 1.8 Hz, =CH_2), 5.68 (s, 1 H, =CH_2), 5.70 - 5.82 (m, 2 H, CH=CH); ^{13}C NMR ($CDCl_3$) δ 14.03, 22.35, 24.48 (aliphatic), 24.97, 39.18, 43.12 (allylic), 60.72 (OC-C-CO), 121.14 (=CH_2), 127.85, 128.57 (CH=CH), 169.57 (BrC=), 169.79 (carbonyl); IR (neat) 2980, 2930, 1725 (C=O), 1220, 1190 cm^{-1}; mass spectrum m/z 358.07723 (calcd for $C_{16}H_{23}O_4Br$, 358.07797).

Compound 2: 80% yield; R_f = 0.44, 7 : 1 hexanes/ethyl acetate; ^{1}H NMR ($CDCl_3$) δ 1.06 - 1.22 (m, 2 H, =CH-CH_2-C$\underline{H}_2$), 1.27 (t, 3 H, J = 6.9 Hz, O-CH_2-C$\underline{H}_3$), 1.28 (t, 3 H, J = 6.9 Hz, O-CH_2-C$\underline{H}_3$), 1.60 - 1.76 (m, 2 H, =CH-CH_2-CH_2-C$\underline{H}_2$), 2.10 -

2.19 (m, 2 H, =CH-C<u>H</u>$_2$), 2.32 (m, 1 H, CH-C<u>H</u>$_2$), 3.15 (s, 2 H, =CBr-CH$_2$), 3.11 - 3.18 (m, 1 H, C<u>H</u>-CH=), 4.16 - 4.26 (m, 4 H, O-C<u>H</u>$_2$-CH$_3$), 5.58 (d, 1 H, J = 1.5 Hz, =CH$_2$), 5.67 (s, 1 H, =CH$_2$), 5.76 (dd, 1 H, J= 4.8 Hz, J = 10.8 Hz, CH$_2$-C<u>H</u>=CH), 5.85 (dt, 1 H, J = 10.8 Hz, J = 5.4 Hz, CH-C<u>H</u>=CH); ^{13}C NMR ($CDCl_3$) δ 13.98, 14.04, 26.01, 27.94, 30.12, 31.59, 41.56, 44.35 (aliphatic), 60.64, 61.22 (O-CH$_2$), 121.79, 127.30, 131.57, 133.26 (olefinic), 169.78, 169.86 (carbonyl); IR (neat) 3000, 2940, 2870, 1735 (C=O), 1630, 1450,1375, 1290, 1230, 1200, 1150, 1050, 900, 862, 702 cm^{-1}; mass spectrum m/z 372.09422 (calcd for $C_{17}H_{25}O_4Br$, 372.09362).

<u>Preparation of compounds 3 and 4</u> Compounds <u>3</u> and <u>4</u> were prepared by double alkylation of ethyl acetoacetate using a modification of the procedure developed by Ho[16]. The preparation of compound <u>3</u> is representative. Ethyl sodium acetoacetate was prepared by adding 0.6507 g (5 mmol) of ethyl acetoacetate to a suspension of oil-free sodium hydride in 10 ml of THF under nitrogen. To the sodium acetoacetate solution at 0°C was added 2.2 ml (5.0 ml) of <u>n</u>-butyllithium dropwise. The solution of dianion was stirred for 30 min, slowly treated with 0.5128 g (5 mmol) of 3-chlorocyclopentene, and then warmed to room temperature for 4 h. The reaction mixture was treated with 0.999 g (5 mmol) of 2,3-dibromo-1-butene at room temperature and was stirred

overnight. The reaction mixture was quenched with water and extracted with ether. The ether extracts were combined, washed with saturated sodium bicarbonate and sodium chloride, dried over anhydrous magnesium sulfate, and concentrated. The resulting yellow liquid was purified by column chromatography using 7 : 1 hexanes/ethyl acetate (R_f = 0.43) to give 0.1652 g (10% yield) of the desired product 3: ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3 H, J = 7.2 Hz, O-CH_2-$C\underline{H}_3$), 1.30 - 1.40 (m, 1 H, CH-$C\underline{H}_2$), 2.07 - 2.20 (m, 1 H, CH-$C\underline{H}_2$), 2.25 - 2.40(m, 2 H, =CH-$C\underline{H}_2$), 2.63 (dd, 1 H, J = 6.9 Hz, J = 17.4 Hz, CH-$C\underline{H}_2$-CO), 2.65 (dd, 1 H, J = 6.9 Hz, J = 17.4 Hz, CH-$C\underline{H}_2$-CO), 2.93 (dd, 1 H, J = 7.2 Hz, J = 14.4 Hz, =CBr-CH_2), 3.00 (dd, 1 H, J = 7.2 Hz, J = 14.4 Hz, =CBr-CH_2), 3.19 (m, 1 H, CH), 3.92 (t, 93% of 1 H, J = 7.2 Hz, OC-C$\underline{H}$-CO, keto form), 4.19 (q, 2 H, J = 6.9 Hz, O-$C\underline{H}_2$-CH_3), 5.45 (d, 1 H, J = 1.8 Hz, CBr=CH_2), 5.61 (m, 1 H, CH_2-C$\underline{H}$=), 5.66 (d, 1 H, J = 1.8 Hz, CBr=CH_2), 5.75 (m, 1 H, CH-C$\underline{H}$=), 13.13 (s, 7% of 1 H, HO-C=C-CO enol form); IR (neat) 3420, 2940, 1735 (C=O), 1710 (C=O), 1630, 1370, 1180, 1020, 895 cm^{-1}; mass spectrum m/z 314.03281 (calcd for $C_{14}H_{19}BrO_3$, 314.05176).

Compound 4: 30% yield; a diastereomeric mixture in a 1.4 : 1 ratio; R_f = 0.43, 7 : 1 hexanes/ethyl acetate. Diastereomer A: ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7.1 Hz, O-CH_2-$C\underline{H}_3$), 1.41 (m, 1 H, CH-$C\underline{H}_2$, cyclopentene ring), 2.12 (m, 1 H, CH-$C\underline{H}_2$, cyclopentene ring), 2.30 - 2.40 (m, 2 H,

=CH-C<u>H</u>$_2$), 2.72 (dd, 2 H, J = 1.0 Hz, J = 2.4 Hz, CO-CH$_2$), 2.86 (m, 2 H, =CBr-CH$_2$), 3.38 (d, 1 H, J = 3.9 Hz, CO-C<u>H</u>-CH), 3.40 (m, 1 H, C<u>H</u>-CH=), 4.20 (q, 2 H, J = 7.2 Hz, O-C<u>H</u>$_2$-CH$_3$), 5.41 (d, 1 H, J = 1.8 Hz, =CH$_2$), 5.34 (ddt, 1 H, J = 5.7 Hz, J = 1.8 Hz, J = 1.8 Hz, CH$_2$-C<u>H</u>=), 5.63 (d, 1 H, J = 1.8 Hz, =CH$_2$), 5.83 (ddt, 1 H, J = 5.7 Hz, J = 2.4 Hz, J = 2.4 Hz, CH-C<u>H</u>=); ^{13}C NMR ($CDCl_3$) δ 14.19, 27.91, 31.83, 35.25, 41.03, 44.99 (aliphatic), 61.40, 64.65 (O-C), 117.80, 131.19, 132.47, 132.84 (olefinic), 168.72, 202.62 (carbonyl).

<u>Diastereomer B</u>: ^{1}H NMR ($CDCl_3$) same except 1.55 (m, 1 H, CH-C<u>H</u>$_2$, cyclopentene ring), 2.08 (m, 1 H, CH-C<u>H</u>$_2$, cyclopentene ring), 3.35 (d, 1 H, J = 4.9 Hz, CO-C<u>H</u>-CH), 5.65 (d, 1 H, CH$_2$-C<u>H</u>=); ^{13}C NMR ($CDCl_3$) same except 27.96, 31.66, 35.19, 40.75, 45.19 (aliphatic), 131.61, 133.17 (olefinic), 202.79 carbonyl).

The spectral data reported below were obtained from the diastereomeric mixture: IR (neat) 3045, 2995, 2940, 2860, 1747 (C=O), 1720 (C=O), 1635, 1370, 1265, 1182, 1155, 1030, 895 cm^{-1}; mass spectrum m/z 314.05205 (calcd for $C_{14}H_{19}BrO_3$, 314.05176).

<u>Preparation of compound 5</u> This compound was prepared by decarboxylation of compound <u>4</u> using a modification of the procedures used by Crimmins and co-worker[17] and Aristoff and co-workers[18]. A flask containing 0.5781 g (1.8 mmol) of

compound 4, 0.4960 g (11.7 mmol) of lithium chloride, 0.28 ml of water, and 10 ml of dimethyl sulfoxide under nitrogen was heated at 140°C for 30 h. The reaction mixture was cooled to room temperature, diluted with ether, washed with saturated sodium chloride, sodium bicarbonate and then water, dried over anhydrous magnesium sulfate, and concentrated. The resulting yellow liquid was purified by column chromatography (R_f = 0.46, 7 : 1 hexanes/ethyl acetate) to give 0.1587 g (0.65 mmol, 36% yield) of compound 5: ^{1}H NMR ($CDCl_3$) δ 1.36 (ddt, 1 H, J = 12.9 Hz, J = 8.7 Hz, J = 6.3 Hz, CH_2-C<u>H</u>$_2$-CH), 2.13 (ddt, 1 H, J = 13.2 Hz, J = 8.1 Hz, J = 5.4 Hz, CH_2-C<u>H</u>$_2$-CH), 2.32 (m, 2 H, =CH-C<u>H</u>$_2$-CH_2), 2.43 (dd, 1 H, J = 16.5 Hz, J = 7.8 Hz, CH-C<u>H</u>$_2$-CO), 2.53 (dd, 1 H, J = 16.5 Hz, J = 6.9 Hz, CH-O<u>H</u>$_2$-CO), 2.69 (m, 4 H, OC-C<u>H</u>$_2$-C<u>H</u>$_2$-CBr=), 3.10 (m, 1 H, CH), 5.41 (d, 1 H, J = 1.8 Hz, =CH_2), 5.62 (d, 1 H, J = 1.8 Hz, =CH_2), 5.63 (ddt, 1 H, J = 5.7 Hz, J = 2.1 Hz, J = 2.1 Hz, CH_2-C<u>H</u>=), 5.75 (ddt, 1 H, J = 5.7 Hz, J = 2.1 Hz, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 29.91, 31.86, 35.48, 41.01, 41.39, 49.23 (aliphatic), 117.53, 131.35, 132.98, 133.84 (olefinic), 208.23 (carbonyl); IR (neat) 2940, 1717, 1632, 1410, 1366, 1095, 890 cm^{-1}.

Preparation of compounds 6 and 7 Compounds 6 and 7 were prepared from a common precursor, compound 8, which was prepared from 2-cyclopentenylacetic acid following the reaction scheme described in eq. 14.

2-(2'-Cyclopentenyl)ethanol To a flask containing 4.75 g of lithium aluminum hydride in 180 ml of ether at 0°C under nitrogen was added a solution of 12.62 g (100 mmol) of 2-cyclopentenylacetic acid dissolved in 150 ml of ether. After slowly warming to room temperature over 3 h, the reaction was quenched with water until a white suspension precipitated. The ether layer was decanted and the remaining alumina was triturated with ether. The ether solutions were combined, washed with saturated sodium bicarbonate and sodium chloride. After the solvent was removed by distillation under atmospheric pressure, the remaining liquid was distilled at 88°C (20 mm Hg) to give 9.93 g (88.6 mmol, 89% yield) of the alcohol: ^{1}H NMR ($CDCl_3$) δ 1.40 (ddt, 1 H, J = 12.9 Hz, J = 9.0 Hz, J = 6.6 Hz, CH_2-C<u>H</u>$_2$-CH), 1.53 (ddt, 1 H, J = 6.9 Hz, J = 6.9 Hz, J = 6.9 Hz, O-CH_2-C<u>H</u>$_2$), 1.64 (ddt, 1 H, J = 6.9 Hz, J = 6.9 Hz, J = 6.9 Hz, O-CH_2-C<u>H</u>$_2$), 2.02 (m, 1 H, CH_2-C<u>H</u>$_2$-CH), 2.27 (m, 1 H, C<u>H</u>-CH=CH), 2.72 (m, 1 H, =CH-C<u>H</u>), 3.63 (t, 1 H, J = 6.9 Hz, O-CH_2), 3.64 (t, 1 H, J = 6.9 Hz, O-CH_2), 5.63 (m, 1 H, CH_2-C<u>H</u>=), 5.70 (m, 1 H, CH-C<u>H</u>=); ^{13}C NMR ($CDCl_3$) δ 29.89, 31.92, 38.95, 42.58 (aliphatic),

61.70 (C-O), 130.52, 134.66 (olefinic); IR (neat) 3340, 3055, 2930, 2858, 1060, 910, 717 cm^{-1}.

2-(2'-Cyclopentenyl)ethyl methanesulfonate To a solution of 4.01 g (35 mmol) of freshly distilled methanesulfonyl chloride and 2.804 g (25 mmol) of 2-(2'-cyclopentenyl)ethanol in 100 ml of THF at 0°C under nitrogen was added 4.05 g (40 mmol) of freshly distilled triethylamine. The reaction gave a white precipitate after the addition was complete. The reaction mixture was stirred for 1 h at 0°C, warmed to room temperature for 2 h, filtered, and then concentrated. The resulting colorless liquid was purified by column chromatography using 2.5 : 1 hexanes/ethyl acetate (R_f = 0.4) to give 4.60 g (97% yield) of methanesulfonate: ^1H NMR ($CDCl_3$) δ 1.42 (ddt, 1 H, J = 12.6 Hz, J = 8.7 Hz, J = 6.3 Hz, $C\underline{H}_2$-CH), 1.73 (ddt, 1 H, J = 13.8 Hz, J = 6.9 Hz, J = 6.9 Hz, O-CH_2-$C\underline{H}_2$), 1.86 (ddt, 1 H, J = 13.8 Hz, J = 6.9 Hz, J = 6.9 Hz, O-CH_2-$C\underline{H}_2$), 2.09 (ddt, 1 H, J = 13.2 Hz, J = 8.1 Hz, J = 5.1 Hz, CH-$C\underline{H}_2$), 2.31 (m, 2 H, =CH-$C\underline{H}_2$), 2.78 (m, 1 H, CH), 2.99 (s, 3 H, CH_3), 4.26 (t, 2 H, J = 6.9 Hz, O-CH_2), 5.64 (ddt, 1 H, J = 1.8 Hz, J = 1.8 Hz, J = 5.7 Hz, CH_2-$C\underline{H}$=), 5.77 (ddt, 1 H, J = 2.4 Hz, J = 2.1 Hz, J = 5.7 Hz, CH-$C\underline{H}$=).

2-(2'-Cyclopentenyl)ethyl chloride To a suspension of 0.70 g (16.5 mmol) of lithium chloride in 10 ml of ether at room temperature under nitrogen was added 2.6230 g of the

methanesulfonate. The reaction was stirred overnight, and an additional 0.70 g (16.5 mmol) of lithium chloride was added. The reaction was stirred for 2 days at room temperature and then refluxed overnight. The reaction was quenched with water and then extracted with ether. The ether extracts were combined, washed with saturated sodium chloride and sodium bicarbonate, and dried over magnesium sulfate. After the solvent was removed by distillation, the residue was distilled at 65°C (25 mm Hg) to give 1.3463 g (10.31 mmol, 75% yield) of the chloride: ^{1}H NMR ($CDCl_3$) δ 1.35 - 1.48 (m, 1 H, CH_2-C<u>H</u>$_2$-CH), 1.69 - 1.82 (m, 1 H, Cl-CH_2-C<u>H</u>$_2$), 1.83 - 1.95 (m, 1 H, Cl-CH_2-C<u>H</u>$_2$), 2.00 - 2.15 (m, 1 H, CH-C<u>H</u>$_2$-CH_2), 2.20 - 2.43 (m, 2 H, =CH-C<u>H</u>$_2$), 2.80 - 2.90 (m, 1 H, =CH-C<u>H</u>), 3.56 (dt, 2 H, J = 6.9 Hz, J = 1.8 Hz, Cl-CH_2), 5.64 - 5.69 (m, 1 H, CH_2-C<u>H</u>=), 5.74 - 5.79 (m, 1 H, =C<u>H</u>-CH).

<u>5-(2'-Cyclopentenyl)-2-pentynyl tetrahydropyranyl ether</u>

This tetrahydropyranyl ether was prepared from the lithium acetylide of THP-protected propargyl alcohol and 2-(2'-cyclopentenyl)ethyl chloride. The preparation of THP-protected propargyl alcohol was accomplished by following a procedure used by Miyashita and co-workers[19]. Thus, a solution of 2.24 g (40 mmol) of propargyl alcohol and 8.4 g (100 mmol) of dihydropyran in 80 ml of methylene chloride at room temperature was treated with 0.0381 g of <u>p</u>-toluenesulfonic acid monohydrate. After stirring for 1.5 h

at room temperature, the reaction was quenched with 100 ml of ether, washed with saturated sodium bicarbonate and sodium chloride, and dried over anhydrous magnesium sulfate. The solvents were removed by distillation and then the residue was distilled at 70°C (13 mm Hg) to give 5.12 g (36.5 mmol, 91% yield) of the protected alcohol: ^{1}H NMR ($CDCl_3$) δ 1.42 - 1.88 (m, 6 H, 3 CH_2 THP group), 2.40 (t, 1 H, J 2.1 Hz, H-C≡), 3.54 (m, 1 H, O-CH_2), 3.84, (ddd, 1 H, J = 3.0 Hz, J = 8.7 Hz, J = 11.7 Hz, O-CH_2), 4.22 (dd, 1 H, J = 2.4 Hz, J = 15.6 Hz, O-CH_2-C≡), 4.30 (dd, 1 H, J = 2.4 Hz, J = 15.6 Hz, O-CH_2-C≡), 4.82 (t, 1 H, J = 2.7 Hz, O-CH-O); ^{13}C NMR ($CDCl_3$) δ 19.04, 25.38, 30.27 (aliphatic), 54.02, 62.00(C-O), 73.97 (HC≡), 79.00 (-C≡), 98.06 (O-CH-O); IR (neat) 3380, 2940, 2880, 1445,1390, 1350, 1265, 1205, 1125, 1035, 815 cm^{-1}.

The lithium acetylide was prepared by stirring 1.4455 g (10.31 mmol) of the THP-protected propargyl alcohol in 6 ml of hexamethylphosphoramide and 4.6 ml (2.24 M) of n-butyllithium at 0°C for 2 h. The acetylide solution at 0°C under nitrogen was treated with 1.3462 g (10.31 mmol) of 2-(2'-cyclopentenyl)ethyl chloride over a 10 min period. The reaction mixture was stirred overnight, quenched with water, and extracted with ether. The ether extracts were combined, washed with saturated sodium chloride and sodium bicarbonate, dried over anhydrous magnesium sulfate, and concentrated. The resulting yellow liquid was purified by column

chromatography using 10 : 1 hexanes/ethyl acetate (R_f = 0.37) to give 1.88 g (8.0 mmol, 78% yield) of the desired product: ^{1}H NMR ($CDCl_3$) δ 1.40 - 2.40 (m, 14 H, aliphatic) 2.76 (m, 1 H, C<u>H</u>-CH=CH), 3.53 (m, 1H, O-CH_2), 3.84 (m, 1 H, O-CH_2), 4.19 (dt, 1 H, J = 15 Hz, J = 2.1 Hz, ≡C-CH_2-O), 4.28(dt, 1 H, J = 15 Hz, J = 2.1 Hz, ≡C-CH_2-O), 4.80 (t, 1 H, J = 3.3 Hz, O-CH-O), 5.66 (m, 1 H, CH_2-C<u>H</u>=), 5.72 (m, 1 H, CH-CH=); ^{13}C NMR ($CDCl_3$) δ 17.23, 19.10, 25.39, 29.40, 30.27, 31.86, 34.71, 44.72 (aliphatic), 54.54, 61.85 (C-O), 75.38, 86.46 (C≡C), 96.54 (O-CH-O), 130.63, 134.23 (CH=CH).

<u>2-(2-Cyclopentenyl)-2-pentyn-1-ol (8)</u> This alcohol was prepared from the corresponding THP ether following the procedure developed by Corey and co-workers[20]. To a solution of 1.87 g (8.0 mmol) of the THP ether in 20 ml of methanol at room temperature was added 0.0152 g (1%) of <u>p</u>-toluenesulfonic acid monohydrate. The reaction was stirred for 10 h at room temperature. After the methanol was removed, the residue was dissolved with 100 ml of ether. The ether solution was washed with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, and then concentrated. The resulting liquid was purified by column chromatography using 3 : 1 hexanes/ethyl acetate (R_f = 0.37) to give 1.017 g (6.8 mmol, 85% yield) of the alcohol <u>8</u>: ^{1}H NMR ($CDCl_3$) δ 1.35 - 1.45 (m, 1 H, CH_2-C<u>H_2</u>-CH), 1.49 (m, 1 H, ≡C-CH_2-C<u>H_2</u>-CH), 1.57 (s, 1 H, OH), 1.66 (m, 1 H, ≡C-CH_2-C<u>H_2</u>-

CH), 2.06 (m, 1 H, CH-C<u>H</u>$_2$-CH$_2$), 2.20 - 2.40 (m, 4 H, =CH-C<u>H</u>$_2$ and ≡C-CH$_2$), 2.76 (m, 1 H, =CH-C<u>H</u>), 4.24 (t, 2 H, J = 3.3 Hz, O-CH$_2$-C≡), 5.66 (ddt, 1 H, J = 5.7 Hz, J = 2.4 Hz, J = 1.82 Hz, =C<u>H</u>-CH$_2$), 5.74 (ddt, 1 H, J = 4.2 Hz, J = 2.4 Hz, J = 2.1 Hz, =C<u>H</u>-CH); ^{13}C NMR ($CDCl_3$) δ 17.27, 29.53, 31.99, 34.84, 44.83 (aliphatic), 51.50 (C-O), 78.42, 86.60 (C≡C), 130.90, 134.27 (CH=CH); IR (neat) 3350 (OH), 3060, 2940, 2860, 2300, 2230, 1140, 1020, 720 cm^{-1}.

<u>Z-5-(2'-Cyclopentenyl)-3-iodo-2-pentene-1-ol (6)</u> This iodo alcohol was prepared from the propargylic alcohol <u>8</u> by the procedure used by Cowell and Stille[21]. To a solution of 0.300 g (2.0 mmol) of the propargylic alcohol and 0.2214 g (4.10 mmol) of sodium methoxide in 6 ml of THF at 0°C under nitrogen was added 1.3 ml (1.57 M in THF) of lithium aluminum hydride. The reaction mixture turned milky white. The reaction was stirred for 3 h while slowly warming to room temperature. Excess lithium aluminum hydride was destroyed by adding 1 ml of ethyl acetate to the reaction mixture at 0°C and stirring for 30 min at 0°C. After cooling to -78°C, the reaction mixture was treated with a solution of 0.9 g (3.54 mmol) of iodine in 5 ml of THF. The reaction was warmed to room temperature over 1 h, quenched with ether, and washed with 5% HCl. The water was back-extracted with ether. The ether extracts were combined, washed with saturated sodium bicarbonate and sodium sulfite, dried over anhydrous

magnesium sulfate, and then concentrated. The resulting liquid was purified by column chromatography using 2.5 : 1 hexane/ethyl acetate (R_f = 0.37) to give 0.3124 g (1.12 mmol, 56% yield) of compound 6: ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 1 H, CH_2-C<u>H</u>$_2$-CH), 1.53 (m, 1 H, CH-C<u>H</u>$_2$-CH_2-CI=), 1.62 (m, 1 H, CH-C<u>H</u>$_2$-CH_2-CI=), 2.05 (m, 2 H, C<u>H</u>$_2$-CH_2-CH and OH), 2.14 - 2.36 (m, 2 H, C<u>H</u>$_2$-CH=), 2.54 (t, 2 H, J = 7.8 Hz, =CI-CH_2), 2.66 (m, 1 H, CH), 4.18 (d, 2 H, J = 6 Hz, O-CH_2), 5.65 (ddt, 1 H, J = 2.1 Hz, J = 2.1 Hz, J = 5.7 Hz, C<u>H</u>=CH-CH), 5.74 (ddt, 1 H, J = 2.4 Hz, J = 2.1 Hz, J = 5.4 Hz, CH=C<u>H</u>-CH), 5.84 (tt, 1 H, J = 1.2 Hz, J = 6.0 Hz, CI=CH); ^{13}C NMR ($CDCl_3$) δ 29.67, 31.99, 35.59, 43.67, 44.29 (aliphatic), 67.29 (C-O), 110.48, 130.86, 133.39, 134.36 (olefinic); IR (neat) 3300, 3040, 2920, 2840, 1640, 1440, 1065, 1000, 710 cm^{-1}; mass spectrum m/z 278.01737 (calcd for $C_{10}H_{15}OI$, 278.01677).

<u>Z-5-(2'-Cyclopentenyl)-2-iodo-2-penten-1-ol (7)</u> This compound was prepared from propargylic alcohol <u>8</u> by the procedure developed by Corey and co-workers[22]. To a solution of 0.4507 g (3.0 mmol) of propargylic alcohol <u>8</u> in 3 ml of ether at -20°C under nitrogen were added 1.35 ml (2.23 M in hexane) of <u>n</u>-butyllithium and 1.6 ml (9.0 mmol) of diisobutylaluminum hydride. After warming to room temperature over 2 h, the reaction mixture was heated at 35°C for 48 h. Excess hydride reagent was destroyed by treating the reaction mixture with 0.6 ml of anhydrous ethyl acetate

and stirring for 20 min at room temperature. The reaction mixture was cooled to -78°C, treated with 6.8 g (27 mmol) of iodine dissolved in 15 ml of ether, and stirred for 30 min at -78°C. The reaction mixture was poured into ice, extracted with ether. The ether extracts were combined, washed with saturated sodium sulfite and sodium bicarbonate, dried over anhydrous magnesium sulfate, and concentrated. The resulting liquid was purified by column chromatography using 3 : 1 hexanes/ethyl acetate (R_f = 0.54, 2 : 1 hexanes/ethyl acetate) to give 0.25 g (0.9 mmol, 30% yield) of compound 7: ^{1}H NMR ($CDCl_3$) δ 1.36 - 1.47 (m, 2 H, CH-C$\underline{H}_2$-CH_2-CH= and CH-C$\underline{H}_2$-CH_2-CH=CI), 1.52 (m, 1 H, CH-C$\underline{H}_2$-CH_2-CH=CI), 2.06 (ddt, 1 H, J = 12.9 Hz, J = 5.1 Hz, J = 8.4 Hz, CH-C$\underline{H}_2$-CH_2-CH=), 2.12 (s, 1 H, OH), 2.19 (t, 1 H, J = 7.2 Hz, CI=CH-C$\underline{H}_2$), 2.21 (t, 1 H, J = 7.2 Hz, CI=CH-C$\underline{H}_2$), 2.25 - 2.38 (m, 2 H, CH=CH-C$\underline{H}_2$), 2.67 (m, 1 H, CH), 4.24(s, 2 H, O-CH_2), 5.68(m, 1 H, CH=C$\underline{H}$-CH_2), 5.73 (m, 1 H, =C$\underline{H}$-$CH_)$, 5.90 (t, 1 H, J = 6.6 Hz, CI=C$\underline{H}$-CH_2); ^{13}C NMR ($CDCl_3$) δ 29.79, 32.01, 34.18, 34.32, 45.11 (aliphatic), 71.65 (C-O), 108.14, 130.70, 134.62, 136.34 (olefinic); IR (neat) 3340 (OH), 3060, 2930, 2860, 1460, 1090, 720 cm^{-1}; Exact mass m/z 278.01686 (calcd for $C_{10}H_{15}OI$, 278.01677).

The cyclization reactions were run using the procedures listed in Table 3 (footnote). Variations in the procedure for the cyclization of compound 1 and 6 are listed in Table 1 and Table 2 respectively. The following compounds were obtained from the cyclization reactions.

Compound 9:

Allylic isomer: ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3 H, J = 7.2 Hz, O-CH_2-C$\underline{H}_3$), 1.27 (t, 3 H, J = 7.2 Hz, O-CH_2-C$\underline{H}_3$), 1.32 - 1.40 (m, 2 H, CH-C$\underline{H}_2$), 2.04 (m, 2 H, =CH-C$\underline{H}_2$), 2.83 (d, 1 H, J = 17.7 Hz, =C-CH_2), 2.84 (ddd, 1 H, J = 12.6 Hz, J = 6.3 Hz, J = 3.3 Hz, =CH-CH-C$\underline{H}$-CH_2, ring juncture), 3.22 (br s, 1 H, =CH-CH, ring juncture), 3.32 (ddd, 1 H, J = 2.7 Hz, J = 2.7 Hz J = 17.7 Hz, =C-CH_2), 4.08 - 4.30 (m, 4 H, O-C$\underline{H}_2$-CH_3), 4.82 (d, 1 H, J = 2.1 Hz, =CH_2), 4.97 (s, 1 H, =CH_2), 5.73 (m, 1 H, CH_2-C$\underline{H}$=), 5.87 (m, 1 H, CH-C$\underline{H}$=); ^{13}C NMR ($CDCl_3$) δ 14.02, 14.14, 21.28, 24.53, 37.79, 42.70, 43.20 (aliphatic), 61.12 (CH=CH-$\underline{C}$H-C=), 61.37, 62.47 (C-O), 107.37, 126.37, 126.56, 151.28 (olefinic), 169.69, 171.76 (carbonyl); IR (neat) 3420, 2980, 2940, 1725, 1450, 1370, 860 cm^{-1}; mass spectrum m/z 278.15231 (calcd for $C_{16}H_{22}O_4$, 278.15181).

Homoallylic isomer: ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3 H, J = 7.2 Hz, O-CH_2-C$\underline{H}_3$), 1.27 (t, 3 H, O-CH_2-C$\underline{H}_3$), 1.50 - 1.65 (m, 1 H, C$\underline{H}_2$-CH=CH), 1.70 - 1.85 (m, 1 H, C$\underline{H}_2$-CH=CH), 2.10 - 2.22 (m, 1 H, C$\underline{H}_2$-CH=CH), 2.25 - 2.38 (m, 1 H, C$\underline{H}_2$-CH=CH), 2.75 -

2.86 (m, 3 H, C<u>H</u>-C<u>H</u>-CH_2 and =C-C<u>H_2</u>), 3.30 (d, 1 H, J = 17.7 Hz, =C-CH_2), 4.08 - 4.30 (m, 4 H, O-C<u>H_2</u>-CH_3), 4.88 (d, 1 H, J = 2.1 Hz, =CH_2), 5.52 (m, 2 H, CH=CH); ^{13}C NMR ($CDCl_3$) δ 14.00, 14.11, 22.31, 24.20, 37.13, 40.47, 40.55 (aliphatic), 61.37, 61.71 (C-O), 105.01, 124.29, 124.71, 149.64 (olefinic), 169.94, 171.79 (carbonyl).

<u>Compound 11</u>:

<u>Allylic isomer</u>: ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 6 H, J = 7.2 Hz, O-CH_2-C<u>H_3</u>), 1.40 - 1.52 (m, 2 H, CH-C<u>H_2</u>), 1.67 - 1.81 (m, 2 H, =CH-CH_2-C<u>H_2</u>), 1.90 - 2.10 (m, 2 H, =CH-C<u>H_2</u>), 2.80 (d, 1 H, J = 18.2 Hz, =C-C<u>H_2</u>), 2.87 (ddd, 1 H, J = 11.1 Hz, J = 7.8 Hz, J = 2.6 Hz, C<u>H</u>-CH-CH=, ring juncture), 3.19 (ddd, 1 H, J = 18.2 Hz, J = 2.0 Hz, J = 2.0 Hz, =CH-C<u>H_2</u>), 3.54 (m, 1 H, =CH-C<u>H</u>, ring juncture), 4.10 - 4.28 (m, 4 H, O-C<u>H_2</u>-CH_3), 4.84 (dt, J = 2.0 Hz, J = 2.0 Hz, =CH_2), 4.93 (dt, J = 2.0 Hz, J = 2.0 Hz, =CH_2), 5.56 (ddt, 1 H, J = 11.9 Hz, J = 5.9 Hz, J = 1.5 Hz, CH_2-C<u>H</u>=), 5.72 (ddt, 1 H, J = 11.9 Hz, J = 5.2 Hz, J = 1.5 Hz, CH-C<u>H</u>=).

<u>Homoallylic isomer</u>: ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 6 H, J = 7.2 Hz, O-CH_2-C<u>H_3</u>), 1.28 - 1.39 (m, 2 H, CH-C<u>H_2</u>), 2.10 - 2.33 (m, 4 H, C<u>H_2</u>-CH=CH-C<u>H_2</u>), 2.39 (m, 1 H, =C-CH, ring juncture), 2.72 (ddd, 1 H, J = 17.6 Hz, J = 2.6 Hz, J = 2.6 Hz, =C-C<u>H_2</u>), 3.12 (d, 1 H, J =17.6 Hz, =C-C<u>H_2</u>), 3.27 (m, 1 H, CH, ring juncture), 4.10 - 4.30 (m, 4 H, O-C<u>H_2</u>-CH_3), 4.93 (dt, 1 H, J

= 2.0 Hz, J = 2.0 Hz, $=CH_2$), 4.99 (dt, 1 H, J = 2.0 Hz, J = 2.0 Hz, $=CH_2$), 5.76 - 5.93 (m, 2 H, C<u>H</u>=C<u>H</u>).

The spectral data reported below were obtained from the mixture: IR (neat) 2930, 1730, 1448, 1370, 1250 cm^{-1}; mass spectrum m/z 292.16792 (calcd for $C_{13}H_{24}O_4$, 292.16747).

<u>Compound 14</u>:

<u>Allylic isomer</u>: ^1H NMR ($CDCl_3$) δ 2.20 - 2.80 (m, 8 H, aliphatic), 3.10 (m, 1 H, CH_2-C<u>H</u>-CH_2, ring juncture), 3.53 (br d, 1 H, J = 9.0 Hz, =CH-C<u>H</u>-CH, ring juncture), 4.88 (s, 1 H, $=CH_2$), 4.99 (s, 1 H, $=CH_2$), 5.61 (1 H, CH-C<u>H</u>=CH), 5.82 (m, 1 H, CH_2-C<u>H</u>=CH); GC mass spectrum m/z (relative intensity) 162 (M^+, 10), 147 (18), 144 (21), 133 (15), 129 (25), 119 (41), 105 (57), 91 (100), 79 (54), 77 (50).

<u>Homoallylic isomer</u>: ^1H NMR ($CDCl_3$) same except 4.96 (s, 1 H, $=CH_2$), 5.07 (s, 1 H, $=CH_2$), 5.76 (m, 2 H, CH=CH); GC mass spectrum m/z (relative intensity) 162 (M^+, 39), 119 (29), 105 (57), 96 (24), 91 (100), 79 (81), 77 (52), 67 (74).

<u>Compound 10</u>:

<u>Allylic isomer</u>: ^1H NMR ($CDCl_3$) δ 1.38 (s, 1 H, OH), 1.43 (ddt, 1 H, J = 10.4 Hz, J = 5.2 Hz, J = 5.2 Hz, CH-C<u>H_2</u>-CH_2), 1.81 (ddt, 1 H, J = 12.3 Hz, J = 7.2 Hz, J = 7.2 Hz, CH-C<u>H_2</u>-CH_2), 2.11 (dddd, 1 H, J = 17.4 Hz, J = 4.1 Hz, J = 2.0 Hz, J = 2.0 Hz, =C-C<u>H_2</u>-CH_2), 2.26 (m, 2 H, =CH-C<u>H_2</u>-CH), 2.62

(dddd, 1 H, J = 17.4 Hz, J = 8.2 Hz, J = 4.1 Hz, J = 2.0 Hz, =CH-C$\underline{H}_2$-CH), 2.80 (m, 1 H, =CH-CH-C$\underline{H}$, ring juncture), 3.72 (br d, 1 H, J = 5.8 Hz, =CH-C$\underline{H}$, ring juncture), 4.23 (m, 2 H, -O-C$\underline{H}_2$-CH=), 5.49 (m, 2 H, C$\underline{H}$=C$\underline{H}$ and =C$\underline{H}$-CH_2-O), 5.62 (m, 1 H, C$\underline{H}$=CH); IR (neat) 3380 (br, OH), 3060, 2950, 2880, 2860, 1000, 685 cm^{-1}; mass spectrum m/z 150.10464 (calcd for $C_{10}H_{14}O$, 150.10447).

Homoallylic isomer: ^1H NMR ($CDCl_3$) same except δ 3.25 (br t, 1 H, J = 7.8 Hz, C$\underline{H}$-CH_2, ring juncture), 3.33 (m, 1 H, C$\underline{H}$-CH_2-C=, ring juncture).

Compound 15: ^1H NMR ($CDCl_3$) δ 1.34 - 1.61 (m, 3 H, OH and =CH-CH_2-C$\underline{H}_2$, cyclohexene ring), 1.93 - 2.06 (m, 2 H, =CH-C$\underline{H}_2$, cyclopentene ring), 2.06 (m, 1 H, =CH-C$\underline{H}_2$, cyclohexene ring), 2.40 - 2.57 (m, 2 H, =CH-C$\underline{H}_2$, cyclohexene ring and =CH-CH-C$\underline{H}$, ring juncture), 3.20 (m, 1 H, =C-C$\underline{H}$), 4.11 (s, 2 H, O-C$\underline{H}_2$-C=), 5.70 (m, 1 H, O-CH_2-C=C$\underline{H}$), 5.76 - 5.83 (m, 2 H, C$\underline{H}$=C$\underline{H}$); ^{13}C NMR ($CDCl_3$) δ 23.27, 26.00, 36.00, 38.19, 45.85 (aliphatic), 66.58 (C-O), 124.08, 129.64, 132.15, 138.80 (olefinic); IR (neat) 3315, 2920, 2843, 1445, 1443, 1038, 1002, 791, 716, 665 cm^{-1}; mass spectrum m/z 150.10464 (calcd for $C_{10}H_{14}O$, 150.10447).

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SUMMARY

In this work, π-allylpalladium compounds have been prepared from alkenylcycloalkanes bearing 3- and 4-membered rings by reaction with organomercurials and dilithium tetrachloropalladate through a novel palladium-promoted ring-opening process. In the second part of the thesis, π-allylpalladium compounds prepared in situ from various acetoxy-substituted dienes and functionally substituted organomercurials react with base to provide a new route to dihydrobenzofurans and lactones. In the part three of the thesis, cyclic alkenes bearing vinylic halides have been shown to undergo facile, palladium catalyzed cyclization to afford a wide variety of bicyclic cycloalkenes. This methodology allows one to close a 5- or 6-membered ring onto 5-, 6-, and 7-membered ring cyclic alkenes.

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