1990

Palladium-catalyzed arylation and vinylation of cyclic alkenes

William H. Gong
Iowa State University

Order Number 9100439

Palladium-catalyzed arylation and vinylation of cyclic alkenes

Gong, William H., Ph.D.

Iowa State University, 1990

U·M·I
300 N. Zeeb Rd.
Ann Arbor, MI 48106

Palladium-catalyzed arylation and vinylation of cyclic alkenes

by

William H. Gong

A Dissertation Submitted to the

Graduate Faculty in Partial Fulfillment of the

Requirements for the Degree of

DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

Approved: Members of the Committee:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

For the Major Department

Signature was redacted for privacy.

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa
1990

TABLE OF CONTENTS

DEDICATION

I would like to dedicate this work to the only person who took this naive, young, college sophomore, chemistry major seriously when he said he was considering graduate school as a future possibility. Since that evening in the spring of 1982 outside of Milner Library of Illinois State University, she has been very supportive of me throughout this incredible journey. To my wife Melinda.

GENERAL INTRODUCTION

The research in each part is related in that it all discusses the development of a palladium-based synthetic method. The primary focus of Part One is the development of an improved palladium-catalyzed procedure for allylic arylation of cyclic alkenes. Existing methods for this synthetic transformation have a variety of shortcomings, one of which is the incompatibility of the reaction conditions with certain organic functional groups. The improved procedure discussed in Part One eliminates this difficulty, and the desired cross-coupled products are afforded in high yields.

The focus of Part Two is the use of the improved procedure in a 3-step synthesis of a number of *trans*-2,5-diaryltetrahydrofurans, known to be potent inhibitors of platelet activating factor. Previous processes for synthesizing these valuable compounds are lengthy and the biologically inactive *cis* isomer is also formed. The process discussed in this part employs, in the first step, procedure C, followed by procedure B and subsequent hydrogenation to generate the desired tetrahydrofuran derivatives.

The focus of Part Three is on the development of a palladium-catalyzed intermolecular vinylation of cyclic alkenes to afford 1,4-dienes. A number of different vinylic iodides containing electron-donating and withdrawing groups were examined. Three different palladium procedures, as well as a variety of cyclic alkenes, have been explored in this reaction. The scope and limitations of this synthetic transformation have been determined and will be discussed.

In the final part, the reaction conditions employed in all three previous parts have been employed in the intramolecular vinylation of cyclic alkenes. The purpose again is to determine the scope and limitations of these procedures for making a variety of carbo- and heterocycles.

TABLE OF ABBREVIATIONS

Ac	Acetyl
bp	Boiling point
^{13}C NMR	Carbon-13 nuclear magnetic resonance
DEAD	Diethyl azodicarbonamide
DHP	3,4-Dihydro-2*H*-pyran
DIBAL	Diisobutylaluminum hydride
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dd	Double of doublets
dt	Doublet of triplets
Et	Ethyl
g	Grams
GC	Gas chromatograph
GC-MS	Gas chromatography - mass spectrometry
HMPA	Hexamethylphosphoramide
^{1}H NMR	Proton nuclear magnetic resonance
HRMS	High resolution mass spectrometry
IR	Infrared
LDA	Lithium diisopropylamide
M	Molar
m	multiplet
MCPBA	Meta-chloroperbenzoic acid

Me	Methyl
mL	Milliliters
mmol	Millimoles
mp	Melting point
Ms	Methanesulfonyl
Ph	Phenyl
PPTS	Pyridinium para-toluenesulfonate
PTSA	Para-toluenesulfonic acid
Pyr	Pyridine
rt	Room temperature
q	Quartet
s	Singlet
t	Triplet
TBAC	Tetra-*n*-butylammonium chloride
TBDMS	*Tert*-butyldimethylsilane
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetate
Tf_2O	Trifluoromethanesulfonyl anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Tolyl	Toluene

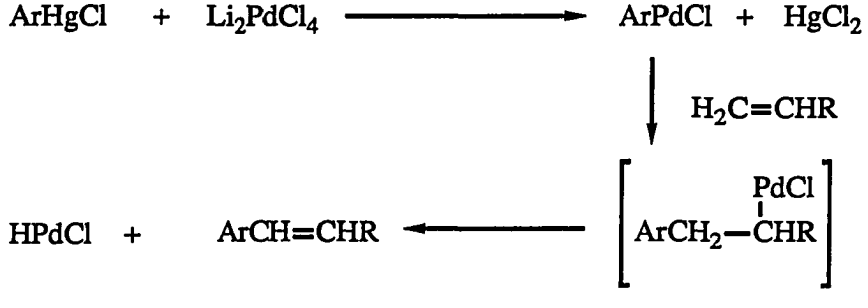
PART I. AN IMPROVED PROCEDURE FOR PALLADIUM-CATALYZED ARYLATION OF CYCLIC ALKENES

INTRODUCTION

Within the last three decades, many advances have been made in the area of organometallic chemistry as applied to organic synthesis. Organopalladium chemistry is one such example as determined by the vast number of publications. There are basically three reasons why Pd-based methodologies have been so widely explored. First, these palladium-based processes are generally not oxygen and moisture sensitive. Secondly, these processes can accommodate a wide variety of important organic functional groups. Lastly, palladium has the ability to catalyze a number of novel organic transformations.[1,2]

In 1967, R.F. Heck reported a novel Pd(II)-mediated arylation of acyclic alkenes with arylmercurials under very mild reaction conditions[3]. Since that initial discovery, many researchers have extensively explored this area.[4-15] The reaction basically proceeds via the mechanism outlined in Scheme I, which begins by a metathesis reaction between an

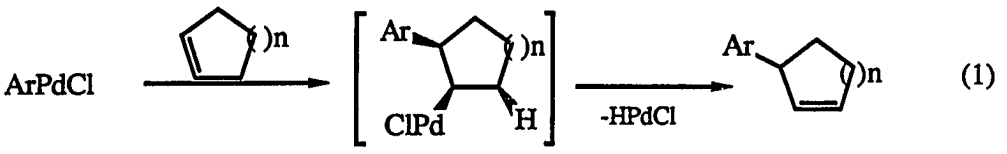
Scheme I



arylmercurial and a Pd(II) salt under very mild reaction conditions (0 - 25 °C) to afford a reactive arylpalladium intermediate. This intermediate then adds in a *syn* 1,2-fashion

across an alkene to afford a new, σ-organopalladium intermediate, followed by bond rotation so that a β-hydrogen is *cis* to the palladium. Subsequent *syn* elimination of palladium hydride affords the vinyl hydrogen substitution product.

When cyclic alkenes are employed, no bond rotation is possible after the 1,2-addition. Thus, there is a *syn* elimination of palladium hydride away from the initial addition site to afford only the allylic isomer (eq 1). While this process is very mild, there are two major

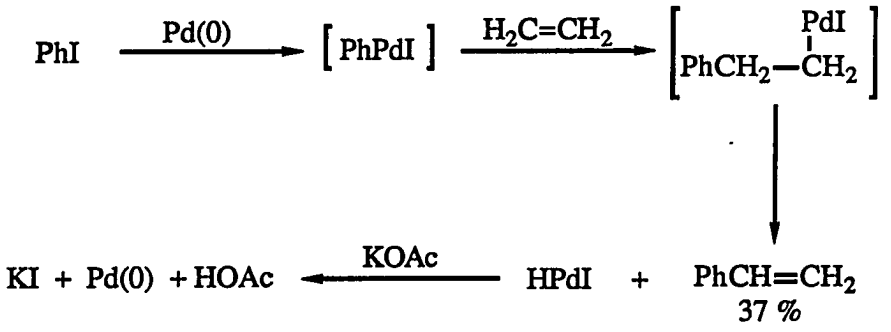


(1)

disadvantages associated with it. There is the need for a stoichiometric amount of expensive Pd(II) salts and toxic organomercurials. Limited success has been achieved in making these reactions catalytic in Pd (1 - 20 mole %). In the presence of a copper(II) salt, such as copper(II) chloride, the Pd(0) is oxidized to Pd(II), and the latter then re-enters the catalytic cycle. One major drawback to this catalytic approach is having to work with thick slurries of copper and mercury salts.

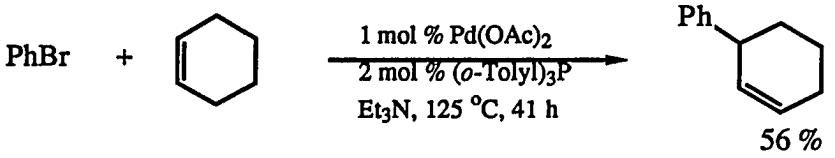
Two groups[16,17] independently discovered a Pd(0)-catalyzed procedure for the arylation of alkenes using aryl halides, and this catalytic process has circumvented the need for large amounts of Pd(II) salts and toxic organomercurial starting materials (Scheme II). The reaction proceeds by oxidative addition of an aryl iodide onto zerovalent palladium to afford the reactive arylpalladium species. This species then adds to the alkene to afford a new, unstable σ-organopalladium species, followed by elimination to afford the expected product and hydridopalladium iodide. This unstable Pd species then reductively

Scheme II



eliminates in the presence of KOAc[16] or Et_3N[17] to afford a salt and Pd(0), which re-enters the catalytic cycle. Since then, many chemists have researched this catalytic process as applied to acyclic alkenes. There are comparatively fewer examples of cyclic alkenes undergoing this reaction, and these examples will now be discussed.

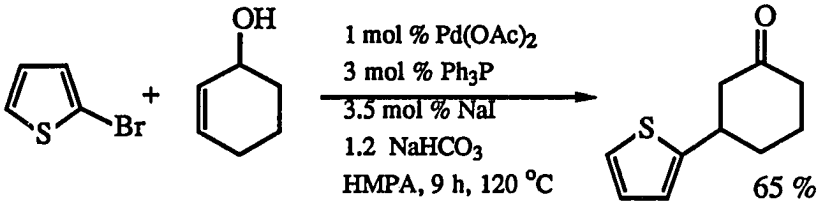
In 1978 Cortese, Ziegler Jr., Hrnjez, and Heck[18] reported a Pd(0)-catalyzed procedure for the phenylation of cyclohexene (eq 2). This group found that it was necessary to



(2)

employ a triarylphosphine as a co-catalyst when bromobenzene was used. However, if iodobenzene was the phenyl source, the conditions were milder (100 °C, 15 h), and the desired product was produced in a higher yield (72 %).

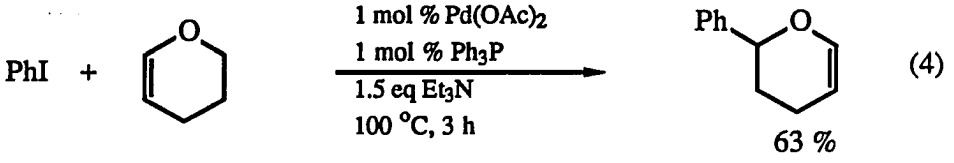
Also in 1978, Tamaru, Yamada, and Yoshida[19] reported an approach to 3-aryl-cyclohexanones (eq 3). This reaction parallels the reaction previously reported by



(3)

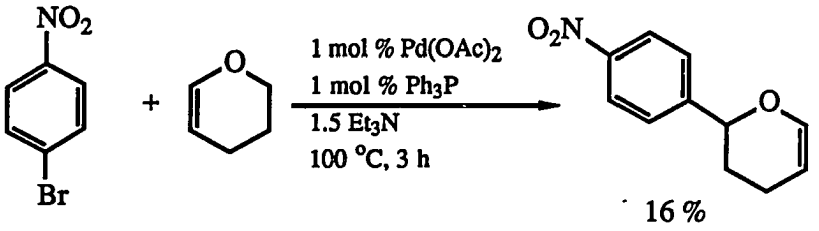
Heck[3b] where arylmercurials were employed. Tamaru had also discovered that when acyclic allylic alcohols were employed, the regioselectivity of this process was greatly influenced by the choice of solvents. The role of NaI is unclear, except that the authors indicated that in reactions containing this salt, there was an increase in the turnover of the catalyst.

Arai and Daves [20] preliminarily reported in 1979 a Pd(0)-catalyzed phenylation of 3,4-dihydro-2*H*-pyran (eq 4). Migration of the double bond occurred, probably due to the



(4)

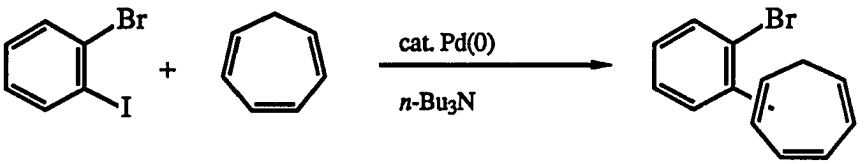
high temperature employed (100 °C) in this reaction. Furthermore, only the α-phenylated isomer was isolated each time. Later in 1987, Andersson, Hallberg, and Daves,[21] followed up on their earlier report with a fairly comprehensive study of this process. In this follow up, they found that when 3,4-dihydro-2*H*-pyran was arylated with 4-iodonitrobenzene, only nitrobenzene and 4,4'-dinitrobiphenyl were formed. However, when the corresponding bromonitrobenzene was employed, the desired arylated product was isolated in a low 16 % yield, but an unspecified amount of 4-bromonitrobenzene remained unreacted (eq 5). Interestingly, when acyclic enol ethers were arylated,



(5)

there was a complex regioisomeric mixture of products. It appears that a variety of factors governs the regioselectivity of the arylation.

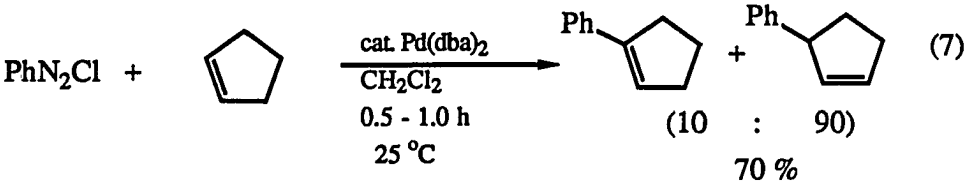
Yamamura and co-workers[22] employed a Pd(0)-catalyzed arylation procedure to synthesize a precursor to *o*-tropyliobiphenyl tetrafluoroborate, a compound useful in studying intramolecular charge-transfer interactions (eq 6). Although no yield was



(6)

reported for this isomeric mixture, it was interesting to note that there was selectivity for the aryl iodide, and furthermore, this is the only example of an arylation of a cyclopolyene.

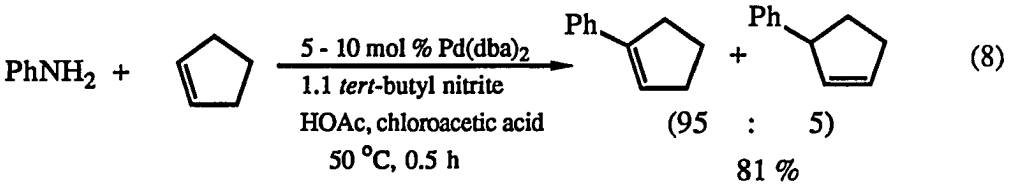
Kikukawa and co-workers[23] reported a Pd(0)-catalyzed arylation procedure of alkenes using arenediazonium salts (eq 7). Although the yield for phenylcyclopentene is



(7)

good, the reaction fast, and the conditions mild, there are several problems associated with this process that severely limit its use in organic synthesis. The product is a mixture of two isomers, with the isomerized, conjugated product present in the greatest amount. Kikukawa observed that diazonium salts tend to be sensitive to temperatures above 25 °C, and this is indicated by the formation of tarry material. When a less reactive cyclic alkene such as 1-pyrrolidinylcyclopentene is employed, the reaction fails to proceed at 25 °C. It appears that the solvent, functional groups present in the arenediazonium salt, and the amounts of Pd catalyst are all very critical in obtaining the desired product. Even with only partial formation of tarry materials, the catalyst is greatly deactivated. Finally, the selection of a base, NaOAc in this case, is critical or the end result is tar.

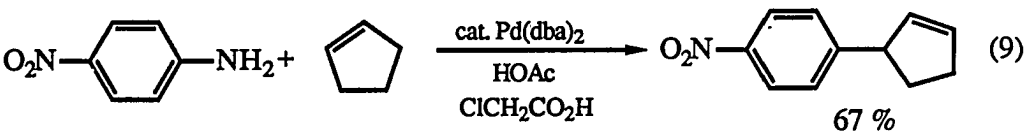
In 1980, Kikukawa and co-workers[24] reported a Pd(0)-catalyzed procedure for the arylation of alkenes with arylamines and *tert*-butyl nitrite (eq 8). Unlike their previous



(8)

work discussed above, the arenediazonium salt is generated *in situ* from the corresponding arylamine. This is an improvement over their previously reported procedure. With this improvement, the researchers were able to manipulate the reagents above room

temperature where otherwise, the arenediazonium salt would have easily decomposed. 4-Nitroaniline can be employed in this procedure to afford 3-(4-nitrophenyl)cyclopentene in good yield (eq 9), while the corresponding arenediazonium salt did not react in the

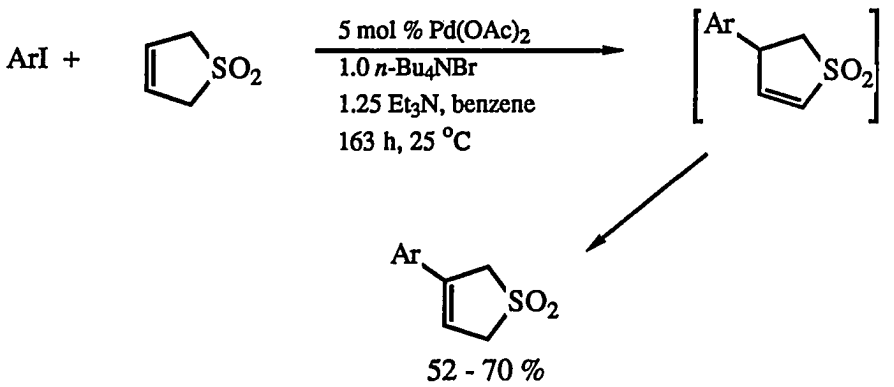


(9)

previous procedure to produce any of the desired product. The disadvantages to this approach could be that certain substrates may be sensitive to the acidic medium, and when cyclopentene and cyclohexene[25] were employed, bad isomeric product mixtures were usually afforded.

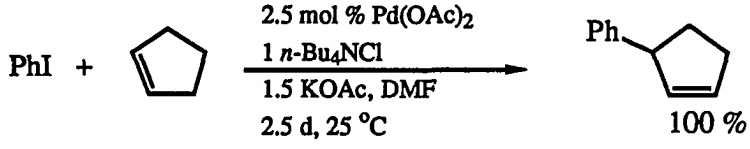
In 1987, Harrington and Di Fiore[26] reported a Pd(0)-catalyzed approach to 3-aryl-2,5-dihydrothiophene-1,1-dioxides from aryl iodides and 2,5-dihydrothiophene-1,1-dioxides (Scheme III). These researchers have explored this reaction with a variety of aryl

Scheme III



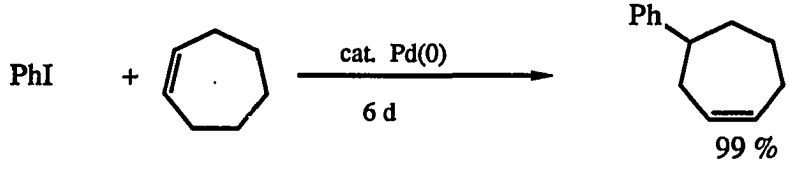
iodides. The phase transfer conditions employed by Harrington were a modification of Jeffrey's conditions.[27-29] From the results reported, the authors have observed 4-iodonitrobenzene to be inert, and aryl iodides bearing electron-donating groups tend to retard the reaction rate.

Most recently in 1988, Larock and Baker[30] developed a general procedure for arylating a wide variety of cyclic alkenes (eq 10). This procedure is a modification of



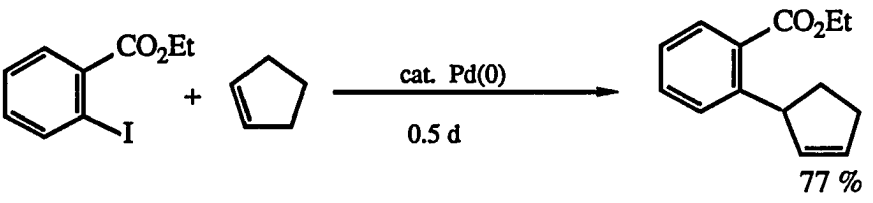
(10)

Jeffrey's phase transfer conditions.[27-29] The authors have found the base and solvent employed to be critical to the yield and overall rate of the reaction. The alkali metal acetates have proven superior as bases to all others examined. Cycloalkenes of ring size 5 through 8 are readily accommodated. Unexpectedly, when iodobenzene and cycloheptene were allowed to react under these reaction conditions, only the homoallylic isomer was afforded in 99 % GC yield (eq 11). Contrary to Harrington's conclusions, electron-



(11)

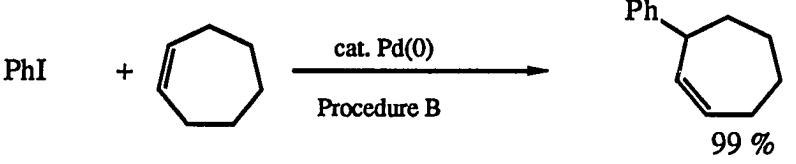
withdrawing groups, whether in the ortho or para position, do not deactivate the arene toward substitution. In fact, Larock's results seem to indicate the opposite. Indeed, when ethyl 2-iodobenzoate and cyclopentene were allowed to react under these reaction conditions, the desired arylated product was produced in 0.5 day in high yield (eq 12).



(12)

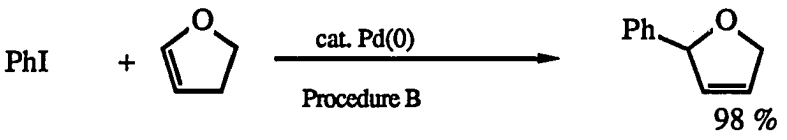
When an electron-rich aryl iodide, such as 2-iodoanisole, was allowed to react with cyclopentene, the reaction required heating to 80 °C for complete conversion of the aryl iodide. However, in agreement with Harrington's findings, 2- and 4-iodonitrobenzene were found to be inert.

Baker's subsequent investigation[31] has revealed that aryl iodides containing a number of important organic functional groups could not be accommodated by his phase transfer procedure (also known as Procedure A: 2.5 mol % $Pd(OAc)_2$, 1 equiv *n*-Bu_4NCl, 3 equiv acetate base, DMF, 25 or 80 °C). Furthermore, certain cyclic alkenes have proven to be problematic by procedure A, because they afford isomeric product mixtures. The aryl iodides that could not be accommodated by procedure A are 2-iodophenol, 2-iodobenzyl alcohol, 2-iodoaniline, 2-iodobenzaldehyde, 2-iodo-*N*-acetyl-aniline, 2-iodo-*N*-tosylaniline, and 2- and 4-iodonitrobenzene. Furthermore, cyclic alkenes such as cycloheptene, 2,3-dihydrofuran, and 3,4-dihydro-2*H*-pyran produced isomeric mixtures. These difficulties caused Baker[31] to employ an alternative procedure[32] for this same synthetic process (known as procedure B: 3 - 4 mole % $Pd(OAc)_2$, 9 mole % PPh_3, 2 equiv. Ag_2CO_3, and CH_3CN at 80 °C). Indeed, when procedure B was employed in the reaction between iodobenzene and cycloheptene, only the desired allylic isomer was afforded in high yield (eq 13). Previously, when procedure A was employed in the

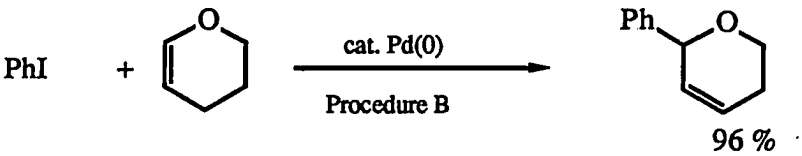


(13)

reaction of iodobenzene and 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran, a high yield of a mixture of two and three isomers was afforded, respectively. When procedure B was employed for these same substrates, only the desired allylic isomer was produced each time in high yields (eqs 14 and 15). While 2- and 4-iodonitrobenzene did not react when

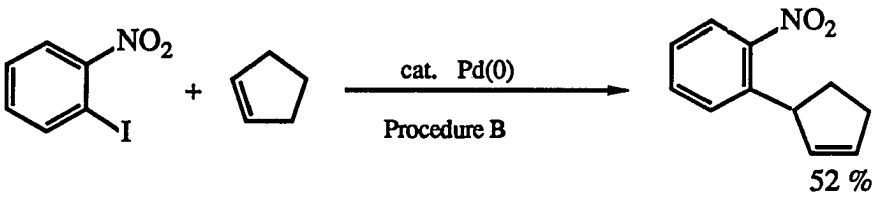


(14)

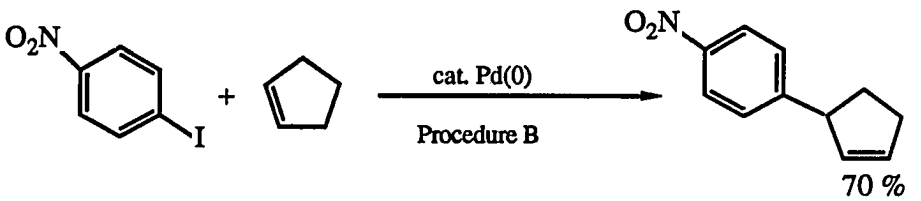


(15)

procedure A was applied, under the reaction conditions of procedure B, the desired product was isolated in good yield (eqs 16 and 17).



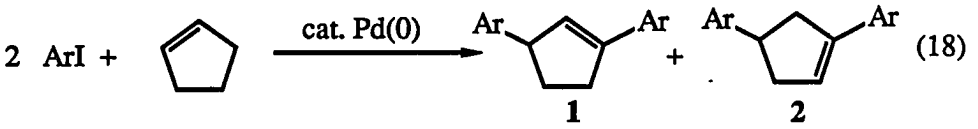
(16)



(17)

Prashad et al.[33] recently reported a convenient Pd(0)-catalyzed synthesis of 1,3-diarylcyclopentenes, which are intermediates to the carbon isosteres of known platelet

activating factor antagonists, *trans*-2,5-diaryltetrahydrofurans (a detailed discussion of these antagonists is found in Part Two) (eq 18). Prashad's approach was a double Heck



(18)

1 **2**

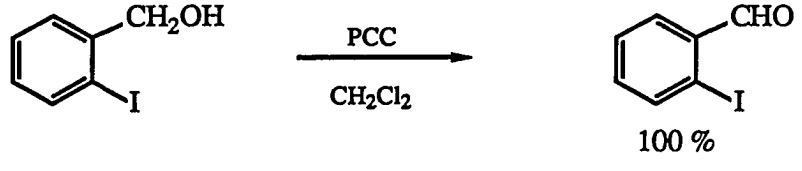
Ar = 3,4,5-trimethoxyphenyl

arylation of cyclopentene using two different sets of reaction conditions to obtain the desired product. When he employed Heck's conditions,[4] a 2 : 1 ratio of the desired allylic product (**1**) to the homoallylic product (**2**) was observed. However, when he employed Larock's procedure A,[30] a 95 : 2.2 ratio for **1** and **2** was observed. He credits Larock's procedure for inhibiting the palladium hydride readdition and subsequent elimination which affords the homoallylic product.

RESULTS AND DISCUSSION

In spite of the success of Baker and Larock's procedures A and B, there still remain a number of aryl iodides containing certain functional groups that are inert to these cycloallylation reactions. The development of an improved procedure to overcome the difficulties encountered in previous procedures is the objective of this section.

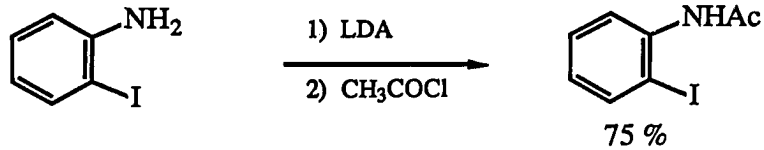
Many of the aryl iodides are commercially available and were used without further purification. 2-Iodobenzaldehyde was prepared by oxidizing the corresponding 2-iodobenzyl alcohol with pyridium chlorochromate (PCC) (eq 19). The aldehyde was



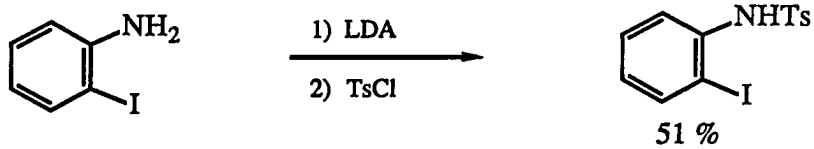
100 % (19)

used immediately as it was found to oxidize slowly upon standing.

2-Iodo-*N*-acetylaniline and 2-iodo-*N*-tosylaniline were obtained by quenching the amide anion of 2-iodoaniline with acetyl and tosyl chloride respectively (eqs 20 and 21).

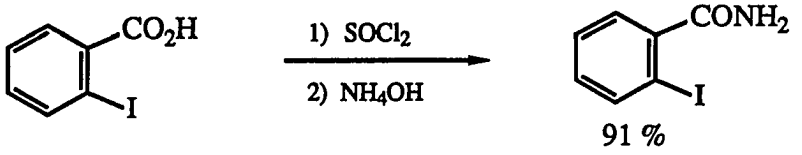


75 % (20)



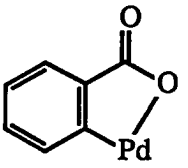
51 % (21)

2-Iodobenzamide was prepared by treating 2-iodobenzoic acid first with thionyl chloride followed by aqueous ammonia (eq 22).



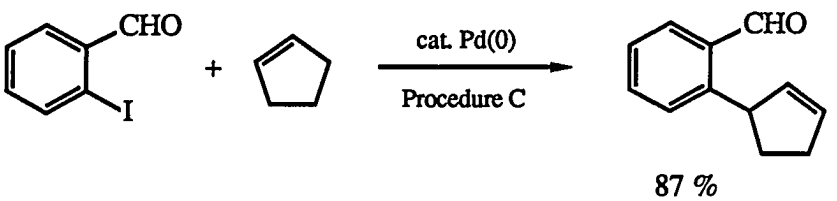
91 % (22)

From a survey of the literature, it's obvious that the Pd(0)-catalyzed processes are more attractive than the Pd(II)-mediated ones employing organomercurials. Of all of the starting materials used in the Pd(0)-catalyzed reactions reviewed thus far, clearly the most attractive ones are aryl iodides. From all of the studies conducted prior to Larock and Baker's work,[30,31] it is clear that the reaction conditions employed are harsh, and frequently the product is afforded in low yield and often contaminated with a regioisomer. The Larock-Baker procedures are attractive in that reaction conditions employed are very mild. When electron-rich aryl iodides are employed, only a slightly higher temperature is necessary. However, from subsequent work by Baker, it was determined that certain aryl iodides could not be accommodated by their method. The unreactive aryl iodides are 2-iodobenzaldehyde, 2-iodobenzyl alcohol, 2-iodo-*N*-tosylaniline, 2-iodo-*N*-acetylaniline, 2-iodoaniline, 2-iodophenol, 2-iodobenzamide, 2-iodobenzoic acid, and 2- or 4-iodonitrobenzene. A possible explanation for this phenomenon could be that some of these aryl iodides may form a stable organopalladium chelate with the palladium catalyst after the oxidative addition step (see Scheme II), thus explaining their failure to react. Baker claimed the presence of a hydrogen atom on a heteroatom must retard the reaction. An excellent example of this chelation is demonstrated with 2-iodobenzoic acid as shown below. As evidence to support this hypothesis, when 2-iodobenzoic acid was esterified



to the ethyl ester, thus removing the acidic hydrogen, the reaction proceeded to afford the desired product in good yield in only 12 hours (eq 12).

Recently, Dr. Colleen Fried, a member of the Larock research group has observed that the presence of a catalytic amount of PPh_3 in reactions using quaternary ammonium salts greatly improves the yields in some intramolecular organopalladium cyclizations. In light of this success, this investigation began by exploring the scope and limitations of a new procedure, procedure C (procedure A plus 2.5 mole % PPh_3). When 2-iodobenzaldehyde and cyclopentene were allowed to react using procedure A, the aryl iodide was found to be completely inert. When procedure C was employed, 2-iodobenzaldehyde was completely converted and 2-(3-cyclopentenyl)benzaldehyde was isolated in a high yield after 1 day (eq 23)! Encouraged by these results, the remaining inert aryl iodides were also examined

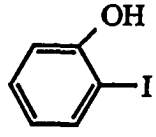
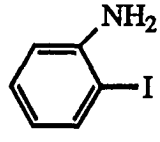
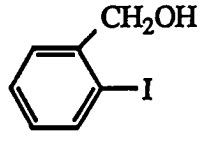
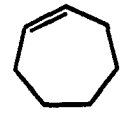


(23)

87 %

using procedure C. The results of this investigation and Baker's results are summarized in Table 1. From the results obtained, the following observations have been made. In the cases where aryl iodides bearing electron - donating groups were allowed to react with cyclopentene, procedure C was found to be superior to procedures A and B in that it reduces the reaction time and / or increases the yield of the desired 3-arylcyclopentene. For example, 2-iodophenol readily reacted with cyclopentene when using procedure C to

Table 1. An improved procedure C for Pd(0)-catalyzed arylation of cyclic alkenes

Entry	Aryl Iodide	Cyclic Alkene	Procedure[a]
1			A
2			B
3			C
4			C
5			A
6			B
7			C
8			C[b]
9			C[c]
10			C[c]
11			A
12			B
13			C
14			C

[a] See text for details of procedures A, B, and C.
[b] 5 Mole % of PPh_3 was used.
[c] 5 Mole % of PPh_3 and 3 equiv of Et_3N were used.
[d] Yield was based on recovered starting material.
[e] Ratio reflects allylic : homoallylic isomer as determined by ^1H NMR spectroscopy.

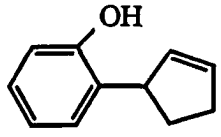
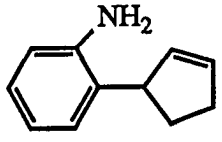
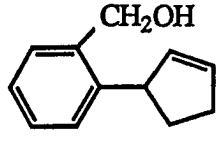
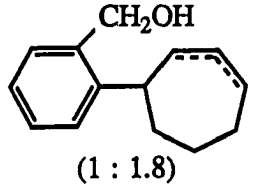
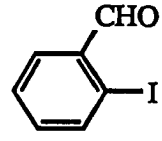
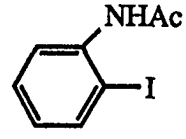
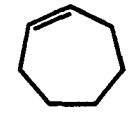
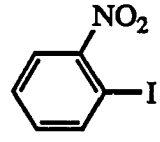
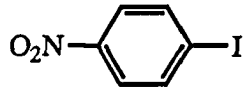
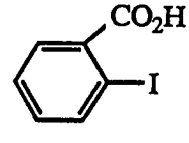
Time (d)	Temp °C	Product	Yield (%)
6.0	80		42
2.0	80		0
4.0	80		66
4.0	100		68
4.5	80		6
6.0	80		0
7.0	80		0
7.0	80		0
7.0	80		52[d]
7.0	100		31
5.0	80		0
5.0	80		0
1.0	80		99
1.0	80	 (1 : 1.8)	99[e]

Table 1. (continued)

Entry	Aryl Iodide	Cyclic Alkene	Procedure[a]
15			A
16			B
17			C
18			A
19			B
20			C
21			C
22			A
23			B
24			C
25			A
26			B
27			C
28			A
29			B
30			C

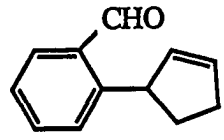
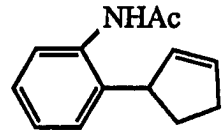
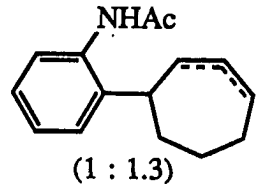
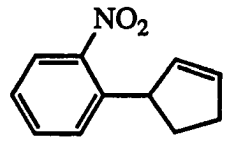
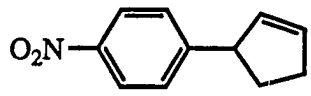
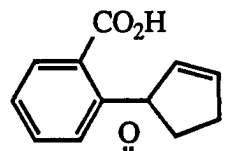
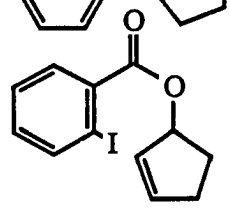
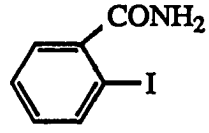
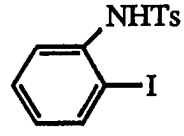
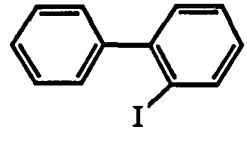
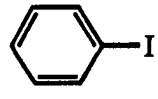
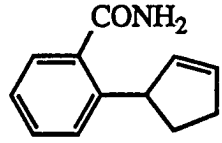
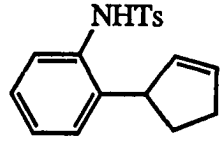
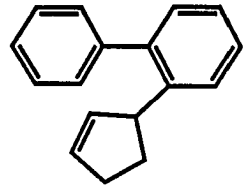
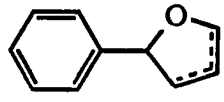
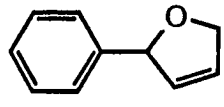
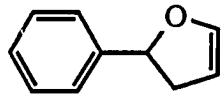
Time (d)	Temp °C	Product	Yield (%)
7.0	80		0
5.0	80		0
1.0	80		87
2.0	80		0
5.0	80		0
1.0	80		76
1.0	80	 (1 : 1.3)	80
4.0	80		0
2.0	80		70
1.0	80		90
4.0	80		0
2.0	80		52
1.0	80		85
5.0	80		0
3.5	80		0
7.0	80		14

Table 1. (continued)

Entry	Aryl Iodide	Cyclic Alkene	Procedure[a]
31			A
32			B
33			C
34			A
35			B
36			C
37			A
38			C
39			A
40			B
41			C

[f] Reaction never went to completion.

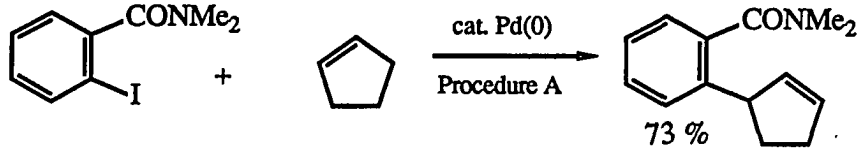
[g] NaOAc was used as the base.

Time (d)	Temp °C	Product	Yield (%)
3.0	80		0
5.0	80		0
7.0	80		0
4.0	80		0
5.0	80		0
7.0	80		0
2.0	80		95
4.0	80		-- [f]
0.5	25	 (5.7 : 1)	100[e,g]
2.0	80		98
1.0	80		76

afford the desired product in good yields (compare entries 1 - 3). When the same reaction was run at 100 °C with hopes of reducing the reaction time, only a 2 % improvement in yield was found (entry 4). Also very similar to 2-iodophenol, 2-iodoaniline proved to be inert when previous procedures were employed (entries 5 and 6). When the standard procedure C was employed, there was again no desired product (entries 7 and 8). When the same reaction was rerun using Et_3N as the base, a dramatic improvement in the yield resulted (entry 9). Like the phenol, a higher reaction temperature was also employed with hopes of decreasing the reaction time. Unlike the results obtained from 2-iodophenol, a decrease in the yield of the desired product, plus the formation of unidentified side products were observed (entry 10). 2-Iodobenzyl alcohol was believed to be inert when using procedures A and B due to the formation of a stable chelate with the catalyst, thus hampering the formation of the desired product (entries 11 and 12). If this chelate were indeed involved, procedure C was successful in breaking up or preventing the formation of this chelate and allowed the reaction to proceed to afford the desired product in quantitative yield (entry 13). For reasons which are not obvious, 2-iodobenzaldehyde, 2-iodo-*N*-acetylaniline, and 2- or 4-iodonitrobenzene were completely inert when using procedure A (entries 15, 18, 22, and 25). When procedure B was employed, there was success only in the iodonitrobenzene examples (entries 23 and 26). For reasons which are not obvious, 2-iodobenzaldehyde and 2-iodo-*N*-acetylaniline were inert in procedure A or B. Yet, these same aryl iodides, again for reasons not obvious, reacted quite readily with cyclopentene using procedure C (entries 17 and 20).

In spite of the successes obtained with procedure C, there remain some aryl iodides, such as 2-iodo-*N*-tosylaniline and 2-iodobenzamide, that are inert to these and previously tried reaction conditions. 2-Iodo-*N*-tosylaniline was an especially interesting case (entries

31-33), because the corresponding 2-iodo-*N*-acetylaniline reacted readily with cyclopentene using procedure C (entry 20). Perhaps the acidity of the tosylaniline hydrogen was high enough for the formation of an anion in the presence of KOAc, therefore causing the nitrogen to strongly coordinate to the arylpalladium intermediate. One may also explain why 2-iodobenzamide was inert by using the chelate explanation. This theory is supported by the fact that 2-iodo-*N*,*N*-dimethylbenzamide readily reacted with cyclopentene[31] using procedure A (eq 24). 2-Iodobenzoic acid was a unique example.

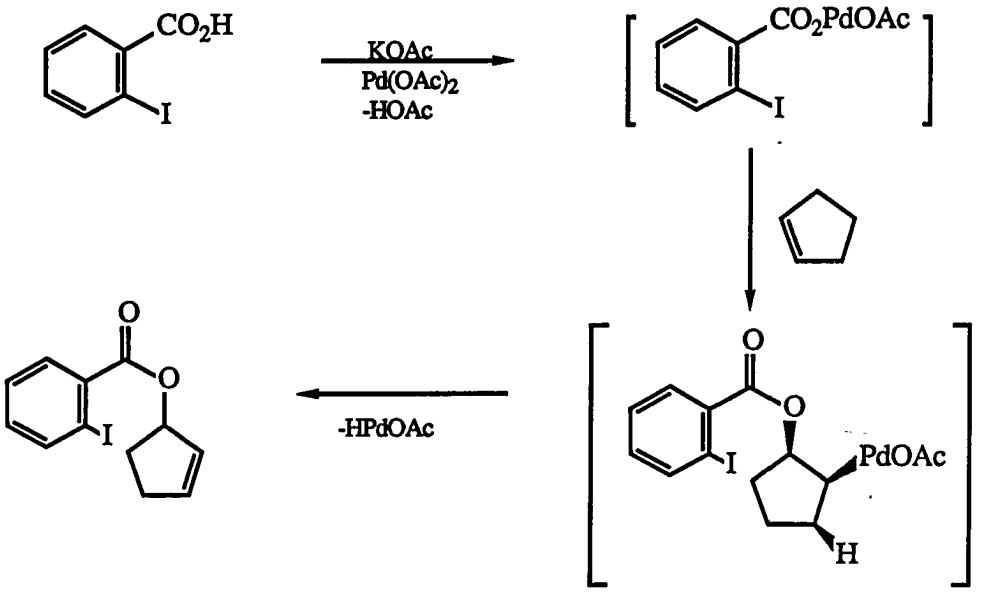


(24)

While it proved to be inert using procedures A and B, by procedure C, it afforded a low yield of 3-cyclopentenyl 2-iodobenzoate. This product could be a result of a Pd(II)-mediated oxypalladation of this carboxylic acid (Scheme IV). This reaction is well precedented the Larock research group. It's reasonable to argue that the ester should only be produced in a 2.5 % yield, but it's quite possible that the Pd(0) generated at the end of the cycle is somehow oxidized to Pd(II) by one of the reagents present or by air present in the reaction vessel. After the catalyst had been recycled a few times, it apparently became deactivated and the reaction stopped after producing the ester in 14 % yield.

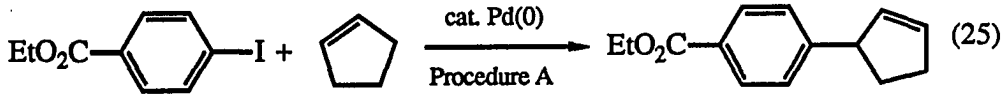
Baker[31] had reported that one of the tremendous benefits of procedure B was the ability of this set of reaction conditions to prevent isomerization of the double bond in reactions employing cycloheptene and 2,3-dihydrofuran. While this is a valuable process, it suffers from having to use two equivalents of expensive silver salts and a large volume of acetonitrile. Procedure C was explored in this area to determine if it was capable of

Scheme IV



inhibiting double bond isomerization, a problem frequently encountered with procedure A. Two aryl iodides were selected for this investigation. When 2-iodobenzyl alcohol and 2-iodo-*N*-acetylaniline were allowed to react with cycloheptene, an isomeric product mixture was isolated in high yield for each of these aryl iodides (entries 14 and 21). Previously, iodobenzene reacted with 2,3-dihydrofuran using procedure A to afford a mixture of two isomers (entry 39). When procedure B was employed, only the desired allylic product was produced in a quantitative yield (entry 40). Surprisingly, procedure C afforded only the homoallylic product (entry 41). This procedure is thus useful in promoting double bond isomerization in the arylation of this enol ether.

Because of the fact that all of the reaction conditions used in the three procedures are mild and the products are afforded in high yield, ethyl 4-(3-cyclopentenyl)benzoate was prepared on a 60 mmole scale using procedure A (eq 25). There were several variations



(25)

used in this preparation, and the results are summarized in Table 2. Several observations have been made based on this series of reactions. First, an attempt was made to accelerate the rate of this reaction by increasing the concentration of the reagents by using only half of the normally required volume of DMF. However, this only serves to create an extremely thick mixture which could not be stirred effectively, and a significant amount of the bis-arylated product **5** was generated at the expense of the desired allylic product **3** (compare entries 2 and 3). Secondly, the crude product mixture could not be distilled since a significant amount of the conjugated isomer **4** was formed at the expense of **3** via thermal isomerization (entries 1 - 3). Lastly, if the number of equivalents of cyclopentene was fewer than five, a significant amount of the product **5** was also generated. Ironically, **5** can easily be separated by distillation, but it was this very process that produced a large amount of **4**. In entry 4, three different approaches were taken to circumvent the above problems. First, by using 120 mL of DMF, which is the same concentration used for the 0.5 mmole scale reactions, the mixture was easily stirred throughout the duration of the reaction. Secondly, the crude product mixture was easily purified by filtering it through a short column of silica gel to afford **3** in a very high yield, plus only 2 % of the conjugated product. Thirdly, by increasing the number of equivalents of cyclopentene to five, the amount of the bis-arylated product **5** was reduced to a trace.

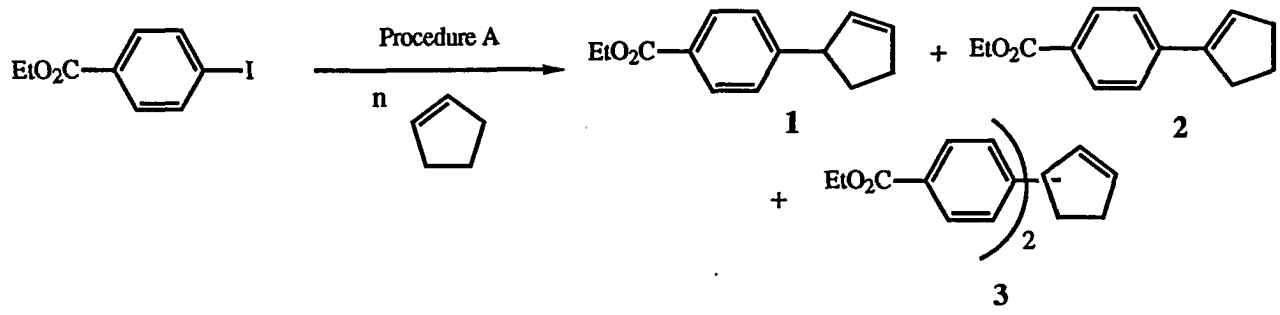


Table 2. Pd(0)-catalyzed preparation of ethyl 4-(3-cyclopentenyl)benzoate

Entry	n	DMF (mL)	Time (d)	1 (%)	2 (%)	3 (%)
1	1.1	60	1.0	58	10	- [a]
2	2.5	60	1.0	70	10	- [a]
3	2.5	120	1.0	92	8	- [a]
4	5.0	120	1.0	94	2	trace

[a] The yield of this product was not determined.

CONCLUSION

While procedures A and B, reported by Larock and Baker, have provided the desired 3-arylcycloalkenes under mild reaction conditions and in high yields, the drawbacks have been that certain organic functional groups could not be accommodated. Procedure C, a simple modification of procedure A, has effectively circumvented this problem, and has become an excellent complement to procedures A and B. Furthermore, procedure C has also pro-moted double bond isomerization in the reaction of iodobenzene and 2,3-dihydrofuran to afford only the homoallylic isomer. This can serve as a selective method for the synthesis of this class of compounds. It was also hoped that procedure C could inhibit the double bond isomerization problem in the arylation of cycloheptene, but preliminary results were not promising. In spite of the success of procedure C, there remain a small number of aryl iodides containing carboxyl, *N*-tosyl, and amido groups that remain inert regardless of the procedures employed.

Lastly, a 60 mmole scale preparation of ethyl 4-(3-cyclopentenyl)benzoate has been achieved at room temperature and in high yield. It is important to note that these reactions can be easily scaled up without compromising the yield of the desired product.

EXPERIMENTAL SECTION

Equipment

All NMR spectra were recorded on a Nicolet NT-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75 MHz for carbon nuclei). Infrared spectra were obtained on an IBM IR/98 FT-IR. Mass spectral data were obtrained on a Kratos high resolution mass spectrometer. Gas chromatographic analyses were performed by using a Varian 3700 or a Hewlett Packard 5890 gas chromatograph equipped with a 3 % OV-101 on Chromasorb W packed column (Varian 3700 or HP 5890) or an HP-1 megabore column (HP 5890).

Reagents

Cyclopentene, 2-iodobenzyl alcohol, 2-iodoaniline, and triphenylphosphine were obtained from Aldrich. Tetra-*n*-butylammonium chloride and ethyl 4-iodobenzoate were obtained from Lancaster Synthesis. *N,N*-dimethylformamide (Fisher) was distilled from calcium hydride (CaH_2) and stored over molecular sieves. 2-Iodobenzaldehyde[34] was prepared according to a literature procedure. 2-Iodo-*N*-acetylaniline and 2-iodo-*N*-tosyl-aniline were generously supplied by Dr. Norman Berrios-Pena and made according to a literature procedure[35]. 2-Iodobenzamide was generously supplied by Dr. L. Wayne Harrison.[36]

The following arylcycloalkenes were prepared from the following procedure, and the reaction time and temperature for the reaction are found in Table 1. In a dry 10 mL round

bottom flask equipped with a side arm and a stirring bar were placed $Pd(OAc)_2$ (0.006 g, 2.5 mol %), PPh_3 (0.007 g, 2.5 mol %), TBAC (0.294 g, 1.0 mmol), KOAc (0.294 g, 3.0 mmol), and the aryl iodide (1.0 mmol). The flask was affixed with a reflux condenser, septa sealed, flushed with nitrogen, and a nitrogen atmosphere was maintained with a bubbler. Cycloalkene (10 mmol) and DMF (2.0 mL) were injected sequentially, and then the reaction mixture was allowed to stir at 80 °C. After analytical gas chromatography or thin-layer chromatography indicated that all of the starting material had been consumed, the mixture was combined with ether (30 mL) and poured into a separatory funnel containing saturated NH_4Cl (50 mL). The aqueous phase was removed, the organic layer was dried over anhydrous $MgSO_4$, vacuum filtered through a fritted funnel, concentrated *in vacuo*, and columned to afford the desired arylcycloalkene.

2-(3-Cyclopentenyl)phenol (entry 3)

This compound was purified over silica gel using hexane / EtOAc (5 : 1).[37] ^1H NMR ($CDCl_3$) δ 1.67 - 1.82 (m, 1 H, C=C-CH_2-C<u>H</u>H), 2.37 - 2.59 (m, 3 H, C=C-C<u>H</u>$_2$-CH<u>H</u>), 4.05 - 4.11 (m, 1 H, Ar-CH-C=C), 5.59 (s, 1H, OH), 5.86 (ddd, 1 H, J = 7.5 Hz, J = 1.8 Hz, J = 1.8 Hz, C<u>H</u>=CH), 6.04 (dd, 1 H, J = 7.5 Hz, J = 2.4 Hz, CH=C<u>H</u>), 6.77 - 6.87 (m, 2 H, aromatic Hs), 7.07 (d, 1 H, J = 7.2 Hz, aromatic H), 7.08 (d, 1 H, J = 7.2 Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 31.59, 32.61, 46.50, 96.50, 115.78, 120.45, 127.34 (2 peaks), 133.29, 133.82, 153.94; IR(neat) 3441, 3055, 2941, 2849, 1604, 1501, 1497, 1269, 1221, 1175, 1094, 1043, 752, 737 cm^{-1}; HRMS: calcd for $C_{11}H_{12}O$ m/z 160.08882, found m/z 160.08880.

2-(3-Cyclopentenyl)aniline (entry 9)

This compound was purified over silica gel using hexane / EtOAc (4 : 1). ^{1}H NMR ($CDCl_3$) δ 1.73 - 1.82 (m, 1 H, C<u>H</u>H), 2.32 - 2.52 (m, 3 H, C=C-C<u>H</u>$_2$-CH<u>H</u>), 3.72 (s, 2 H, NH_2), 3.86 - 3.92 (m, 1 H, Ar-CH-C=C), 5.83 (ddd, 1 H, J = 5.7 Hz, J = 2.1 Hz, J = 2.1 Hz, C<u>H</u>=CH), 5.99 (dd, 1 H, J = 5.7 Hz, J = 2.4 Hz, CH=C<u>H</u>), 6.67 (dd, 1 H, J = 6.6 Hz, J = 6.6 Hz, aromatic H), 6.71 (dd, 1 H, J = 7.5 Hz, J = 7.5 Hz, aromatic H), 7.02 (d, 1 H, J = 7.5 Hz, aromatic H), 7.02 (d, 1 H, J = 7.5 Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 30.43, 31.60, 32.50, 47.04, 115.89, 118.55, 126.99, 127.76, 132.55, 133.22, 144.13; IR (neat) 3462, 3377, 3053, 2934, 2851, 1620, 1582, 1495, 1456, 1288, 1254, 750, 733, 646 cm^{-1}; HRMS: calcd for $C_{11}H_{13}N$ m/z 159.10480, found m/z 159.10443.

2-(3-Cyclopentenyl)benzyl alcohol (entry 13)

This compound was purified over silica gel by using hexane / EtOAc (4 : 1). ^{1}H NMR ($CDCl_3$) δ 2.35 - 2.50 (m, 4 H, C=C-CH_2-CH_2), 2.85 (s, 1 H, OH), 4.10 - 4.15 (m, 1 H, Ar-CH-C=C), 4.65 (dd, 2 H, J = 8.1 Hz, J = 4.2 Hz, Ar-CH_2), 5.69 - 5.72 (m, 1 H, C<u>H</u>=CH), 5.94 (dd, 1 H, J = 5.4 Hz, J = 2.1 Hz, CH=C<u>H</u>), 7.11 - 7.21 (m, 3 H, aromatic Hs), 7.29 (d, 1 H, J = 7.5 Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 32.32, 33.31, 46.25, 62.73, 125.89, 126.65, 127.87, 128.15, 131.92, 133.77, 137.54, 144.33; IR(neat) 3331, 3057, 3028, 2937, 1437, 1452, 1040, 1011, 910, 754, 733 cm^{-1}; HRMS: calcd for $C_{12}H_{14}O$ m/z 174.10445, found m/z 174.10447.

2-(3-Cyclopentenyl)benzaldehyde (entry 17)

This compound was purified over silica gel using hexane / EtOAc (7.5 : 1). ^{1}H NMR ($CDCl_3$) δ 1.60 - 1.72 (m, 2 H, CH_2), 2.43 - 2.62 (m, 2 H, C=C-CH_2), 4.80 - 4.87 (m, 1 H, Ar-CH-C=C), 5.71 - 5.76 (m, 1 H, C<u>H</u>=CH), 5.99 - 6.03 (m, 1 H, CH=C<u>H</u>), 7.35 (dd, 2 H, J = 7.5 Hz, J = 7.5 Hz, aromatic H), 7.51 (ddd, 1 H, J = 7.5 Hz, J = 7.5 Hz, J = 1.2 Hz, aromatic H), 7.82 (d, 1 H, J = 7.5 Hz, aromatic H), 10.38 (s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 32.34, 33.93, 45.96, 126.31, 127.68, 128.54, 131.42, 132.93, 133.29, 133.94, 148.76, 192.34; IR(neat) 3057, 2937, 2851, 1693, 1599, 1572, 1450, 1209, 1186, 1015, 758, 733, 656 cm^{-1}; HRMS: calcd for $C_{12}H_{12}O$ m/z 172.08886, found m/z 172.08882.

2-(3-Cyclopentenyl)-*N*-acetylaniline (entry 20).

This compound was purified over silica gel using hexane / EtOAc (4 : 1). ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3 H, $COCH_3$), 2.26 - 2.42 (m, 4 H, C=C-CH_2-CH_2), 3.87 - 3.98 (m, 1 H, Ar-CH-C=C), 5.67 - 5.69 (m, 1 H, C<u>H</u>=CH), 5.91 - 5.93 (m, 1 H, CH=C<u>H</u>), 6.97 - 7.09 (m, 3 H, aromatic Hs), 7.56 (d, 1 H, J = 8.1 Hz, aromatic H), 7.72 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 23.89, 31.49, 32.46, 47.36, 124.62, 125.44, 126.59, 127.99, 132.74, 133.32, 135.02, 137.22, 168.64; IR (KBr) 3268, 3189, 3132, 2963, 1651, 1532, 1478, 1371, 1013, 748, 712 cm^{-1}; HRMS: calcd for $C_{13}H_{15}NO$ m/z 201.11537, found m/z 201.11554.

2-(3-Cyclopentenyl)-1-nitrobenzene (entry 24)

This compound was purified over silica gel by using hexane / EtOAc (4 : 1) . The spectroscopic data were identical to those reported by Baker.[31]

4-(3-Cyclopentenyl)-1-nitrobenzene (entry 27)

This compound was purified over silica gel by using hexane / EtOAc (4 : 1). The spectroscopic data were identical to those reported by Baker.[31]

2-(3-Cyclopentenyl)biphenyl (entry 37)

This compound was purified over silica gel using hexane. ^{1}H NMR ($CDCl_3$) δ 1.68 - 1.76 (m, 1 H, Ar-CH-C<u>H</u>H), 2.19 - 2.35 (m, 2 H, CH_2), 2.43 - 2.53 (m, 1 H, Ar-CH-CH<u>H</u>), 3.92 - 3.98 (m, 1 H, Ar-CH-C=C), 5.64 - 5.67 (m, 1 H, C<u>H</u>=CH), 5.88 (dt, 1 H, J = 5.7 Hz, J = 2.1 Hz, CH=C<u>H</u>), 7.21 - 7.42 (m, 9 H, aromatic Hs); ^{13}C NMR ($CDCl_3$) δ 32.47, 34.54, 47.39, 125.54, 126.67, 127.10, 127.67, 127.89, 129.41, 129.64, 131.46, 134.67, 141.32, 141.86, 144.07; IR(neat) 3057, 3022, 2930, 1597, 1477, 1460, 1072, 1016, 1009, 748, 702, 617 cm^{-1}; HRMS: calcd for $C_{17}H_{16}$ m/z 220.12520, found m/z 220.12526.

2-Phenyl-2,3-dihydrofuran (entry 41)

This compound was purified over silica gel using hexane / EtOAc (10 : 1).[38] ^{1}H NMR ($CDCl_3$) δ 2.58 (dddd, 1 H, J = 12.9 Hz, J = 8.4 Hz, J = 2.4 Hz, J = 2.4 Hz, Ph-CH-C<u>H</u>H-C=C), 3.38 (dddd, 1 H, J = 12.9 Hz, J = 10.2 Hz, J = 2.4 Hz, J = 2.4 Hz, Ph-CH-CH<u>H</u>-C=C), 4.92 (ddd, 1 H, J = 2.7 Hz, J = 2.7 Hz, J = 2.7 Hz, Ph-C<u>H</u>-CH_2), 5.49 (dd, 1 H, J = 10.8 Hz, J = 8.4 Hz, C<u>H</u>=CH-O), 6.43 (dd, 1 H, J = 5.0 Hz, J = 2.6 Hz, CH=C<u>H</u>-O), 7.23 - 7.34 (m, 5 H, aromatic Hs); ^{13}C NMR ($CDCl_3$) δ 37.79, 62.24, 98.91, 125.48, 127.50, 128.40, 142.94, 145.21; IR(neat) 3087, 3062, 3031, 2932, 1728, 1620, 1495, 1450, 1136, 1051, 1001, 941, 758, 698 cm^{-1}; HRMS: calcd for $C_{10}H_{10}O$ m/z 146.07317, found m/z 146.07317.

Ethyl 4-(3-cyclopentenyl)benzoate (see Table 2)

This compound was purified over silica gel by using hexane / EtOAc (8 : 1). The spectroscopic data were identical to those reported by Baker.[31]

REFERENCES

1. (a) Tsuji, J. "Organic Synthesis with Palladium Compounds"; Springer Verlag: New York, 1980. (b) Heck, R.F. "Palladium Reagents in Organic Synthesis"; Academic Press: New York, 1985.

2. Maitlis, P.M. "The Organic Chemistry of Palladium"; Academic Press: New York, 1973; Vols. 1 & 2.

3. (a) Heck, R.F. *J. Am. Chem. Soc.* **1968**, *90*, 5518.

   (b) Heck, R.F. *J. Am. Chem. Soc.* **1968**, *90*, 5526.

   (c) Heck, R.F. *J. Am. Chem. Soc.* **1968**, *90*, 5535.

   (d) Heck, R.F. *J. Am. Chem. Soc.* **1968**, *90*, 5538.

   (e) Heck, R.F. *J. Am. Chem. Soc.* **1968**, *90*, 5542.

   (f) Heck, R.F. *J. Am. Chem. Soc.* **1968**, *90*, 5546.

4. Heck, R.F. *Organomet. Chem. Synth.* **1972**, *1*, 455.

5. Henry, P. M.; Ward, G.A. *J. Am. Chem. Soc.* **1972**, *94*, 673.

6. Heck, R.F. *J. Am. Chem. Soc.* **1971**, *93*, 6896.

7. Horino, H.; Arai, M.; Inoue, N. *Bull Chem. Soc. Jpn.* **1974**, *47*, 1683.

8. Horino, H.; Inoue, N. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3210.

9. Saito, R.-I.; Isumi, T.; Kasahara, A. *Bull Chem. Soc. Jpn.* **1973**, *46*, 1776.

10. Lee, T.D.; Daves, D.G., Jr. *J. Org. Chem.* **1983**, *48*, 399.

11. Kasahara, A.; Isumi, T.; Yodono, M.; Saito, R.-I.; Takeda, T.; Sugawara, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1220.

12. Horino, H.; Inoue, N. *J. Chem. Soc., Chem. Commun.* **1976**, 500.

13. Kasahara, A.; Isumi, T.; Saito, G.; Yodono, M. *Bull Chem. Soc. Jpn.* **1972**, *45*, 895.

14. Outten, R.A.; Daves, D.G., Jr. *J. Org. Chem.* **1987**, *52*, 5064.

15. Garves, K. *J. Org. Chem.* **1970**, *35*, 3273.

16. Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

17. Heck, R.F.; Nolley, J.P., Jr. *J. Org. Chem.* **1972**, *37*, 2320.

18. Cortese, N.A.; Ziegler, C.B. Jr.; Hrnjez, B.J. ; Heck, R.F. *J. Org. Chem.* **1978**, *43*, 2952.

19. Tamaru, Y.; Yamada, Y.; Yoshida, Z.-I. *Tetrahedron* **1979**, *35*, 329.

20. Arai, I.; Daves, G.D. Jr. *J. Org. Chem.* **1979**, *44*, 21.

21. Andersson, C.-M.; Hallberg, A.; Daves, G.D. Jr. *J. Org. Chem.* **1987**, *52*, 3529.

22. Yamamura, K.; Nakatsu, K.; Nakao, K.; Nakazawa, T.; Murata, I. *Tetrahedron Lett.* **1979**, 4999.

23. Kikukawa, K.; Nagira, K.; Wada, F.; Matsuda, T. *Tetrahedron* **1981**, *37*, 31.

24. Kikukawa, K.; Maemura, K.; Kiseki, Y.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1981**, *46*, 4885.

25. Wada, F.; Matsuda, T. *J. Org. Chem.* **1981**, *46*, 4885.

26. Harrington, P.J.; Di Fiore, K.A. *Tetrahedron Lett.* **1987**, *28*, 495.

27. Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287.

28. Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667.

29. Jeffery, T. *Synthesis* **1987**, 70.

30. Larock, R.C.; Baker, B.E. *Tetrahedron Lett.* **1988**, *29*, 905.

31. Baker, B.E., Ph.D. Dissertation, Iowa State University, 1988.

32. Abelman, M.M.; Oh, T.; Overman, L.E. *J. Org. Chem.* **1987**, *52*, 4130.

33. Prashad, M.; Tomesch, J.C.; Wareing, J.; Smith, H.W.; Cheon, S.H. *Tetrahedron Lett.* 1989, 30, 2877.

34. Corey, E.J.; Suggs, J.W. *Tetrahedron Lett.* **1975**, 2647.

35. Polya, J.B.; Spotwood, T.M. *Rec. Trav. Chim.* **1948**, *67*, 927.

36. Harrison, L.W., Ph.D. Dissertation, Iowa State University, 1983.

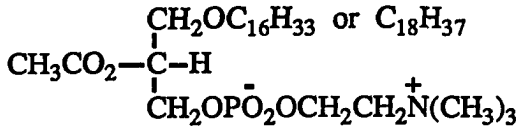
37. Dai, S.H.; Lin, C.Y.; Rao, D.V.; Stuber, F.A.; Carleton, P.S.; Ulrich, H. *J. Org. Chem.* **1985**, *50*, 1722.

38. Scribe, P.; Wieman, J. *Bull Chim. Soc. Fr.* **1971**, 2268.

PART II. PALLADIUM-CATALYZED SYNTHESIS OF TRANS-2,5-DIARYL-TETRAHYDROFURANS, POTENT INHIBITORS OF PLATELET ACTIVATING FACTOR

INTRODUCTION

Platelet activating factor (PAF) is a fundamental mediator of mammalian cell functions.[1] PAF has been identified as an acetyl glycero ether phosphorylcholine, 1-*O*-hexadecyl / octadecyl-2-acetyl-*sn*-glycero-3-phosphorylcholine (**1**).[2-4] PAF is



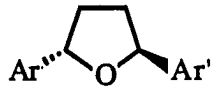
1

synthesized and secreted by a variety of cells involved in inflammatory responses, including basophils, neutrophils, platelets, macrophages, endothelial cells, and IgE-sensitized bone marrow mast cells.[5] PAF has been implicated as an important mediator of pathophysiological reactions in animal and human diseases.[6] PAF initiates its actions first by binding to its receptor sites.[7-9] Receptor sites in rabbit plasma membrane,[10] guinea pig smooth muscle membranes,[7] human platelets,[8,9] and human lung tissues[11] have already been identified using [^{3}H] PAF. Furthermore, the nature of PAF binding sites and the supposed conformation of PAF have already been discussed.[12] The wide variety of biological actions PAF exerts includes *inter alia* smooth muscle contraction, neutrophil degranulation, gastro-intestinal dysfunction,[13-15] acute allergy, inflammation, and toxic shock.[16,17] Researchers have recently learned that PAF may play a major role in asthma,[18,19] and possibly late asthmatic responses.[20,21] In animal model studies, PAF induces bronchoconstriction,[6] neutropenia, [22] systematic hypotension, [23] increased vascular permeability,[24] and elevated plasma lysosomal hydrolase levels.[25] Most recently, Etienne and co-workers[26] have uncovered evidence suggesting the possible

involvement of PAF in endotoxin-induced abortion in mice. Indeed, endotoxemia induces a massive release of PAF during endotoxic shock, which induces a high level of miscarriages in women and in animal models.[27] It is believed that PAF is the mediator involved in the increase in permeability at the site of ovoimplantation. Besides PAF's primary role in the inflammatory process, this phospholipid has also been reported to be a chemotactic[28] as well as a tumor-cytotoxic agent.[10]

The synthesis of therapeutically effective antagonists to the binding of PAF to its receptor sites remains a challenge for synthetic organic chemists.[12] In Table 1, a summary of synthetic compounds known to inhibit the binding of PAF to its receptor sites is presented.[29-35] Table 2 is a summary of natural products known to have some anti-PAF activities.[36-45]

Synthetic analogues of a series of neolignans known as diaryltetrahydrofurans (**2**)



2

have received much attention within the last six years as PAF antagonists.[17] Biftu and co-workers [46,47] reported a multi-step synthetic process to afford a number of these compounds, and their approach is represented by the synthesis of two of the more potent PAF antagonists **3** and **4** (Scheme I). The multi-step synthesis of these compounds begins with an oxidative coupling reaction of **5** or **6** mediated by copper(II) to afford the desired diketones **7** and **8** in modest yields. The ketones, **7** and **8**, are then reduced in excellent yields to the corresponding diols, **9** and **10**, respectively. Treatment of the diol **9** with mesyl chloride and triethylamine produces **3** as a mixture of *cis* and *trans* isomers. Treatment of diol **10** with trifluoroacetic acid in chloroform affords **4** also as a *cis / trans*

Table 1. Known synthetic PAF antagonists

Entry	Compound[a]	Reference
1	CV 3988	29
2	CV 6209	30
3	Ono 6240	31, 32
4	SRI 63-119	31, 32
5	SRI 63-072	33
6	SRI 63-073	34 - 36
7	48740RP	34 - 36
8	52629RP	37
9	52770RP	37
10	WEB 2086	32
11	Kadsurenone - Ginkgolide hybrid	38
12	2,5-diarylcyclopentanol	39

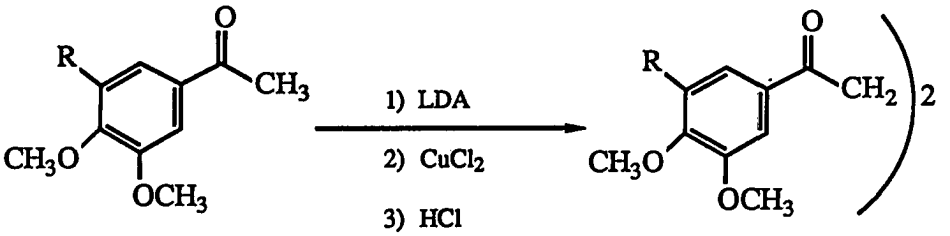
[a] Compound number or name is given.

Table 2. Natural products with PAF antagonists activities

Entry	Compound[a]	Source	Reference
1	BN 52020	Ginkgo biloba	40
2	BN 52021	Ginkgo biloba	40
3	BN 52022	Ginkgo biloba	40
4	BN 52023	Ginkgo biloba	40
5	BN 52024	Ginkgo biloba	40
6	Kadsurenone	Piper futokadsurae	41
7	Presteganes A	Steganotaenia aralacea	42
8	Presteganes B	Steganotaenia aralacea	42
9	FR-900452	S. Phacofaciens	43 - 45
10	FR-49175	P. tertikowskii	43 - 45

[a] Compound number or name is given.

Scheme I

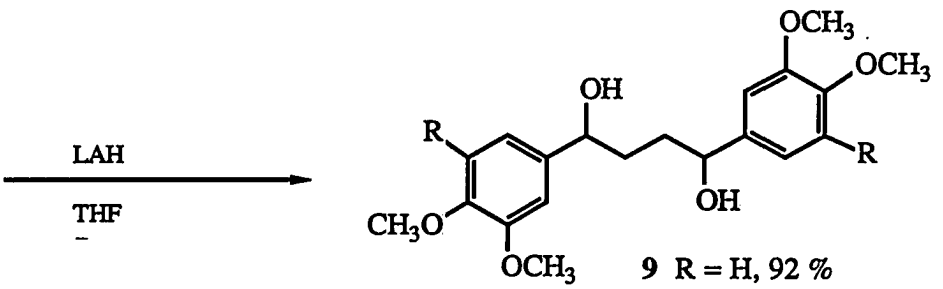


5 R = H

6 R = OCH_3

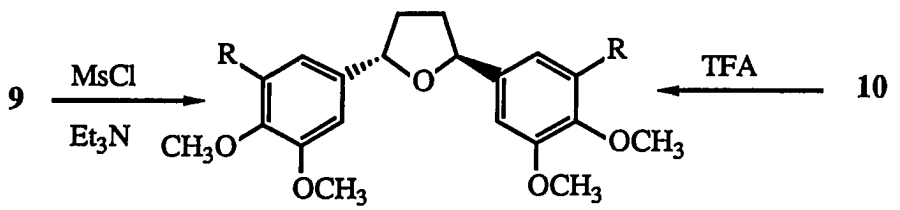
7 R = H, 25 %

8 R = OCH_3, 49 %



9 R = H, 92 %

10 R = OCH_3, 83 %

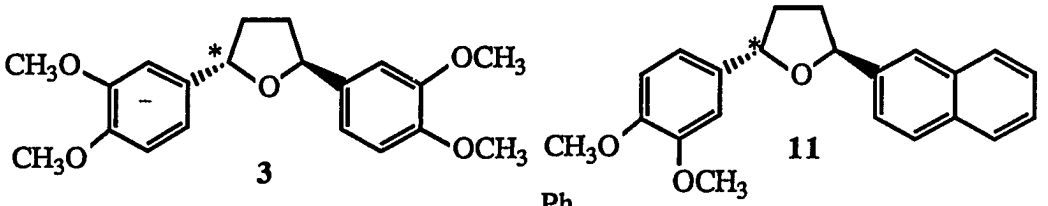


3 R = H, 64 % (22 % cis)

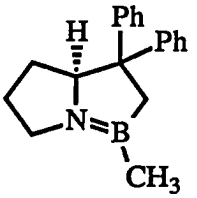
4 R = OCH_3, 52 % (22 % cis)

mixture. Analysis of **3** and **4** has indicated that the *trans* isomer is the only isomer that exhibited any anti-PAF activity.[46,48] Furthermore, by decreasing the number of methoxy groups from 6 (**4**) to 4 (**3**), the anti-PAF activity also correspondingly decreased.[47] Biftu and co-workers [46,47] also synthesized a number of analogues of **3** and **4** and their anti-PAF activities has been evaluated by a number of researchers (Table 3).[48-57] Unfortunately, Biftu's approach suffers from a lengthy synthesis and low overall yields of these important compounds. Moreover, the desired *trans* isomer is not the exclusive isomer produced and it is not easily separated from the *cis* isomer.

Corey and co-workers[58] recently communicated an enantioselective synthesis of **3** and *trans*-2-(2-naphthyl)-5-(3,4-dimethoxyphenyl)tetrahydrofuran (**11**) using his "CBS" catalyst **12** (Scheme II). Corey's multi-step approach begins with an enantioselective



3 **11**



12

reduction of the ketoester **13** to afford the corresponding alcohol **14** in a quantitative yield. Treatment of the chiral alcohol **14** with sodium hydride then provides the chiral lactone **15**. The lactone is reduced with DIBAL to afford the desired lactol as a 1 : 1 mixture. Treatment of the lactol with trimethylsilyl bromide generates the unstable bromide, which when coupled with the appropriate arylmagnesium bromide provides a

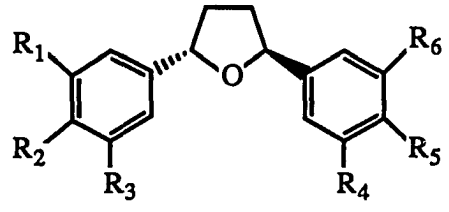
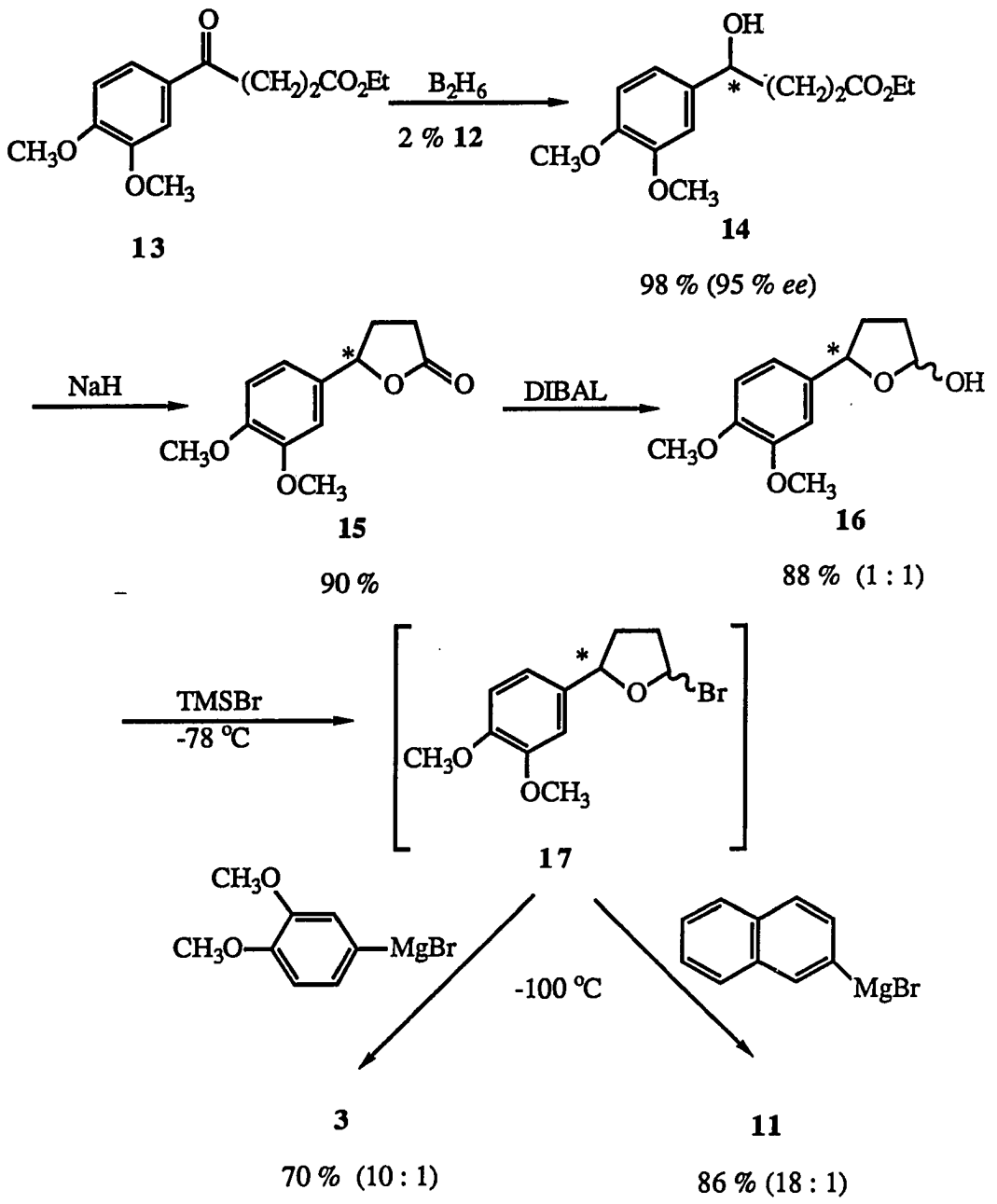


Table 3. *trans*-2,5-Diaryltetrahydrofurans as PAF antagonists

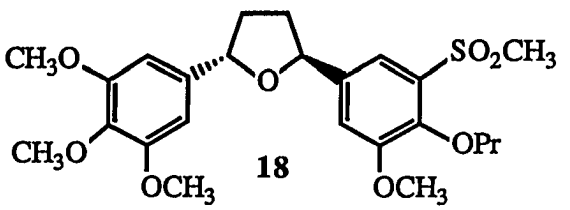
Entry	R_1	R_2	R_3	R_4	R_5	R_6	References
1	CH_3O	CH_3O	CH_3O	CH_3O	CH_3O	CH_3O	49 - 56
2	CH_3O	CH_3	CH_3O	CH_3O	HO	CH_3O	46, 48
3	CH_3O	EtO	CH_3O	CH_3O	EtO	CH_3O	48
4	CH_3O	*i*-PrO	CH_3O	CH_3O	EtO	CH_3O	48
5	CH_3O	*i*-PrO	CH_3O	CH_3O	*i*-PrO	CH_3O	48
6	CH_3O	CH_3O	CH_3O	CH_3O	H	CH_3O	48
7	H	CH_3O	CH_3O	CH_3O	CH_3O	H	59

Scheme II


O
(CH2)2CO2Et
B2H6
2 % 12
OH
(CH2)2CO2Et
CH3O
OCH3
13
14
98 % (95 % ee)
NaH
DIBAL
OH
15
16
90 %
88 % (1 : 1)
TMSBr
-78 °C
Br
17
MgBr
-100 °C
3
11
70 % (10 : 1)
86 % (18 : 1)

mixture of *cis* and *trans* isomers of antagonists **3** and **11**, respectively, in good overall yields. By using the other enantiomer of catalyst **12**, the enantiomers of **3** and **11** were also obtained in parallel syntheses. In a later communcation, Corey et al.[59] reported the biological activities of both *R* and *S* enantiomers of **3** and **11**. Surprisingly, there was almost no difference in their anti-PAF activities, and Corey also echoed what Biftu[46,48] had reported earlier about the relative inactivities of the *cis* isomers toward inhibiting the binding of PAF to its receptor sites. While Corey's approach is more versatile in that enantiomers are produced in high yields, like Biftu's approach, the *trans* isomer is not the exclusive isomer produced.

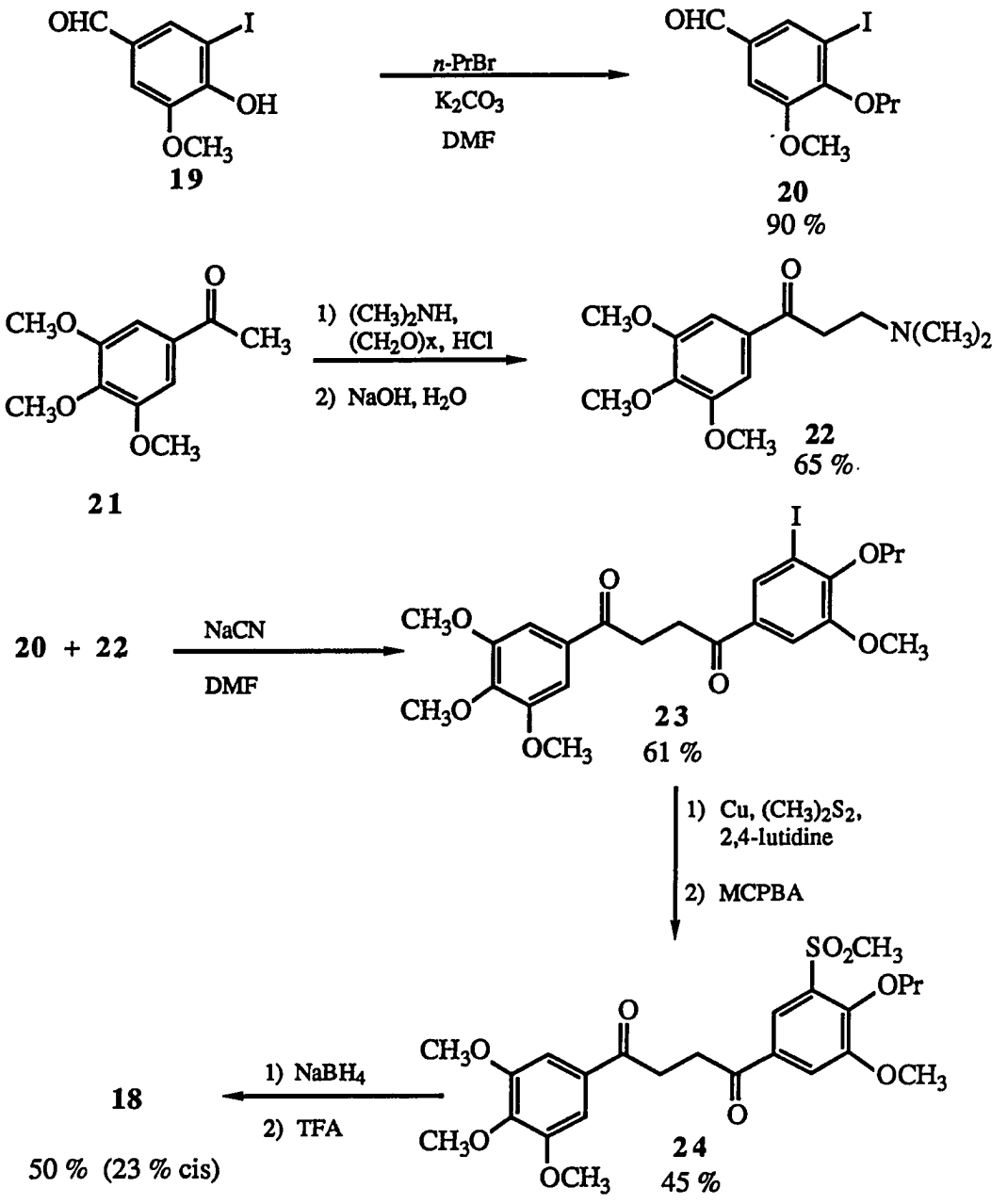
Most recently, Pompipom et al.[60] reported the synthesis of *trans*-2-(3-methoxy-5-methylsulfonyl-4-propoxyphenyl)-5-(3,4,5-trimethoxyphenyl)tetrahydrofuran (**18**), another *trans*-2,5-diaryltetrahydrofuran effective as a PAF antagonist (Scheme III). Their synthesis begins with an alkylation of 5-iodovanillin (**19**) and ketone **21** to afford



18

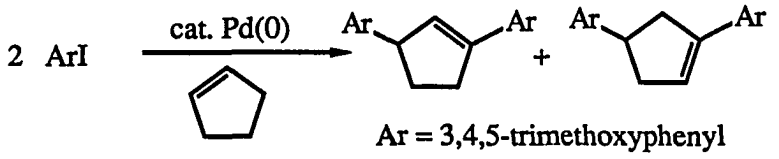
the propylvanillin **20** and ketone **22**, respectively. Vanillin (**20**) and ketone **22** are then coupled using sodium cyanide in DMF to afford the diketone **23**. Treatment of diketone **23** with copper, dimethyldisulfide, and 2,4-lutidine produces the corresponding methyl sulfide, which in the presence of MCPBA provides the diketone sulfone **24**. This diketone is then reduced to the corresponding diol with sodium borohydride in ethanol, followed by treatment with trifluoroacetic acid to afford the desired antagonist **18** in 50 %

Scheme III


OHC
I
OH
OCH3
19
n-PrBr
K2CO3
DMF
OHC
I
OPr
OCH3
20
90 %
CH3O
O
CH3
CH3O
OCH3
21
1) (CH3)2NH,
(CH2O)x, HCl
2) NaOH, H2O
CH3O
O
N(CH3)2
CH3O
OCH3
22
65 %
20 + 22
NaCN
DMF
I
OPr
O
CH3O
OCH3
CH3O
O
OCH3
23
61 %
1) Cu, (CH3)2S2,
2,4-lutidine
2) MCPBA
SO2CH3
OPr
O
CH3O
OCH3
CH3O
O
OCH3
24
45 %
1) NaBH4
2) TFA
18
50 % (23 % cis)

yield, plus 23 % of the inactive *cis* isomer.

Recently, Prashad et al.[61] reported a palladium(0)-catalyzed synthesis of 1,3-diaryl-cyclopentenes which are intermediates to 1,3-diarylcyclopentane and are carbon isosteres of 2,5-diaryltetrahydrofurans. Prashad's synthetic approach was a double Heck arylation of cyclopentene using either Heck's[62] reaction conditions or Larock and Baker's[63] procedure A (eq 1). When he employed the former procedure, a 2 : 1 ratio of the desired

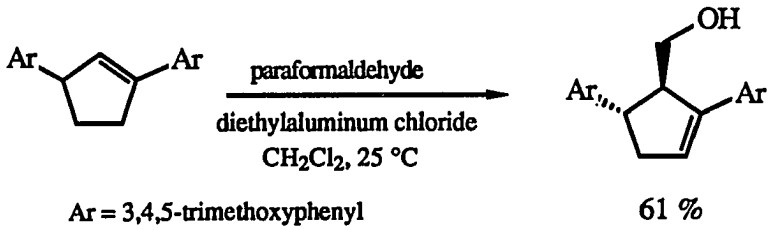


(1)

Ar = 3,4,5-trimethoxyphenyl

allylic product (1,3-diaryl-1-cyclopentene) to homoallylic product (1,4-diaryl-1-cyclopentene) was observed. However, when he employed Larock's procedure A, a 95 : 2.2 ratio of the same products was observed. He credits Larock's procedure for inhibiting the palladium hydride readdition and subsequent elimination to the alkene which provides the undesired homoallylic product. In this same publication, Prashad did not report hydrogenating these intermediates in order to obtain 1,3-diarylcyclopentanes in spite of the fact that he indicated that these alkenes are the necessary intermediates to 1,3-diarylcyclopentanes.

It was only in a later publication that Prashad et al.[61b] reported using these 1,3-diaryl-1-cyclopentenes in a Lewis acid catalyzed ene reaction with paraformaldehyde to afford a variety of *trans*-2,5-diaryl-2-cyclopentene-1-methanols (eq 2). The latter compounds are



Ar = 3,4,5-trimethoxyphenyl

61 %

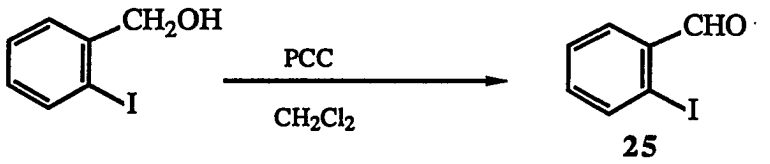
(2)

precursors to 2,5-diaryl-2-cyclopentane-1-methanol, which are potential PAF inhibitors.

RESULTS AND DISCUSSION

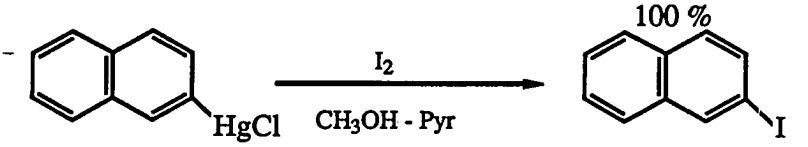
In this section, the development of a convient procedure for the synthesis of a variety of 2-aryl-2,3-dihydrofurans, and the use of this procedure in an efficient three-step, stereoselective synthesis of a variety of *trans*-2,5-diaryltetrahydrofurans are described.

Most of the aryl iodides used were commercially available and used without further purification. 2-Iodobenzaldehyde was obtained from the corresponding benzyl alcohol (eq 3). 2-Iodonaphthalene was obtained from iodination of 2-naphthylmercuric chloride (eq 4). 4-Iodo-1,2-dimethoxybenzene was obtained from iodination of 1,2-dimethoxy-



25
100 %

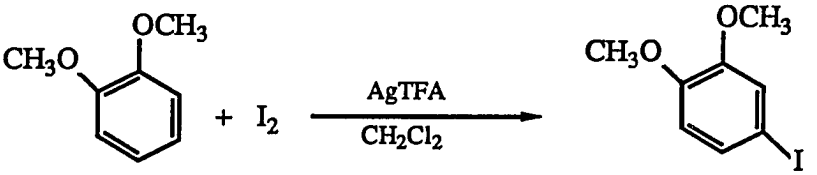
(3)



26
91 %

(4)

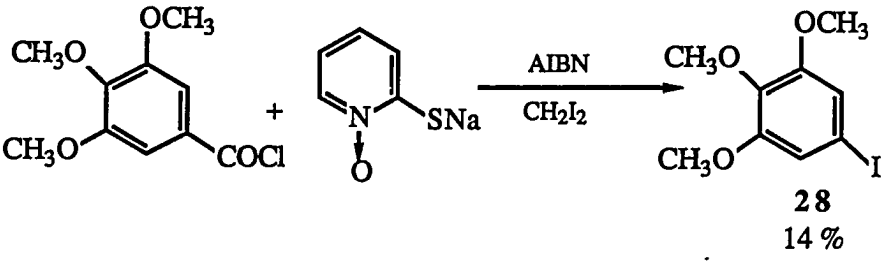
benzene (eq 5). 1-Iodo-3,4,5-trimethoxybenzene was obtained in a low yield from 3,4,5-



27
99 %

(5)

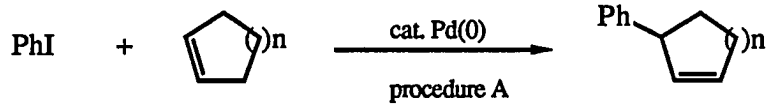
trimethoxybenzoyl chloride as a variety of other products were also present (eq 6).



28
14 %

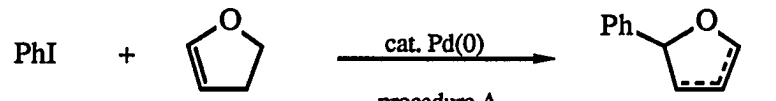
(6)

As discussed in part I of this dissertation, three different palladium procedures (procedure A: 2.5 mole % $Pd(OAc)_2$, 1 equiv *n*-Bu_4NCl, 3 equiv KOAc, DMF at 25 °C or 80 °C; procedure B: 3-4 mole % $Pd(OAc)_2$, 9 mole % PPh_3, 2 equiv Ag_2CO_3, CH_3CN at 80 °C; procedure C: procedure A plus 2.5 mole % PPh_3) have been used for the arylation of cyclic alkenes (eq 7). Larock and Baker's procedure A[63] is a



(7)

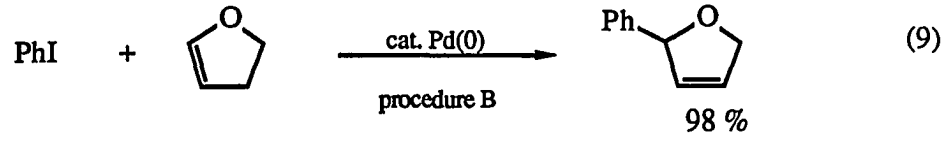
general procedure for the arylation of cyclic alkenes, but certain aryl iodides containing important organic functional groups were found to be inert when using this procedure. Furthermore, certain cyclic alkenes such as cycloheptene, 2,3-dihydrofuran, and 3,4-dihydro-2*H*-pyran produced mixtures of allylic and homoallylic isomers. For example, when iodobenzene was allowed to react with 2,3-dihydrofuran using procedure A, a mixture of the allylic and homoallylic isomers was generated in a 5.7 to 1 ratio (eq 8).



100 %
(5.7 : 1)

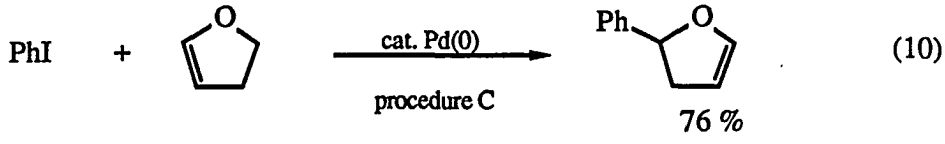
(8)

This has caused Larock and Baker[63] to use procedure B,[64,65] which circumvents some of the functional group and isomerization difficulties (eq 9). In spite of the



(9)

improvements procedure B offered, there are still a number of aryl iodides that remain inert under those conditions. As a result, Larock and Gong[66] have developed procedure C that effectively eliminated the functional group difficulties. It was also important to determine if procedure C would also eliminate the double bond isomerization problem seen in eq 8 when procedure A was employed, since this would offer a less expensive alternative to procedure B. Unexpectedly, procedure C afforded only the homoallylic isomer (eq 10).



(10)

Encouraged that procedure C might provide a general route to 2-aryl-2,3-dihydrofurans, a number of aryl iodides were used to determine the scope and limitations of this synthetic process, and the results are summarized in Table 4. From the results obtained, the following conclusions can be made. All of the reactions, except the one reported in entry 5, were complete in 24 hours. In all cases, except entry 1, the aryl iodides afforded only a trace of the allylic isomer. Fortunately, both isomers were easily separated using flash column chromatography.

Motivated by the success obtained in this study, the application of this chemistry in the synthesis of *trans* -2,5-diaryltetrahydrofurans is envisioned in Scheme IV. Three PAF-antagonists (**3**, **4**, and **11**) were selected as synthetic targets. The first step employed procedure C to generate the necessary 2-aryl-2,3-dihydrofuran (Table 5). In all three cases, only a trace of the allylic isomer was produced. Without exception, all three

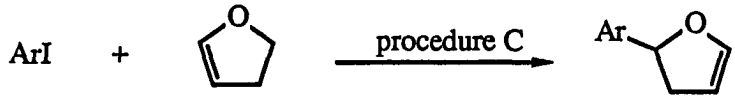
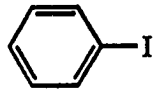
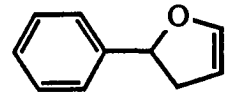
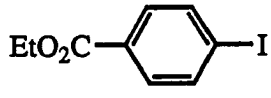
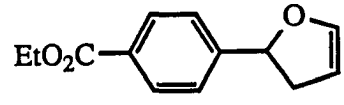
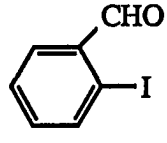
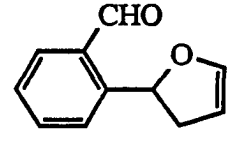
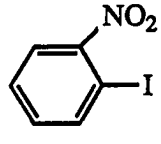
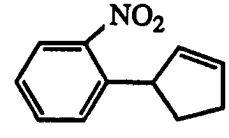
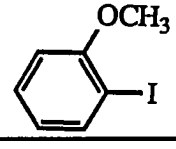
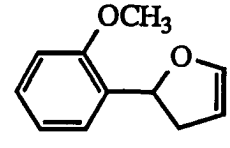


Table 4. Arylation of 2,3-dihydrofuran

Entry	Aryl iodide	Product	Yield (%)
1			76
2			70
3			61
4			53
5			53[a]

[a] This reaction required 3 days to complete.

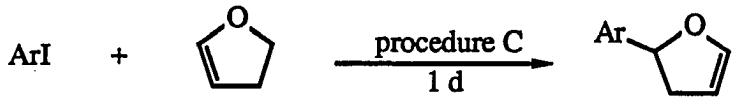
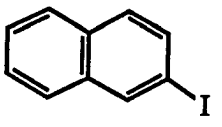
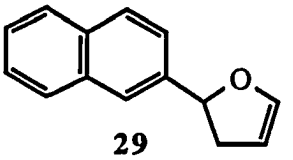
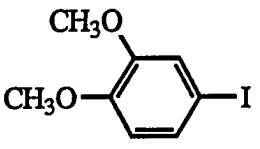
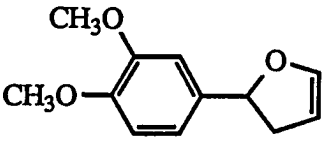
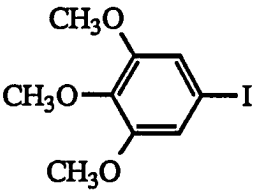
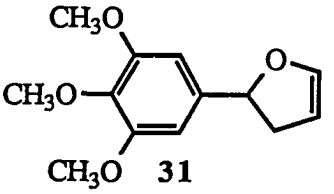
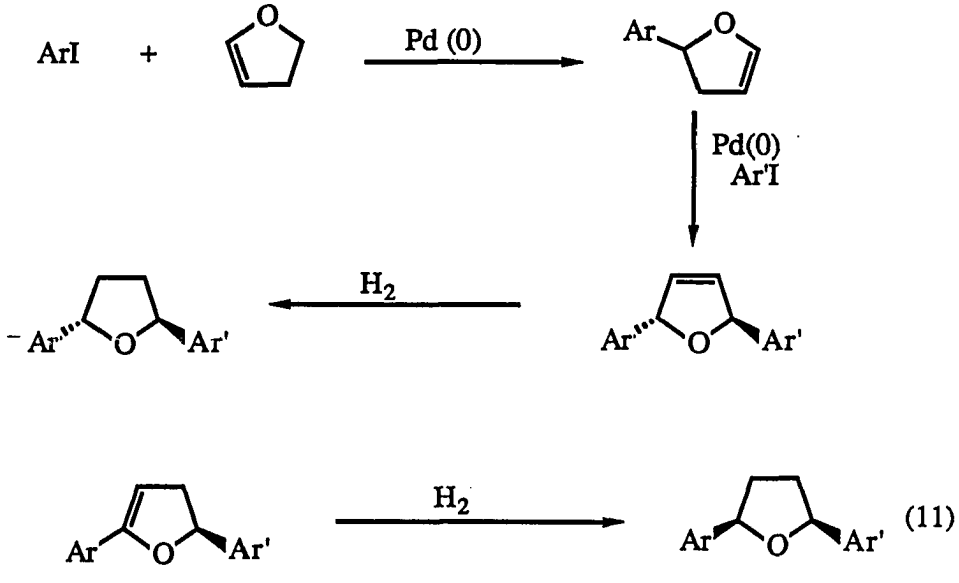


Table 5. Synthesis of 2-aryl-2,3-dihydrofurans using procedure C

Entry	Aryl iodide	Product	Yield (%)
1		 **29**	68
2		 **30**	78
3		 **31**	63

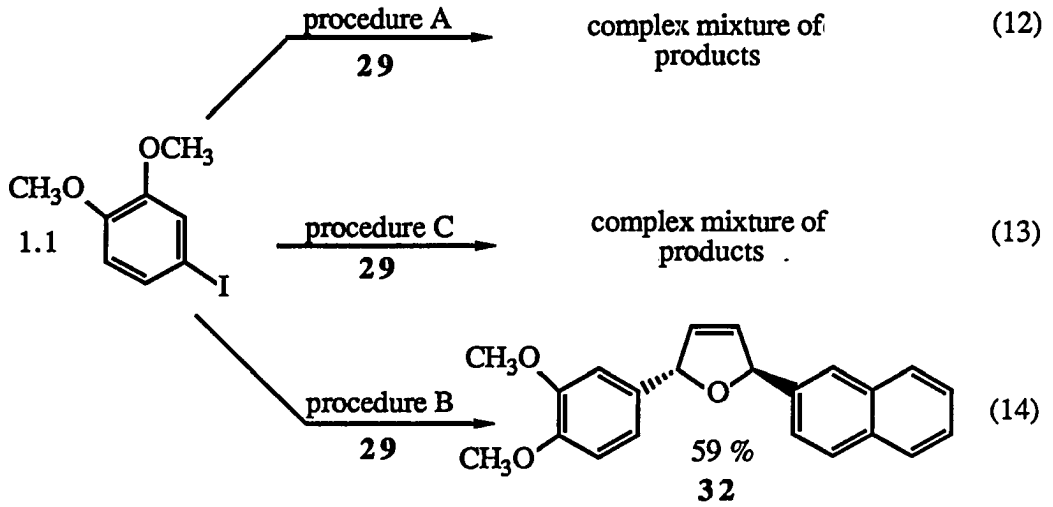
reactions were easily completed in a period of 24 hours. The second step of this approach must fulfill two criteria. First, the palladium procedure employed must afford only the allylic isomer. If not, the hydrogenation step of this sequence would produce the inactive *cis* -isomer[46] (eq 11). Secondly, this second arylation step must employ as few

Scheme IV



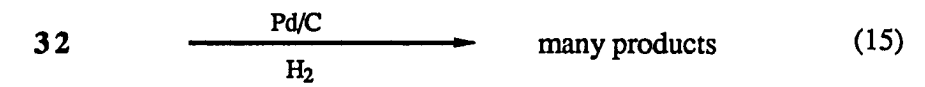
(11)

equivalents of the valuable 2-aryl-2,3-dihydrofuran as possible. The coupling of 1-iodo-3,4-dimethoxybenzene and 2-(2-naphthyl)-2,3-dihydrofuran was employed in this investigation to determine the optimal palladium procedure (eqs 12 - 14). Procedure B



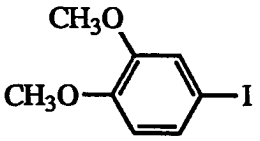
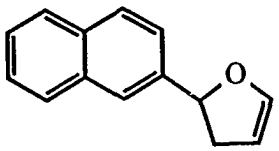
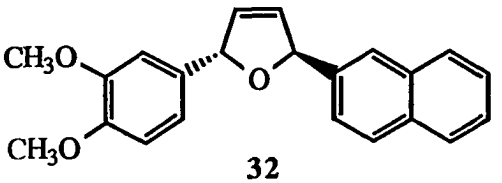
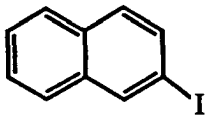
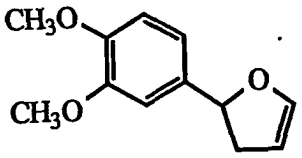
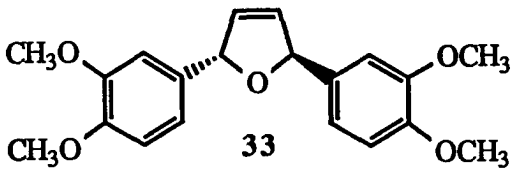
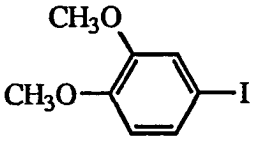
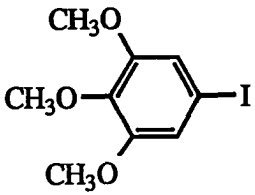
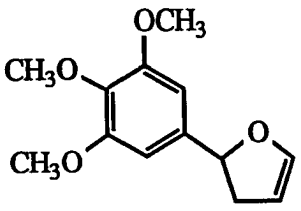
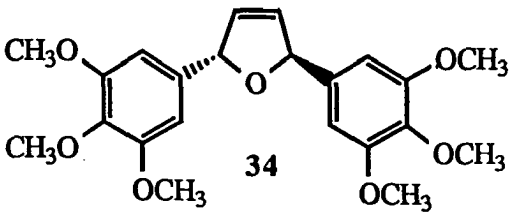
easily fulfilled both criteria by affording only the allylic isomer. Furthermore, this step required only a 10 % excess of the aryl iodide. Having established the optimal conditions from this study, the other substrates were then coupled under these same reaction conditions, and the results are summarized in Table 6. In all cases, the reactions were completed in only 24 hours. In entry 2, by reversing the order in which the dihydrofuran was arylated, a higher yield of **32** was obtained, and this reaction was also found to contain fewer side products than entry 1. It's important to note that these diaryldihydrofurans will aromatize to the corresponding furans if the reactions are allowed to run beyond 24 hours.

Although the final step of this synthesis may appear to be trivial, the actual chemistry was not. Compound **32** was used in this hydrogenation procedure employing palladium on charcoal (eq 15). Unfortunately, no desired product was recovered. What in fact



occurred was that **11** was initially generated, but under the reaction conditions, the benzyl ether linkages were also reduced. With this complication in mind, an alternative such as

Table 6. Arylation of 2-aryl-2,3-dihydrofuran using procedure B

Entry	Aryl Iodide	Alkene	Product	Yield (%)
1			 **32**	59
2			 **33**	93
3				82
4			 **34**	56

diimide was considered (eq 16). Once again, **32** was not fully converted, and

$$\mathbf{32} \xrightarrow[\substack{\text{HOAc}\\ \text{CH}_3\text{OH}\\ \text{24 h}}]{4\ KO_2CN{=}NCO_2K} \mathbf{32} + \mathbf{11} \quad (3 : 2) \qquad (16)$$

the inseparable mixture was again hydrogenated using 10 equivalents of dipotassium diazodicarboxylate (eq 17). Once again, incomplete hydrogenation was observed.

$$\mathbf{32} + \mathbf{11} \xrightarrow[\text{HOAc}]{10\ KO_2CN{=}NCO_2K} \mathbf{32} + \mathbf{11} \quad (1 : 1) \qquad (17)$$

A survey of the literature revealed that platinum(IV) oxide is a milder and more selective catalyst than palladium on charcoal. Moreover, the survey also revealed that platinum oxide tends not to isomerize the double bonds of alkenes, and the activity of the catalyst is highly dependent on the polarity of the solvent. Thus, by increasing the polarity of the solvent, the activity of the catalyst also increases. Since greater selectivity was desired in this hydrogenation step, a less polar solvent, EtOAc, was employed. When this hydrogenation system was employed on **32**, the desired PAF - antagonist was finally obtained in 93 % yield (eq 18). The remaining *trans* -2,5-diaryl-2,5-dihydro-

$$\mathbf{32} \xrightarrow[\substack{\text{EtOAc}\\ \text{100 min}}]{23\ \%\ PtO_2,\ H_2} \mathbf{11} \quad 93\ \% \qquad (18)$$

furans were then hydrogenated using these hydrogenation conditions (eqs 19 and 20).

$$\mathbf{33} \xrightarrow[\substack{\text{EtOAc}\\ \text{60 min}}]{23\ \%\ PtO_2,\ H_2} \mathbf{3} \quad 69\ \% \qquad (19)$$

$$\mathbf{34} \xrightarrow[\substack{\text{EtOAc}\\ \text{20 min}}]{23\ \%\ PtO_2,\ H_2} \mathbf{4} \quad 78\ \% \qquad (20)$$

CONCLUSION

Procedure C is a valuable synthetic tool in the arylation of cyclic alkenes. When the alkene is 2,3-dihydrofuran, isomerization of the double bond of the product is promoted by this catalyst system, and the predominate isomer is the homoallylic isomer. The scope and limitations of this procedure for the arylation of this enol ether are discussed. Application of this useful procedure in a three-step synthesis of a number of *trans* -2,5-diaryltetrahydrofurans, which are potent PAF antagonists, has been successful. This synthetic process is far superior to literature procedures at the present time in that the reactions are simple, high yielding, and limited only by the availability of the aryl iodides. Furthermore, only the biologically active *trans* isomer is afforded each time.

EXPERIMENTAL SECTION

Equipment

All NMR spectra were recorded on a Nicolet NT-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75 MHz for carbon nuclei). Infrared spectra were obtained on an IBM IR/98 FT-IR. Mass spectral data were obtained on a Kratos high resolution mass spectrometer. Gas chromatographic analyses were performed by using a Varian 3700 or a Hewlett Packard 5890 gas chromatograph equipped with a 3 % OV-101 on Chromasorb W packed column (Varian 3700 or HP 5890) or an HP-1 megabore column (HP 5890).

Reagents

1,2-Dimethoxybenzene, 3,4,5-trimethoxybenzoyl chloride, iodobenzene, 2-iodonitrobenzene, 2-iodoanisole, 2,3-dihydrofuran, potassium acetate, silver carbonate, silver trifluoroacetate, platinum(V) oxide, and PPh_3 were all obtained from Aldrich. Tetra-*n*-butylammonium chloride was purchased from Lancaster synthesis. *N,N* - Dimethylformamide, methylene chloride, and acetonitrile (Fisher) were all distilled from calcium hydride and stored over anhydrous molecular sieves. Toluene (Fisher) was distilled from sodium metal and stored over anhydrous molecular sieves. 2-Iodobenzaldehyde was prepared according to a literature procedure.[67]

2-Iodonaphthalene (26)[68]

In a 250 mL round bottom flask containing a stirring bar were added methanol (194 mL), β-naphthylmercuric chloride (3.63 g, 10.0 mmol), and pyridine (4.9 mL). Once the stirring began, I_2 (2.79 g, 11.0 mmol) was added in small portions. The solution was allowed to stir for 5 hours before it was poured into a separatory funnel containing saturated sodium chloride (100 mL) and hexane (100 mL). The aqueous layer was removed, and freshly prepared saturated aqueous $Na_2S_2O_3$ (100 mL) was added. The aqueous layer was removed and the hexane layer was washed with saturated sodium chloride, dried over anhydrous $MgSO_4$, filtered through a fritted funnel, concentrated *in vacuo*, and purified over silica gel using hexane to afford 2-iodonaphthalene in a 91 % yield (mp 55 - 56 °C, lit mp[69] 53 - 54 °C). ^1H NMR ($CDCl_3$) δ 7.46 - 7.51 (m, 2 H, aromatic Hs), 7.57 (d, 1 H, J = 8.1 Hz, aromatic H), 7.70 - 7.72 (m, 1 H, aromatic H), 7.79 (dd, 2 H, J = 6.0 Hz, J = 3.3 Hz, aromatic Hs), 8.23 (s, 1 H, aromatic H).

1,2-Dimethoxy-4-iodobenzene (27)[70]

In a flame-dried 3-necked round bottom flask under a nitrogen atmosphere equipped with a stirring bar, a reflux condenser, and an addition funnel were placed silver trifluoroacetate (4.00 g, 18.2 mmol) and 1,2-dimethoxybenzene (2.51 g, 18.2 mmol). The suspension was stirred for one minute before I_2 (4.62 g, 19.2 mmol) dissolved in methylene chloride (100 mL) was added over a period of two hours. After the addition was completed, the mixture was stirred for two additional hours before the mixture was filtered through a plug of Celite, and the solids were washed with methylene chloride (3 x 20 mL). The organic layer was extracted once with water, saturated Na_2CO_3, and freshly prepared 10 % $Na_2S_2O_3$. The organic layer was dried over anhydrous $MgSO_4$,

concentrated *in vacuo*, filtered through a fritted funnel, and columned over silica gel using 3 : 1 hexane / EtOAc to afford the desired aryl iodide in 99 % yield. ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.59 (d, 1H, J = 8.4 Hz, aromatic H), 7.09 (d, 1H, J = 1.8 Hz, aromatic H), 7.21 (dd, 1H, J = 8.4 Hz, J = 1.8 Hz, aromatic H).

1-Iodo-3,4,5-trimethoxybenzene (28)[71]

In a flame-dried 3-necked round bottom flask equipped with a stirring bar, addition funnel, and a reflux condenser was placed anhydrous 2-mercaptopyridine *N*-oxide sodium salt (3.29 g, 22 mmol). After the flask had been flushed with dry nitrogen, an atmosphere of nitrogen was maintained. Toluene (60 mL) was introduced via the addition funnel and methylene iodide (5.90 g, 22 mmol) was then injected. In a separate flask were placed AIBN (0.5 g), 3,4,5-trimethoxybenzoyl chloride (4.61 g, 20 mmol) and toluene (100 mL). This mixture was swirled until the solids were all dissolved and then transferred to the addition funnel. The toluene solution in the flask was heated to reflux before the AIBN and the acid chloride dissolved in toluene were added dropwise over a 30 minute period. After the addition, the solution was heated for 15 more minutes. The toluene was removed *in vacuo* , and the residue was columned over silica gel using 3 : 1 hexane / EtOAc to afford the desired aryl iodide in 14 % yield. ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H, OCH_3), 3.84 (s, 6H, OCH_3's), 6.89 (s, 2H, aromatic Hs).

General procedure for the arylation of 2,3-dihydrofuran

In a 10 mL round bottom flask equipped with a side arm were placed palladium acetate (0.006 g, 2.5 mol %), PPh_3 (0.007 g, 2.5 mol %), tetra-*n*-butylammonium chloride (0.294 g, 1.06 mmol), potassium acetate (0.294 g, 3.00 mmol), and the aryl iodide (1.00

mmol). The flask was affixed with a reflux condenser and sealed by a septum. The flask was flushed with a rapid stream of dry nitrogen and a nitrogen atmosphere was maintained throughout the course of the reaction. 2,3-Dihydrofuran (0.70 g, 0.76 mL, 10 mmol) and DMF (2 mL) were injected sequentially. The reaction was heated to 80 °C and monitored by thin layer chromatography. Once all of the starting material had been consumed, the mixture was combined with ether (25 mL) and poured into a separatory funnel containing saturated ammonium chloride (50 mL). The organic layer was isolated, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and columned over silica gel using either hexane or a mixture of hexane and EtOAc.

2-Phenyl-2,3-dihydrofuran (Table 4, entry 1)[62]

This compound was purified over silica gel using 10 : 1 hexane / EtOAc. ^{1}H NMR ($CDCl_3$) δ 2.58 (dddd, 1 H, J = 12.9 Hz, J = 8.4 Hz, J = 2.4 Hz, J = 2.4 Hz, C<u>H</u>H-C=C), 3.38 (dddd, 1 H, J = 12.9 Hz, J = 10.2 Hz, J = 2.4 Hz, J = 2.4 Hz, CH<u>H</u>-C=C), 4.92 (ddd, 1 H, J = 2.7 Hz, J = 2.7 Hz, J = 2.7 Hz, Ph-CH), 5.49 (dd, 1 H, J = 10.8 Hz, J = 8.4 Hz, C<u>H</u>=CH-O), 6.43 (dd, 1 H, J = 5.0 Hz, J = 2.6 Hz, CH=C<u>H</u>-O), 7.23 - 7.34 (m, 5 H, aromatic Hs); ^{13}C NMR ($CDCl_3$) δ 37.79, 62.24, 98.91, 125.48, 127.50, 128.40, 142.94, 145.21; IR(neat) 3087, 3062, 3031, 2932, 1728, 1620, 1495, 1450, 1136, 1051, 1001, 941, 758, 698 cm^{-1}; HRMS: calcd for $C_{10}H_{10}O$ m/z 146.07317, found m/z 146.07317.

(4-Ethoxycarbonylphenyl)-2,3-dihydrofuran (Table 4, entry 2)

This compound was purified over silica gel using 4 : 1 hexane / EtOAc. ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3 H, J = 6.9 Hz, CH_3), 2.56 (dddd, 1 H, J = 15 Hz, J = 8.1 Hz, J = 2.4 Hz, J = 2.4 Hz, C=C-C<u>H</u>H), 3.12 (dddd, 1 H, J = 15 Hz, J = 11.1 Hz, J = 2.4 Hz, J

= 2.4 Hz, C=C-CHH), 4.37 (q, 2 H, J = 6.9 Hz, CO_2CH_2), 4.96 (dd, 1 H, J = 5.1 Hz, J = 2.7 Hz, Ar-CH-C=C), 5.56 (dd, 1 H, J = 10.8 Hz, J = 5.1 Hz, CH=CHO), 6.46 (dd, 1 H, J = 5.1 Hz, J = 2.4 Hz, CH=CHO), 7.41 (d, 2 H, J = 8.4 Hz, aromatic Hs), 8.03 (d, 2 H, J = 8.4 Hz, aromatic Hs); ^{13}C NMR ($CDCl_3$) δ 14.32, 37.95, 60.89, 81.63, 98.97, 127.26, 128.63, 128.77, 145.24, 148.05, 166.80; IR (neat) 3101, 2982, 2937, 1717, 1622, 1612, 1367, 1275, 1177, 1136, 1103, 1051, 770, 706 cm^{-1}; HRMS calc for $C_{13}H_{14}O_3$ m/z 218.09430, found m/z 218.09411; Anal calc for $C_{13}H_{14}O_3$: C, 71.56; H, 6.42. Found: C, 71.80; H, 6.26

2-(2-Formylphenyl)-2,3-dihydrofuran (Table 4, entry 3)

This compound was purified over silica gel using 4 : 1 hexane / EtOAc to afford the desired product. ^{1}H NMR ($CDCl_3$) δ 2.16 (dddd, 1 H, J = 12 Hz, J = 4.5 Hz, J = 2.4 Hz, J = 2.4 Hz, CHH-C=C), 3.33 (dddd, 1 H, J = 12 Hz, J = 4.8 Hz, J = 2.4 Hz, J = 2.4 Hz, CHH-C=C), 4.86 (dd, 1 H, J = 5.1 Hz, J = 2.4 Hz, Ar-CH), 6.24 (dd, 1 H, J = 11.1 Hz, J = 7.5 Hz, CH=CH-O), 6.45 (dd, 1 H, J = 2.4 Hz, J = 2.4 Hz, CH=CH-O), 7.43 (ddd, 1 H, J = 7.5 Hz, J = 7.5 Hz, J = 1.5 Hz, aromatic H), 7.56 (ddd, 1 H, J = 7.5 Hz, J = 7.5 Hz, J = 1.5 Hz, aromatic H), 7.62 (dd, 1 H, J = 7.5 Hz, J = 1.2 Hz, aromatic H), 7.79 (dd, 1 H, J = 7.5 Hz, J = 1.2 Hz, aromatic H), 10.07 (s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 38.12, 79.20, 99.00, 125.49, 127.40, 131.90, 133.98, 134.55, 144.89, 145.80 (missing aldehydic carbon); IR(neat) 3101, 3072, 3033, 2927, 2740, 1703, 1622, 1601, 1573, 1450, 1200, 1139, 1051, 935, 947, 756, 735 cm^{-1}; HRMS : calcd for $C_{11}H_{10}O_2$ m/z 174.06808, found m/z 174.06823; Anal calc for $C_{11}H_{10}O_2$: C, 75.86; H, 5.75. Found C: 70.61; H, 5.52. (Apparently this sample decomposed during shipping to Galbraith Laboratory for elemental analysis.)

2-(2-Nitrophenyl)-2,3-dihydrofuran (Table 4, entry 4)

This compound was purified over silica gel using 8 : 1 hexane / EtOAc. ^{1}H NMR ($CDCl_3$) δ 2.44 (dddd, 1 H, *J* = 15.6 Hz, *J* = 7.2 Hz, *J* = 2.4 Hz, *J* = 2.4 Hz, C<u>H</u>H-C=C), 3.40 (dddd, 1 H, *J* = 15. 6 Hz, *J* = 10.8 Hz, *J* = 2.4 Hz, *J* = 2.4 Hz, CH<u>H</u>-C=C), 4.95 (dd, 1 H, *J* = 5.1 Hz, *J* = 2.4 Hz, Ar-CH), 6.09 (dd, 1 H, *J* = 10.8 Hz, *J* = 7.2 Hz, C<u>H</u>=CH-O), 6.50 (dd, 1 H, *J* = 5.1 Hz, *J* = 2.4 Hz, CH=C<u>H</u>-O), 7.44 (ddd, 1 H, *J* = 8.4 Hz, *J* = 8.4 Hz, *J* = 1.5 Hz, aromatic H), 7.65 (ddd, 1 H, *J* = 8.4 Hz, *J* = 8.4 Hz, *J* = 1.5 Hz, aromatic H), 7.73 (dd, 1 H, *J* = 7.8 Hz, *J* = 1.5 Hz, aromatic H), 8.08 (dd, 1 H, *J* = 8.4 Hz, *J* = 1.2 Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 38.23, 78.35, 99.21, 124.77, 126.98, 127.98, 132.88, 139.64, 144.05, 146.38; IR(neat) 3107, 2930, 2862, 1624, 1610, 1526, 1342, 1136, 1049, 1016, 939, 854, 789, 766, 708 cm^{-1}; HRMS: calcd for $C_{10}H_9NO_3$ m/z 191.05825, found m/z 191.05781; Anal calc for $C_{10}H_9NO_3$: C, 62.83; H, 4.71. Found: C, 63.45; H, 4.83. (Apparently this sample decomposed during shipping to Galbraith Laboratory for elemental analysis.)

2-(2-Methoxyphenyl)-2,3-dihydrofuran (Table 4, entry 5)

This compound was purified over silica gel using 8 : 1 hexane / EtOAc. ^{1}H NMR ($CDCl_3$) δ 2.42 (dddd, 1 H, *J* = 15 Hz, *J* = 8.1 Hz, *J* = 2.4 Hz, *J* = 2.4 Hz, C<u>H</u>H-C=C), 3.11 (dddd, 1 H, *J* = 15 Hz, *J* = 10.8 Hz, *J* = 2.4 Hz, *J* =2.4 Hz, CH<u>H</u>-C=C), 3.82 (s, 3 H, OCH_3), 4.91 (dd, 1 H, *J* = 5.1 Hz, *J* = 2.7 Hz, Ar-CH), 5.79 (dd, 1 H, *J* = 10.8 Hz, *J* = 8.1 Hz, C<u>H</u>=CH-O), 6.46 (dd, 1 H, *J* = 4.8 Hz, *J* = 2.4 Hz, CH=C<u>H</u>-O), 6.86 (d, 1 H, *J* = 8.1 Hz, aromatic H), 6.95 (dd, 1 H, *J* = 7.2 Hz, *J* = 7.2 Hz, aromatic H), 7.24 (ddd, 1 H, *J* = 8.1 Hz, *J* = 8.1 Hz, *J* = 1.5 Hz, aromatic H), 7.39 (dd, 1 H, *J* = 8.1 Hz, *J* = 8.1 Hz, *J* = 1.5 Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 36.93, 55.25,

77.44, 99.19, 110.11, 120.43, 125.35, 128.17, 131.42, 144.97, 155.75; IR(neat) 3066, 3004, 2937, 2860, 1620, 1603, 1491, 1475, 1286, 1242, 1138, 1053, 935, 754, 706 cm^{-1}; HRMS: calcd for $C_{11}H_{12}O_2$ m/z 176.08373, found m/z 176.08399; Anal calc for $C_{11}H_{12}O_2$: C, 75.00; H, 6.82. Found: C, 68.82, H, 6.50. (Apparently this sample decomposed during shipping to Galbraith Laboratory for elemental analysis.)

2-(2-Naphthyl)-2,3-dihydrofuran (29) (Table 5, entry 1)

This compound was columned over silica gel using 15 : 1 hexane / EtOAc. ^1H NMR ($CDCl_3$) δ 2.65 (dddd, 1 H, J = 15.3 Hz, J = 8.4 Hz, J = 2.4 Hz, J = 2.4 Hz, C=C-CHH), 3.11 (dddd, 1 H, J = 15.3 Hz, J = 10.8 Hz, J = 2.4 Hz, J = 2.4 Hz, C=C-CHH), 4.97 (dd, 1 H, J = 5.1 Hz, J = 2.7 Hz, Ar-CH-O), 5.66 (dd, 1 H, J = 10.8 Hz, J = 8.4 Hz, CH=CH-O), 6.50 (dd, 1 H, J = 5.1 Hz, J = 2.4 Hz, CH=CH-O), 7.41 - 7.47 (m, 3 H, aromatic Hs), 7.77 - 7.83 (m, 4 H, aromatic Hs); ^{13}C NMR ($CDCl_3$) δ 37.81, 82.40, 99.07, 123.60, 124.20, 125.79, 126.10, 127.59, 127.90, 128.47, 132.88, 133.09, 140.19, 145.33; IR (mull) 1622, 1462, 1053, 1016, 816, 747, 721 cm^{-1}; HRMS: calcd for $C_{14}H_{12}O$ m/z 196.08882, found m/z 196.08906.

2-(3,4-Dimethoxyphenyl)-2,3-dihydrofuran (30) (Table 5, entry 2)

This compound was columned over silica gel using 3 : 1 hexane / EtOAc. ^1H NMR ($CDCl_3$) δ 2.62 (dddd, 1 H, J = 15.0 Hz, J = 8.4 Hz, J = 2.4 Hz, J = 2.4 Hz, C=C-CHH), 3.04 (dddd, 1 H, J = 15.0 Hz, J = 10.5 Hz, J = 2.4 Hz, J = 2.4 Hz, C=C-CHH), 3.90 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.97 (dd, 1 H, J = 5.1 Hz, J = 2.4 Hz, Ar-CH-O), 5.46 (dd, 1 H, J = 10.5 Hz, J = 8.7 Hz, CH=CH-O), 6.44 (dd, 1 H, J = 4.8 Hz, J = 2.4 Hz, CH=CH-O), 6.83-6.92 (m, 3 H, aromatic Hs); ^{13}C NMR ($CDCl_3$) δ 37.53,

55.68, 55.74, 82.21, 98.97, 108.70, 110.86, 117.89, 135.30, 145.05, 148.40, 148.94; IR(neat) 3103, 3003, 2937, 2837, 1620, 1593, 1518, 1466, 1443, 1263, 1236, 1163, 1138, 1051, 1020, 914, 731 cm^{-1}; HRMS: calcd for $C_{12}H_{14}O_3$ m/z 206.09430, found m/z 206.09456.

2-(3,4,5-Trimethoxyphenyl)-2,3-dihydrofuran (31) (Table 5, entry 3)

This compound was purified over silica gel using 3 : 1 hexane / EtOAc. ^1H NMR ($CDCl_3$) δ 2.62 (dddd, 1 H, J = 15.3 Hz, J = 9.6 Hz, J = 2.4 Hz, J = 2.4 Hz, C=C-CHH), 3.06 (dddd, 1 H, J = 15.3 Hz, J = 10.8 Hz, J = 2.4 Hz, J = 2.4 Hz, C=C-CHH), 3.84 (s, 3 H, OCH_3), 3.87 (s, 6 H, OCH_3's), 4.97 (dd, 1 H, J = 5.1 Hz, J = 2.7 Hz, Ar-CH-O), 5.45 (dd, 1 H, J = 10.8 Hz, J = 8.7 Hz, CH=CH-O), 6.45 (dd, 1 H, J = 5.1 Hz, J = 2.4 Hz, CH=CH-O), 6.59 (s, 2 H, aromatic Hs); ^{13}C NMR ($CDCl_3$) δ 37.75, 55.97, 60.73, 82.39, 99.14, 102.29, 137.11, 138.54, 145.11, 153.20; IR(neat) 3050, 1620, 1593, 1508, 1464, 1420, 1360, 1236, 1130, 1053, 1011, 731, 708 cm^{-1}; HRMS: calcd for $C_{13}H_{16}O_4$ m/z 236.10486, found m/z 236.10501.

General procedure for the arylation of 2-aryldihydrofuran

In a dry 25 mL round bottom flask equipped with a side arm and a stirring bar were placed palladium acetate (0.0035 g, 3.0 mol %), PPh_3 (0.12 g, 9.0 mol %), silver carbonate (0.276 g, 1.00 mmol), the 2-aryl-2,3-dihydrofuran (0.50 mmol), and the aryl iodide (0.55 mmol). The flasked was affixed with a reflux condenser, the apparatus was sealed, flushed with nitrogen, and a positive atmosphere of nitrogen was maintained with a bubbler. Acetonitrile (6 mL) was injected, the mixture was heated to 80 °C and the reaction was followed by thin layer chromatography. Once all of the starting alkene has

been consumed, the reaction mixture was filtered through a plug of Celite to remove the silver salts, and the solids were washed with ether (3 x 25 mL). The filtrate was poured into a separatory funnel and washed with saturated ammonium chloride (50 mL). The organic layer was isolated, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and columned over silica gel to afford the desired *trans*-2,5-diaryl-2,5-dihydrofuran. The results are found in Table 6.

***trans*-2-(2-Naphthyl)-5-(3,4-dimethoxyphenyl)-2,5-dihydrofuran (32)** (entry 1).

This compound was purified over silica gel using 5 : 1 hexane / EtOAc. ^1H NMR ($CDCl_3$) δ 3.89 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 6.08 - 6.09 (m, 2 H, Ar-CH-O's), 6.15 - 6.20 (m, 2 H, HC=CH), 6.87 - 6.98 (m, 3 H, aromatic Hs), 7.46 - 7.52 (m, 3 H, aromatic Hs), 7.82 - 7.87 (m, 4 H, aromatic Hs); ^{13}C NMR ($CDCl_3$) δ 55.85, 55.94, 88.17, 88.22, 109.86, 111.14, 118.93, 124.35, 125.14, 125.88, 126.05, 127.62, 127.89, 128.34, 130.28, 130.38, 133.12, 133.31, 133.97, 138.20, 148.86, 149.18; IR(neat) 3057, 3005, 2937, 1602, 1516, 1464, 1261, 1235, 1155, 1142, 1059, 1028, 910, 858, 817, 790, 754, 730 cm^{-1}; HRMS: calcd for $C_{22}H_{20}O_3$ m/z 332.14125, found m/z 332.14091.

***trans*-2,5-bis(3,4-Trimethoxyphenyl)-2,5-dihydrofuran (33)** (entry 3).

This compound was purified over silica gel using 2 : 1 : 1 hexane / EtOAc / methylene chloride. ^1H NMR ($CDCl_3$) δ 3.88 (s, 6 H, OCH_3's), 3.90 (s, 6 H, OCH_3's), 5.98 (s, 2 H, Ar-CH-O's), 6.08 (s, 2 H, CH=CH), 6.85 - 6.94 (m, 6 H, aromatic Hs); ^{13}C NMR ($CDCl_3$) δ 55.59, 55.70, 87.64, 109.50, 110.79, 118.71, 130.12, 133.68, 148.57,

148.87; IR (neat) 3008, 1591, 1518, 1466, 1448, 1267, 1234, 1151, 1140, 1055, 1024, 854, 810, 733 cm^{-1}; HRMS: calcd for $C_{20}H_{22}O_5$ m/z 342.14673, found 342.14660.

***trans*-2,5-bis(3,4,5-Trimethoxyphenyl)-2,3-dihydrofuran** (entry 4)

This compound was purified over silica gel using 2 : 1 : 1 hexane / EtOAc / methylene chloride. ^1H NMR ($CDCl_3$) δ 3.79 (s, 6 H, OCH_3's) 3.84 (s, 12 H, OCH_3's), 5.94 (s, 2 H, Ar-CH-O's), 6.06 (s, 2 H, CH=CH), 6.57 (s, 4 H, aromatic Hs); ^{13}C NMR ($CDCl_3$) δ 55.94, 60.24, 60.65, 88.18, 103.30, 130.19, 136.65, 153.28; IR(neat) 3078, 2999, 2941, 2839, 1593, 1506, 1464, 1420, 1327, 1234, 1126, 1009, 912, 733 cm^{-1}; HRMS: calcd for $C_{22}H_{26}O_7$ m/z 402.16786, found m/z 402.16741.

General procedure for hydrogenating the *trans*-2,5-diaryl-2,5-dihydrofurans

In a 50 mL round bottom flask equipped with a side arm with a Teflon stopcock and a stirring bar was weighed platinum oxide (23 mol %). The flask was injected with EtOAc (3 mL) and flushed with hydrogen gas for five minutes. Stirring was initiated and the catalyst was flushed with hydrogen for another five minutes before a gas buret was attached to the flask via the side arm. With the stopcock closed and the gas buret attached, the stirring was stopped for ten minutes to check for leaks. The alkene (0.75 mmole), dissolved in EtOAc (3 mL), was then injected via the side arm. Stirring began immediately and the reaction was stopped when the theoretical amount of hydrogen had been taken up. The reaction mixture was filtered through a plug of silica gel and concentrated *in vacuo*. The crude product was then columned over silica gel using hexane and EtOAc, and concentrated *in vacuo* to afford the desired product.

***trans*-2-(2-Naphthyl)-5-(3,4-dimethoxyphenyl)tetrahydrofuran (11)**[58]

This compound was purified over silica gel using 5 : 1 hexane / EtOAc. ^{1}H NMR ($CDCl_3$) δ 1.97 - 2.12 (m, 2 H, CH_2), 2.4 - 2.57 (m, 2 H, CH_2), 3.87 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 5.27 (t, 1 H, J = 7.2 Hz, Ar-CH-O), 5.42 (t, 1 H, J = 7.2 Hz, Ar'CH-O), 6.85 (d, 1 H, J = 8.4 Hz, aromatic H), 6.95 - 7.01 (m, 2 H, aromatic Hs), 7.43 - 7.51 (m, 3 H, aromatic Hs), 7.80 -7.87 (m, 4H, aromatic Hs); ^{13}C NMR ($CDCl_3$) (there are some overlapping signals) δ 35.60, 55.83, 81.22, 81.33, 108.69, 110.79, 117.75, 123.82, 125.51, 125.96, 127.59, 127.77, 128.08, 132.65, 133.17, 135.81, 141.01, 148.07, 148.83; IR(neat) 3055, 2964, 2907, 1514, 1462, 1448, 1258, 1124, 1028, 910, 860, 818, 737, 704, 662 cm^{-1}; HRMS: calcd for $C_{22}H_{22}O_3$ m/z 334.15690, found 334.15678; Anal calc for $C_{22}H_{22}O_3$: C, 79.04; H, 6.59. Found: C, 78.77; H, 6.75.

***trans*-2,5-bis(3,4-Dimethoxyphenyl)tetrahydrofuran (3)**[46,58]

This compound was purified over silica gel using 2 : 1 : 1 hexane / EtOAc / methylene chloride. ^{1}H NMR ($CDCl_3$) δ 1.85 - 1.91 (m, 2 H, CH_2), 2.29 - 2.37 (m, 2 H, CH_2), 3.76 (s, 6 H, OCH_3's), 3.80 (s, 6 H, OCH_3's), 5.10 (t, 2 H, J = 6.6 Hz, Ar-CH-O's), 6.73 - 6.88 (m, 6 H, aromatic Hs); ^{13}C NMR ($CDCl_3$) δ 35.37, 55.57 (two peaks), 80.82, 108.48, 110.59, 117.48, 139.76, 147.79, 148.57; HRMS: calcd for $C_{20}H_{24}O_5$ m/z 344.16238, found m/z 344.16215; Anal. calc for $C_{20}H_{24}O_5$: C, 69.76; H, 6.98, found: C, 69.81; H, 7.01.

***trans*-2,5-bis(3,4,5-Trimethoxyphenyl)tetrahydrofuran (4)**[46]

This compound was columned over silica gel using 2 : 1 : 1 hexane / EtOAc / methylene chloride. ^{1}H NMR ($CDCl_3$) δ 1.89 - 1.95 (m, 2 H, CH_2), 2.38 - 2.41 (m, 2 H, CH_2), 3.78 (s, 6 H, OCH_3's), 3.80 (s, 12 H, OCH_3's), 5.13 (t, 2 H, J = 6.9 Hz, Ar-CH-O's), 6.56 (s, 4 H, aromatic Hs); ^{13}C NMR ($CDCl_3$) δ 35.53, 56.00, 60.72, 81.30, 102.22, 136.86, 139.11, 153.12; IR(neat) 3005, 2941, 2839, 1591, 1506, 1464, 1418, 1329, 1234, 1126, 1070, 1039, 910, 783, 734 cm^{-1}; HRMS: calcd for $C_{22}H_{28}O_7$ m/z 404.18351, found m/z 404.18349.

REFERENCES

1. Hanahan, D.J. *Ann. Rev. Biochem.* **1986**, *55*, 483.
2. Hanahan, D.J. *J. Biol. Chem.* **1980**, *255*, 5514.
3. Demopoulos, C.A.; Pinckard, R.N.; Hanahan, D.J. *J. Biol. Chem.* **1979**, *254*, 5514.
4. Benveniste, J.; Tence, M.; Bidault, J.; Boullet, C.; Varence, D.; Polonsky, J. *C.R. Seances Acad. Sci. Ser. D* **1979**, *289*, 1037.
5. Benveniste, J.; Arnoux, A. "Platelet - activating Factor and Structurally Related Ether -lipids," *INSERM Symposium* no. 23, Elsevier Science: Amsterdam, 1983.
6. Vargaftig, B.B.; Lefort, J.; Chignard, M.; Benveniste, J. *Eur. J. Pharmacol.* **1980**, *65*, 185.
7. Hwang, S.-B.; Lee, C.-S.; Cheah, M.J.; Shen, T.-Y. *Biochemistry* **1983**, *22*, 4756.
8. Valone, F.-H.; Coles, E.; Reinhold, V.R.; Goetzl, E.J. *J. Immunol.* **1982**, *129*, 1637.
9. Kloprogge, E.; Akkerman, J.W. *INSERM Symposium*, **1983**, *23*, 153.
10. Honma, Y.; Kasukabe, T.; Hozumi, M.; Tsuschima, S.; Nomura, H. *Cancer Res.* **1981**, *41*, 3211.
11. Hwang, S.-B.; Lam, M.-H.; Shen, T.-Y. *Biochem. Biophys. Res. Commun.* **1985**, *128*, 972.
12. Godfroid, J.J.; Braquet, P. *Trends Pharmacol. Sci.* **1986**, *7*, 368.
13. Venuti, M.C. *Ann. Rev. Med. Chem.* **1985**, *20*, 193.
14. Vargaftig, B.B.; Chignard, M.; Benveniste, J.; Veefort, J.; Wal, F. *Ann. N.Y. Acad. Sci.* **1981**, *370*, 119.
15. Pinckard, R.N.; McManus, N.L.; Hanahan, D.J. *Adv. Inflammation Res.* **1982**, *4*, 147.
16. Braquet, P.; Godfroid, J.J. *Trends Pharmacol. Sci.* **1986**, *7*, 397.

17. Braquet, P.; Touqui, L.; Shen, T.-Y.; Varfatig, B.B. *Pharmacol. Rev.* **1987**, *39*, 98.

18. Page, C.P.; Morley, J. *Pharmacol. Res. Commun.* (suppl) **1986**, *18*, 217.

19. Morley, J. *Agents and Agents* **1986**, *19*, 100.

20. Nakamura, T.; Page, C.P.; Sanjar, S. *Int. Arch. Allergy Appl. Immunol.* **1985**, *7*, 73.

21. Nakamura, T.; Morita, Y.; Kuriyama, M.; Shihara, K.; Ito, K.; Miyamoto, T. *Int. Arch. Allergy Appl. Immunol.* **1987**, *82*, 57.

22. McManus, L.M.; Hanahan, D.J.; Demopoulos, C.A.; Pinckard, R.N. *J. Immunol.* **1980**, *124*, 2919.

23. Blank, M.L.; Snyder, F.; Byers, L.W.; Brooks, B.; Muirhead, E.E. *Biochem. Biophys. Res. Commun.* **1979**, *90*, 1194.

24. Sanchez - Crespo, M.; Alonso, F.; Inarrea, P.; Alvarez, V.; Egido, J. *Immunopharmacology* **1982**, *4*, 173.

25. Doebber, T.W.; Wu, M.S.; Shen, T.-Y. *Biochem. Biophys. Res. Commun.* **1984**, *125*, 980.

26. Etienne, A.; Hecquet, F.; Braquet, P. *Progress Clinical Biol. Res.* **1988**, *272*, 135.

27. Doebber, T.W.; Wu, M.S.; Robbins, J.C.; Machoay, B.; Chary, M.N.; Shen, T.-Y. *Biochem. Biophys. Res. Commun.* **1985**, *127*, 799.

28. Munder, P.B.; Weltzien, H.O.; Modolell, M. *7th International Symposium on Immunopathology,* Miescher, P.A.; Ed.; Basel, 1976, p. 411.

29. Terashita, Z.; Tsushima, B.; Yoshioka, Y.; Nomura, H.; Inada, Y.; Nishikawa, K. *Life Sci.* **1983**, 1975.

30. Hartung, H.-P. *FEBS Lett.* **1983**, *160*, 209.

31. Handley, D.A.; Van Valen, R.G.; Saunders, R.N. *Immunopharmacology* **1986**, *11*, 175.

32. Winslow, C.M.; Vallespir, S.R.; Frisch, G.E.; D'aries, F.J.; DeLillo, A.K.; Houlihan, W.J.; Parrino, V.; Schmitt, G.; Saunders, R.N. *Prostaglandins* **1985**, *30*, 697.

33. Lee, M.L.; Winslow, C.M.; Jaeggi, C.; D'ares, F.; Frisch, G.; Farley, C.; Melden, M.K.; Handley, D.A.; Saunders, R.N. *Prostaglandins* **1985**, *30*, 690.

34. Lefort, J.; Sedivy, P.; Desquand, S.; Randon, J.; Coeffier, E.; Maridonneau - Parini, I.; Floch, A.; Benveniste, J.; Vargaftig, B.B. *Eur. J. Pharmacol.* **1984**, *69*, 257.

35. Sedivy, P.; Caillard, C.G.; Carruette, A.; Deregnaucourt, J.; Mondat, S. In *Advances in Inflammation Research*, Russo - Marie, F.; Mencia - Huerta, J.M.; Chignard, M., Ed.; Raven Press: New York, 1985, pp. 171 - 173.

36. Sedivy, P.; Caillard, G.C.; Floch, A.; Folliard, R.; Mondat, S.; Robault, C.; Terlain, B. *Prostaglandins* **1985**, *30*, 688.

37. Cavero, L.; Lave, D.; Marquis, O.; Robault, C. *Br. J. Pharmacol.* **1987**, *90*, 116.

38. Schreiber, S.L.; Desmaele, D.; Porco, J.A. Jr. *Tetrahedron Lett.* **1988**, *29*, 6689.

39. Chiang, Y.C.P.; Biftu, T.; Graham, D.W.; Yang, S.S.; Chang, M.N.; Chabala, J.C.; Thompson, K.L. European Patent EP-257921-A, 1988.

40. Braquet, P. In *Advances in Prostaglandin, Thromboxane, and Leukotriene Research*, Raven Press: New York, 1986, pp. 179 - 198.

41. Ponpipom, M.M.; Bugianesi, R.L.; Brooker, D.R.; Yue, B.-Z.; Hwang, S.-B.; Shen, T.-Y. *J. Med. Chem.* **1987**, *30*, 136.

42. Braquet, P.; Esanu, A.; Etienne, A.; Robin, J.P. In *Proceedings of the First Sandoz Research Symposium*, "New Horizons in Platelet - activating Factor Research," Winslow, C.M.; Lee, M.L., Ed.; J. Wiley: London, 1987.

43. Okamoto, M.; Yoshida, K.; Nishikawa, M.; Ando, T.; Iwami, M.; Kohsaka, M.; Aoki, H. *J. Antibiot.* **1986**, *39*, 198.

44. Okamoto, M.; Yoshida, K.; Uchida, I.; Kohsaka, M.; Aoki, H. *Chem. Pharm. Bull.* **1986**, *34*, 345.

45. Okamoto, M.; Yoshida, K.; Uchida, I.; Nishikawa, M.; Kohsaka, M.; Aoki, H. *Chem. Pharm. Bull.* **1986**, *34*, 340.

46. Biftu, T.; Gamble, N.F.; Doebber, T.; Hwang, S.-B.; Shen, T.-Y.; Snyder, J.; Spring, J.P.; Stevenson, R. *J. Med. Chem.* **1986**, *29*, 1917.

47. Biftu, T.; Hwang, S.-B.; Doebber, T.W.; Beattie, T.R.; Shen,T.-Y. European Patent Appl. EP 199324; *Chem. Abstr.* **1987**, *106*, 50026r.

48. Hwang, S.-B.; Lam, L.-H.; Biftu,T.; Beatti, T.R.; Shen, T.-Y. *J. Biol. Chem.* **1985**, *260*, 15639.

49. Tahraoui, L.; Floch, A.; Mondot, S.; Cavero, I. *Mol. Pharmacol.* **1988**, *34*, 145.

50. Junier, M.P.; Tiberghien, C.; Rougeot, C.; Fafeur, V.; Dray, F. *Endocrinology* **1988**, *123*. 72.

51. O'Donnell, S.R.; Barnett, C.J.K. *Br. J. Pharmacology* **1988**, *94*, 437.

52. Ward, S.G.; Westwick, J. *Br. J. Pharmacology* **1988**, *93*, 769.

53. Vercellotti, G.M.; Yin, H.Q.; Gustafson, K.S.; Nelson, R.D.; Jacob, H.S. *Blood* **1988**, *71*, 1100.

54. Myers, A.K.; Nakanishi, T.; Ramwell, P. *Prostaglandins* **1988**, *35*, 447.

55. Marquis, O.; Robaut, C.; Cavero, I. *J. Pharmacol. Exp. Ther.* **1988**, *244*, 709.

56. Robaut, C.; Durand, G.; James, C.; Lave, D.; Cavero, I.; LeFur, G. *Biochem. Pharmacol.* **1987**, *36*, 3221.

57. Sonenberg, M.; Huang, J.T.; Ren, Y.F.; Su, T.L.; Watanabe, K.A.; Haspel, H.C.; Crin, R.E.; Hoffer, A.P. *Contraception* **1988**, *37*, 247.

58. Corey, E.J.; Bakshi, R.K.; Shibata, S.; Chen, C.-P.; Singh, V.K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

59. Corey, E.J.; Chen, C.P.; Parry, M.J. *Tetrahedron Lett.* **1988**, *29*, 2899.

60. Pompipom, M.M.; Hwang, S.-B.; Doebber, T.W.; Acton, J.J.; Alberts, A.W.; Biftu, T.; Brooker, D.R.; Bugianesi, R.L.; Chabala, J.C.; Gambler, N.L.; Graham, D.W.; Lam, M.- L.; Wu, M.S. *Biochem. Biophys. Res. Commun.* **1988**, *150*, 1213.

61. a) Prashad, M.; Tomesch, J.C.; Wareing, J.R.; Smith, H.C.; Cheon, S.H. *Tetrahedron Lett.* **1989**, *30*, 2877; b) Prashad, M.; Tomesch, J.C.; Shapiro, M.J. *Tetrahedron Lett.* **1989**, *30*, 4757.

62. Heck, R.F. *Organomet. Chem. Synth.* **1972**, *1*, 455.

63. Larock, R.C.; Baker, B.E. *Tetrahedron Lett.* **1988**, *29*, 905.

64. Abelman, M.M.; Oh, T.; Overman, L.E. *J. Org. Chem.* **1987**, *52*, 4130.

65. Baker, B.E., Ph.D. Dissertation, Iowa State University, 1988.

66. Larock, R.C.; Gong, W. *Tetrahedron Lett.* **1989**, *30*, 2603.

67. Corey, E.J.; Suggs, J.W. *Tetrahedron Lett.* **1975**, 2647.

68. Uemura, S.; Miyoshi, H.; Okano, M. *J. Chem. Soc., Perkin Trans. I* **1980**, 1098.

69. Suzuki, H.; Kondo, A.; Inouye, M.; Ogawa, T. *Synthesis* **1986**, 121.

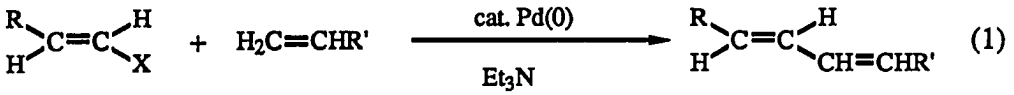
70. Janssen, D.E.; Wilson, C.V. *Organic Synth. Coll. Vol. 4,* **1963,** 547.

71. Barton, D.H.R.; Lacher, B.; Zard, S.Z. *Tetrahedron* **1987,** *43,* 4321.

PART III. PALLADIUM-CATALYZED INTERMOLECULAR VINYLATION OF CYCLIC ALKENES

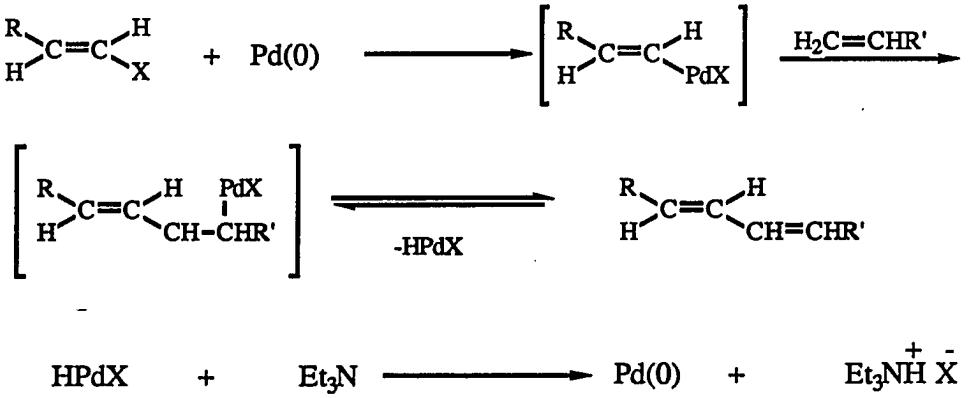
INTRODUCTION

There are many examples of palladium(0)-catalyzed cross-coupling reactions of vinylic halides and acyclic alkenes (eq 1).[1-3] This reaction (Scheme I) begins by oxidative



(1)

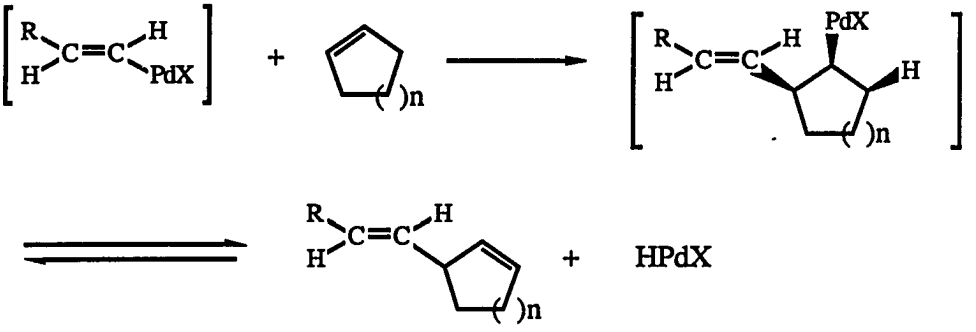
Scheme I



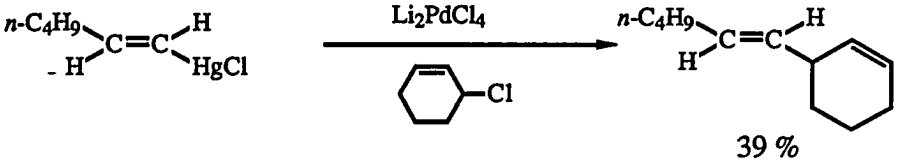
addition of a vinylic halide onto zerovalent Pd to afford a reactive alkenyl-palladium halide species. The latter then adds in a *syn* 1,2-fashion across the double bond of an acyclic alkene to afford a new, σ-organopalladium species, followed by bond rotation so that a β-hydrogen is *cis* to the palladium, and subsequent *syn* elimination of palladium hydride affords the 1,3-diene.

When cyclic alkenes are employed, no bond rotation is possible after the 1,2-addition. Thus, there is a *syn* elimination of palladium hydride away from the vinylic group to afford only 1,4-diene (Scheme II).

Scheme II



There are comparatively fewer examples of the Pd-mediated or catalyzed vinylation of cyclic alkenes, and these few examples will now be discussed. Larock, Bernhardt, and Driggs[4] reacted 3-chlorocyclohexene with (*E*)-1-butenylmercuric chloride catalyzed by Li_2PdCl_4 to afford (*E*)-1-(3-cyclohexenyl)hexene in fair yield (eq 2). This

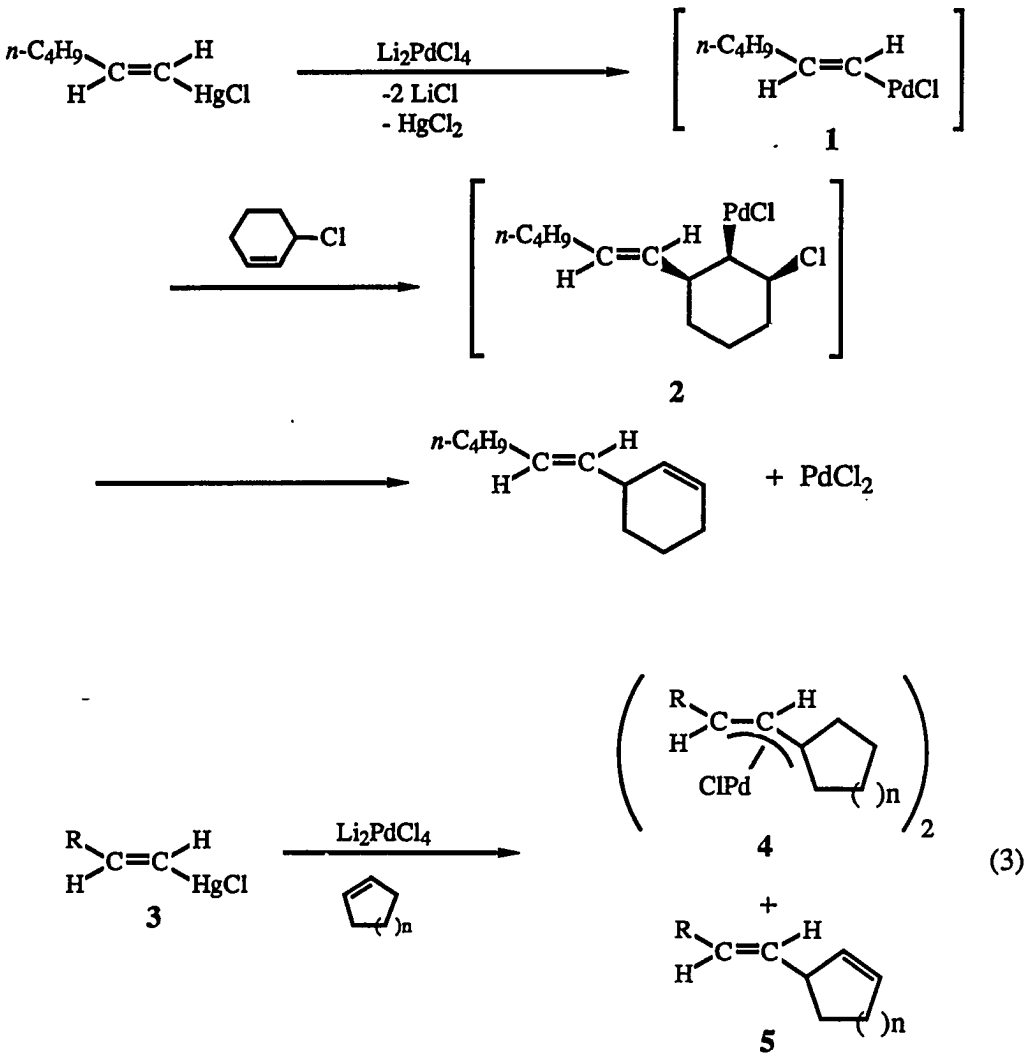


39 % (2)

interesting reaction (Scheme III) begins with a transmetallation reaction between the vinylmercurial and $PdCl_4^{2-}$ to generate a vinylpalladium species **1**. The latter then adds in a *syn* 1,2-fashion to the double bond of the allylic chloride to generate **2**, which eliminates $PdCl_2$ to afford the 1,4-diene. The mechanism suggests that this reaction is catalytic in Pd(II) and in fact it is.

Larock and Takagi[5] observed that 1,4-dienes **5** were formed as side products in their synthesis of π-allylpalladium complexes **4** from the reaction of a vinylmercurial, Li_2PdCl_4, and cyclic alkenes (eq 3). Furthermore, Larock observed that when the reaction

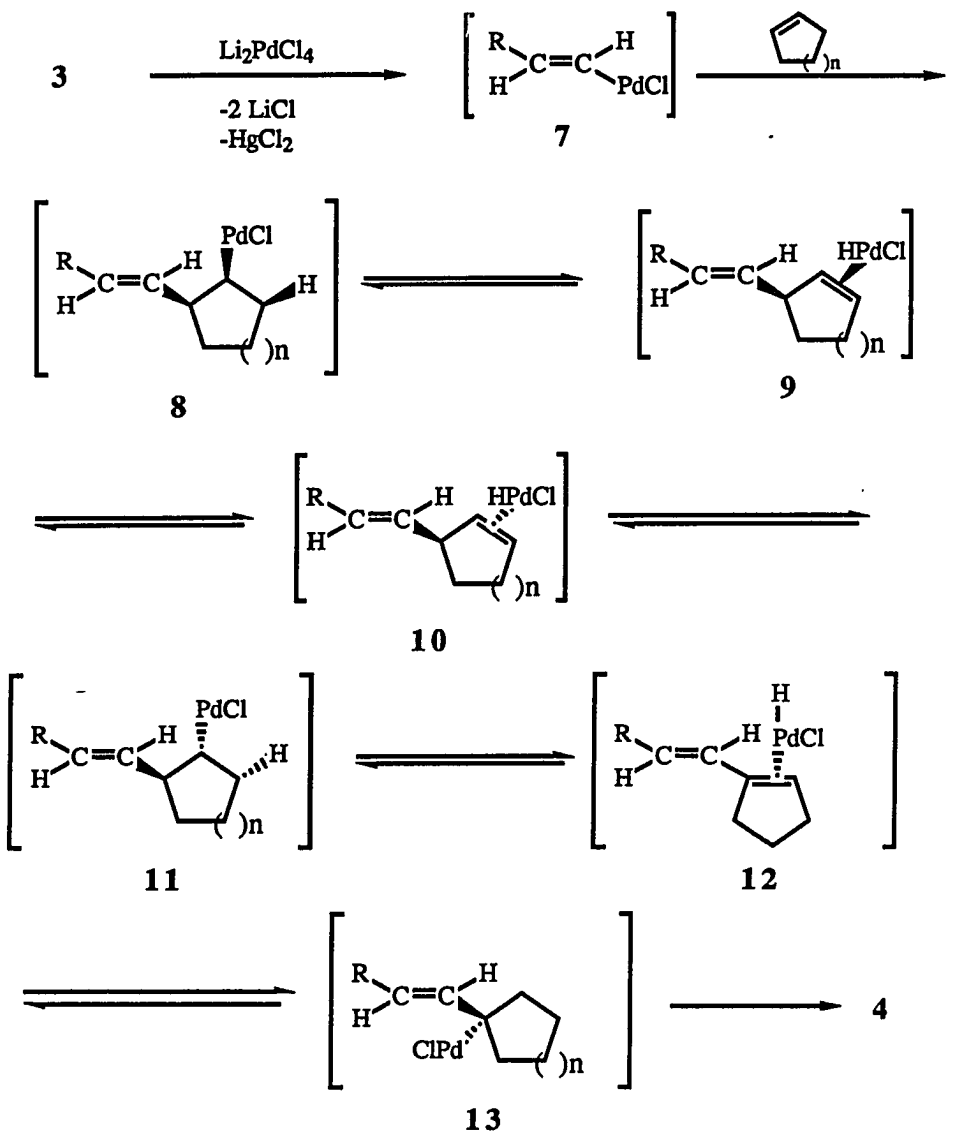
Scheme III



(3)

is run in the presence of Et_3N, 1,4-dienes were formed exclusively. The mechanism for the formation of **4** is interesting and deserves additional attention (Scheme IV). The reaction begins with a transmetallation reaction between the vinylmercurial and $PdCl_4^{2-}$ to generate vinylpalladium species **7**. The latter then adds in a *syn* 1,2-fashion to the double bond of the cyclic alkene to afford an alkylpalladium species **8**, which eliminates

Scheme IV



palladium hydride to generate a π-complex **9**. The latter then dissociates, and the palladium hydride complexes to the face of the alkene opposite to the vinyl group to afford π-complex **10**. Through a series of elimination and re-addition reactions of palladium

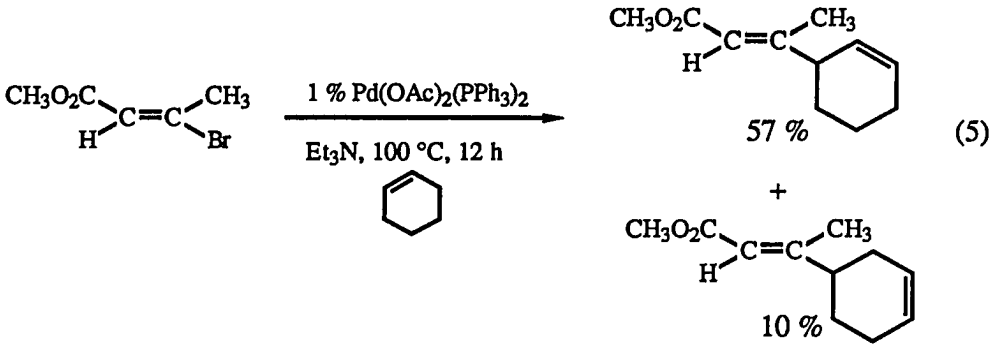
hydride, σ-allylpalladium chloride **13** is finally generated, and the latter then collapses to the stable π-allylpalladium complex **4**.

The formation of **5** presumably came from the decomposition of π-complex **9** or **10** (eq 4). Larock postulated that the addition of a good ligand or base such as Et_3N to

(4)

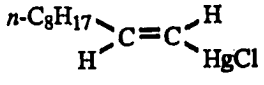
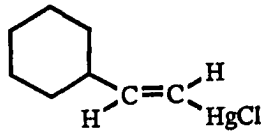
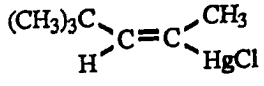
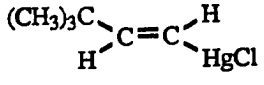
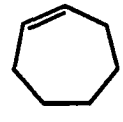
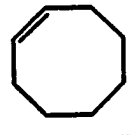
destroy the π-complex or neutralize the HCl generated from the reductive elimination of palladium hydride would increase the rate of formation of **5**. Table 1 summarizes the results of Larock and Takagi's efforts. Only **5** is generated in the presence of Et_3N (entries 4 and 7). In the absence of this base, the rate of formation of **4** is competitive to that of **5**. Cyclopentene and cycloheptene afford high yields of 1,4-diene (entries 2, 4, 7, and 9). Cyclooctene is relatively unreactive (entry 10), and cyclohexene proved to be inert (entry 8).

There are only two examples of the Pd(0)-catalyzed vinylation of cyclic alkenes affording the corresponding 1,4-diene. Kim et al.[6] reported a cross-coupling reaction between a vinylic bromide and cyclohexene (eq 5).

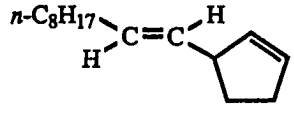
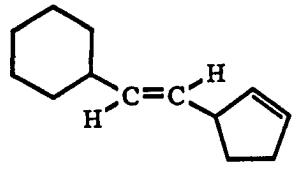
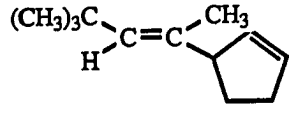
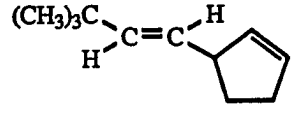
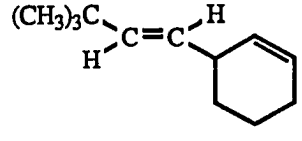
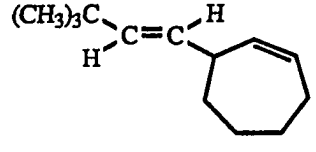
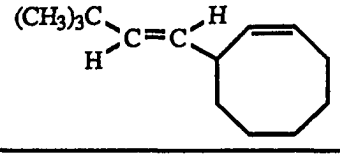


(5)

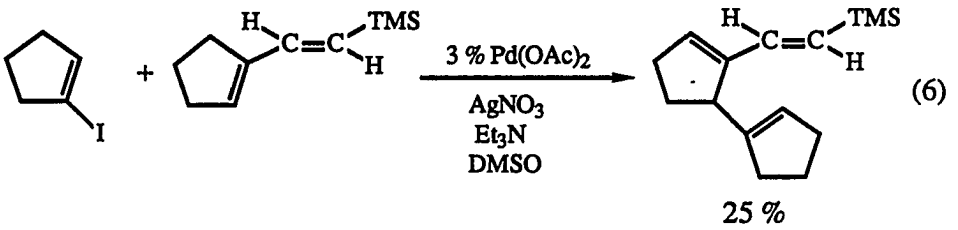
Table 1. Palladium-assisted vinylation of cyclic alkenes

Entry	Organomercurial	Cyclic Alkene	Base
1			none
2			Et_3N
3			none
4			Et_3N
5			none
6			none
7			Et_3N
8			Et_3N
9			Et_3N
10			Et_3N

[a] Yields in parentheses are GC yields.

Product	Yield (%) [a]
	20 66 (96)
	23 (84)
	10
	0 66 (96)
	3
	67
	18

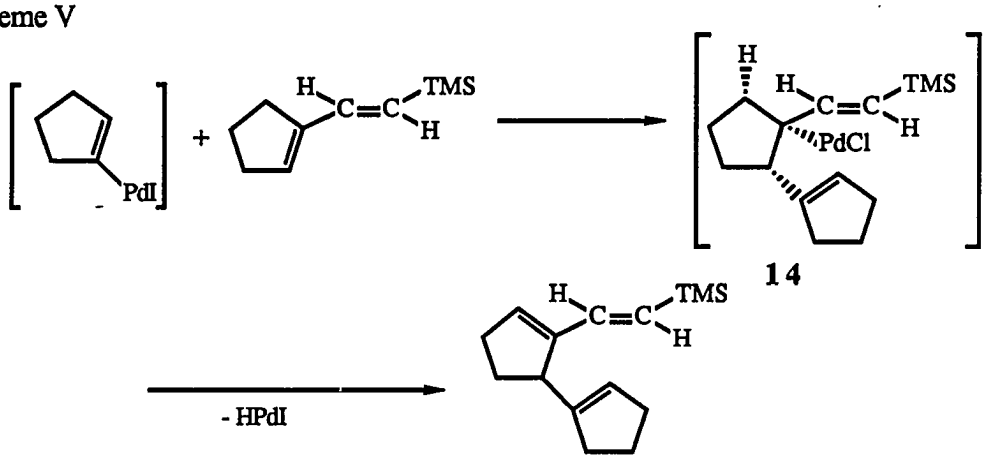
Karabelas and Hallberg[7] reported a cross-coupling between 1-iodo-1-cyclopentene and a trmethylvinylsilane (eq 6). Interestingly, a σ-allylpalladium intermediate **14** was



(6)

proposed in this reaction mechanism, but surprisingly, there wasn't any π-allylpalladium species generated in this reaction (Scheme V).

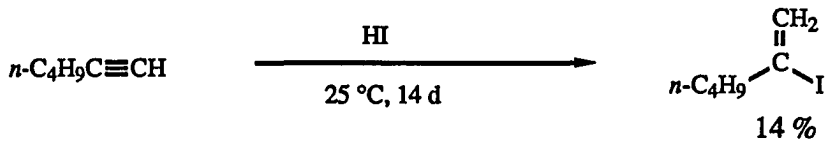
Scheme V



Inspite of the potential usefulness of this Pd-based process for generating a variety of 1,4-dienes, the vinylation of cyclic alkenes hasn't been fully explored by anyone. This fact prompted this author to explore the scope and limitations of this important methodology, and the results of this investigation are now reported.

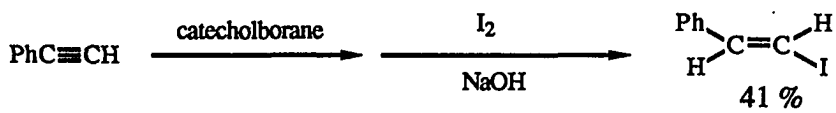
RESULTS AND DISCUSSION

All vinylic iodides and triflates employed in this investigation were synthesized in the following manner. 2-Iodo-1-hexene was prepared from 1-hexyne using the published procedure of Kim, Patel, and Heck[6] (eq 7). (*E*)-2-Iodostyrene was prepared from phenyl-



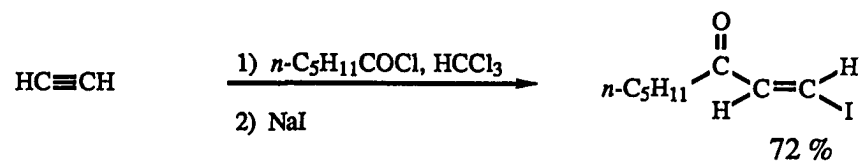
(7)

acetylene using the published procedure of Brown, Hamaoka, and Ravindran[8] (eq 8).



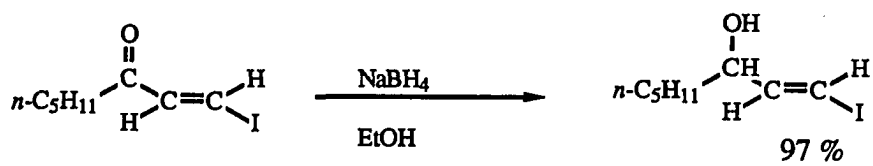
(8)

(*E*)-1-Iodo-1-octen-3-one[9] was prepared from the reaction of acetylene and hexanoyl chloride followed by NaI[10] (eq 9). (*E*)-1-Iodo-1-octen-3-ol[10] was prepared from the



(9)

reaction of the corresponding enone with $NaBH_4$ (eq 10). 1-Iodo-2-methylpropene[11] was

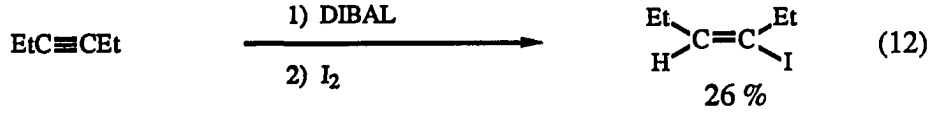


(10)

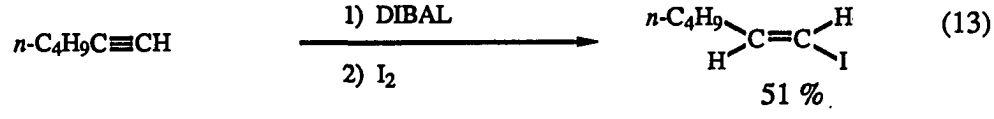
prepared from the reaction of the corresponding vinylic bromide and Mg turnings in THF followed by I_2 (eq 11). (*E*)-3-Iodo-3-hexene, (*E*)-1-iodo-1-hexene, and (*E*)-3,3-

(11)

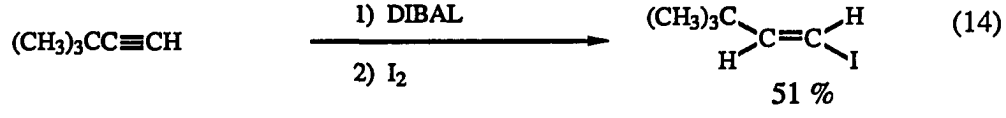
dimethyl-1-iodo-1-butene[12] were all prepared by the hydroalumination-iodination of the corresponding alkynes (eqs 12 - 14). (*Z*)-1-Iodo-1-hexene was prepared from 1-hexyne



(12)

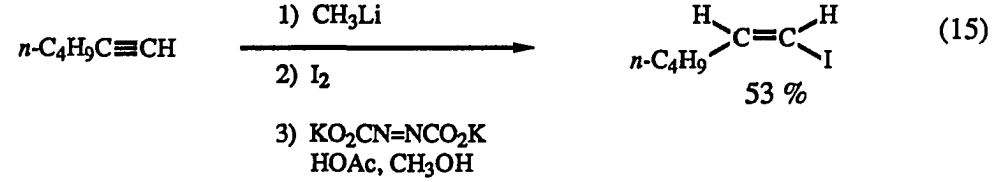


(13)



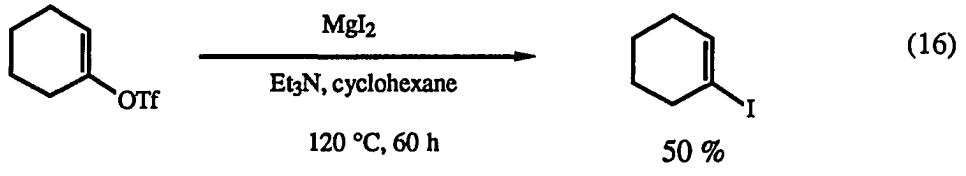
(14)

using the published procedure of Dieck and Heck[13] (eq 15). 1-Iodo-1-cyclohexene was



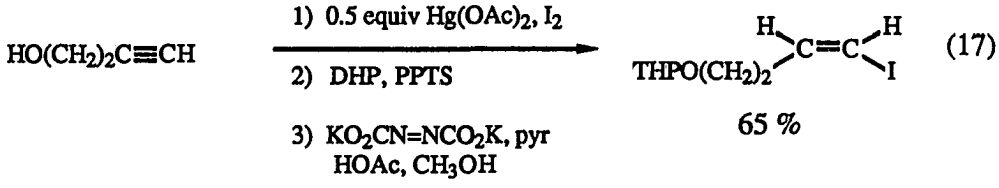
(15)

prepared from the corresponding triflate using a procedure developed by Martinez, Alvarez, and Fraite[14] (eq 16). (*Z*)-1-Iodo-4-(2-tetrahydropyranoxy)-1-butene[15-17] was



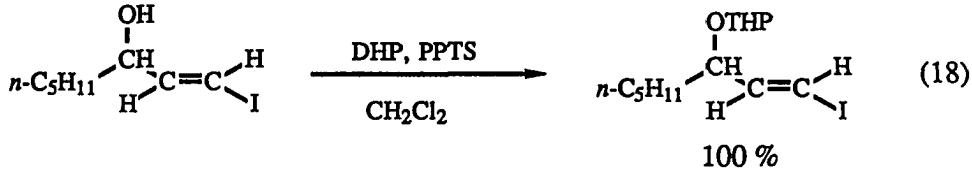
(16)

prepared from 3-butyn-1-ol (eq 17). (*E*)-1-Iodo-3-(2-tetrahydropyranoxy)-1-octene[16]



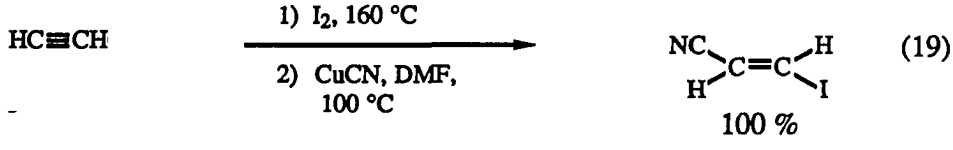
(17)

was prepared from the corresponding alcohol and 3,4-dihydro-2*H*-pyran (eq 18). *Trans*-



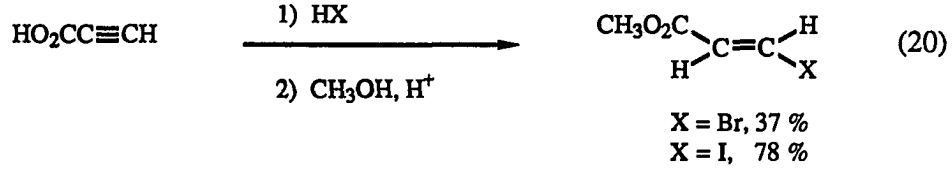
(18)

β-iodoacrylonitrile[18] was prepared from iodine and acetylene followed by CuCN (eq 19).



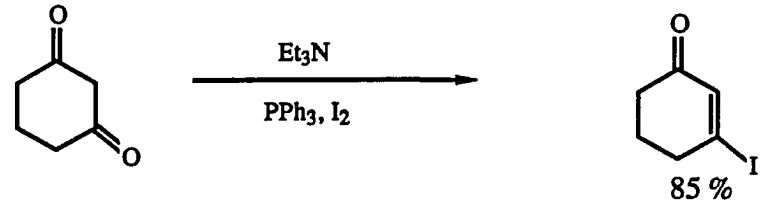
(19)

Methyl (*E*)-3-bromopropenoate and the corresponding vinylic iodide[19] were prepared from the reaction of propiolic acid and the appropriate aqueous hydrohalic acid (eq 20). 3-



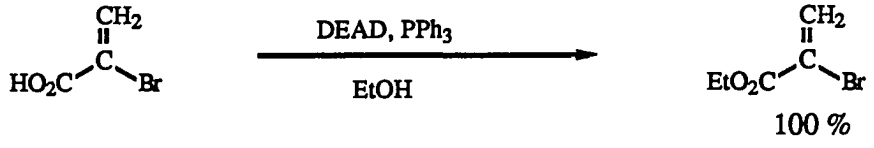
(20)

Iodo-2-cyclohexen-1-one was prepared from the reaction of 1,3-cyclohexanedione using a procedure developed by Piers and Nagakura[20] (eq 21). Ethyl 2-bromopropenoate[21] was



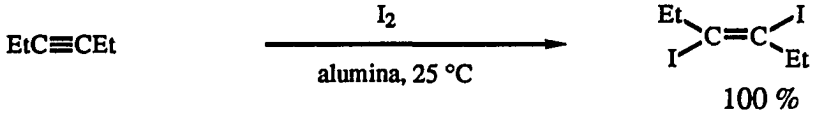
(21)

prepared from 2-bromopropenoic acid, DEAD, PPh_3, and EtOH (eq 22). (*E*)-1,2-

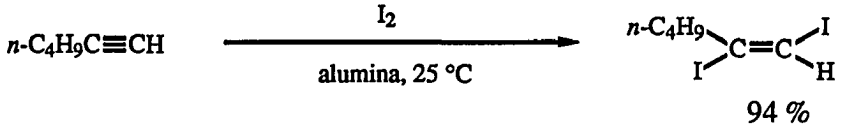


(22)

Diiodo-3-hexene and (*E*)-1,2-diiodo-1-hexene were prepared from 3-hexyne and 1-hexyne, respectively, using a procedure developed by Larson, Luidhardt, Kabalka, and Pagni[22] (eqs 23 and 24). 2-Bromo-2-cyclohexen-1-one[23] was prepared from 2-

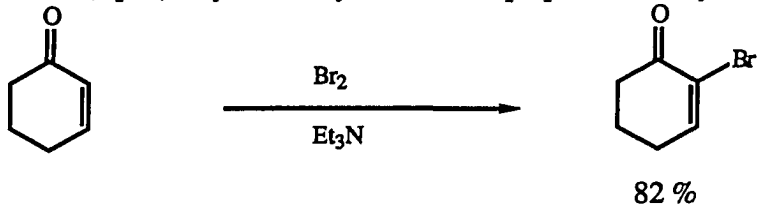


(23)



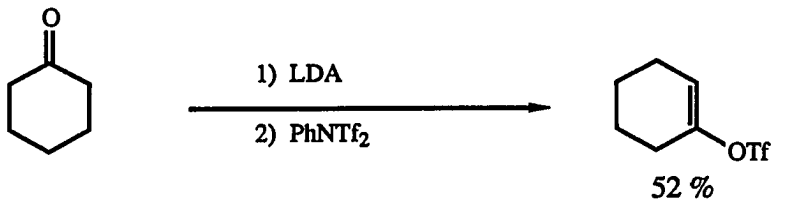
(24)

cyclohexen-1-one (eq 25). Cyclohexenyl triflate was prepared from cyclohexanone using



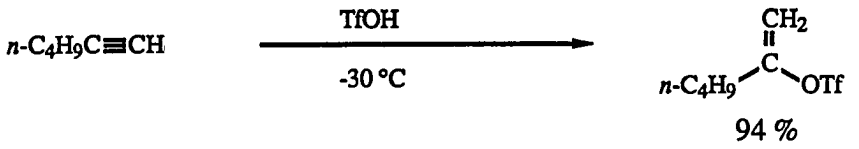
(25)

the published procedure of McMurray and Scott[24] (eq 26). 2-Hexenyl triflate was



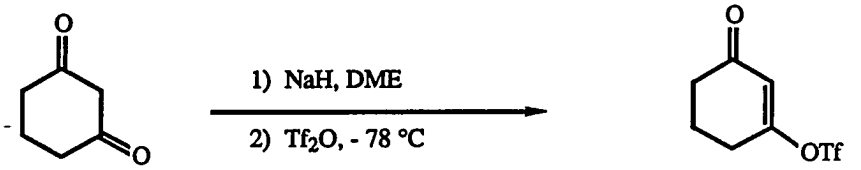
(26)

prepared from 1-hexyne using the published procedure of Summerville, Senklar, Schleyer, Dueber, and Stang[25] (eq 27). 3-(Trifluoromethylsulfonyloxy)cyclohex-2-en-1-



(27)

one was prepared from 1,3-cyclohexanedione using the procedure developed by Martinez, Alvarez, Casado, Subramanian, and Hanack[26] (eq 28).



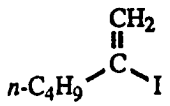
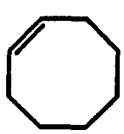
(28)

Vinylic iodides bearing electron-donating groups, as well as vinylic iodides bearing electron-withdrawing groups, were studied. Cycloalkenes of ring size 5 through 8, as well as 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran, were employed in this study to determine the scope and limitations of this Pd(0)-catalyzed process. Three different Pd(0) procedures were studied: procedure A[27] (2.5 mol % $Pd(OAc)_2$, 1 equiv TBAC, 3 equiv KOAc or NaOAc, DMF, at 25 °C or 80 °C), procedure B[28,29] (3.0 mol % $Pd(OAc)_2$, 9.0 mol % PPh_3, 2.0 equiv Ag_2CO_3, CH_3CN at 25 °C or 80 °C), and procedure C[29] (procedure A plus 2.5 mol % PPh_3).

Initially, all reactions were conducted at 25 °C, and at 80 °C if the reaction at the former temperature was too sluggish. The results of this investigation are summarized in Table 2. The following observations have been made in the course of this investigation. Using procedure A, simple alkyl-containing vinylic iodides react sluggishly at 25 °C, but when the reactions are heated to 80 °C, the reactions easily go to completion. Cyclopentene is the most reactive of all the alkenes employed in this investigation as it produced cross-coupled products even at room temperature, and good to excellent yields of 1,4-dienes are generally obtained. Cycloheptene has proven less reactive and tends to produce bad mixtures of 1,4-and 1,5-dienes. The latter product presumably arises from the readdition of HPdI to the alkene and elimination to afford the 1,5-diene. Cyclooctene is unreactive and gives bad mixtures usually containing several products. Cyclohexene and 3,4 - dihydro-2*H*-pyran are essentially inert. 2,3-Dihydrofuran produces two to three different products. The more highly substituted the vinylic iodide is, the slower the reaction (entries 43 - 48). In these cases, the fact that (*E*)-1-iodo-2-methylpropene and (*E*)-3-iodo-3-hexene are also unstable at 80 °C may also explain why many unidentified products and none of the 1,4-dienes were produced.

Certain functional groups also appeared to inhibit the reaction. For example (*E*)-1-iodo-1-octen-3-ol (entries 38 - 42) and *trans*-β-iodoacrylonitrile (entries 102 - 105) apparently inhibited the cross-coupling reaction. When the former vinylic iodide was converted to a THP ether, the desired product was produced in good yields (entries 97 - 101). If the alkyl group is rather large, the reaction tends to be slower and the yield of the 1,4-diene is also lower (entries 77 and 78).

Table 2. Palladium(0)-catalyzed intermolecular vinylation of cyclic alkenes

Entry	Vinylic Halide	Cyclic Alkene	Base	Procedure[a]
1			KOAc	A
2			NaOAc	A
3			KOAc	A
4			NaOAc	A
5			Ag_2CO_3	B
6			KOAc	A
7			NaOAc	A
8			Ag_2CO_3	B
9			KOAc	A
10			NaOAc	A
11			Ag_2CO_3	B

[a] See text for explanation of procedures.
[b] All ratios reflect the ratio of 1,4- to 1,5-dienes.
[c] Ratio was determined by gas chromatography.
[d] Some 2-butyl-1-octene-3-yne was also observed.

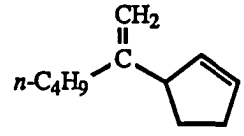
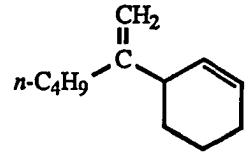
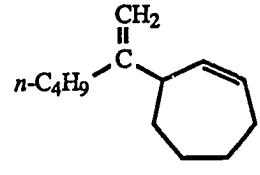
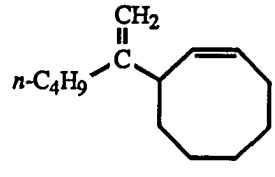
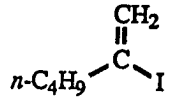
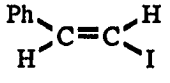
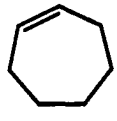
Time (h)	Temp (°C)	Product [b]		Yield (%)
216	25			56
216	25			71
216	25			0
216	25			0
24	80			0
48	25		(1 : 1)	10 [c,d]
48	25		(2 : 1)	10 [c,d]
24	80			81
24	80			0
24	80			0
24	80			0

Table 2. (continued)

Entry	Vinylic Halide	Cyclic Alkene	Base	Procedure[a]
12			Ag_2CO_3	B
13			KOAc	A
14			NaOAc	A
15			KOAc	A
16			NaOAc	A
17			KOAc	A
18			NaOAc	A
19			KOAc	A
20			NaOAc	A
21			Ag_2CO_3	B
22			KOAc	A
23			NaOAc	A
24			KOAc	A
25			NaOAc	A

[e] 5 % $Pd(OAc)_2$ was employed in this reaction.
[f] Only vinylic iodide and its dimer were recovered.

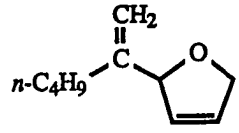
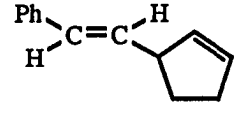
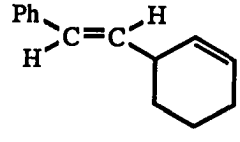
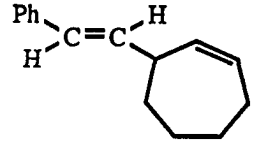
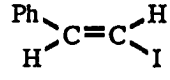
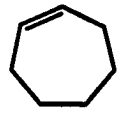
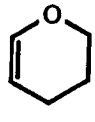
Time (h)	Temp (°C)	Product [b]		Yield (%)
24	80			42
168	25			77
168	25			94
216	25			0
216	25			0
216	80			0
216	80			0
216	80			0 [e,f]
216	80			0 [e,f]
48	80			47
216	25			0
216	25			0
48	80		(3 : 1)	94
48	80		(1 : 1)	80

Table 2. (continued)

Entry	Vinylic Halide	Cyclic Alkene	Base	Procedure[a]
26			Ag_2CO_3	B
27			KOAc	A
28			NaOAc	A
29			KOAc	A
30			NaOAc	A
31			Ag_2CO_3	B
32			KOAc	A
33			NaOAc	A
34			Ag_2CO_3	B
35			KOAc	A
36			NaOAc	A
37			Ag_2CO_3	B

[g] Two isomers of mono-vinylated and two isomers of bis-vinylated cyclooctene were observed by GC/MS. The yield was not determined.

[h] A trace of the symmetrical 1,3-diene was also produced.

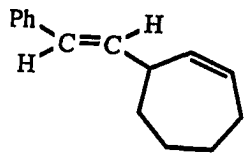
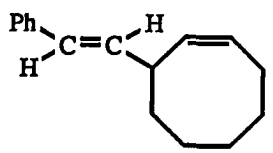
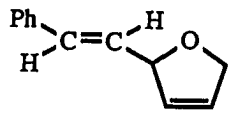
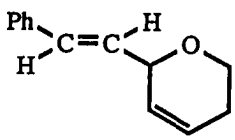
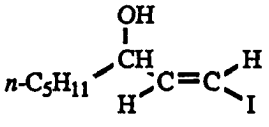
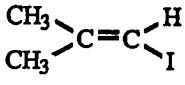
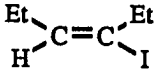
Time (h)	Temp (°C)	Product [b]	Yield (%)
24	80		86
216	25		0
216	25		0
48	80		--- [g]
48	80		--- [g]
48	80		0
24	80		68 [h]
24	80		60 [h]
24	80		52
96	80		0
96	80		0
48	80		34

Table 2. (continued)

Entry	Vinylic Halide	Cyclic Alkene	Base	Procedure[a]
38			KOAc	A
39			NaOAc	A
40			KOAc	A
41			NaOAc	A
42			Ag_2CO_3	B
43			KOAc	A
44			NaOAc	A
45			KOAc	A
46			NaOAc	A
47			KOAc	A
48			NaOAc	A
49			KOAc	A
50			NaOAc	A

[i] Only the dimer of the vinylic iodide was observed.

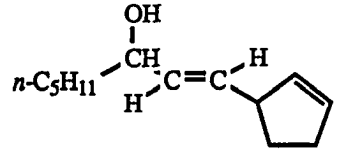
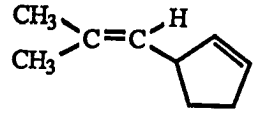
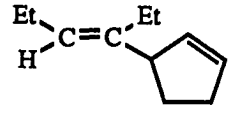
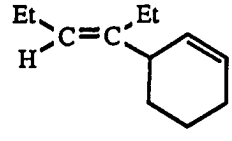
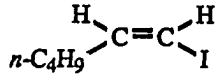
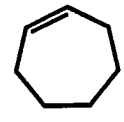
Time (h)	Temp (°C)	Product [b]	Yield (%)
216	25		0
216	25		0
96	80		0
96	80		0
96	80		0
96	80		0
96	80		0
216	25		0
216	25		0
24	80		--- i
24	80		--- i
24	80		--- i
24	80		--- i

Table 2. (continued)

Entry	Vinylic Halide	Cyclic Alkene	Base	Procedure[a]
51			KOAc	A
52			NaOAc	A
53			KOAc	A
54			NaOAc	A
55			KOAc	A
56			KOAc	A
57			KOAc	A
58			KOAc	A
59			NaOAc	A
60			Ag_2CO_3	B
61			KOAc	A
62			NaOAc	A
63			Ag_2CO_3	B
64			Ag_2CO_3	B

[j] HMPA was employed as the solvent in this reaction.

[k] CH_3CN was employed as the solvent in this reaction.

[l] A combination of HMPA / CH_3CN / DMF (1 : 1 : 1) was employed as the solvent in this reaction.

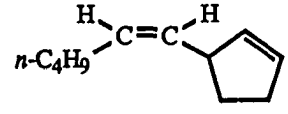
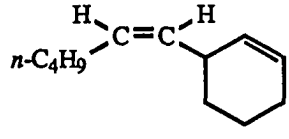
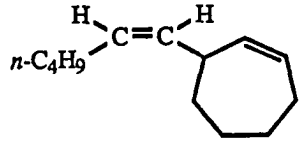
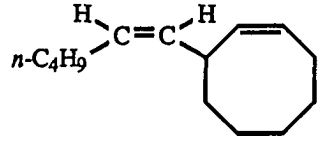
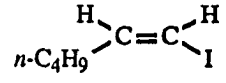
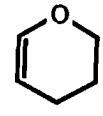
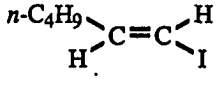
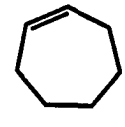
Time (h)	Temp (°C)	Product [b]	Yield (%)
216	25		96
216	25		77
24	80		66
24	80		17
48	80		87 [j]
48	80		96 [k]
48	80		87 [l]
216	80		0
216	80		0
24	80		55
216	25	 (1 : 1)	60
216	25	(1 : 1)	56
24	80		81
48	80		0

Table 2. (continued)

Entry	Vinylic Halide	Cyclic Alkene	Base	Procedure[a]
65			Ag_2CO_3	B
66			Ag_2CO_3	B
67			KOAc	A
68			Ag_2CO_3	B
69			Ag_2CO_3	B
70			Ag_2CO_3	B

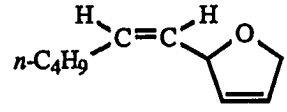
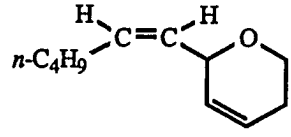
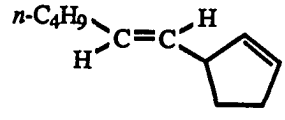
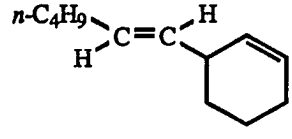
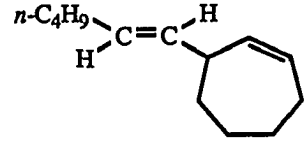
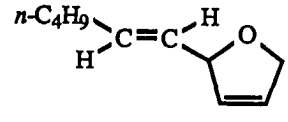
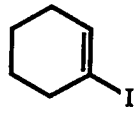
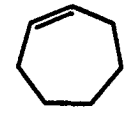
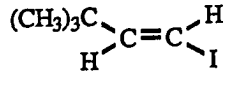
Time (h)	Temp (°C)	Product [b]	Yield (%)
24	80		51
48	80		0
24	80		79
48	80		51
24	80		88
24	80		43

Table 2. (continued)

Entry	Vinylic Halide	Cyclic Alkene	Base	Procedure[a]
71			KOAc	A
72			NaOAc	A
73			KOAc	A
74			NaOAc	A
75			Ag_2CO_3	B
76			Ag_2CO_3	B
77			KOAc	A
78			NaOAc	A
79			Ag_2CO_3	B

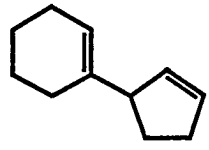
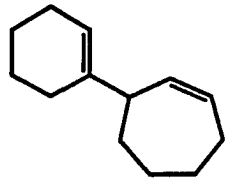
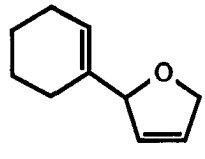
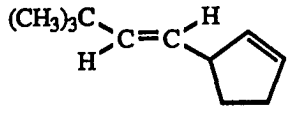
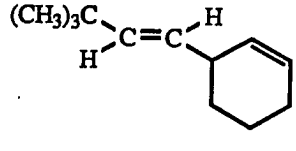
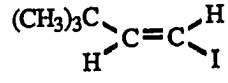
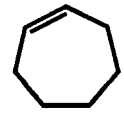
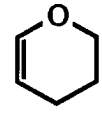
Time (h)	Temp (°C)	Product [b]	Yield (%)
72	25		66
72	25		61
72	25		61 [k]
72	25		56 [k]
24	80		37
24	80		58
72	80		62
72	80		45
24	80		0

Table 2. (continued)

Entry	Vinylic Halide	Cyclic Alkene	Base	Procedure[a]
80			KOAc	A
81			NaOAc	A
82			Ag_2CO_3	B
83			KOAc	A
84			NaOAc	A
85			Ag_2CO_3	B
86			KOAc	A
87			NaOAc	A
88			Ag_2CO_3	B
89			KOAc	A
90			NaOAc	A
91			Ag_2CO_3	B

[m] A mixture of many inseparable products was observed.

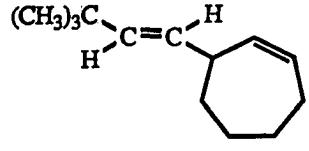
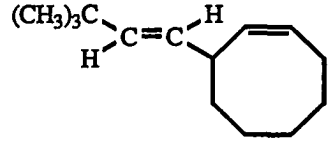
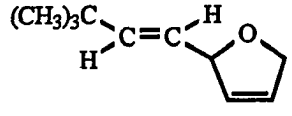
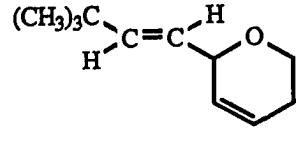
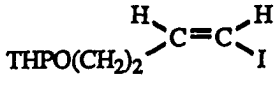
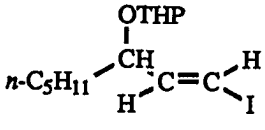
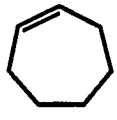
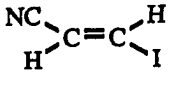
Time (h)	Temp (°C)	Product [b]		Yield (%)
48	80		(1 : 1)	86
48	80		(1 : 1)	63
24	80			65
96	80			--- g
96	80			--- g
48	80			--- g
24	80			--- m
24	80			--- m
24	80			52
96	80			0
96	80			0
72	80			34

Table 2. (continued)

Entry	Vinylic Halide	Cyclic Alkene	Base	Procedure[a]
92			KOAc	A
93			NaOAc	A
94			KOAc	A
95			NaOAc	A
96			Ag_2CO_3	B
97			KOAc	A
98			NaOAc	A
99			KOAc	A
100			NaOAc	A
101			Ag_2CO_3	B
102			KOAc	A
103			NaOAc	A

[n] A complex mixture of diastereomers was afforded.

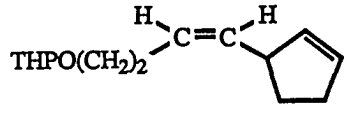
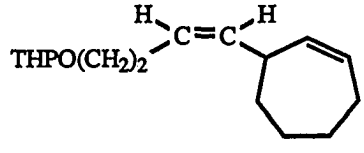
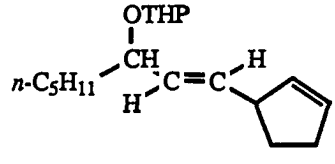
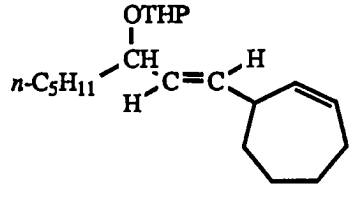
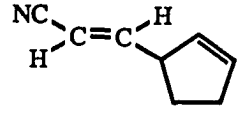
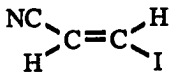
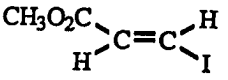
Time (h)	Temp (°C)	Product(s)		Yield (%)
96	80			79 [n]
96	80			49 [n]
48	80		(1 : 1)	100 [n]
48	80		(1 : 1.5)	75 [n]
24	80		(1 : 1.5)	86 [n]
72	80			74 [n]
72	80			60 [n]
48	80		(1 : 3)	98 [n]
48	80		(1 : 2)	80 [n]
48	80			77 [n]
72	25			0
72	25			0

Table 2. (continued)

Entry	Vinylic Halide	Cyclic Alkene	Base	Procedure[a]
104			KOAc	A
105			NaOAc	A
106			KOAc	A
107			NaOAc	A
108			CsOAc	A
109			KOAc	A
110			NaOAc	A
111			KOAc	A
112			NaOAc	A
113			KOAc	A
114			NaOAc	A

[o] The ratio reflects the ratio of 1,3- to 1,4-diene.
[p] This diene was contaminated with an unknown product.

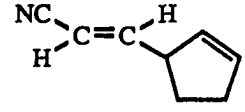
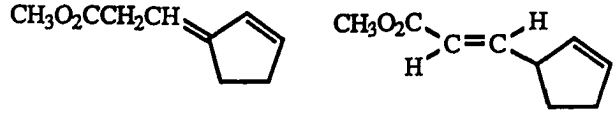
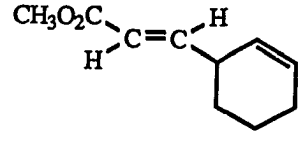
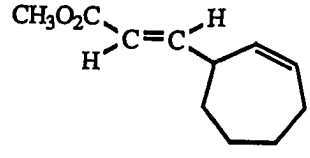
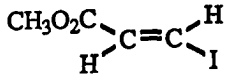
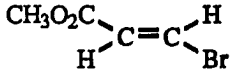
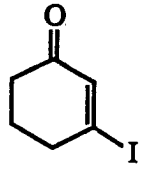
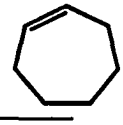
Time (h)	Temp (°C)	Product [b]	Yield (%)
72	80		0
72	80		0
48	25	 (1 : 12)	100 [o]
72	25	(1 : 2)	96 [o]
120	25	(1 : 99)	100 [o]
216	25		0
216	25		0
216	80		0
216	80		0
48	25		62 [p]
72	25		56 [p]

Table 2. (continued)

Entry	Vinylic Halide	Cyclic Alkene	Base	Procedure[a]
115			KOAc	A
116			NaOAc	A
117			Ag_2CO_3	B
118			KOAc	A
119			NaOAc	A
120			KOAc	A
121			NaOAc	A
122			CsOAc	A
123			Na_2CO_3	A
124			KOAc	A
125			NaOAc	A
126			KOAc	A

[q] Only a tarry substance was afforded in this reaction.

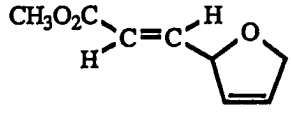
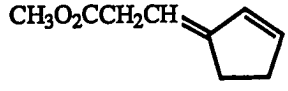
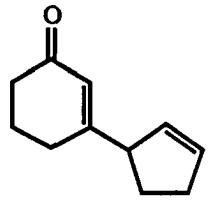
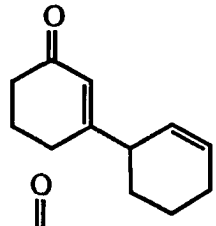
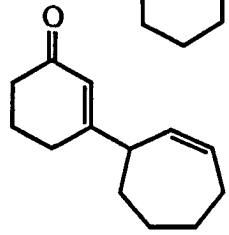
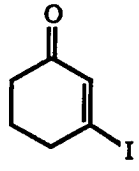
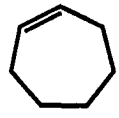
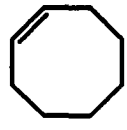
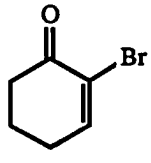
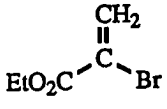
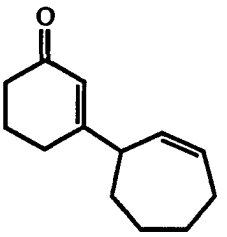
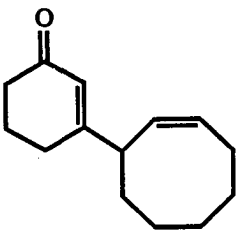
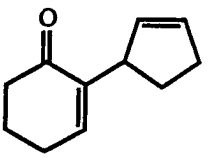
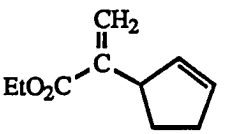
Time (h)	Temp (°C)	Product [b]		Yield (%)
24	25			--- m
24	80			--- m
24	25			--- m
24	25			100
24	25			96
3	25		(1 : 4)	23
3	25		(3 : 1)	66
20	25			--- q
24	25			--- q
192	80			0
192	80			0
72	25			0 q

Table 2. (continued)

Entry	Vinylic Halide	Cyclic Alkene	Base	Procedure[a]
127			NaOAc	A
128			KOAc	A
129			NaOAc	A
130			KOAc	A
131			KOAc	A

[r] Only 2-bromophenol was observed by GC-MS.

Time (h)	Temp (°C)	Product [b]	Yield (%)
72	25		--- [q]
120	25		--- [q]
120	25		--- [q]
24	25		0 [r]
24	25		33

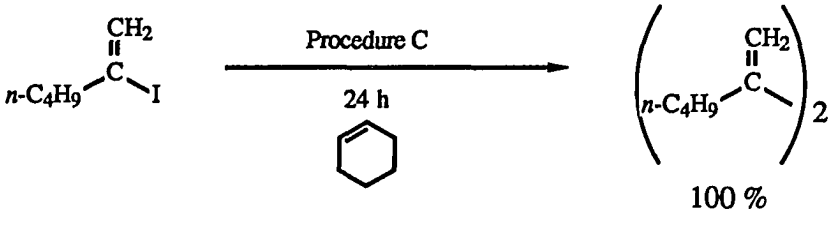
It is important to note that there is retention of stereochemistry in these reactions. For example, the reaction between (*Z*)-1-iodo-1-hexene and cyclopentene produced only the *cis* isomer (entries 51-57, 60-63, and 65).

Vinylic halides bearing electron-withdrawing groups ("activated vinylic halides") are more reactive in these reactions when using procedure A than vinylic iodides bearing electron-donating groups. In fact, activated vinylic bromides will even react with cyclopentene at 25 °C. Unfortunately, in almost all of these cases, mixtures of regioisomers are produced when cyclopentene is employed (entries 106-108, 120, and 121). This complication is so severe in several cases that the regioisomer is the major isomer produced (entries 106 and 107) and in one case, it is the exclusive isomer produced (entries 118 and 119). Larock and Baker[27] observed that CsOAc was effective in stopping the isomerization reaction in the synthesis of 3-phenylcyclooctene. Thus CsOAc was employed in entry 108. Unfortunately, the undesired isomer was produced with only a trace of the desired product. With methyl (*E*)-3-iodopropenoate, cycloheptene is less reactive than cyclopentene and tends to require a longer reaction period and bad mixtures of side products are also produced (entries 113 and 114).

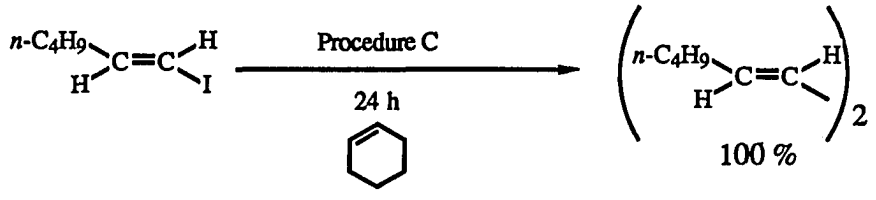
One example of the incompatibility of these "activated vinylic halides" with this process is the reaction of 2-bromo-2-cyclohexen-1-one with cyclopentene (entry 130). In this case, the sole product is 2-bromophenol. The mechanism of this unusal reaction presumably involves a Pd-catalyzed dehydrogenation process. Perhaps the only positive result coming from the reaction of an activated vinylic halide is in the reaction of ethyl 2-bromopropenoate with cyclopentene to produce only the desired product in 33 % yield (entry 131).

Procedure B solves many of the problems encountered with procedure A. For example, cyclohexene, which is inert when the latter procedure was employed, reacted smoothly with alkyl-containing vinylic iodides under the conditions of procedure B to produce the desired 1,4-diene in a short period of time (entries 21, 60, and 68). As reported by Larock, Gong, and Baker,[29] procedure B when employed with aryl halides inhibited the formation of regioisomers arising from palladium hydride re-addition to the 3-aryl cycloalkene. In this investigation, procedure B also effectively suppressed the isomerization reaction associated with the vinylation of cycloheptene (entries 8, 26, 63, 75, and 82), 2,3-dihydrofuran (entries 12, 34, 65, 76, and 88), and 3,4-dihydro-2*H*-pyran (entries 37 and 91) when using procedure A. The only exception appears to be entry 96 in which two isomers were produced! Currently, there is no good explanation for this observation. Procedure B was ineffective in promoting the vinylation of cyclooctene, as this alkene was once again too inert to produce any desired product (entries 11, 31, 64, and 85). Procedure B also proved to be ineffective in overcoming the difficulties encountered when activated vinylic halides were employed as vinylating agents, as they are easily dimerized to symmetrical 1,3-dienes under these reaction conditions.

Procedure C was briefly investigated as an alternative to procedure B since the latter employs expensive Ag_2CO_3. Preliminary results indicated that only the symmetrical dimers of the vinylic iodides were formed as observed by GC-MS (eqs 27 and 28). A



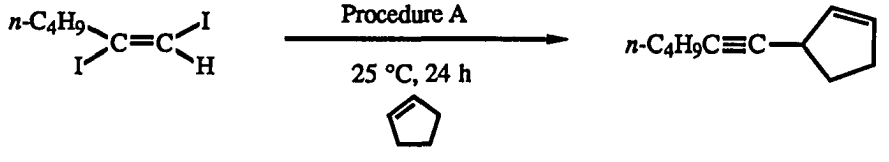
100 % (27)



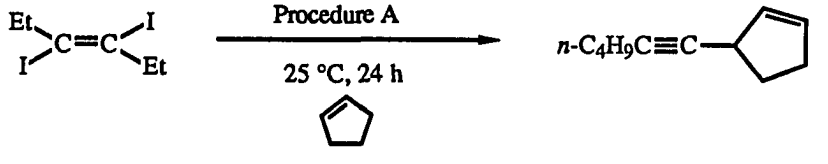
(28)

possible explanation is that the PPh_3 is somehow promoting the dimerization reaction since this phenomenon is not observed when using procedure A.

Vinylic diiodides were also investigated in this Pd-catalyzed process with hopes of obtaining triene products. While (*E*)-1,2-diiodo-1-hexene and (*E*)-3,4-diiodo-3-hexene reacted readily at 25 °C with cyclopentene using procedure A, a number of products were observed by GC/MS. What's stiking about this reaction is that the major product produced in both reactions is 1-(3-cyclopentenyl)hexyne (eqs 29 and 30). This compound



(29)



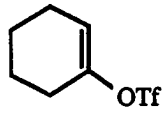
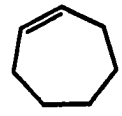
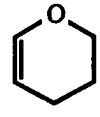
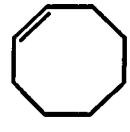
(30)

was identified by comparing its mass spectrum with the mass spectrum of an authentic sample provided by Mr. Peter Johnson. It's presumed that the vinyl palladium iodide intermediate generated initially must somehow have eliminated an iodine atom and

migrated to the terminal end of the molecule before it finally adds as an alkynyl palladium iodide to cyclopentene.[30]

Vinylic triflates were also investigated since they are often easier to prepare than the corresponding iodide. The results of this research are summarized in Table 3. The following observations have been made in the course of this investigation. Once again, cyclopentene is the most reactive of all of the cyclic alkenes used as it cross-coupled even at room temperature (entries 1, 13, 19, and 20). In only two cases did cyclopentene fail to produce any of the desired product (entries 8 and 9). It is believed that the triflate decomposed under the phase-transfer reaction conditions affording the volatile, undetected alkyne. The decomposition reaction was inhibited when procedure B was employed for this reaction, and a good yield of the desired 1,4-diene was afforded (entry 10). Apparently, the choice of base is also critical. This is seen in entry 16 when NaOAc was used and the desired product was produced. KOAc apparently decomposed the triflate (entry 18). Cycloheptene produced high yields of regioisomers no matter what procedure was employed. Cyclohexene and cyclooctene proved to be unreactive.

Table 3. Palladium(0)-catalyzed vinylation of cyclic alkenes with vinyl triflates

Entry	Vinyl Triflate	Cyclic Alkene	Base	Procedure[a]
1			KOAc	A
2			KOAc	A
3			KOAc	A
4			Ag_2CO_3	B
5			Ag_2CO_3	B
6			Ag_2CO_3	B
7			Ag_2CO_3	B

[a] See text for explanation of procedures.
[b] Ratio in parentheses reflects the amount of 1,4- to 1,5-dienes observed.
[c] Many unidentifiable products were produced.

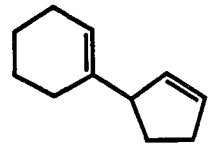
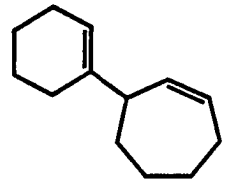
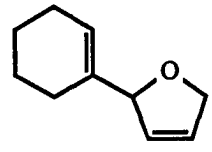
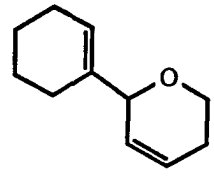
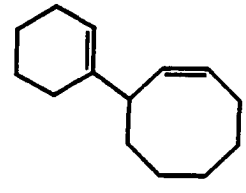
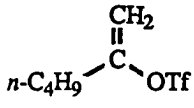
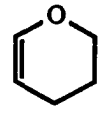
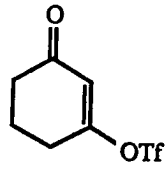
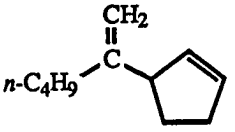
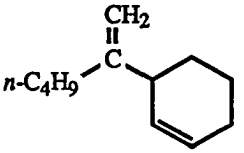
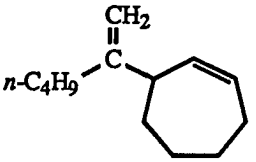
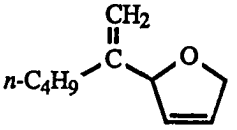
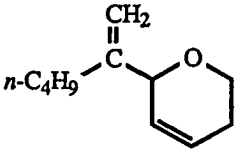
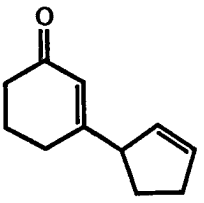
Time (h)	Temp (°C)	Product [b]		Yield (%)
72	25			58
2	80		(1 : 2.6)	100
48	25		(1 : 3)	100
24	80		(1 : 5)	82
48	80			--- [c]
48	80			--- [c]
48	80			--- [c]

Table 3. (continued)

Entry	Vinyl Triflate	Cyclic Alkene	Base	Procedure[a]
8			KOAc	A
9			NaOAc	A
10			Ag_2CO_3	B
11			Ag_2CO_3	B
12			Ag_2CO_3	B
13			Ag_2CO_3	B
14			Ag_2CO_3	B
15			KOAc	A
16			NaOAc	A
17			Ag_2CO_3	B

[d] No starting material or product was recovered. The triflate probably decomposed.
[e] A trace amount of the triflate was recovered.

Time (h)	Temp (°C)	Product		Yield (%)
24	25			--- [d]
24	25			--- [d]
24	80			65
24	80			--- [c]
24	80		(2 : 1)	81
24	80			67
24	80			--- [d]
24	25			--- [d]
24	25			26[e]
24	25			59

CONCLUSION

A Pd(0)-catalyzed procedure for the vinylation of cyclic alkenes has been developed. This process using procedure A or B is the first generally useful procedure for preparing 1,4-dienes in high yields under very mild reaction conditions. In procedure A, the choice of base is somewhat critical; KOAc in a vast majority of cases is far superior to NaOAc. The drawback to this procedure is that it tends to produce a mixture of regioisomers with some alkenes, and cyclohexene has been found to be unreactive. Procedure B effectively inhibits the isomerization reaction frequently encountered when using procedure A. Furthermore, cyclohexene has been successfully vinylated in a short period of time under these reaction conditions. The major drawback to procedure B is the employment of expensive Ag_2CO_3. A number of functional groups can be accommodated in both procedures, but vinylic iodides bearing a hydroxyl or a nitrile group apparently inhibit the reaction. Vinylic iodides also bearing electron-withdrawing groups β to the iodide tend to produce bad mixtures of products regardless of the procedure employed. This process has also been found to retain the stereochemistry of the vinylic iodide. Thus stereoselective synthesis of 1,4-dienes is also possible.

EXPERIMENTAL SECTION

Equipment

NMR spectra were recorded on a Nicolet NT-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75 MHz for carbon nuclei). Infrared spectra were obtained on an IBM IR/98 FT-IR. Mass spectral data were obtained on a Kratos high resolution mass spectrometer. Gas chromatographic analyses were performed by using a Varian 3700 or a Hewlett Packard 5890 gas chromatograph equipped with a 3 % OV-101 on Chromasorb W packed column (Varian 3700 or HP 5890) or an HP-1 megabore column (HP 5890). Spectral information is provided only if the compound is not found in the literature, or if the spectral data available are less accurate. Initially, some of the 1,4-dienes were submitted to Galbraith Laboratories for elemental analyses, but in all cases, the alkenes decomposed during shipping. Consequently, none of the following compounds have elemental analyses.

Reagents

The palladium acetate was donated by Johnson Matthey Co. Cyclopentene, cycloheptene, cyclooctene, 2,3-dihydrofuran, 1-hexyne, 3-hexyne, phenylacetylene, *n*-butyllithium, catecholborane, hexanoyl chloride, silver carbonate, propiolic acid, copper(I) iodide, copper(I) cyanide, 1,3-cyclohexanedione, triphenylphosphine, 3-butyn-1-ol, cyclohexanone, trifluoromethanesulfonic acid, and trifluoromethanesulfonic anhydride, tetra-*n*-butylammonium chloride, and 3,4-dihydro-2*H*-pyran were all obtained from Aldrich Chemical Company and used without further purification. *N,N*- Dimethyl-

formamide and acetonitrile were distilled from calcium hydride (CaH_2) and stored over anhydrous molecular sieves.

2-Iodo-1-hexene[6]

In a 50 mL round bottom flask containing a stirring bar were added 1-hexyne (3.28 g, 40 mmol, 4.60 mL) and HI (47 % in water, 11 mL). The flask was sealed, wrapped in aluminum foil, and stirred rapidly for 10 days at room temperature. The solution was poured into a separatory funnel containing water (50 mL) and ether (50 mL). The organic layer was separated and washed with water, saturated Na_2CO_3, freshly prepared 10 % $Na_2S_2O_3$, and water. The organic layer was dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and distilled (88 - 92 °C, 82 mm Hg) to afford the desired product in 14 % yield. ^1H NMR ($CDCl_3$) δ 0.83 (t, 3 H, J = 7.5 Hz, CH_3), 1.23 (sextet, 2 H, J = 7.5 Hz, CH_2-C<u>H</u>$_2$-CH_3), 1.40 (quintet, 2 H, J = 7.5 Hz, CH_2-C<u>H</u>$_2$-CH_2), 2.29 (t, 2 H, J = 7.5 Hz, C=C-CH_2), 5.59 (d, 1 H, J = 1.5 Hz, C=C<u>H</u>H), 5.19 (d, 1 H, J = 1.5Hz, C=CH<u>H</u>); IR (neat) 3087, 2959, 2932, 1720, 1616, 1466, 1427, 1379, 1213, 1151, 1134, 1045, 891 cm^{-1}.

(*E*)-2-Iodostyrene[8]

In a dry 100 mL round bottom flask containing a stirring bar were added phenylacetylene (5.10 g, 50.0 mmol, 5.48 mL) and catecholborane (6.00 g, 50.0 mmol, 5.33 mL). The mixture was stirred under a nitrogen atmosphere at 70 °C for two hours. After the mixture was cooled to room temperature, water (50 mL) was added, and the mixture was stirred for two hours at room temperature. The resulting solid boronic acid was collected by filtration, and washed free of catechol with ice-cold water (3 x 50 mL).

The boronic acid was then dissolved in ether (50 mL) and placed in a 500 mL round bottom flask. The solution was cooled to 0 °C, and aqueous sodium hydroxide (50 mL, 3*N*) was then added, followed by I_2 (15.2 g, 60.0 mmol) in ether (150 mL). The mixture was stirred for 30 minutes at 0 °C. The excess I_2 was destroyed with freshly prepared 5 % sodium thiosulfate. The organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate. After the organic layer was filtered, and concentrated, the residue was distilled (74 °C, 1 mm Hg) to afford the desired vinylic iodide in 41 % yield. ^{1}H NMR ($CDCl_3$) δ 6.82 (d, 1 H, J = 15.0 Hz, C<u>H</u>=CHPh), 7.27 - 7.35 (m, 5 H, aromatic HS), 7.43 (d, 1 H, J = 15.0 Hz, CH=C<u>H</u>Ph); IR (neat) 3101, 3059, 1595, 1570, 1495, 1171, 1018, 947, 727, 689, 667 cm^{-1}.

(*E*)-1-Iodo-1-octen-3-one[9,10]

A 250 mL round bottom flask precooled to 0 °C was flushed with acetylene for five minutes. Anhydrous carbon tetrachloride (100 mL) was added and acetylene was bubbled into it for five minutes. The flow of acetylene was stopped and aluminum chloride (15.6 g, 117 mmol) was added to the mixture. Bubbling of this solution with acetylene resumed for another five minutes before hexanoyl chloride (13.5 g, 14.1 mL, 100 mmol) was added over a period of 20 minutes. Acetylene bubbling was resumed at 0 °C for four additional hours. The mixture was poured into crushed ice and water (300 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 x 50 mL). To the combined extracts was added hydroquinone (0.32 g) and the solution was dried over calcium chloride. The organic layer was filtered and the calcium chloride was washed with fresh carbon tetrachloride (25 mL). Hydroquinone (0.32 g) was added to the filtrate and the solvent was concentrated *in vacuo* to afford a greenish-yellow oil.

Fractional distillation (60 °C, 1 mm Hg) of the crude product afforded (*E*)-1-chloro-1-octen-3-one in 77 % yield. To a solution of NaI (16.3 g, 108 mmol) in acetone (100 mL) was added (*E*)-1-chloro-1-octen-3-one (12.35 g, 77.0 mmol). The contents were heated to reflux for four hours. The solids were then filtered and the bulk of the acetone was concentrated *in vacuo*. To this solution was added water (50 mL) which was then extracted with ether (4 x 50 mL). The combined extracts were washed with water, 5 % sodium thiosulfate and water again, dried over anhydrous MgSO4, filtered, and concentrated *in vacuo* to afford the crude iodoenone. Recrystallization of the crude product from hexane afforded the desired (*E*)-1-iodo-1-octen-3-one (mp 37 - 38 °C) in 93 % yield. ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3 H, J = 6.9 Hz, CH_3), 1.23 - 1.24 (m, 4 H, CH_2's), 1.43 - 1.47 (m, 4 H, CH_2's), 6.26 (d, 1 H, J = 14.4 Hz, ICH=CH), 6.50 (d, 1 H, J = 14.4 Hz, ICH=CH).

(*E*)-1-Iodo-1-octen-3-ol[10]

To a 250 mL round bottom flask was added ethanol (70 mL). The flask was precooled to 0 °C with stirring for five minutes before sodium borohydride (0.40 g, 10.6 mmol) was added. Stirring was continued for two additional minutes and then a solution of (*E*)-1-iodo-1-octen-3-one (7.56 g, 30.0 mmol) in 10 mL of ethanol was added over a period of 1.5 - 2.0 hours. After the addition was complete, the solution was stirred for 6 additional hours at 0 °C. The solution was concentrated *in vacuo* at 10 °C, and the residue was combined with pentane (100 mL) and water (50 mL). The aqueous layer was separated and extracted with pentane (3 x 50 mL). The combined pentane layers were washed once with sat. NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford the pure product (as established by GC and TLC) in 97 % yield. ^{1}H NMR

($CDCl_3$) δ 0.89 (t, 3 H, J = 6.9 Hz, CH_3), 1.30 (br s, 6 H, CH_2's), 1.50 - 1.60 (m, 2 H, CH_2), 4.06 - 4.14 (m, 1 H, C<u>H</u>-O), 6.34 (dd, 1 H, J = 0.9 Hz, J = 14.4 Hz, IC<u>H</u>=CH), 6.58 (dd, 1 H, J = 6.3 Hz, J = 14.4 Hz, ICH=C<u>H</u>); IR (neat) 3342, 3047, 2957, 2858, 1607, 1466, 1379, 1340, 1271, 1231, 1169, 1126, 1055, 945 cm^{-1}.

1-Iodo-2-methylpropene[11]

In a flame-dried 100 mL round bottom flask equipped with an addition funnel and a stirring bar were placed magnesium turnings (1.07 g, 44.0 mmol) and THF (50 mL). 1-Bromo-2-methylpropene (5.36 g, 40.0 mmol) in THF (10 mL) was added dropwise over a 30 minute period. After the addition was complete, the contents were refluxed for one hour. The solution was then cooled to 0 °C and was quenched with I_2 (11.2 g, 44.0 mmol) dissolved in THF (15 mL). The solution was allowed to come to room temperature overnight before it was quenched with saturated NH_4Cl and the organic and aqueous layers were separated. The aqueous layer was extracted with ether (2 x 50 mL). The organic layers were combined, washed with 5 % $Na_2S_2O_3$, saturated NaCl, water, dried over Na_2SO_4, filtered, concentrated *in vacuo*, and the residue was distilled under vacuum (60 °C, 100 mm Hg) to afford the vinylic iodide in 67 % yield. ^1H NMR ($CDCl_3$) δ 1.80 (s, 6H, CH_3's), 5.85 (s, 1 H, CH=C).

1-Iodo-1-hexyne[13]

A flame-dried 500 mL 3-necked round bottom flask equipped with an addition funnel, a reflux condenser, and a stirring bar was flushed with nitrogen and a positive nitrogen atmosphere was maintained. 1-Hexyne (10.2 g, 125 mmol) and ether (100 mL) were injected. Then methyllithium (102 mL, 1.40 *M*, 143 mmol) was added at such a rate so as

to cause gentle refluxing. Iodine (29.0 g, 114 mmol) dissolved in ether (75 mL) was added dropwise to the solution. After the addition was completed, the reaction was allowed to come to room temperature slowly, and the reaction was allowed to stir at room temperature overnight. Water (60 mL) was added and the mixture was poured into a separatory funnel containing more water (90 mL). The layers were separated and the aqueous phase was extracted with ether (2 x 30 mL). The ether layers were combined, washed with freshly prepared 10 % $Na_2S_2O_3$ (90 mL), dried over anhydrous MgSO4, filtered, and concentrated *in vacuo* to afford a yellow oil. The crude product was distilled (75 °C, 20 mm Hg) to afford the desired alkynyl iodide as a colorless oil in 80 % yield. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 7.2 Hz, CH_3), 1.34 - 1.50 (m, 4 H, CH_2's), 2.33 (t, 2 H, J = 6.6 Hz, CH_2); IR(neat) 2959, 2934, 2187 cm^{-1}.

(Z)-1-Iodo-1-hexene[13]

In a 3-necked round bottom flask was added water (70 mL). The flask was cooled to -10 °C, and blanketed by a slow stream of nitrogen. Potassium hydroxide (28.1 g, 502 mmol) was added and the alkaline solution was cooled back to -10 °C. Azodicarbonamide (23.4 g, 201 mmol) was added in portions at such a rate that the temperature of the mixture was never above 10 °C. After the addition was complete, the yellow mixture was allowed to stir for three hours at 0 - 5 °C. Ice-cold methanol (50 mL) was then added to the mixture at 0 °C. The bright yellow dipotassium azodicarboxylate was vacuum filtered with a fritted funnel. The bright yellow solid was washed several times with ice-cold methanol to remove excess potassium hydroxide. The solid was then transferred to a 500 mL round bottom flask containing a stirring bar. To the flask were added methanol (104 mL) and 1-iodo-1-hexyne (5.20 g, 25.0 mmol). An addition funnel containing a mixture

of glacial acetic acid (20 mL) and methanol (52 mL) and a reflux condenser were attached to the flask. This mixture was added dropwise to the rapidly stirring dipotassium azodicarboxylate and iodoalkyne. After the addition was complete, the mixture was combined with ether (100 mL), and the organic layer was washed with water, and saturated Na_2CO_3, concentrated *in vacuo*, and stirred in *n*-butylamine (15 mL) for one hour. The solution was diluted with ether (50 mL), washed with 5 % hydrochloric acid (50 mL) and then saturated Na_2CO_3 (50 mL), dried over anhydrous $MgSO_4$, filtered, and finally concentrated *in vacuo* to afford the desired vinylic iodide in 53 % overall yield. ^1H NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 6.9 Hz, CH_3), 1.32 - 1.35 (m, 4 H, CH_2's), 2.05 - 2.08 (m, 2 H, $C{=}CCH_2$), 6.07 - 6.10 (m, 2 H, CH=CH); IR (neat) 3066, 1739, 1610, 1010, 933 cm^{-1}.

(*E*)-1-Iodo-1-hexene[12]

To a solution of 1-hexyne (2.50 g, 30.5 mmol) in dry heptane (15 mL) was added diisobutylaluminum hydride (1.5 *M*, 20 mL, 30.0 mmol) at a rate such that the temperature of the reaction remained below 40 °C. The resulting solution was heated to 50 °C for 2.5 hours, and then the heptane was removed under reduced pressure. The residue was diluted with dry THF (15 mL), cooled to -50 °C, and a solution of I_2 (7.62 g, 30.0 mmol) in THF (15 mL) was added. The cooling bath was removed, and the reaction mixture was warmed to room temperature and stirred overnight. The reaction was cooled to 0 °C and quenched by dropwise addition of sulfuric acid (20 %) until the evolution of isobutane ceased. The mixture was then poured into ice containing sulfuric acid (20 %), and the mixture was extracted with hexane (2 x 50 mL). The hexane extracts were washed with saturated $Na_2S_2O_3$ (20 mL) and 5 % Na_2CO_3 (20 mL), dried over anhydrous

$MgSO_4$, and concentrated *in vacuo* to afford the crude product. Bulb-to-bulb distillation of the residue (68 - 71 °C, 18 mm Hg) provided the desired vinylic iodide in 51 % yield. ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 5.8 Hz, CH_3), 1.22 - 1.47 (m, 4 H, CH_2's), 2.02 - 2.14 (m, 2 H, C=C-CH_2), 5.97 (dt, 1 H, J = 14.4 Hz, J = 1.5 Hz, C=CHI), 6.51 (dt, 1 H, J = 14.4 Hz, J = 7.2 Hz, C<u>H</u>=CHI); IR (neat) 3049, 3007, 2928, 1607, 1466, 1435, 1379, 1219, 1180, 1018, 949, 922, 860 cm^{-1}.

(*E*)-1-Iodo-3,3-dimethyl-1-butene

This vinylic iodide was prepared in 56 % yield by the same procedure used to synthesize (*E*)-1-iodo-1-hexene. ^1H NMR ($CDCl_3$) δ 1.00 (s, 9 H, *t*-Bu), 5.95 (d,1 H, J = 15.9 Hz, *t*-BuC<u>H</u>=CH), 6.56 (d, 1 H, J = 15.9 Hz, *t*-BuCH=C<u>H</u>); IR (neat) 3071, 2961, 2903, 1599, 1259, 935 cm^{-1}.

(*E*)-3-Iodo-3-hexene

This vinylic iodide was prepared in 26 % yield by the same procedure used to synthesize (*E*)-1-iodo-1-hexene. ^1H NMR ($CDCl_3$) δ 0.99 (t, 3 H, J = 7.2 Hz, CH_3), 1.04 (t, 3 H, J = 7.2 Hz, CH_3), 2.06 (q, 2 H, J = 7.2 Hz, CH_2), 2.41 (q, 2 H, J = 7.2 Hz, CH_2), 6.15 (t, 1 H, J = 9.7 Hz, C=CH); IR (neat) 3024, 1630, 1134, 1065, 852 cm^{-1}.

1-Iodo-1-cyclohexene[15]

In a dry pyrex culture tube equipped with a stirring bar was weighed magnesium iodide (1.66 g, 11 mmol). Then 1-cyclohexenyl triflate (1.20 g, 5.5 mmol), Et_3N (0.56 g, 5.5 mmol), and cyclohexane (50 mL) were added sequentially. The tube was sealed

and heated to 120 °C for 60 hours. The solution was concentrated *in vacuo*, and the residue was columned over silica gel using hexane as the eluent to afford the desired product in 50 % yield. The ^{1}H NMR spectral data matched the data reported in the literature.[31]

4-Iodo-3-butyn-1-ol[15]

In a 500 mL round bottom flask equipped with a stirring bar were added ether (150 mL), mercury acetate (9.56 g, 30.0 mmol), and 3-butyn-1-ol (4.20 g, 4.60 mL, 60.0 mmol). Solid iodine (15.3 g, 60.0 mmol) was added slowly in portions to the rapidly stirred mixture. After the addition was complete, the flask was sealed with a septum and the contents were stirred for 48 hours at room temperature in the absence of light. The mercuric iodide was removed by filtering the reaction mixture through a short column of Celite. The solids were then washed with ether (3 x 50 mL). The filtrate was washed with saturated Na_2CO_3 (2 x 75 mL), $Na_2S_2O_3$ (5 %, 75 mL), and the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford a light green oil in 100 % yield. ^{1}H NMR ($CDCl_3$) δ 2.63 (t, 2 H, J = 6.3 Hz, C$\underline{H_2}$CH$_2$OH), 3.73 (t, 2 H, J = 6.3 Hz, CH$_2$OH); IR (neat) 3358, 1713, 1047 cm^{-1}.

4-(2-Tetrahydropyranoxy)-1-iodo-1-butyne[16]

In a 250 mL round bottom flask equipped with a stirring bar were added anhydrous CH_2Cl_2 (210 mL), and 4-iodo-3-butyn-1-ol (5.88 g, 30 mmol) and 3,4-dihydro-2*H*-pyran (3.36 g, 40.0 mmol). Once the contents were stirring, PPTS (0.753 g, 3.00 mmol) was added all at once. After the solution was stirred for four hours, it was combined with ether (200 mL) and washed with saturated NaCl (200 mL). The aqueous layer was

discarded and the remaining organic layer was washed with water. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford the desired product in 99 % yield. ^{1}H NMR ($CDCl_3$) δ 1.53 - 1.84 (m, 6 H, CH_2's), 2.67 (t, 2 H, J = 6.9 Hz, CH_2), 3.54 - 3.84 (m, 4 H, CH_2-O's), 4.64 (t, 1 H, J = 1.8 Hz, O-CH-O); IR (neat) 2943, 2872, 1732, 1200, 1136 cm^{-1}.

(*Z*)-3-(2-Tetrahydropyranoxy)-1-iodo-1-butene

Freshly prepared dipotassium azodicarboxylate (14.4 g, 74.0 mmol) was added to a 250 mL round bottom flask equipped with a large stirring bar, addition funnel, and a reflux condenser. To the flask were also added pyridine (15 mL), methanol (30 mL), and 3-(2-tetrahydropyranoxy)-1-iodo-1-butyne (5.64 g, 20.0 mmol). A mixture of acetic acid (18 mL) and methanol (18 mL) was added to the addition funnel. The methanol-acetic acid mixture was added dropwise at room temperature at such a rate as to cause only a gentle reflux. After the addition, the mixture was stirred for 24 hours. The mixture was poured into a 500 mL round bottom flask containing ether (200 mL). The contents were stirred rapidly as ice-cold 5 % HCl (100 mL) was slowly added. The layers were separated and the aqueous layer was extracted with ether (2 x 50 mL). The combined ether layers were washed with saturated Na_2CO_3 and water. The organic layer was concentrated *in vacuo* and the residue was added *n*-butylamine (10 mL), and the mixture was stirred for three hours at room temperature to remove the over reduced product. The mixture was added to ether (75 mL), washed with water (2 x 100 mL), cold 5 % HCl (150 mL), and water (100 mL). The ether layer was dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and columned over basic alumina using hexane as the eluent to afford the desired product in 66 % yield. ^{1}H NMR ($CDCl_3$) δ 1.57 - 1.75 (m, 6 H,

CH_2's), 2.45 (dt, 2 H, J = 7.2 Hz, J = 7.2 Hz, CH_2), 3.46 - 3.90 (m, 4 H, CH_2O's), 4.61 (dd, 1 H, J = 1.8 Hz, J = 1.8 Hz, O-CH-O), 6.30 - 6.32 (m, 2 H, CH=CHI); IR (neat) 3019, 2939, 2868, 1200, 1136, 1121, 1074, 1034, 984 cm^{-1}.

(*E*)-3-(2-Tetrahydropyranoxy)-1-iodo-1-octene

This vinylic iodide was prepared from the corresponding alcohol, (*E*)-1-iodo-1-octen-3-ol, and 3,4-dihydro-2*H*-pyran using a procedure identical to the procedure used for the preparation of 3-(2-tetrahydropyranoxy)-1-iodo-1-butyne (100 %). ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 7.2 Hz, CH_3), 1.16 - 1.92 (m, 14 H, CH_2's), 3.46 - 3.52 (m, 1 H, C<u>H</u>H-O), 3.80 - 3.87 (m, 1 H, CH<u>H</u>-O), 3.99 - 4.16 (m, 1 H, CH-OTHP), 4.61 - 4.57 (m, 1 H, O-CH-O), 6.23 - 6.40 (m, 1 H, C<u>H</u>=CHI), 6.51 - 6.61 (m, 1 H, CH=C<u>H</u>I); IR (neat) 2934, 2910, 1261, 1200, 1022 cm^{-1}.

***trans*-β-iodoacrylonitrile**[18]

In a bomb apparatus was placed I_2 (15 g, 60 mmol). After the bomb was sealed, acetylene was passed through it for five minutes before the bomb was pressurized to 250 psi, and the bomb was heated to 140 - 160 °C for 24 hours. The bomb was cooled to room temperature and the excess acetylene was released. The resulting dark solids were added ether, filtered, added activated charcoal, and filtered. After the ether was removed, the crude yellow solid, (*E*)-1,2-diiodoethene, was used without purification. In a 250 mL round bottom flask were placed (*E*)-1,2-diiodoethene (10 g, 36 mmol), CuCN (3.0 g, 33 mmol), and dry DMF (40 mL). The heterogeneous mixture was flushed with N_2 and a positive N_2 atmosphere was maintained. The contents were heated to 100 °C for 24 hours, then the mixture was allowed to cool to room temperature before it was added to

ether (200 mL). The solution was filtered through Celite, and the solids were washed with more ether. The filtrate was washed with water (3 x 100 mL), dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and the dark yellow solid was recrystallized from hexane to afford the desired vinylic iodide in 50 % yield. NOTE: THIS COMPOUND IS A POWERFUL IRRITANT, THUS IT MUST BE HANDLED WITH CAUTION! ^1H NMR ($CDCl_3$) δ 5.23 (d, 1 H, J = 15.5 Hz, IC<u>H</u>=CHCN), 6.22 (d, 1 H, J = 15.5 Hz, ICH=C<u>H</u>CN).

Methyl (*E*)-3-bromopropenoate[19]

Propiolic acid (4.90 g, 4.30 mL, 70.0 mmol) was added dropwise to aqueous HBr (48 % in water, 28 mL) and then the solution was heated to reflux for 1.5 hours. When the solution was cooled in an ice bath, (*E*)-3-bromopropenoic acid crystallized from the solution. The solid was collected by filtration and transferred to a 250 mL round bottom flask containing a stirring bar and methanol (50 mL). After a few drops of concentrated sulfuric acid were added, the solution was heated to reflux for 24 hours. The contents were diluted with ether, extracted twice with 10 % NaOH, and then the organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo* to afford an oil. The latter was distilled bulb-to-bulb (48 - 50 °C, 10 mm Hg) to afford the desired ester in 37 % yield. ^1H NMR ($CDCl_3$) δ 3.75 (s, 3 H, OCH_3), 6.53 (d, 1 H, J = 14.4 Hz, C<u>H</u>=CHBr), 7.60 (d, 1 H, J = 14.4 Hz, CH=C<u>H</u>Br); IR (neat) 3082, 3001, 2955, 1728, 1609, 1437, 1306, 1261, 1028, 941 cm^{-1}.

Methyl (*E*)-3-iodopropenoate

This vinylic iodide was prepared in 78 % yield using a procedure identical to the one used in the preparation of the corresponding vinylic bromide. ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3 H, OCH_3), 6.81 (d, 1 H, J = 14.7 Hz, C<u>H</u>=CHI), 7.83 (d, 1 H, J = 14.7 Hz, CH=C<u>H</u>I); IR (neat) 3063, 2999, 2843, 1724, 1591, 1302, 1265, 1219, 1148, 947 cm^{-1}.

3-Iodo-2-cyclohexen-1-one[20]

To a stirred solution of recrystallized PPh_3 (1.73 g, 6.60 mmol) in dry acetonitrile (60 mL) was added I_2 (1.68 g, 6.60 mmol), and the mixture was stirred at room temperature for two hours. To this yellow-orange suspension was added sequentially Et_3N (0.667 g, 0.92 mL, 6.60 mmol) and 1,3-cyclohexanedione (0.672 g, 6.00 mmol). The mixture was heated to reflux for 9 hours, concentrated *in vacuo*, and filtered through a short column of silica gel (50 g) using ether as the eluent. The filtrate was concentrated *in vacuo* and the residue was columned over silica gel using hexane / EtOAc (4 : 1) to afford the desired iodoenone in 85 % yield. ^{1}H NMR ($CDCl_3$) δ 2.03 (quintet, 2 H, J = 6.3 Hz, CH_2), 2.43 (t, 2 H, J = 6.3 Hz, CH_2), 2.91 (dt, 2 H, J = 7.8 Hz, J = 1.5 Hz, CH_2), 6.81 (t, 1 H, J = 1.5 Hz, CH=CI); IR (mull) 1675, 1595 cm^{-1}.

Ethyl 2-bromopropenoate[21]

In a dry 100 mL round bottom flask containing a stirring bar were placed DEAD (1.46 g, 1.32 mL, 8.40 mmol), 2-bromopropenoic acid (1.05 g, 7.00 mmol), and ether (23 mL). In a separate flask were placed PPh_3 (2.02 g, 7.70 mmol), EtOH (0.483 g, 1.63 mL, 10.5 mmol), and ether (10 mL). The contents of the latter flask were added dropwise

into the stirring solution of the other flask, and after the addition was complete, stirring was continued overnight. The solution was washed with saturated Na_2CO_3 (50 mL), dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and columned over silica gel using hexane / EtOAc (6 : 1) as the eluent to afford the desired vinylic bromide in 100 % yield. ^1H NMR ($CDCl_3$) δ 1.34 (t, 3 H, J = 7.2 Hz, CH_3), 4.29 (q, 2 H, J = 7.2 Hz, CH_2), 6.27 (d, 1 H, J = 1.8 Hz, C<u>H</u>H=CBr), 6.96 (d, 1 H, J = 1.8 Hz, CH<u>H</u>=CBr); IR (neat) 3117, 2986, 2934, 1736, 1239, 1101, 1022, 937 cm^{-1}.

(*E*)-1,2-Diiodo-1-hexene[22]

In a 50 mL round bottom flask containing a stirring bar were placed activated, neutral alumina (9.46 g) and I_2 (3.07 g, 12.1 mmol). After the flask was septum sealed, pentane (21 mL) and 1-hexyne (0.82 g, 1.15 mL, 10.0 mmol) were injected sequentially. The mixture was stirred rapidly for 5 hours before the contents were vacuum filtered. The alumina was washed once with pentane and the filtrate was concentrated *in vacuo* to afford the desired diiodo compound in 94 % yield. ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 7.2 Hz, CH_3), 1.36 (tq, 2 H, J = 7.2 Hz, J = 7.2 Hz, CH_2), 1.53 (quintet, 2 H, J = 7.2 Hz, CH_2), 2.51 (t, 2 H, J = 7.2 Hz, CH_2), 6.80 (s, 1 H, CH=C); IR (neat) 3071, 2957, 2932, 1464, 1427, 1205, 1109, 968, 951, 768 cm^{-1}.

(*E*)-3,4-Diiodo-3-hexene[22]

This compound was prepared in 100 % yield from 3-hexyne by a procedure identical to the one used for preparing (*E*)-1,2-diiodo-1-hexene. ^1H NMR ($CDCl_3$) δ 1.04 (t, 6 H, J = 7.2 Hz, CH_3), 2.69 (q, 4 H, J = 7.2 Hz, CH_2); IR (neat) 2970, 2932, 2851, 1454, 1433, 1371, 1313, 1261, 1074, 906, 795 cm^{-1}.

2-Bromo-2-cyclohexenone[23]

In a dry 50 mL round bottom flask equipped with a stirring bar and an addition funnel were placed CH_2Cl_2 (11 mL) and 2-cyclohexenone (1.92 g, 1.93 mL, 20.0 mmol). The solution was cooled to 0 °C before a solution of Br_2 (3.16 g, 1.02 mL, 20 mmol) in CH_2Cl_2 (1 mL) was added dropwise. Stirring was continued for 1 hour before Et_3N (3.03 g, 4.17 mL, 30.0 mmol) was added, and the solution was allowed to stir and come to room temperature overnight. The organic layer was washed with saturated NaCl, water, and dried over anhydrous $MgSO_4$. After the solvent was removed *in vacuo*, the solid residue was recrystallized from EtOH and water to afford the desired product as brown crystals (mp. 69 - 72 °C) in 82 % yield. ^1H NMR ($CDCl_3$) δ 2.08 (quintet, 2 H, J = 6.6 Hz, CH_2), 2.44 - 2.49 (m, 2 H, CH_2), 2.64 (t, 2 H, J = 6.6 Hz, CH_2), 7.43 (t, 1 H, J = 4.5 Hz, C=CH); IR (nujol) 3040, 1680, 1597, 1124, 991, 972, 916 cm^{-1}.

Cyclohexenyl triflate[24]

To a -78 °C solution of diisopropylamine (0.545 g, 5.40 mmol) in THF (10 mL) was added *n*-butyllithium (2.30 mL, 2.35 *M*). The solution was stirred at -78 °C for 10 minutes, 0 °C for 10 minutes, and then cooled back down to -78 °C before freshly distilled cyclohexanone (0.490 g, 5.00 mmol) was injected. The resulting solution was stirred at -78 °C for 30 minutes, 0 °C for 30 minutes, and then cooled back down to -78 °C before *N*-phenyltrifluoromethanesulfonimide (1.90 g, 5.30 mmol) in THF (10 mL) was added. The contents were stirred at -78 °C for one hour, 0 °C for one hour, and then at room temperature for two hours. Once analysis by thin-layer chromatography indicated that all of the cyclohexanone has been consumed, the reaction was quenched by the addition of saturated NH_4Cl and extracted with ether. The ether extracts were washed with water (25

mL) and saturated NaCl (25 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude product. The residue was purified by filtration through a short column of silica gel using hexane as the eluent followed by bulb-to-bulb distillation (82 - 85 °C,18 mm Hg) to afford the desired triflate in 52 % yield. ^1H NMR ($CDCl_3$) δ 1.23 - 1.83 (m, 4 H, CH_2's), 1.87 - 2.40 (m, 4 H, CH_2's), 5.60 - 5.76 (m, 1 H, C=CH); IR (neat) 1690 cm^{-1}.

2-Hexenyl triflate[25]

In a 100 mL round bottom flask equipped with a stirring bar were added 1-hexyne (9.98 g, 14.0 mL, 122 mmol) and pentane (25 mL). After the solution was cooled to -30 °C, trifluoromethanesulfonic acid was added dropwise over a period of 15 minutes using an addition funnel. After the addition was complete, the solution was allowed to warm quickly to 0 °C, and then a solution of saturated Na_2CO_3 (20 mL) was added. After the aqueous solution layer was removed, the organic layer was washed twice with saturated Na_2CO_3, and then dried over K_2CO_3. After the organic layer was filtered, and concentrated *in vacuo*, the residue was distilled (67 - 69 °C, 15 mm Hg) to afford the desired triflate in 94 % yield. ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 7.2 Hz, CH_3), 1.39 (quintet, 2 H, J = 7.5 Hz, CH_2), 1.53 (quintet, 2 H, J = 7.5 Hz, CH_2), 2.34 (t, 2 H, J = 7.5 Hz, CH_2), 4.93 (d, 1 H, J = 3.6 Hz, C=C<u>H</u>H), 5.09 (d, 1 H, J = 3.6 Hz, C=CH<u>H</u>); IR (neat) 3138, 2964, 1672, 1470, 1420, 1250, 1211, 1173, 1101, 949, 906, 840, 702, 705 cm^{-1}.

3-(Trifluoromethylsulfonyloxy)cyclohex-2-en-1-one[26]

To a stirred solution of NaH (50 % in oil, 1.77 g, 36.3 mmol) in DME (78 mL) was added dropwise a solution of 1,3-cyclohexanedione (4.30 g, 38.4 mmol). After the evolution of hydrogen gas ceased, the mixture was stirred for an additional 25 minutes, cooled to -78 °C and trifluoromethanesulfonic acid anhydride (10.0 g, 35.5 mmol) was slowly added to the solution. After stirring for two hours at -78 °C, the mixture was warmed to room temperature, the DME removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (160 mL). The organic layer was washed with saturated solutions of Na_2CO_3 (100 mL), NaCl, and then water, dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure at 0 °C. The residue was chromatographed over silica gel using chloroform as the eluent (160 mL). Removal of the solvent under reduced pressure at 0 °C afforded the triflate in 52 % yield. THIS TRIFLATE IS QUITE UNSTABLE AT ROOM TEMPERATURE. THIS TRIFLATE MUST ALSO BE DILUTED WITH AN ORGANIC SOLVENT BEFORE IT CAN BE STORED IN THE FREEZER. ^{1}H NMR ($CDCl_3$) δ 2.13 (tt, 2 H, J = 6.6 Hz, J = 6.3 Hz, CH_2), 2.45 (t, 2 H, J = 6.3 Hz, CH_2), 2.69 (dt, 2 H, J = 6.3 Hz, J = 1.2 Hz, CH_2), 6.06 (t, 1 H, J = 1.2 Hz, C=CH); ^{13}C NMR ($CDCl_3$) δ 20.60, 28.24, 29.53, 36.12, 118.94, 167.27, 197.03; IR (neat) 2955, 2926, 1701, 1647, 1462, 1377, 1248, 1219, 1142, 1072, 1043, 908, 798 cm^{-1}.

Procedure A

In a dry 10 mL round bottom flask equipped with a stirring bar were added $Pd(OAc)_2$ (0.003 g, 2.5 mol %), TBAC (0.147 g, 0.530 mmol), anhydrous KOAc (0.147 g, 1.50 mmol), and the vinylic halide or triflate (0.500 mmol). The flask was sealed with a

septum (for 25 °C reactions) or was affixed with a condenser sealed with a septum (for 80 °C reactions). The contents were flushed with N_2 for two minutes and then a positive N_2 atmosphere was maintained with a balloon or a bubbler. Cycloalkene (2.5 mmol) and anhydrous DMF (1.0 mL) were sequentially injected, and the mixture was stirred for the length of time and at the temperature indicated in Tables 2 or 3. After gas chromatographic analysis indicated that all of the vinylic halide or triflate had been consumed, the mixture was added to a separatory funnel containing ether (25 mL) and saturated aqueous NH_4Cl (25 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and columned over silica gel using hexane or hexane / EtOAc mixture to afford the desired 1,4-diene.

Procedure B

In a dry 25 mL round bottom flask equipped with a stirring bar were added $Pd(OAc)_2$ (0.0035 g, 3.0 mol %), PPh_3 (0.012 g, 9.0 mol %), Ag_2CO_3 (0.276 g, 1.00 mmol) and the vinylic halide or triflate (0.500 mmol). The flask was sealed with a septum or a reflux condenser equipped with a septum. The contents were flushed with nitrogen for two minutes, and a positive nitrogen atmosphere was maintained. Cycloalkene (2.5 mmol) and anhydrous acetonitrile (6.0 mL) were sequentially injected. The mixture was stirred for the length of time and at the temperature indicated in Tables 2 or 3. After gas chromatographic analysis indicated that all of the vinylic halide or triflate had been consumed, the mixture was diluted with ether (10 mL). The mixture was filtered through a small plug of Celite and the solids were washed with ether (3 x 10 mL). The filtrate was poured into a separatory funnel containing saturated NH_4Cl, and the ether layer was

dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and columned over silica gel using either hexane or hexane / EtOAc mixture to afford the desired 1,4-diene.

2-(3-Cyclopentenyl)-1-hexene (Table 2, entry 2)

This diene was purified over silica gel using hexane as the eluent. ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 7.2 Hz, CH_3), 1.20 - 1.67 (m, 6 H, CH_2's), 2.00 - 2.20 (m, 2 H, C=C-CH_2), 2.23 - 2.59 (m, 2 H, C=C-CH_2), 3.30 (br s, 1 H, C=C-CH-C=C), 4.69 (m, 1 H, C=C(H)H), 4.73 (br s, 1H, C=C(H)H), 5.58 - 5.69 (m, 1 H, CH=CH), 5.73 - 5.88 (m, 1 H, CH=CH); ^{13}C NMR ($CDCl_3$) δ 14.02, 22.89, 30.34, 32.17, 34.59, 37.95, 51.69, 107.22, 129.83, 131.29, 133.62; IR (neat) 3296, 3274, 2964, 1717, 1677, 1020 cm^{-1}; HRMS: calcd for $C_{11}H_{18}$ m/z 150.14085, found m/z 150.14104.

2-(3-Cycloheptenyl)-1-hexene (Table 2, entry 8)

This diene was purified over silica gel using hexane as the eluent. ^1H NMR($CDCl_3$) δ 0.94 (t, 3 H, J = 7.2 Hz, CH_3), 1.29 - 1.73 (m, 10 H, CH_2's), 2.05 (t, 2 H, J = 7.2 Hz, C=CCH_2), 2.13 - 2.17 (m, 2 H, C=CCH_2), 2.90 - 2.92 (m, 1 H, C=CCHC=C), 4.75 (d, 1 H, J = 1.5 Hz, C=C(H)H), 4.82 (t, 1 H, J = 1.5 Hz, C=C(H)H), 5.61 (dd, 1 H, J = 4.5 Hz, J = 1.2 Hz, CH=CH), 5.76 - 5.83 (m, 1 H, CH=CH); ^{13}C NMR ($CDCl_3$) δ 14.08, 22.70, 27.07, 28.64, 30.21 (2 peaks), 32.95, 34.43, 47.01, 107.93, 131.26, 137.53, 154.26; IR (neat) 3080, 3018, 2957, 2923, 1641, 1466, 1445, 1379, 1020, 889, 737, 687 cm^{-1}; HRMS: calcd for $C_{13}H_{22}$ m/z 178.17215, found m/z 178.17201.

2-(2-Hexenyl)-2,5-dihydrofuran (Table 2, entry 12)

This diene was purified over silica gel using hexane / EtOAc (10 : 1) as the eluent. ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3 H, J = 7.2 Hz, CH_3), 1.27 - 1.53 (m, 4 H, CH_2's), 1.95 - 2.09 (m, 2 H, C=C-CH_2), 4.63 - 4.71 (m, 2 H, CH_2-O), 4.83 (dd, 1 H, J = 1.5 Hz, J = 3 Hz, C=C(H)H), 5.03 (dt, 1 H, J = 3 Hz, J = 3 Hz, C=C(H)H), 5.21 - 5.24 (m, 1 H, O-CH-O), 5.73 - 5.77 (m, 1 H, dihydrofuran CH=CH), 5.90 - 5.96 (m, 1 H, dihydrofuran CH=CH); ^{13}C NMR ($CDCl_3$) δ 13.92, 22.58, 30.11, 30.50, 75.55, 89.69, 110.17, 126.92, 128.87, 149.68; IR (neat) 3082, 2959, 2930, 1647, 1620, 1466, 1458, 1261, 1138, 1070, 1020, 901, 804, 758, 735, 683 cm^{-1}; HMRS: calcd for $C_{10}H_{16}O$ m/z 152.12012, found m/z 152.12010.

2-(3-Cyclopentenyl)styrene (Table 2, entry 14)

This diene was purified over silica gel using hexane as the eluent. ^{1}H NMR ($CDCl_3$) δ 1.67 - 1.68 (m, 2 H, CH_2), 2.18 - 2.20 (m, 1 H, C=C-C(H)H), 2.93 - 2.95 (m, 1 H, C=CC(H)H), 3.40 - 3.46 (m, 1 H, C=C-CH-C=C), 5.68 - 5.77 (m, 1 H, cyclopentenyl CH=CH), 5.82 - 5.83 (m, 1 H, cyclopentenyl CH=CH), 6.15 (d, 1 H, J = 15.9 Hz, PhCH=CH), 6.36 (d, 1 H, J = 15.9 Hz, PhCH=CH), 7.26 - 7.37 (m, 5 H, aromatic HS); ^{13}C NMR ($CDCl_3$) δ 31.09, 32.47, 49.12, 126.29 (2 peaks), 128.69 (2 peaks), 131.98, 133.83, 134.60, 137.96; IR (neat) 3057, 3026, 2937, 2849, 1649, 1601, 964, 748, 723, 692 cm^{-1}; HRMS: calcd for $C_{13}H_{14}$ m/z 170.10955, found m/z 170.10922.

2-(3-Cyclohexenyl)styrene (Table 2, entry 21)

This diene was purified over silica gel using hexane as the eluent. ^{1}H NMR ($CDCl_3$) δ 1.43 - 2.03 (m, 6 H, CH_2's), 2.93 - 2.95 (m, 1 H, C=C-CH-C=C), 5.55 - 5.61 (m, 1

H, cyclohexenyl CH=CH), 5.76 - 5.81 (m, 1 H, cyclohexenyl CH=CH), 6.17 (dd, 1 H, J = 15.9 Hz, J = 7.2 Hz, PhCH=CH), 6.37 (d, 1 H, J = 15.9 Hz, PhCH=CH), 7.18 (d, 1 H, J = 7.5 Hz, aromatic H), 7.27 (dd, 2 H, J = 7.5 Hz, J = 7.5 Hz, aromatic HS), 7.34 (d, 2 H, J = 7.5 Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 25.52, 26.08, 29.25, 38.63, 125.97, 126.80, 127.99, 128.38, 128.99, 129.41, 134.59, 137.72; IR (neat) 3059, 3020, 2926, 2856, 1649, 1598, 1495, 1447, 962, 906, 746, 723 cm^{-1}; HRMS: calcd for $C_{14}H_{16}$ m/z 184.12520, found m/z 184.12552.

2-(3-Cycloheptenyl)styrene (Table 2, entry 26)

This compound was purified over silica gel using hexane as the eluent. ^{1}H NMR ($CDCl_3$) δ 1.38 - 1.79 (m, 6 H, CH_2's), 2.09 - 2.18 (m, 2 H, C=CCH_2), 3.09 - 3.12 (m, 1 H, C=C-CH-C=C), 5.68 (dd, 1 H, J = 11.1 Hz, J = 4.5 Hz, cycloheptenyl CH=CH), 5.79 - 5.87 (m, 1 H, cycloheptenyl CH=CH), 6.28 (dd, 1 H, J = 15.6 Hz, J = 7.2 Hz, PhCH=CH), 6.38 (d, 1 H, J = 15.6 Hz, PhCH=CH), 7.14 - 7.35 (m, 5 H, aromatic HS); ^{13}C NMR ($CDCl_3$) (one missing C-13 signal) δ 27.02, 28.77, 29.44, 33.87, 43.50, 125.99, 126.80, 128.40, 128.54, 131.78, 134.82, 137.79; IR (neat) 3082, 3058, 2920, 2851, 1599, 1495, 1447, 1070, 1028, 964, 781, 744, 692 cm^{-1}; HRMS: calcd for $C_{15}H_{18}$ m/z 198.14085, found m/z 198.14129.

2-(2-Styrenyl)-2,5-dihydrofuran (Table 2, entry 34)

This compound was purified over silica gel using hexane / EtOAc (10 : 1). ^{1}H NMR ($CDCl_3$) δ 4.58 - 4.73 (m, 2 H, C=C-CH_2-O), 5.32 - 5.51 (m, 1 H, C=C-CH-C=C), 5.73 - 5.75 (m, 1 H, dihydrofuran CH=CH), 5.89 - 5.91 (m, 1 H, dihydrofuran CH=CH), 6.08 (dd, 1 H, J = 15.9 Hz, J = 7.2 Hz, PhCH=CH), 6.52 (d, 1 H, J = 15.9

Hz, PhC<u>H</u>=CH), 7.16 (d, 1 H, J = 7.2 Hz, aromatic H), 7.23 (t, 2 H, J = 7.2 Hz, aromatic HS), 7.31 (d, 2 H, J = 7.2 Hz, aromatic H); ^{13} C NMR ($CDCl_3$) δ 75.20, 86.67, 126.50, 127.02, 127.58, 128.41, 128.75, 129.19, 130.80, 136.56; IR (neat) 3352, 3084, 3060, 3028, 2962, 2925, 2902, 1600, 1577, 1494, 1448, 1353, 1265, 1119, 1088, 1061, 966, 866, 825, 795, 692, 662 cm^{-1}; HRMS: calcd for $C_{12}H_{12}O$ m/z 172.08882, found m/z 172.08872.

2-(2-Styrenyl)-5,6-dihydro-2*H*-pyran (Table 2, entry 37)

This compound was purified over silica gel using hexane / EtOAc (10 : 1). ^{1}H NMR ($CDCl_3$) δ 2.09 - 2.26 (m, 2 H, CH_2), 3.99 (ddd, 1 H, J = 11.4 Hz, J = 6.3 Hz, J = 3.9 Hz, C=C-CH-C=C), 3.96 - 4.03 (m, 1 H, C<u>H</u>H-O), 4.30 - 4.76 (m, 1 H, CH<u>H</u>-O), 5.71 - 5.76 (m, 1 H, dihydropyran C<u>H</u>=CH), 5.91 - 5.98 (m, 1 H, dihydropyran CH=C<u>H</u>), 6.21 (dd, 1 H, J = 15.9 Hz, J = 6.3 Hz, PhCH=C<u>H</u>), 6.61 (d, 1 H, J = 15.9 Hz, PhC<u>H</u>=CH), 7.23 (d, 1 H, J = 7.2 Hz, J = 7.2 Hz, aromatic HS), 7.30 (t, 2 H, J = 7.2 H, aromatic HS), 7.39 (d, 2 H, J = 7.2 Hz, aromatic H); ^{13}C NMR ($CDCl_3$) δ 25.10, 62.31, 74.09, 125.30, 126.44, 127.57, 128.43, 128.46, 128.77, 131.69, 136.69; IR (neat) 3050, 2964, 1599, 1448, 1414, 1261, 1180, 1080, 1020, 798, 746, 690 cm^{-1}; HRMS: calcd for $C_{13}H_{14}O$ m/z 186.10447, found m/z 186.10467.

(*Z*)-1-(3-Cyclopentenyl)-1-hexene (Table 2, entry 51)

This diene was purified over silica gel using hexane as the eluent. ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3 H, J = 6.6 Hz, CH_3), 1.29 - 1.38 (m, 4 H, CH_2's), 1.70 - 1.74 (m, 2 H, CH_2), 1.96 - 2.10 (m, 4 H, C=C-CH_2's), 3.10 - 3.19 (m, 1 H, C=C-CH-C=C), 5.21 - 5.40 (m, 2 H, *n*-BuCH=CH), 5.58 - 5.69 (m, 1 H, C<u>H</u>=CH), 5.73 - 5.88 (m, 1 H,

CH=C<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 13.98, 23.60, 30.94, 31.74, 32.30, 34.18, 48.76, 130.04, 131.03, 134.84, 135.87; IR (neat) 3049, 2965, 2918, 1612, 1466, 1376, 912 cm^{-1}; HRMS: calcd for $C_{11}H_{18}$ m/z 150.14085, found m/z 150.14070.

(*Z*)-1-(3-Cyclopentenyl)-1-hexene (Table 2, entry 60)

This diene was purified over silica gel using hexane as the eluent. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3 H, *J* = 6.9 Hz, CH_3), 1.30 - 1.39 (m, 6 H, CH_2's), 1.74 - 1.78 (m, 2 H, CH_2), 1.97 - 2.10 (m, 4 H, C=C-CH_2's), 3.04 - 3.12 (m, 1 H, C=C-CH-C=C), 5.21 - 5.40 (m, 2 H, *n*-BuCH=CH), 5.44 - 5.49 (m, 1 H, C<u>H</u>=CH), 5.69 - 5.74 (m, 1 H, CH=C<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 13.98, 21.17, 22.37, 24.88, 27.08, 29.63, 32.16, 33.09, 127.05, 129.15, 130.78, 139.94; IR (neat) 3020, 3005, 2958, 2929, 1652, 1465, 1456, 910, 737, 694, 669 cm^{-1}; HRMS: calcd for $C_{12}H_{20}$ m/z 164.15650, found m/z 164.15636.

(*Z*)-1-(3-Cycloheptenyl)-1-hexene (Table 2, entry 63)

This diene was purified over silica gel using hexane as the eluent. ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H, *J* = 6.9 Hz, CH_3), 1.30 - 1.66 (m, 10 H, CH_2's), 1.98 - 2.00 (m, 2 H, C=CCH_2), 2.09 - 2.12 (m, 2 H, C=C-CH_2), 2.88 - 2.90 (m, 1 H, C=CCHC=C), 5.35 - 5.50 (m, 2 H, *n*-BuCH=CH), 5.59 (dd, 1 H, *J* = 4.2 Hz, *J* = 11.4 Hz, C<u>H</u>=CH), 5.70 - 5.79 (m, 1 H, CH=C<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 13.96, 22.23, 27.18, 28.83, 29.60, 31.87, 32.26, 34.21, 43.27, 128.38, 130.99, 134.59, 136.21; IR (neat) 3017, 2957, 2872, 1647, 1466, 1445, 1379, 986, 908, 858, 737, 690, 683 cm^{-1}; HRMS: calcd for $C_{13}H_{22}$ m/z 178.17215, found m/z 178.17193.

2-((*Z*)-1-hexenyl)-2,5-dihydrofuran (Table 2, entry 65)

This diene was purified over silica gel using hexane / EtOAc (10 : 1) as the eluent. ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3 H, J = 6.6 Hz, CH_3), 1.20 - 1.36 (m, 4 H, CH_2's), 2.08 (t, 2 H, J = 6.6 Hz, C=C-CH_2), 4.55 - 4.59 (m, 2 H, C=C-CH_2-O), 4.66 - 4.69 (m, 1 H, C=C-CH-C=C), 5.30 (dd, 1 H, J = 10.5 Hz, J = 9 Hz, *n*-BuCH=C<u>H</u>), 5.43 - 5.50 (m, 1 H, *n*-Bu<u>CH</u>=CH), 5.63 - 5.66 (m, 1 H, dihydrofuran <u>CH</u>=CH), 5.87 - 5.89 (m, 1 H, dihydrofuran CH=<u>CH</u>); ^{13}C NMR ($CDCl_3$) δ 13.85, 22.22, 27.18, 31.83, 74.84, 81.47, 126.59, 129.16, 129.40, 132.36; IR (neat) 3015, 2959, 2874, 1446, 1261, 1101, 1070, 1020, 905, 802, 754, 733, 687 cm^{-1}; HRMS: calcd for $C_{10}H_{16}O$ m/z 152.12012, found m/z 152.12038.

(*E*)-1-(3-Cyclopentenyl)-1-hexene (Table 2, entry 67)

This diene was purified over silica gel using hexane as the eluent. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.9 Hz, CH_3), 1.27 - 1.35 (m, 4 H, CH_2's), 1.95 - 2.12 (m, 4 H, CH_2's), 2.27 - 2.36 (m, 2 H, C=C-CH_2), 3.20 - 3.26 (m, 1 H, C=C-CH-C=C), 5.29 - 5.46 (m, 2 H, *n*-BuCH=CH), 5.57 - 5.61 (m, 1 H, cyclopentenyl <u>CH</u>=CH), 5.72 - 5.76 (m, 1 H, cyclopentenyl CH=<u>CH</u>); ^{13}C NMR ($CDCl_3$) δ 13.98, 22.26, 22.71, 30.95, 31.81, 32.20, 48.56, 129.03, 130.77, 133.91, 134.47; IR (neat) 3055, 2959, 1612, 1466, 1458, 1379, 1286, 1088, 966, 912, 721 cm^{-1}; HRMS: calcd for $C_{11}H_{18}$ m/z 150.14085, found m/z 150.14104.

(*E*)-1-(3-Cyclohexenyl)-1-hexene (Table 2, entry 68)

This diene was purified over silica gel using hexane as the eluent. ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 6.9 Hz, CH_3), 1.25 - 1.42 (m, 4 H, CH_2's), 1.48 - 1.53 (m, 2 H,

CH_2), 1.70 - 1.75 (m, 2 H, CH_2), 1.96 - 2.06 (m, 4 H, C=C-CH_2's), 2.68 - 2.73 (m, 1 H, C=C-CH-C=C), 5.36 - 5.41 (m, 2 H, *n*-BuCH=CH), 5.52 - 5.56 (m, 1 H, C<u>H</u>=CH), 5.65 - 5.71 (m, 1 H, CH=C<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 13.97, 20.69, 22.23, 25.15, 29.58, 31.84, 32.30, 38.39, 127.18, 129.67, 130.55, 134.30; IR (neat) 3020, 2957, 2874, 1466, 1456, 966, 908, 737, 723, 677 cm^{-1}; HRMS: calcd for $C_{12}H_{20}$ m/z 164.15650, found m/z 164.15644.

(*E*)-1-(3-Cycloheptenyl)-1-hexene (Table 2, entry 69)

This diene was purified over silica gel using hexane as the eluent. ^1H NMR ($CDCl_3$) δ 0.89 (t, 3 H, *J* = 6.9 Hz, CH_3), 1.30 - 1.66 (m, 10 H, CH_2's), 1.98 - 2.00 (m, 2 H, C=CCH_2), 2.09 - 2.12 (m, 2 H, C=CCH_2), 2.88 - 2.90 (m, 1 H, C=CCHC=C), 5.35 - 5.50 (m, 2 H, *n*-BuCH=CH), 5.59 (dd, 1 H, *J* = 4.2 Hz, *J* = 11.4 Hz, C<u>H</u>=CH), 5.70 - 5.79 (m, 1 H, CH=C<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 13.96, 22.22, 27.18, 28.83, 29.60, 31.87, 32.26, 34.21, 43.27, 128.38, 130.99, 134.59, 136.21; IR (neat) 3017, 2957, 2872, 1647, 1466, 1445, 1379, 986, 908, 858, 737, 690, 683 cm^{-1}; HRMS: calcd for $C_{13}H_{22}$ m/z 178.17215, found m/z 178.17193.

2-((*E*)-1-hexenyl)-2,5-dihydrofuran (Table 2, entry 70)

This diene was purified over silica gel using hexane / EtOAc (10 : 1) as the eluent. ^1H NMR ($CDCl_3$) δ 0.89 (t, 3 H, *J* = 6.9 Hz, CH_3), 1.29 - 1.39 (m, 4 H, CH_2's), 2.04 (dt, 2 H, *J* = 6.9 Hz, *J* = 6.9 Hz, C=CCH_2), 4.58 - 4.72 (m, 2 H, CH_2O), 5.17 (br s, 1 H, C=CCHC=C), 5.41 (dd, 1 H, *J* = 6.9 Hz, *J* = 15.3 Hz, *n*-BuCH=C<u>H</u>), 5.65 - 5.74 (m, 2 H, *n*-BuC<u>H</u>=CH and dihydrofuran C<u>H</u>=CH), 5.90 (d, 1 H, *J* = 5.7 Hz, dihydropyran CH=C<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 14.30, 22.61, 31.57, 32.19, 75.32, 87.31, 126.98,

129.76, 130.12, 133.63; IR (neat) 3082, 2958, 2928, 2873, 2854, 1666, 1618, 1466, 1458, 1352, 1261, 1086, 1061, 1020, 968, 908, 800, 735, 694 cm^{-1}; HRMS: calcd for $C_{10}H_{16}O$ m/z 152.12012, found m/z 152.11998.

1-(3-Cyclopentenyl)-1-cyclohexene (Table 2, entry 71)

This diene was purified over silica gel using hexane as the eluent. ^1H NMR ($CDCl_3$) δ 1.52 - 1.65 (m, 4 H, CH_2's), 1.88 - 2.11 (m, 6 H, CH_2's), 2.27 - 2.36 (m, 2 H, C=C-CH_2), 3.19 - 3.24 (m, 1 H, C=CCHC=C), 5.41 (br s, 1 H, CH=C), 5.59 - 5.63 (m, 1 H, C<u>H</u>=CH), 5.76 - 5.80 (m, 1 H, CH=C<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 22.75, 23.12, 25.26, 26.43, 29.32, 32.37, 52.96, 119.70, 131.13, 133.61, 140.90; IR (neat) 3051, 2993, 2923, 1664, 1614, 1458, 1446, 1375, 1350, 1134, 1013, 920, 802, 754, 727 cm^{-1}; HRMS: calcd for $C_{11}H_{16}$ m/z 148.12520, found m/z 148.12497.

3-(Cyclohexenyl)-1-cycloheptene (Table 2, entry 75)

This diene was purified over silica gel using hexane as the eluent. ^1H NMR ($CDCl_3$) δ 1.48 - 1.69 (m, 10 H, CH_2's), 1.90 - 2.02 (m, 4 H, C=CCH_2's), 2.12 - 2.19 (m, 2 H, C=CCH_2), 2.76 - 2.79 (m, 1 H, C=C-CH-C=C), 5.44 (br s, 1 H, CH=C), 5.58 (dd, 1 H, J = 3.9 Hz, J = 11.4 Hz, C<u>H</u>=CH), 5.72 - 5.81 (m, 1 H, CH=C<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 22.78, 23.26, 25.28, 26.44, 27.09, 28.67, 30.16, 32.59, 48.49, 120.15, 131.09, 136.55, 142.03; IR (neat) 3016, 2925, 2854, 2837, 1745, 1666, 1645, 1494, 1446, 1269, 1136, 1084, 956, 931, 879, 788 cm^{-1}; HRMS: calcd for $C_{13}H_{20}$ m/z 176.15650, found 176.15642.

2-(1-Cyclohexenyl)-2,5-dihydrofuran (Table 2, entry 76)

This diene was purified over silica gel using hexane / EtOAc (10 : 1) as the eluent. ^{1}H NMR ($CDCl_3$) δ 1.56 - 1.64 (m, 4 H, CH_2's), 2.02 - 2.03 (m, 4 H, C=CCH_2's), 4.63 - 4.69 (m, 2 H, CH_2-O), 5.12 (br s, 1 H, C=CCHC=C), 5.68 - 5.71 (m, 2 H, CH=CH), 5.92 - 5.95 (m, 1 H, CH=C); ^{13}C NMR ($CDCl_3$) δ 22.52 (two overlapping signals), 23.36, 25.05, 75.61, 90.53, 124.14, 127.02, 128.77, 137.99; IR (neat) 3078, 2923, 28.35, 1456, 1446, 1436, 1379, 1350, 1282, 1259, 1174, 1082, 1053, 1022, 920, 837, 797, 719, 649 cm^{-1}; HRMS: calcd for $C_{10}H_{14}O$ m/z 150.10447, found 150.10467.

(*E*)-1-(3-Cyclopentenyl)-3,3-dimethyl-1-butene (Table 2, entry 77)

This diene was purified over silica gel using hexane as the eluent. ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 9 H, *t*-Bu), 1.45 - 1.56 (m, 2 H, CH_2), 2.03 - 2.38 (m, 2 H, C=C-CH_2), 3.19 - 3.24 (m, 1 H, C=CCHC=C), 5.26 (dd, 1 H, *J* = 15. 6 Hz, *J* = 7.8 Hz, *t*-BuCH=C<u>H</u>), 5.44 (d, 1 H, *J* = 15.6 Hz, *t*-Bu<u>C</u>H=CH), 5.59 - 5.60 (m, 1 H, cyclopentenyl C<u>H</u>=CH), 5.73 - 5.76 (m, 1 H, cyclopentenyl CH=C<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 29.85, 31.04, 32.18, 32.61, 48.48, 128.55, 130.66, 134.67, 140.20; IR (neat) 3060, 3010, 2960, 2870, 1470, 1455, 1360, 1270, 1195, 970, 720 cm^{-1}; HRMS: calcd for $C_{11}H_{18}$ m/z 150.14085, found m/z 150.14082.

(*E*)-1-(3-Cycloheptenyl)-3,3-dimethyl-1-butene (Table 2, entry 82)

This diene was purified over silica gel using hexane as the eluent. ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9 H, *t*-Bu), 1.32 - 1.48 (m, 2 H, CH_2), 1.54 - 1.69 (m, 2 H, CH_2), 1.84 - 1.92 (m, 2 H, CH_2), 2.09 - 2.11 (m, 2 H, C=C-CH_2), 2.85 - 2.89 (m, 1 H, C=C-CH-C=C), 5.35 (dd, 1 H, *J* = 15.6 Hz, *J* = 9.9 Hz, *t*-BuCH=C<u>H</u>), 5.45 (d, 1 H, *J* = 15.6

Hz, *t*-BuC<u>H</u>=CH), 5.59 (dd, 1 H, J = 11.4 Hz, J = 4.5 Hz, cycloheptenyl C<u>H</u>=CH), 5.76 (ddd, 1 H, J = 6.3 Hz, J = 4.5 Hz, J = 1.8 Hz, cycloheptenyl CH=C<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 27.14, 28.82, 29.64, 29.85, 32.68, 34.33, 43.16, 129.13, 131.03, 136.47, 140.02; IR (neat) 3017, 2961, 2862, 1475, 1462, 1391, 1362, 1267, 1204, 970, 737, 689 cm^{-1}; HRMS: calcd for $C_{13}H_{22}$ m/z 178.17215, found m/z 178.17198.

2-((*E*)-3,3-Dimethyl-1-butenyl)-2,5-dihydrofuran (Table 2, entry 88)

This diene was purified over silica gel using hexane / EtOAc (10 : 1) as the eluent. ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 9 H, *t*-Bu), 4.48 - 4.66 (m, 2 H, CH_2O), 5.08 (br s, 1 H, C=C-CH-C=C), 5.25 (dd, 1 H, J = 15.3 Hz, J = 7.8 Hz, *t*-BuCH=C<u>H</u>), 5.63 - 5.67 (m, 1 H, dihydrofuran C<u>H</u>=CH), 5.63 (d, 1 H, J = 15. 3 Hz, *t*-BuC<u>H</u>=CH), 5.81 - 5.85 (m, 1 H, dihydrofuran CH=C<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 29.37, 32.80, 74.93, 87.31, 124.52, 126.00, 129.51, 144.03; IR (neat) 3005, 2959, 2903, 1475, 1462, 1364, 1263, 1088, 1065, 1020, 970, 800 cm^{-1}; HRMS: calcd for $C_{10}H_{16}O$ m/z 152.12012, found m/z 152.12039.

(Z)-1-(3-Cyclopentenyl)-4-(2-tetrahydropyranoxy)-1-butene (Table 2, entry 92)

This diene was isolated as a mixture of two diastereomers and was purified over silica gel using hexane / EtOAc (5 : 1). ^{1}H NMR ($CDCl_3$) δ 1.41 - 1.80 (m, 6 H, CH_2's), 1.94 - 2.10 (m, 2 H, C=C-CH_2), 2.02 - 2.36 (m, 4 H, C=C-CH_2's), 3.29 - 3.45 (m, 2 H, C=C-CH_2-C<u>H</u>$_2$-O), 3.52 - 3.57 (m, 1 H, C=C-CH-C=C), 3.62 - 3.71 (m, 1 H, C(<u>H</u>)H-O), 3.75 - 3.83 (m, 1 H, C(H)<u>H</u>-O), 4.52 (dd, 1 H, J = 6.9 Hz, J = 3.3 Hz, O-CH-O), 5.20 - 5.29 (m, 2 H, THPOCH_2CH_2-C<u>H</u>=C<u>H</u>), 5.43 - 5.52 (m, 1 H,

cyclopentenyl C<u>H</u>=CH), 5.65 - 5.70 (m, 1 H, cyclopentenyl CH=C<u>H</u>); (there are overlapping ^{13}C signals); ^{13}C NMR ($CDCl_3$) δ 19.37, 25.35, 28.00, 30.81, 30.91, 31.90, 32.05, 32.75, 43.29, 48.33, 61.92, 66.89, 67.01, 98.36, 98.41, 124.43, 124.79, 130.74, 133.91, 134.01, 135.66, 135.84; IR (neat) 3051, 3005, 2941, 2869, 1652, 1076, 966 cm^{-1}; HRMS: calcd for $C_{14}H_{22}O_2$ m/z 222.16198, found m/z 222.16165.

(*E*)-1-(3-Cyclopentenyl)-3-(2-tetrahydropyranoxy)-1-octene (Table 2, entry 97)

This diene was isolated as a mixture of 3 diastereomers and was purified over silica gel using hexane / EtOAc (4 : 1) as the eluent. ^1H NMR ($CDCl_3$) δ 0.88 - 2.33 (m, 21 H, CH_2's and CH_3), 3.29 - 3.30 (m, 1 H, CH-O), 3.35 - 3.49 (m, 1 H, C=C-CH-C=C), 3.87 - 3.88 (m, 1 H, C(<u>H</u>)H-O), 4.03 - 4.66 (m, 1 H, C(H)<u>H</u>-O), 4.67 (s, 1 H, O-CH-O), 5.20 (dd, 1 H, J = 15.3 Hz, J = 8.4 Hz, C_5-CH=C<u>H</u>), 5.50 - 5.59 (m, 2 H, C_5-C<u>H</u>=CH and cyclopentenyl C<u>H</u>=CH), 5.76 - 5.77 (m, 1 H, cyclopentenyl CH=C<u>H</u>); (there are overlapping ^{13}C signals) ^{13}C NMR ($CDCl_3$) δ 19.52, 19.77, 19.93, 22.56, 24.83, 25.30, 25.50, 25.63, 30.67, 30.78, 30.86, 31.80, 32.62, 34.78, 35.81, 48.04, 48.10, 61.98, 62.41, 75.71, 75.77, 77.75, 94.29, 97.46, 97.52, 128.62, 130.00, 131.05, 131.09, 131.26, 135.56, 133.65, 133.83, 135.02, 135.10, 137.80; IR (neat) 3053, 1664, 1284, 1261, 1201, 1184, 1161, 1130, 1112, 1078, 1035, 1020, 985, 937, 910 cm^{-1}; HRMS: calcd for $C_{18}H_{30}O_2$ m/z 278.22459, found m/z 278.22448.

Methyl cyclopent-2-enylideneacetate (Table 2, entry 108)

This diene was purified over silica gel using hexane / EtOAc (4 : 1) as the eluent. ^{1}H NMR ($CDCl_3$) δ 2.48 - 2.52 (m, 4 H, CH_2's), 3.08 (d, 2 H, J = 7.2 Hz, C=C-CH_2-C=O), 3.67 (s, 3 H, OCH_3), 5.45 (t, 1 H, J = 7.2 Hz, C=C<u>H</u>-CH_2), 6.05 - 6.07 (m, 1 H, cyclopentenyl C<u>H</u>=CH), 6.14 (d, 1 H, J = 5.7 Hz, cyclopentenyl CH=C<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 25.83, 31.70, 34.75, 51.44, 109.64, 133.86, 137.62, 150.12, 172.21; IR (neat) 3157, 3057, 2953, 2930, 1740, 1612, 1259, 991, 914 cm^{-1}; HRMS: calcd for $C_9H_{12}O_2$ m/z 152.08373, found m/z 152.08362.

Ethyl 2-(3-cyclopentenyl)propenoate (Table 2, entry 131)

This diene was purified over silica gel using hexane / EtOAc (4 : 1) as the eluent. ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3 H, J = 7.2 Hz, CH_3), 2.28 - 2.37 (m, 4 H, CH_2's), 3.76 (br s, 1 H, C=C-CH-C=C), 4.25 (q, 2 H, J = 7.2 Hz, O-CH_2), 5.49 (d, 1 H, J = 1.2 Hz, C=C(<u>H</u>)H), 5.63 - 5.65 (m, 1 H, cyclopentenyl C<u>H</u>=CH), 5.88 - 5.91 (m, 1 H, cyclopentenyl CH=C<u>H</u>), 6.12 (d, 1 H, J = 1.2 Hz, C=C(H)<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 14.14, 31.16, 31.74, 46.22, 6049, 122.48, 132.00, 132.57, 144.43, 167.20; IR (neat) 3055, 2982, 2963, 1718, 1628, 1261 cm^{-1}; HRMS: calcd for $C_{10}H_{14}O_2$ m/z 166.21996, found m/z 166.09938.

3-(3-Cyclopentenyl)-2-cyclohexenone (Table 3, entry 17)

This diene was purified over silica gel using hexane / EtOAc (4 : 1) as the eluent. ^{1}H NMR ($CDCl_3$) δ 2.41 - 2.59 (m, 10 H, CH_2's), 3.59 - 3.70 (m, 1 H, C=C-CH-C=C), 5.74 - 5.77 (m, 1 H, cyclopentenyl C<u>H</u>=CH), 6.02 (s, 1 H, C=CH-C=O), 6.06 - 6.09 (m, 1 H, cyclopentenyl CH=C<u>H</u>); ^{13}C NMR ($CDCl_3$) δ 22.68, 27.74, 29.17, 32.09,

37.29, 52.67, 123.28, 130.51, 133.52, 169.27, 200.12; IR (neat) 3053, 2943, 2868, 1668 cm^{-1}; HRMS: calcd for $C_{11}H_{14}O$ m/z 162.10447, found m/z 162.10424.

REFERENCES

1. Heck, R. F. *Org. React.* **1982**, *27*, 345.
2. Jeffrey, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287.
3. Jeffrey, T. *Tetrahedron Lett.* **1985**, *26*, 2667.
4. Larock, R. C.; Bernhardt, J. C.; Driggs, R. J. *J. Organomet. Chem.* **1978**, *156*, 45.
5. Larock, R. C.; Takagi, K. *J. Org. Chem.* **1988**, *53*, 4329.
6. Kim, J-I. I.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1981**, *46*, 1067.
7. Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1988**, *53*, 4909.
8. Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 5786.
9. Price, C. C.; Pappalardo, J. A. *Org. Synth. Coll. Vol. IV* **1963**, 186.
10. Luo, F-T.; Negishi, E-I. *J. Org. Chem.* **1985**, *50*, 4762.
11. MacLeod, A. J.; Rossiter, J. T. *J. Chem. Soc., Perkin Trans. I* **1983**, 717.
12. Zweifel, G.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *102*, 2753.
13. Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083.
14. Martinez, A. G.; Alvarez, R. M.; Fraite, A. G. *Synthesis* **1986**, 222.
15. Shostakovskii, M. F.; Komarov, N. V.; Yarosh, O. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1968**, 908.
16. Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
17. Michelot, D. *Synthesis* **1983**, *2*, 130.
18. Private communication from Dr. Kris Narayanan.
19. Brouwer, H.; Stothers, J. B. *Can. J. Chem.* **1972**, *50*, 601.
20. Piers, E.; Nagakura, I. *Synth. Commun.* **1975**, *5*, 193.
21. Baker, B. E. *Ph.D. Dissertation*, Iowa State, 1988.
22. Larson, S.; Luidhardt, T.; Kabalka, G. W.; Pagni, R. M. *Tetrahedron Lett.* **1988**, *29*, 35.

23. Janssen, C. G. M.; Simons, L. H. J. G.; Godroi, E. F. *Synthesis* **1982**, 389.

24. McMurray, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

25. Summerville, R. H.; Senklar, C. A. Schleyer, P. V. R.; Dueber, T. E.; Stang, P. J. *J. Am. Chem. Soc.* **1974**, *96*, 1100.

26. Martinez, A. G.; Alvarez, R. M.; Casado, M. M.; Subramanian, L. R.; Hanack, M. *Tetrahedron Lett.* **1987**, *43*, 275.

27. Larock, R. C. Baker, B .E. *Tetrahedron Lett.* **1988**, *29*, 905.

28. Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.

29. Larock, R. C.; Gong, W. H.; Baker, B. E. *Tetrahedron Lett.* **1989**, *30*, 2603.

30. Johnson, P. L. *M.S. Thesis* , Iowa State University, 1989.

31. Pross, A.; Sternhall, S. *Aust. J. Chem.* **1970**, *23*, 989

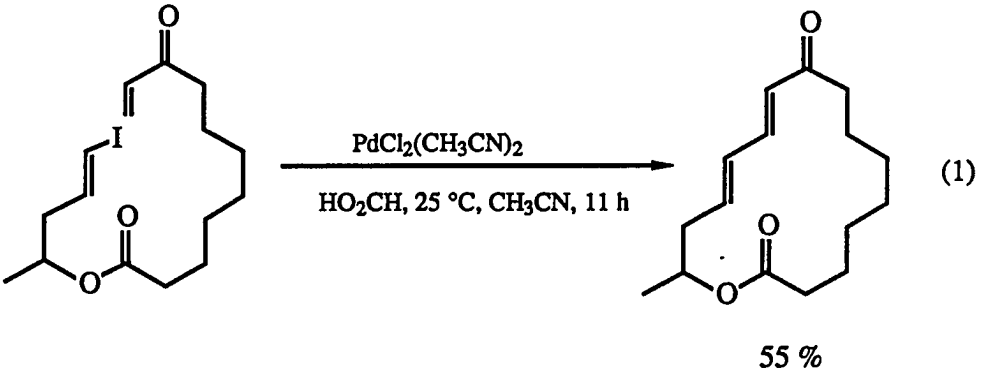
PART IV. PALLADIUM-CATALYZED INTRAMOLECULAR VINYLATION OF CYCLIC ALKENES

INTRODUCTION

The synthesis of carbo- and heterocycles is a formidable challenge to the organic chemist. Quite frequently, the methodology employed must be stereoselective, mild in reaction conditions, and accommodating to a wide variety of important functional groups present in the molecule. The use of the Heck reaction for forming carbon-carbon bonds is well known in the literature.[1] The exploitation of this methodology for intramolecular arylation of alkenes has been well examined.[2-25] Examples of the intramolecular vinylation of alkenes, on the other hand, have appeared less frequently. In fact, prior to our initiation of the work described in the section entitled Results and Discussion, there were only five reports describing the use of the Heck reaction for making cyclic compounds from dienyl halides. Since 1985, a large number of bi- and polycyclic compounds have been synthesized using this novel methodology, and a review of these reactions follows.

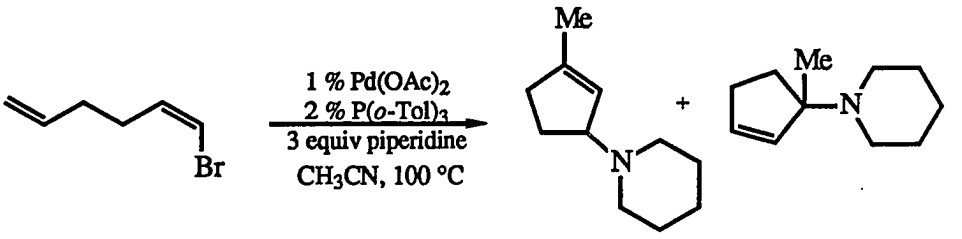
The use of palladium in the intramolecular vinylation of an alkene was first reported by Ziegler et al.[13] An interesting 16-membered ring lactone synthesis was achieved by the reaction of a vinylic iodide with an enone using one equivalent of a palladium salt under very dilute reaction conditions at 25 °C (eq 1).

The above lactone synthesis prompted Narula et al.[14] to develop a Pd-catalyzed intramolecular vinylation process. A number of dienyl bromides were prepared and reacted in the presence of a catalytic amount of a Pd salt and piperidine to afford five-membered ring products in good yields (eqs 2 and 3). Both reactions involve the



(1)

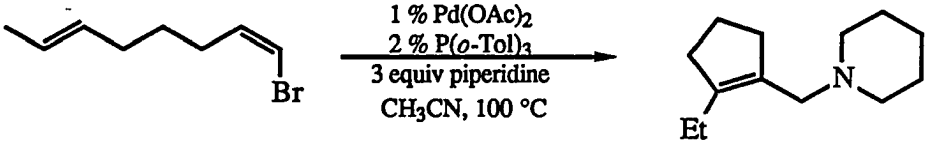
55 %



(2)

1 **2** **3**

68 % 9 %



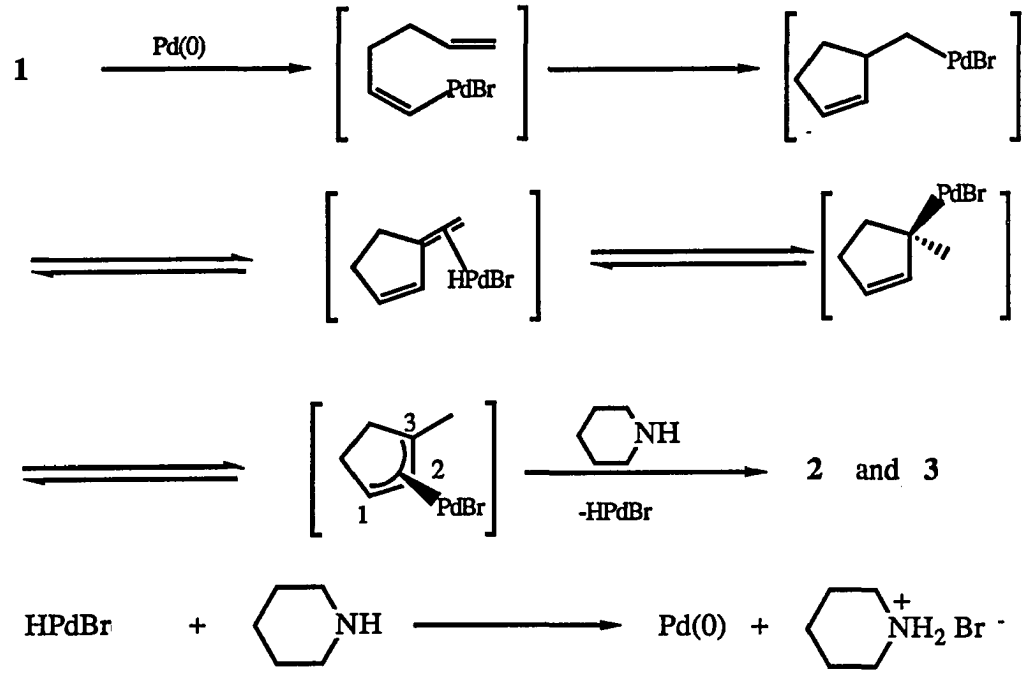
(3)

4 **5**

40 %

formation of a π-allylpalladium intermediate, and this species subsequently reacts with piperidine functioning as the nucleophile to yield **2** and **3** (Scheme I, all ligands were omitted in order to simplify the illustration). Product **2** results from the reaction of piperidine on C-1, while **3** comes from nucleophilic attack on the most hindered carbon of the π-allyl complex, C-3. A most interesting observation was made when a different solvent was employed in the reaction described in eq 2. Indeed, when benzene was used

Scheme I

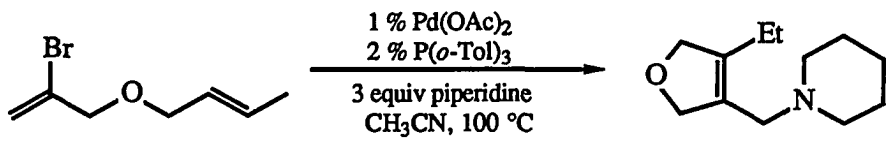


as the solvent, the yield of **3** increased to 29 % at the expense of **2**! The reaction shown in eq 3, however, generated only one isomer from the reaction of piperidine with the least hindered carbon of the π-allyl intermediate (eqs 3 and 4). A notable feature of the above

(4)

reaction is the preferred formation of only five-membered ring compounds. This preference can only occur from attack of the vinylic palladium species onto the internal carbon atom of the alkene. This is unusual in light of the results obtained in the intermolecular Pd-catalyzed cross-coupling of a vinylic bromide with a 1-alkene in which vinylation occurrs selectively at the terminal olefinic carbon atom.[1] When a tertiary amine such as Et_3N was employed as the base, the reaction rates and yields of identifiable products were greatly decreased.

Shi and co-workers[15] prepared a number of bromo dialkenyl ethers and cyclized them under similar Pd conditions (eqs 5 and 6). Again, there was a preference for

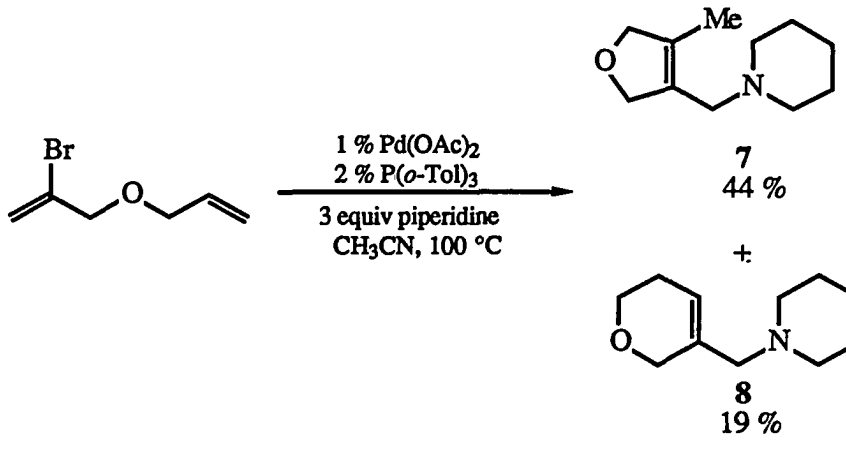


(5)

6

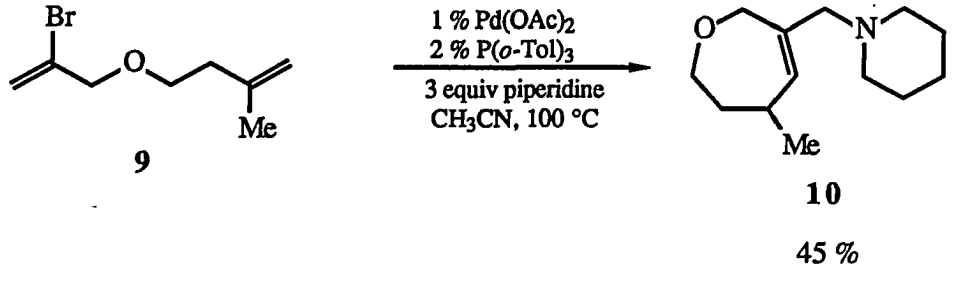
60 %

forming five-membered ring products in both cases, but allyl 2-bromoallyl ether gave a 2 : 1 mixture of five- and six-membered ring products (eq 6). Dihydropyran **8** undoubtedly comes from attack on the terminal carbon atom of the allyl ether moiety producing the six-membered ring product. By increasing the steric hindrance of one of the olefinic carbons,



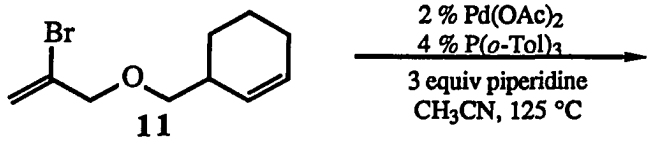
(6)

bromo dialkenyl ether **9** cyclized to produce only a seven-membered cyclic ether **10** (eq 7). Bromoallyl ether **11** which contained a cyclic alkene reacted to produce very little, if



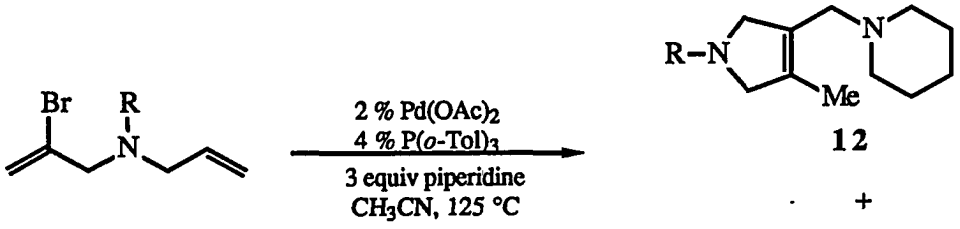
(7)

any, cyclized products (eq 8). The failure to cyclize presumably comes from steric



(8)

hindrance around the cyclic alkene. A number of bromo dialkenylamines were reacted under similar catalytic reaction conditions (eq 9). Generally, low yields and bad mixtures of five- and six-membered cyclic amine products were observed. By increasing the size of the R group, a higher yield of **13** was obtained along with higher overall yields of **12** and **13**. Apparently, by increasing the steric hindrance around the internal olefinic carbon,

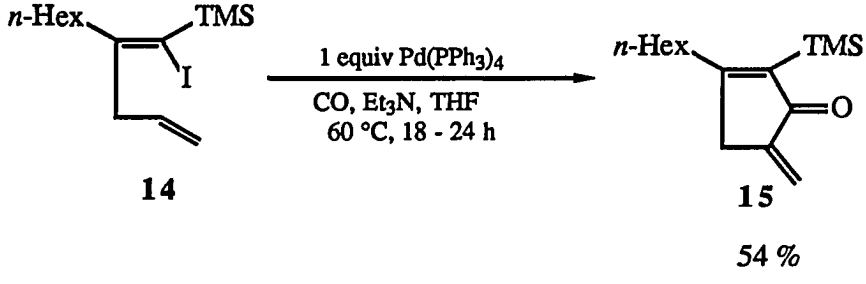


(9)

R	% 12	% 13
H	15	4
Me	33	11
COMe	38	38

vinylation occurred increasingly on the terminal carbon atom. In general, five-membered rings are formed in preference to six-membered rings, whether the dienyl bromide is all carbon or contains an oxygen or a nitrogen atom. However, this preference may be altered if the double bond carbons are not simularly substituted. Unsubstituted olefinic carbons are more reactive than monosubstituted ones, and disubstituted olefinic carbon atoms do not react.

Negishi and Miller[16] developed a novel Pd(0) method for synthesizing cyclopentadienones (eq 10). Dienyl iodide **14**, prepared from the allylzincation of 1-trimethylsilyl-



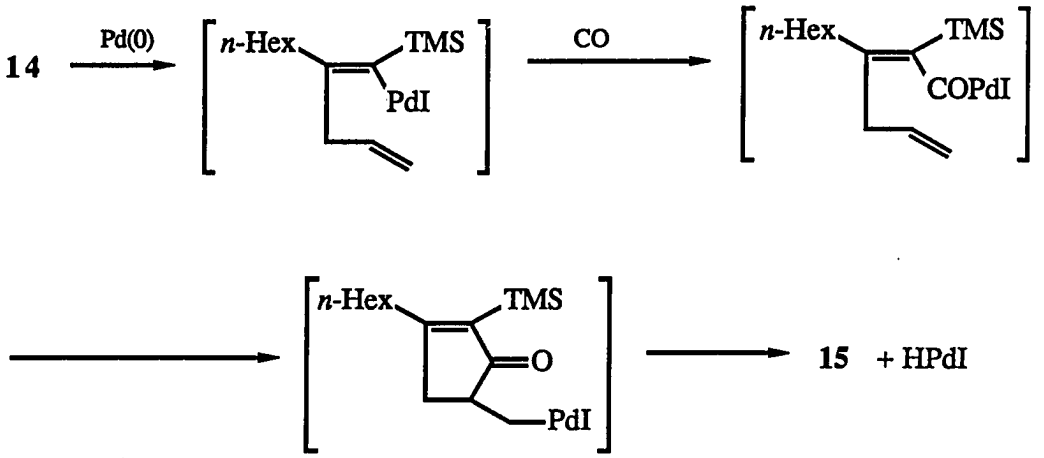
14 **15**

54 %

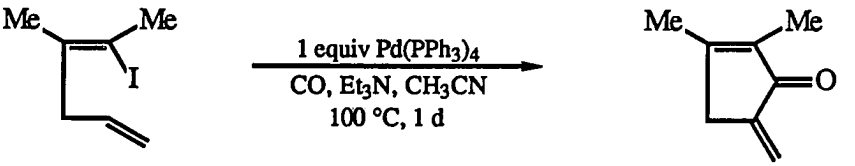
(10)

1-octyne, followed by a number of synthetic transformations, reacted with a stoichiometric amount of $Pd(PPh_3)_4$ under an atmosphere of CO to produce cyclopentadienone **15**. This reaction proceeds by the mechanism illustrated in Scheme II. Oxidative

Scheme II



addition of **14** onto Pd(0) affords a vinylic palladium iodide, which under an atmosphere of CO produces an acylpalladium species. The latter then adds across the alkene double bond, followed by palladium hydride elimination to afford **15**. This methodology was successfully applied to the synthesis of methylenemycin B (**16**) (eq 11). While this is a

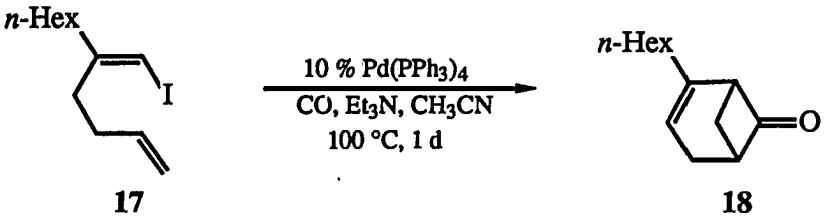


(11)

16
51 %

one-pot process affording the desired product, the major limitation of the reaction is that it is stoichiometric in palladium. All attempts to achieve the same transformation using only a catalytic amount of Pd reportedly failed.

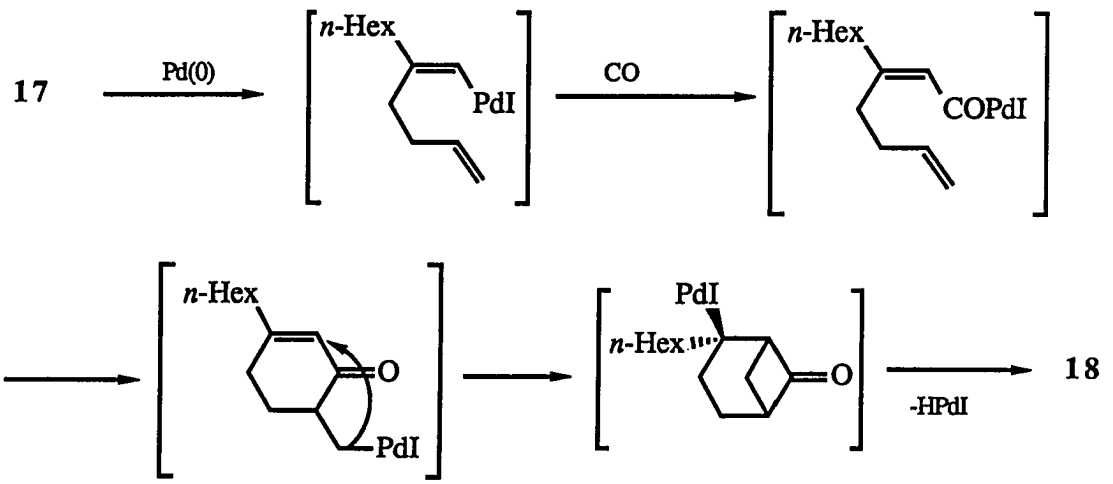
Later in 1985, Tour and Negishi[17] reported limited success in intramolecular acyl-palladation to make a variety of cycloalkenone derivatives (eq 12). This interesting



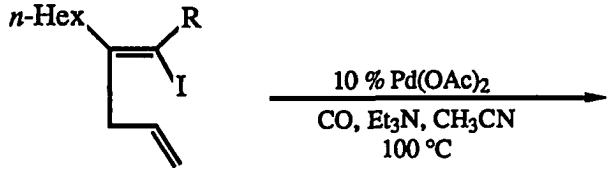
17 18 55 % (12)

reaction merits a closer examination of its mechanism (see Scheme III). Under the same

Scheme III



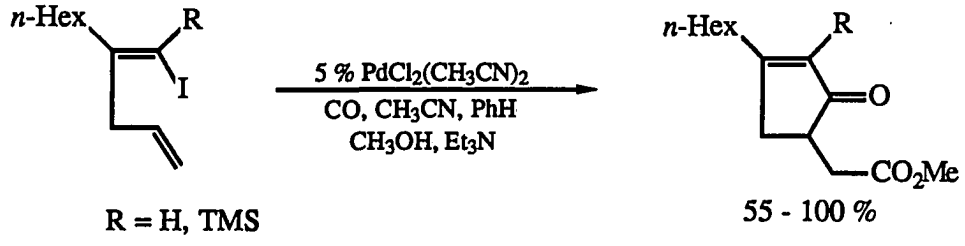
reaction conditions, two other dienyl iodides failed to cyclize and only polymeric material was recovered each time (eq 13). These side reactions were inhibited by running the Pd-



(13)

R = H, TMS

catalyzed carbonylation reactions in the presence of methanol (eq 14). The ester, which

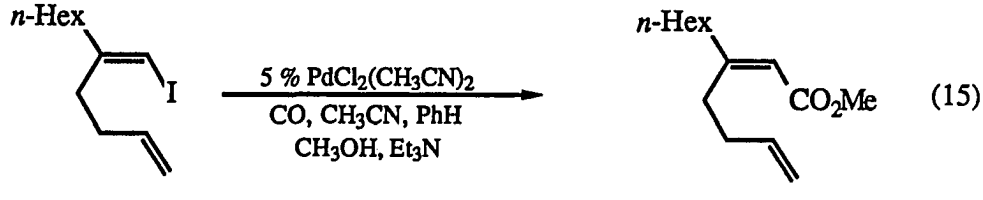


(14)

R = H, TMS

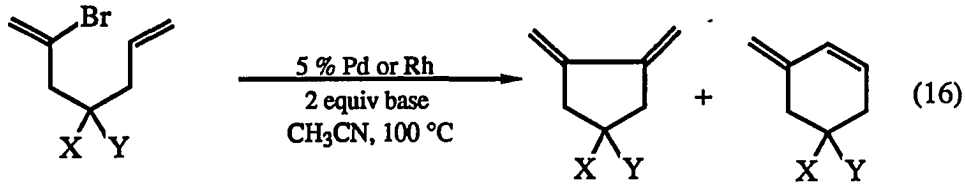
55 - 100 %

was afforded in high yields, resulted from methanolysis of the alkylpalladium intermediate. The following points are worth noting. Both Pd(0) and Pd(II) catalysts, such as $Pd(PPh_3)_4$, $Pd(dba)_2$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, and $PdCl_2$ were effective in the above reactions. The mode of cyclization is only exo trig. No products formed via intramolecular Heck alkenylation were observed. When a longer chain dienyl iodide was employed in the hopes of obtaining large ring systems, the rate of methanolysis was faster than the rate of acylpalladation of the alkene (eq 15).



(15)

Grigg et al.[18] examined the use of Pd and Rh catalysts in the cyclization of bromodienes **19** to determine if this was an efficient method for synthesizing a variety of dienes (eq 16). It was discovered that $Pd(PPh_3)_4$ produced a 1 : 10 ratio of **20** to **21**, while



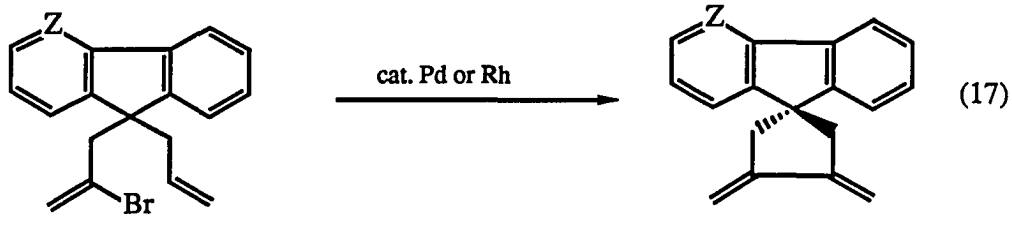
(16)

19 **20** **21**

X = H, CO_2Et, Me, COMe

Y = H, CO_2Et, COPh, COMe

$RhCl(PPh_3)_3$ (Wilkinson's catalyst) produced the same products, but in the opposite ratio. In contrast to the above results, dienyl bromide **22** cyclized to provide only the 5-exo trig product regardless of the catalyst employed (eq 17).



(17)

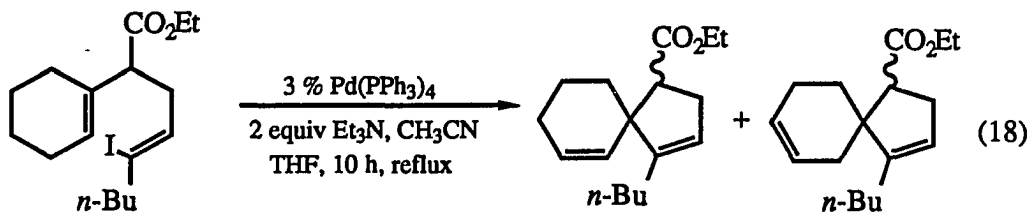
22 **23**

Z= CH, N 70 - 90 %

In a full paper, Grigg et al.[19] extensively investigated the reaction parameters controlling the stereoselectivity of the cyclization of a large number of dienyl bromides. A variety of ligands consisting of monophosphines, diphosphines, and phosphites were examined,

and PPh_3 was found to be the superior ligand in these reactions. Since Jeffrey [20-22] had reported the usefulness of tetra-*n*-butylammonium chloride in Pd-catalyzed arylation and vinylation of alkenes, a variety of tetraethylammonium salts were also examined, with the chloride emerging as the most effective salt. The quaternary ammonium chloride was believed to function as an anion exchange agent which converts the intermediate vinylic palladium bromide to the chloride. The latter intermediate is believed to be a more reactive species in the vinylpalladation or palladium hydride elimination step of this reaction mechanism.

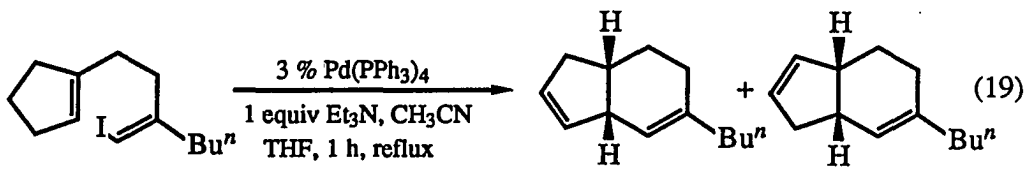
At the same time as our publication of the intramolecular vinylpalladation of cyclic alkenes, Negishi et al.[23] reported on an efficient synthesis of carbocyclic compounds in like manner. A number of dienyl iodides were prepared and reacted under Pd(0) conditions (eqs 18 to 21). In general, all cases proceeded to provide isomeric mixtures of



(18)

(4 : 1)

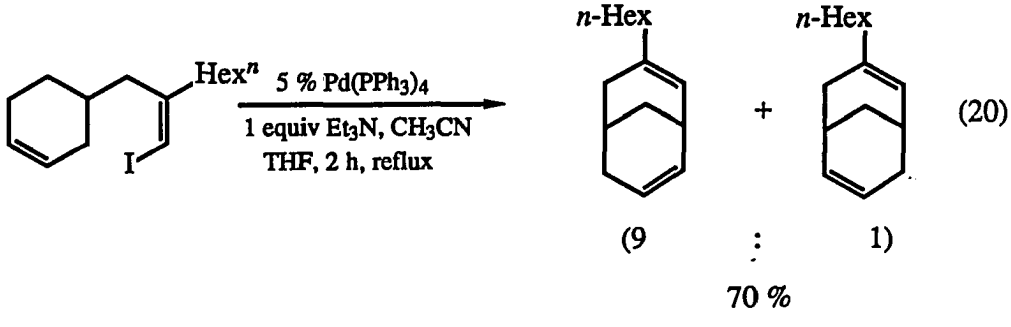
86 %



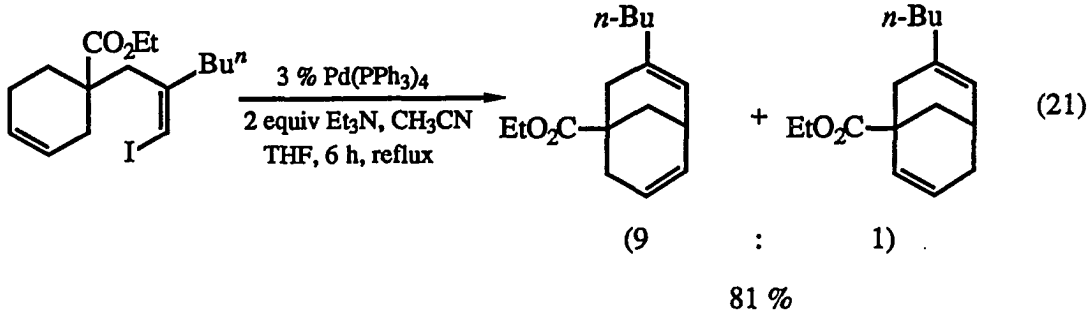
(19)

(9 : 1)

70 %



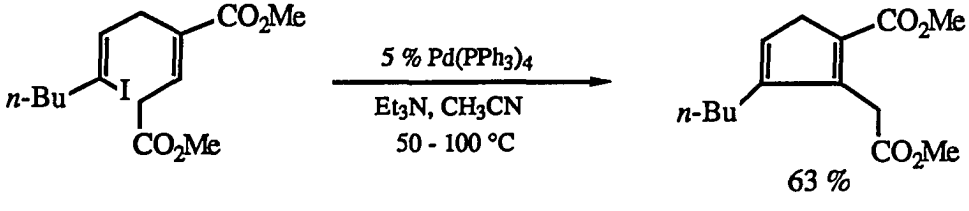
(20)



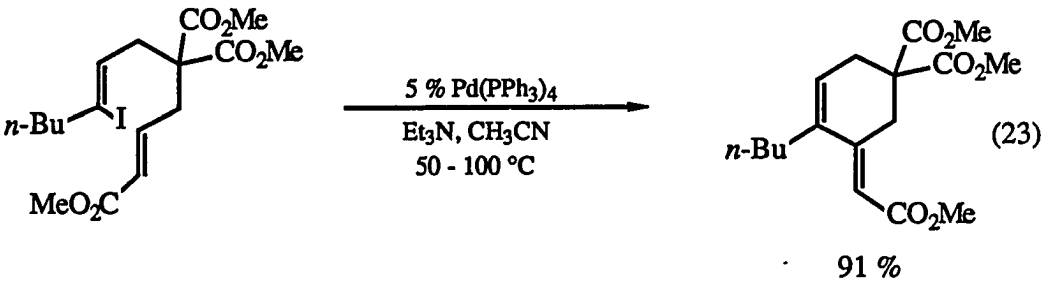
(21)

products in good to excellent yields. The presence of an ester group appears to slow the reaction rate (eqs 18 and 21). In eq 20, substituting Et_3N by two equivalents of NaOAc provided the cyclized products in a combined 97 % yield. Furthermore, the choice of Pd(0) catalyst is critical; using $Pd(dba)_2$ in eq 19 produced less than 10 % of the cyclized products after 10 hours.

O'Connor et al.[24] obtained complete regiocontrol in the vinylation reactions of α,β-unsaturated carbonyl compounds (eqs 22 and 23).

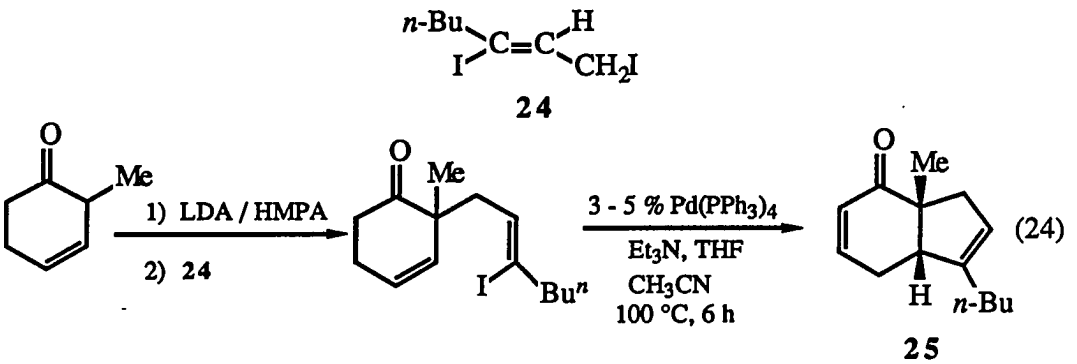


(22)

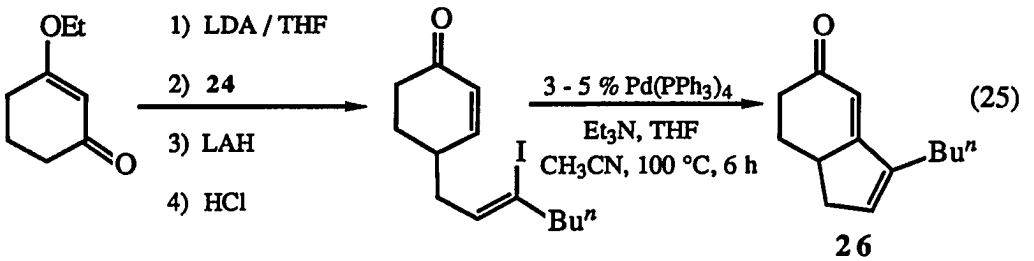


(23)

Using the above methodology, Zhang, O'Connor, and Negishi[25] developed a novel [3 + 2] annulation procedure employing **24** as a 3-carbon synthon (eqs 24 and 25).

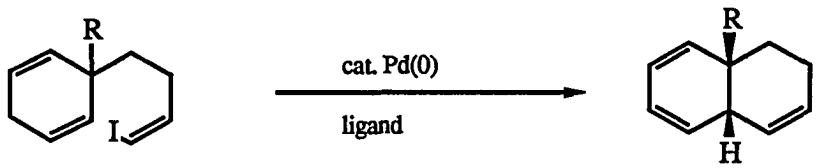


(24)



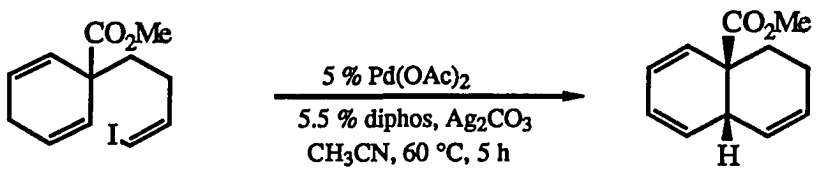
(25)

Recently, Sato and co-workers[26] reported the Pd-catalyzed asymmetric synthesis of a number of *cis*-decalin derivatives employing chiral ligands (eq 26). A number of



27 28 (26)

different Pd salts, ligands, bases, and solvents were first investigated in order to obtain the optimum reaction conditions for the cyclization of **29**. It was discovered that Abelman et al.[4] and Larock et al.[9] silver procedure provided the highest yield of **30** (eq 27). The



29 **30** (27)

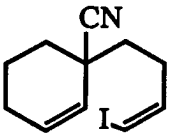
68 %

stereochemistry of the bridgehead groups of **30** was unequivocally determined to be *cis* by ^{1}H NMR (NOE) spectroscopy. Then a variety of optically active bidentate ligands and solvents were examined in order to obtain optimized reaction conditions for the preparation of **30** in high product yield and % ee. After much effort, it was discovered that (*R*)-BINAP[27] and 1-methyl-2-pyrrolidinone as solvent afforded **30** in 74 % yield and 33 % ee.

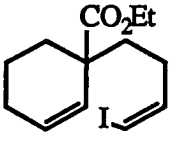
In summary, a wide variety of dienyl halides have been cyclized under a variety of Pd-catalyzed conditions to form bicyclic and polycyclic compounds. Even though reaction conditions have been mild, mixtures of regioisomers are common. It's clear there exists a need to develop a procedure that will provide the desired cyclized product in high yield and under mild conditions. The development of such a procedure is discussed in the following section.

RESULTS AND DISCUSSION

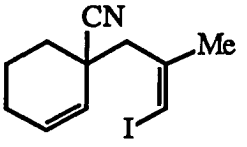
Each of the nine dienyl halides used for this investigation was prepared from a multistep sequence. Nitrile **31** and ester **32** were prepared by quenching the appropriate



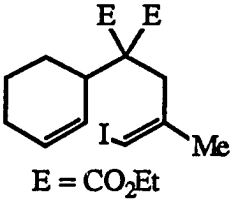
31



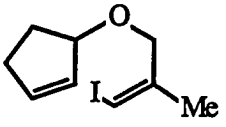
32



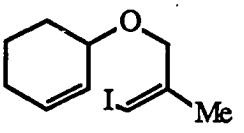
33



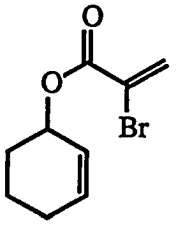
34



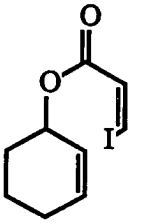
35



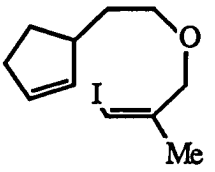
36



37



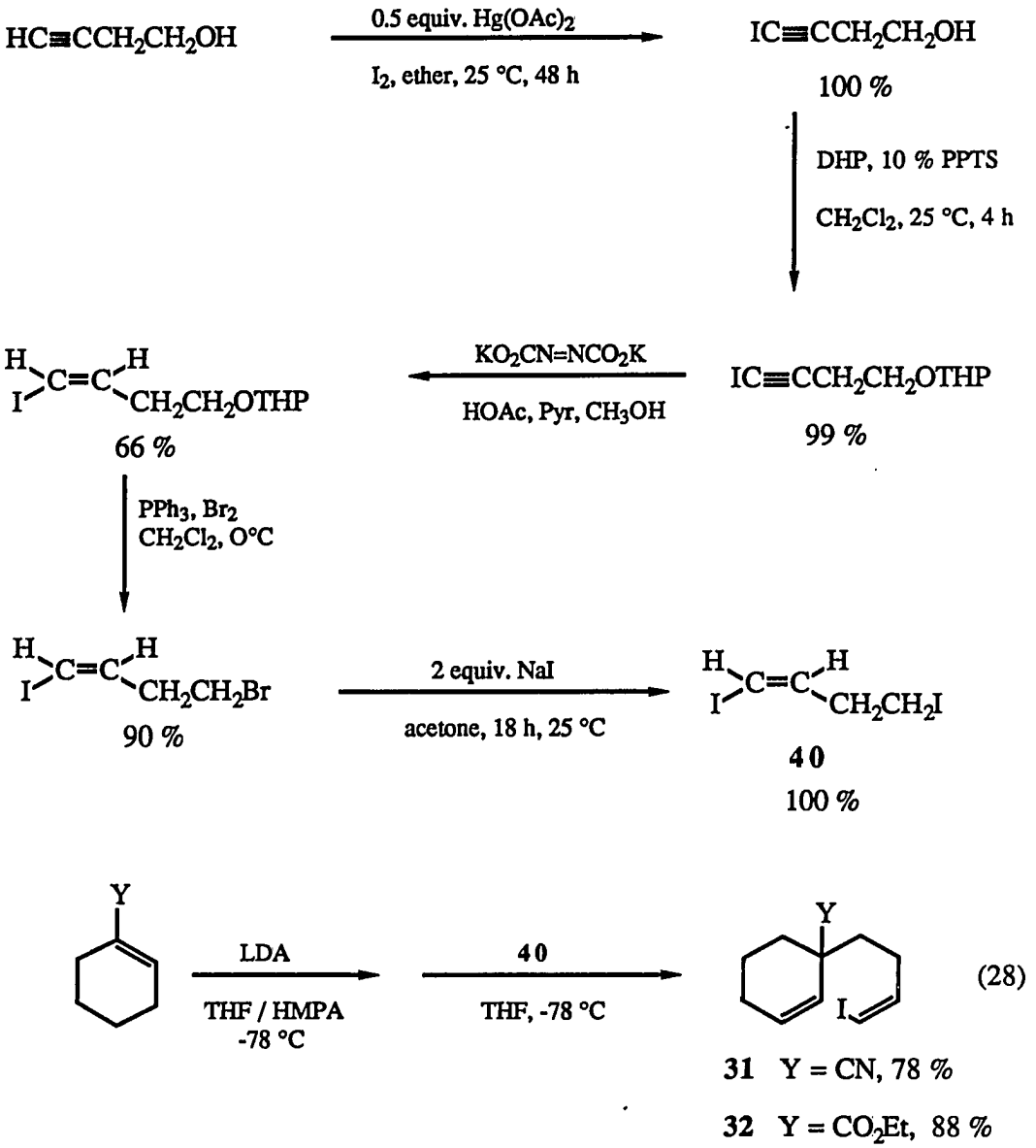
38



39

carbanions with (Z)-1,4-diiodo-1-butene (**40**) prepared as shown in Scheme IV (eq 28).

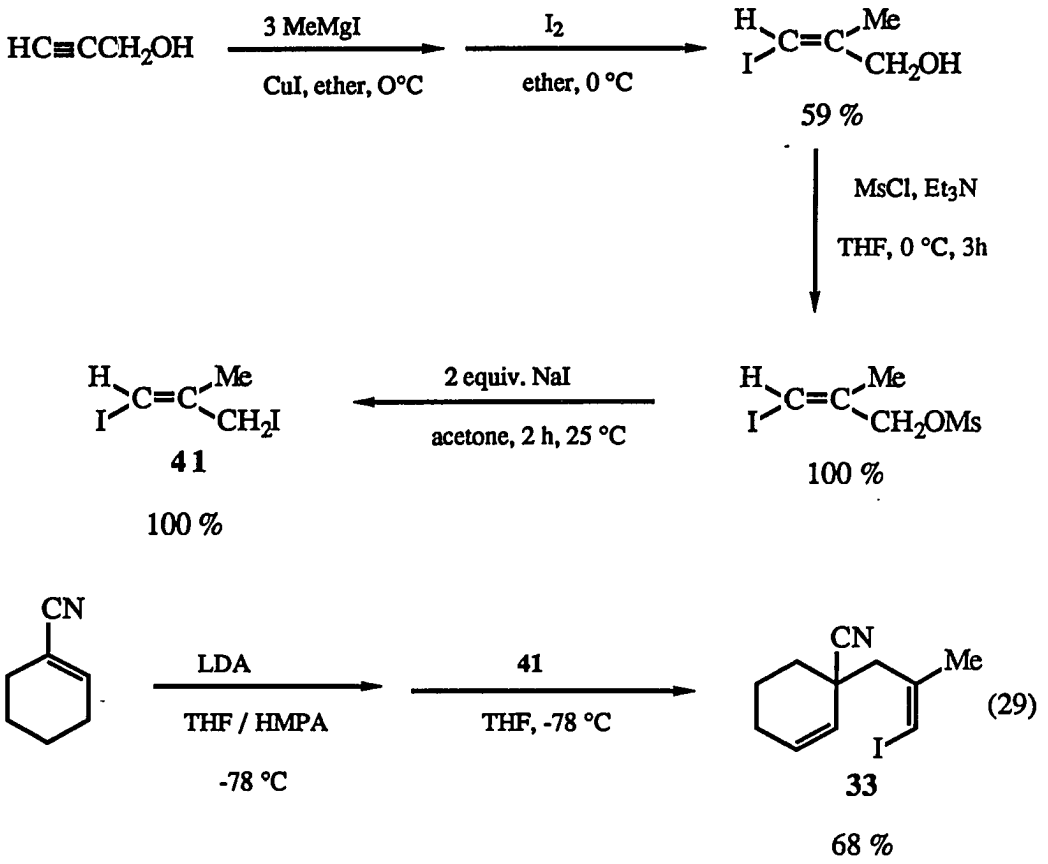
Scheme IV



(28)

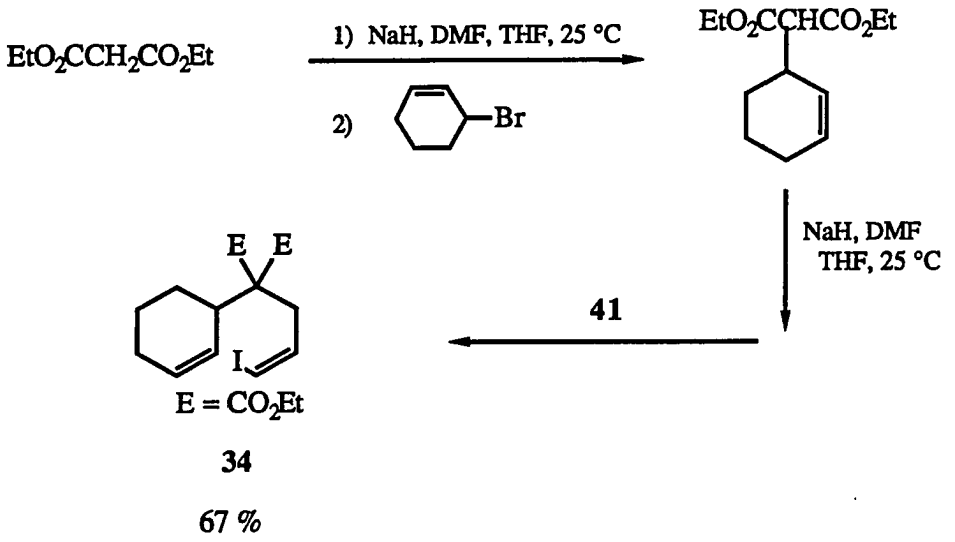
Nitrile **33** was prepared in the same manner as **31** and **32** except (Z)-1,3-diiodo-2-methylpropene (**41**) was used as the halide (see Scheme V and eq 29). Diethyl malonate

Scheme V



34 was prepared from the alkylation of diethyl malonate with 3-bromocyclohexene followed by alkylation by **41** (Scheme VI). Dienyl ethers **35** and **36** were prepared from 2-cyclopenten-1-ol and 2-cyclohexen-1-ol , respectively, in quantitative yields using the

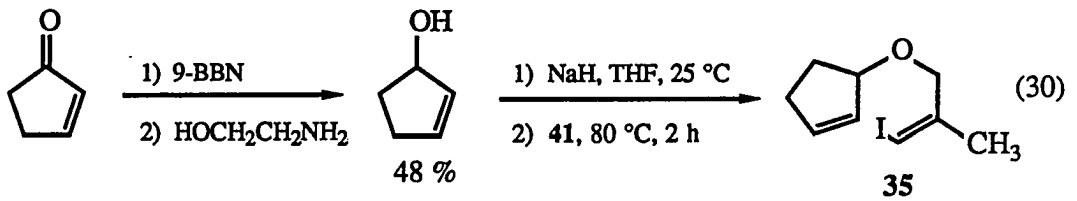
Scheme VI



34

67 %

Williamson ether synthesis (eqs 30 and 31). Esters **37** and **38** were prepared from 2-

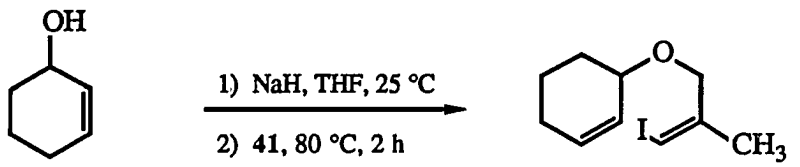


48 %

35

100 %

(30)

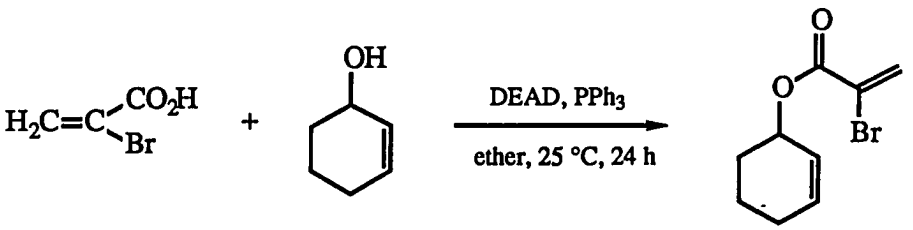


36

100 %

(31)

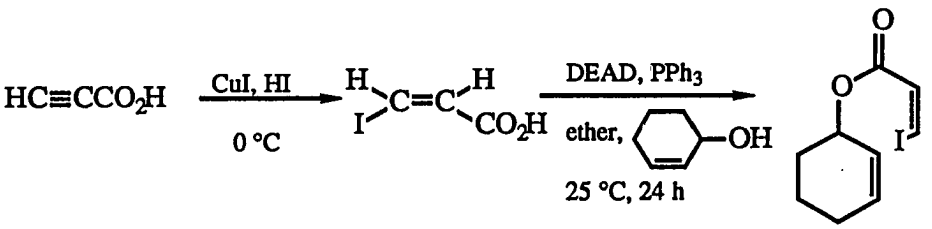
cyclohexen-1-ol and the appropriate carboxylic acids using DEAD and PPh_3 in ether (eqs 32 and 33). Finally, ether **39** was prepared from the coupling of alkyl iodide **42**



(32)

37

100 %



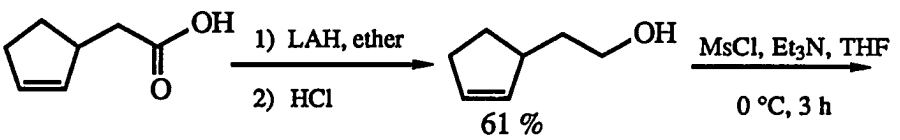
(33)

38

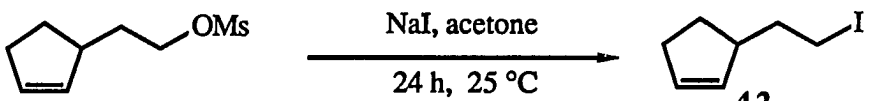
56 %

(Scheme VII) and (Z)-1-iodo-2-methyl-1-propen-1-ol (eq 34).

Scheme VII



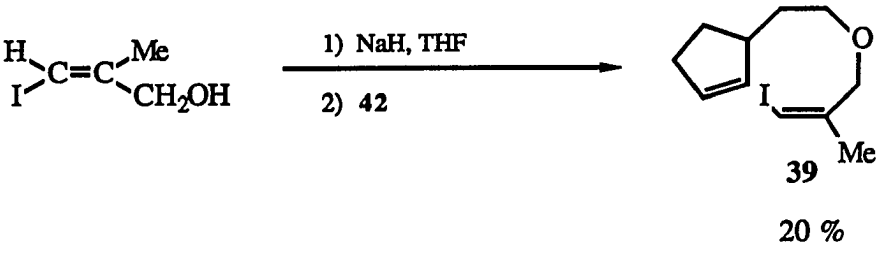
61 %



80 %

42

80 %



(34)

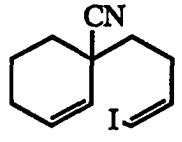
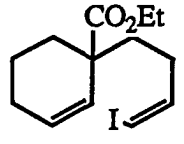
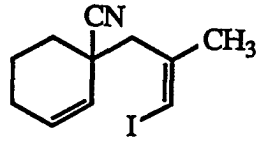
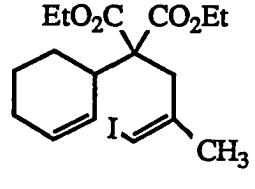
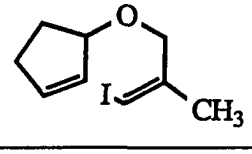
39

20 %

Three different Pd(0) procedures (Procedure A: 2.5 mol % $Pd(OAc)_2$, 1 equiv TBAC, 3 equiv KOAc, DMF at 80 °C; Procedure B: 3 - 6 mol % $Pd(OAc)_2$, 9 - 18 mol % PPh_3, 2 equiv Ag_2CO_3, CH_3CN at 80 °C; Procedure C: Procedure A plus 2.5 mol % PPh_3) were employed in these cyclizations. Table 1 summarizes the results obtained from this study.

Several points are worth noting. Both procedures A and B stereoselectively afford the desired bicyclic compounds in good to excellent yields (entries 1-12). Unfortunately, procedure A[9] provides a bad mixture of regioisomers each time (entries 1, 3, 5, 7, 9, and 11). In fact, in one case, the major isomer (entry 7) was the undesired 1,5 - diene. However, when procedure B[4,9] was employed in cases where cyclization took place when using procedure A, only the desired 1,4-diene was afforded (entries 2, 4, 6, 8, 10, and 12). As Negishi et al.[23] had observed, dienyl iodides **31** and **32** which contained a nitrile and an ester did cyclize more slowly than the other dienyl halides. However, this decelerating effect was not observed in the reaction of **34** (entries 7 and 8). The stereochemistry of bicyclic compounds **43** to **48** has been determined to be *cis* based on NMR spectral data[26], mechanistic arguments, and assignments made by others on similar products.[4,11,29] This method was found to be incompatible with allylic esters, however. For example, ester **37** did not produce any of the desired product when procedure A was applied (entry 14). Instead, only 2-cyclohexenyl acetate was isolated in 52 % yield.

Table 1. Palladium(0)-catalyzed Intramolecular Vinylation of Cyclic Alkenes

Entry	Dienyl Halide	Pd (%)	Procedure
1		2.5	A
2		3.0	B
3		2.5	A
4		6.0	B
5		2.5	A
6		3.0	B
7		2.5	A
8		3.0	B
9		2.5	A
10		3.0	B

[a] The ratio in parentheses reflects the ratio of cyclic 1,4- to 1,5-dienes. If no ratio is reported, the product is essentially pure.

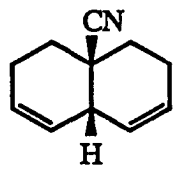
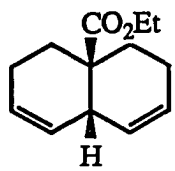
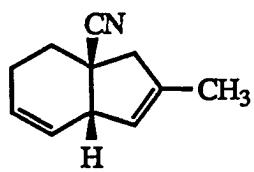
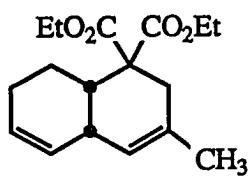
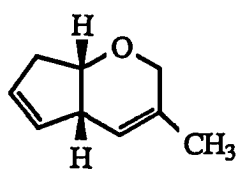
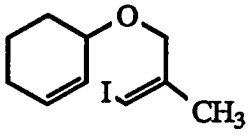
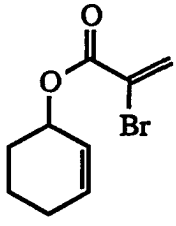
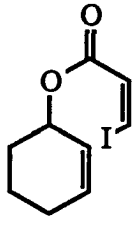
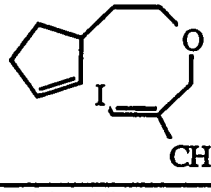
Time (d)	Product [a]		Yield (%)
4 5	 **43**	(1 : 1)	79 56
2 5	 **44**	(1 : 3)	48 68
1 1	 **45**	(1 : 1)	81 77
2 1	 **46**	(1 : 5)	86 96
1 1	 **47**	(2 : 1)	60 60

Table 1. (continued)

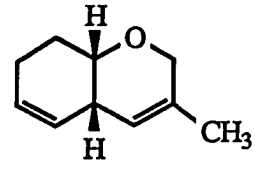
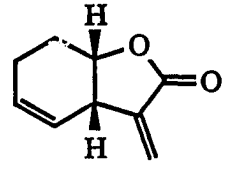
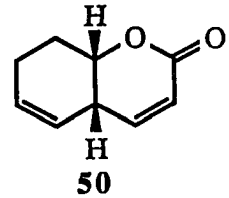
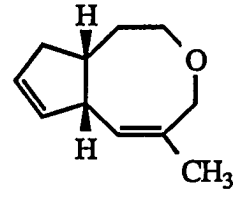
Entry	Dienyl Halide	Pd (%)	Procedure
11		2.5	A
12		3.0	B
13		2.5	C
14		2.5	A
15		3.0	B
16		2.5	C
17		2.5	A
18		3.0	B
19		2.5	C
20		2.5	A
21		3.0	B

[b] Only unidentifiable polymeric material was recovered.

[c] Only 2-cyclohexenyl acetate was recovered in 52 % yield.

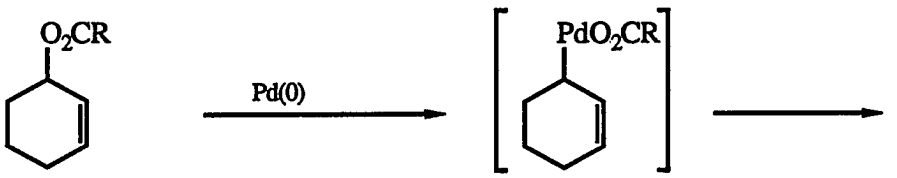
[d] Only the dimer of the dienyl halide was recovered.

[e] The yield of the product was approximated since large amounts of contaminants were also present.

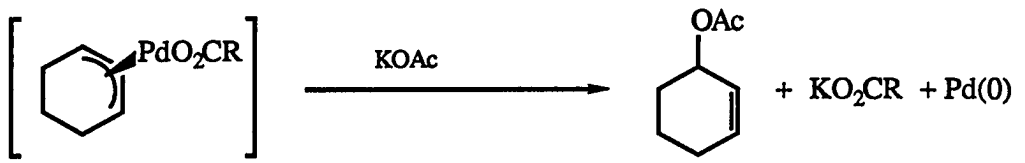
Time (d)	Product [a]		Yield (%)
1		(1.5 : 1)	92
1			69
1	**48**		0[b]
5			0[c]
7			0[b]
1	**49**		0[d]
1			0[b]
1			0[b]
1	**50**		0[d]
1			0[d]
1	**51**		10[d,e]

One possible explanation is that the Pd(0) species did not react with the vinylic bromide, but instead reacted more rapidly with the allylic ester functional group to generate a π-allyl-palladium species which reacted with KOAc functioning as a nucleophile (Scheme VIII). This side reaction is actually well precedented[28] since π-allylpalladium complexes

Scheme VIII

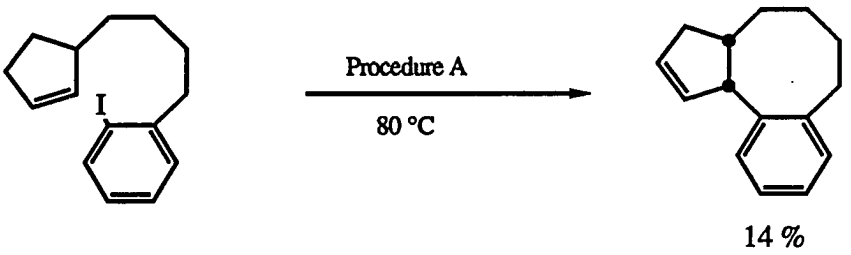


(R = $C(Br)=CH_2$)



are usually made from the reaction of an allylic acetate and Pd(0). When procedure B was applied to ester **37** (entry 15), only unidentifiable polymeric material was generated. The polymerization presumably resulted from the reactive acrylate present in the molecule. Ester **38** produced only polymeric material when using either procedure A or B (entries 17 and 18). It's surprising to find that no 2-cyclohexenyl acetate was produced when procedure A was employed. Procedure C was briefly examined as a possible alternative to procedure B. Dienyl iodide **36** was completely consumed within 24 h when using procedure C, but a mixture of unidentifiable organic products was produced (entry 13). However, when **37** and **38** were allowed to react under these same reaction conditions, a

significant amount of the dimeric 1,3-dienes corresponding to the starting materials was observed by GC/MS each time (entries 16 and 19). An attempt to synthesize a bicyclic compound containing an eight-membered ring also failed under these conditions. Indeed, when **39** was allowed to react using procedure A (entry 20), all of **39** was consumed in one day and only a tarry unidentified substance was recovered. Employing procedure B in this same reaction provided approximately a 10 % yield of the desired compound contaminated with an unknown organic compound (entry 21). In fact, Baker [30] had also encountered the same difficulties in his intramolecular arylation studies (eq 35).



14 %

(35)

CONCLUSION

A general, Pd-catalyzed method useful for the preparation of bicyclic dienes has been developed. This method employing procedure A or B affords bicyclic compounds in high yields and in a stereo- and regioselective manner under mild reaction conditions. Procedure A's major limitation has been the tendency to form large amounts of the undesired homoallylic side product. Procedure B which has been used quite successfully to suppress the formation of the homoallylic product in the intermolecular vinylation of cyclic alkenes, provides the desired bicyclic products in high yields. In the intramolecular vinylation reactions, procedure B proved again to be successful in providing only the desired bicyclic 1,4-dienes. Procedure C proved to be problematical as it tends to produce mixtures of many unidentifiable organic products. The limitations of both procedures A and B appear to be their incompatibility with dienyl iodides containing an allylic ester.

EXPERIMENTAL SECTION

Equipment

NMR spectra were recorded on a Nicolet NT-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75 MHz for carbon nuclei). Infrared spectra were obtained on an IBM IR/98 FT-IR. Mass spectral data were obtained on a Kratos high resolution mass spectrometer. Gas chromatographic analyses were performed by using a Varian 3700 or a Hewlett Packard 5890 gas chromatograph equipped with a 3 % OV-101 on Chromasorb W packed column (Varian 3700 or HP 5890) or an HP-1 megabore column (HP 5890).

Reagents

Propargyl alcohol, 3-butyn-1-ol, cyclohexanone, 2-cyclopenten-1-one, 2-cyclohexen-1-ol, methyl magnesium bromide, copper(I) iodide, triphenylphosphine, silver carbonate, tetra-*n*-butylammonium chloride, *n*-butyllithium, and diisopropylamine were all obtained from Aldrich. Tetra-*n*-butylammonium chloride was purchased from Lancaster Synthesis. Tetrahydrofuran was distilled immediately prior to use from sodium benzophenone. *N,N*-Dimethylformamide, CH_3CN, and CH_2Cl_2 were all distilled from calcium hydride and stored over dry molecular sieves. 2-Cyclopenten-1-ol was prepared by a procedure reported by Krishnamurthy and Brown,[31] and 2-(3-cyclopentenyl)ethanol and 1-iodo-2-(3-cyclopentenyl)ethane were prepared using Dr. Song's procedure (the latter compound was prepared using the iodide instead of the chloride).[32] 1-Cyano-1-cyclohexene[33] and 1-carboethoxy-1-cyclohexene[34] were generously supplied by Dr. Bruce Baker.[30]

4-Iodo-3-butyn-1-ol

In a 500 mL round bottom flask equipped with a stirring bar were added ether (150 mL), $Hg(OAc)_2$ (9.57 g, 30.0 mmol), and 3-butyn-1-ol (4.20 g, 4.60 mL, 60.0 mmol). Solid I_2 (15.3 g, 60.0 mmol) was added slowly in portions to the rapidly stirred mixture. After the addition was complete, the flask was sealed with a septum and the contents were stirred for 48 hours at room temperature in the absence of light. The red mercuric iodide was removed by filtering the reaction mixture through a short column of Celite. The solids were then washed with ether (3 x 50 mL). The filtrate was washed with saturated sodium bicarbonate (2 x 75 mL) and $Na_2S_2O_3$ (5 %, 75 mL), and the organic layer was dried over anhydrous $MgSO_4$. After the solvent was removed, the iodoalkyne was produced in 100 % yield as a light green oil. ^1H NMR ($CDCl_3$) δ 2.63 (t, 2 H, J = 6.3 Hz, $C\underline{H}_2CH_2OH$), 3.73 (t, 2 H, J = 6.3 Hz, $CH_2\underline{C}H_2OH$); IR (neat) 3358, 1713, 1047 cm^{-1}.

1-Iodo-4-(2-tetrahydropyranyloxy)-1-butyne

In a 250 mL round bottom flask equipped with a stirring bar were added dry CH_2Cl_2 (210 mL) and 1-iodo-3-butyn-1-ol (5.88 g, 30.0 mmol). Once the contents were stirring, PPTS (0.753 g, 3.00 mmol) was added all at once. After the solution was stirred for four hours, it was combined with ether (200 mL), and washed with saturated aqueous NaCl (200 mL). The aqueous layer was discarded and the remaining organic layer was washed with water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford the desired product as a light yellow oil in 99 % yield. ^1H NMR ($CDCl_3$) δ 1.53 - 1.84 (m, 6 H, CH_2's), 2.67 (t, 2H, J = 6.9 Hz, CH_2), 3.54 -

3.84 (m, 4 H, CH_2-O's), 4.64 (t, 1 H, J = 1.8 Hz, O-CH-O); IR (neat) 2943, 2872, 1732, 1200, 1136 cm^{-1}.

(Z)-1-Iodo-4-(2-tetrahydropyranyloxy)-1-butene

Freshly prepared dipotassium azodicarboxylate (14.4 g, 74.0 mmol) was added to a 250 mL round bottom flask equipped with a large stirring bar, addition funnel, and a reflux condenser. To the flask were also added pyridine (15 mL), methanol (30 mL), and 1-iodo-4-(2-tetrahydropyranyloxy)-1-butyne (5.64 g, 20.0 mmol). In the addition funnel, a mixture of acetic acid (18 mL) and methanol (18 mL) was added. The methanol - acetic acid mixture was added slowly at such a rate only a gentle reflux was obtained. After the addition, the mixture was stirred at 25 °C for 24 hours. The mixture was poured into a 500 mL round bottom flask containing ether (200 mL). The contents were stirred rapidly as ice - cold aqueous HCl (5 %, 100 mL) was added slowly. The organic layer was separated and the aqueous layer was extracted with ether (2 x 50 mL), saturated Na_2CO_3 (2 x 50 mL), and water (50 mL). The organic layer was concentrated *in vacuo* and the residual oil was added to *n*-butylamine (10 mL), and the mixture was stirred for three hours at room temperature to remove the overreduced product. The mixture was then added to ether (75 mL), washed with water (2 x 100 mL), cold aqueous HCl (5 % 150 mL), and water (100 mL). The ether layer was dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, columned over basic alumina using hexane as the eluent to afford the desired product in 66 % yield. ^1H NMR ($CDCl_3$) δ 1.57 - 1.75 (m, 6 H, $CH_{2's}$), 2.45 (q, 2 H, J = 7.2 Hz, CH_2), 3.46 - 3.90 (m, 4 H, CH_2O's), 4.61 (t, 1 H, J = 1.8 Hz, O-CH-O), 6.30 - 6.32 (m, 2 H, CH=CHI); IR (neat) 3019, 2939, 2868, 1200, 1136, 1121, 1074, 1034, 984 cm^{-1}.

(Z)-4-Bromo-1-iodo-1-butene

In a dry 250 mL round bottom flask equipped with a stirring bar were placed dry methylene chloride (100 mL) and freshly recrystallized PPh_3 (5.76 g, 22.0 mmol). An addition funnel was attached and the contents were stirred and cooled to 0 °C. Bromine (3.48 g, 1.12 mL, 22.0 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise to the solution with rapid stirring. After the addition, the solution was allowed to stir for 30 minutes before (Z)-1-iodo-4-(2-tetrahydropyranyoxyl)-1-butene (5.64 g, 20.0 mmol) in methylene chloride (10 mL) was added dropwise. After the addition, the solution was stirred at 0 °C for two hours, allowed to come to room temperature and then stirred for one more hour. The reaction mixture was washed with water (2 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to a point such that only approximately 25 % of the solvent remained. This solution was then filtered through a short column of silica gel, and eluted using hexane as the eluent to remove the triphenylphosphine oxide. The hexane solution was concentrated *in vacuo* to afford the desired bromide as a light yellow oil in 90 % yield. ^1H NMR ($CDCl_3$) δ 2.76 (dt, 2 H, J = 6.6 Hz, J = 6.9 Hz, CH_2), 3.44 (t, 2 H, J = 6.9 Hz, CH_2), 6.32 (dt, 1 H, J = 7.8 Hz, J = 6.6 Hz, ICH=C<u>H</u>), 6.45 (d, 1 H, J = 7.8 Hz, IC<u>H</u>=CH); IR (neat) 3050, 2955, 2924, 2853, 1615, 1437, 1321, 1285, 1261, 1231 cm^{-1}.

(Z)-1,4-Diiodo-1-butene (40)

In a 50 mL round bottom flask equipped with a stirring bar were placed (Z)-4-bromo-1-iodo-1-butene (4.68 g, 18.0 mmol), reagent grade acetone (30 mL), and sodium iodide (5.40 g, 36.0 mmol). The flask was sealed and the contents were allowed to stir for 24 hours at room temperature. The solution was combined with ether (50 mL) and washed

with water (50 mL). The organic layer was then washed with freshly prepared $Na_2S_2O_3$ (10 %, 50 mL), saturated NaCl (50 mL), dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo, and columned over silica gel using hexane as the eluent to afford the desired alkyl iodide as a colorless oil in 100 % yield. ^1H NMR ($CDCl_3$) δ 2.72 - 2.79 (m, 2 H, CH_2), 3.20 (t, 2 H, J = 6.9 Hz, CH_2), 6.25 (ddd, 1 H, J = 6.9 Hz, J = 6.9 Hz, J = 6.9 Hz, ICH=C<u>H</u>), 6.45 (d, 1 H, J = 6.9 Hz, IC<u>H</u>=CH); IR (neat) 3071, 2955, 2924, 2853, 1285, 1261 cm^{-1}.

(*Z*)-3-Iodo-2-methyl-2-propen-1-ol

In a flame-dried 3-necked round bottom flask equipped with a mechanical stirrer, and an addition funnel were added copper(I) iodide (11.44 g, 60 mmol) and propargyl alcohol (3.36 g, 60 mmol). After ether (224 mL) was added, the contents were cooled to 0 °C with stirring. Methylmagnesium bromide (60 mL, 180 mmol, 3 *M*) was added dropwise and care was taken to add the first 20 mL slowly due to a rapid evolution of hydrogen gas. After the Grignard addition was complete, the reaction was slowly warmed to room temperature and then it was stirred for four hours. The dark green reaction mixture was then cooled to 0 °C, followed by rapid addition of reagent grade I_2 (16.77 g, 66 mmol). The reaction was slowly warmed to room temperature and stirring was continued at room temperature for one hour; then the reaction mixture was cooled back down to 0 °C before saturated NH_4Cl (140 mL) was carefully added. The ether layer was separated and the aqueous layer was extracted with ether (3 x 70 mL). The combined organic layers were washed with freshly prepared 10 % $Na_2S_2O_3$ (140 mL), saturated NaCl (140 mL), dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and the yellow oil was vacuum distilled (52-56 °C, 0.1mm Hg) to afford the desired allylic alcohol in 59 % yield. ^1H

NMR ($CDCl_3$) δ 1.97 (s, 4 H, CH_3 and OH), 4.29 (s, 2 H, CH_2), 5.97 (s, 1 H, HC=C); IR(neat) 3323, 3055, 2970, 1618, 1034, 1013 cm^{-1}.

(*Z*)-2-Methyl-3-iodo-2-propenyl methanesulfonate.

In a dry 25 mL round bottom flask equipped with a stirring bar were added (*Z*)-3-iodo-2-methyl-2-propen-1-ol (1.21 g, 6.10 mmol) and THF (12 mL). The flask was sealed and cooled to 0 °C with stirring. Triethylamine (0.986 g, 9.76 mmol, 1.36 mL) and methanesulfonyl chloride (0.974 g, 8.54 mmol, 0.66 mL) were injected sequentially. The mixture was allowed to warm to room temperature over a period of one hour, and the mixture was allowed to stir at room temperature for three additional hours. The mixture was poured into a separatory funnel containing water (75 mL) and ether (50 mL). The aqueous layer was removed, and the organic layer was washed with saturated NH_4Cl (75 mL), dried over anhydrous $MgSO_4$, filtered through a fritted funnel, concentrated *in vacuo* to afford the crude mesylate in quantitative yield. This mesylate was immediately taken on to the next step without further purification. ^1H NMR ($CDCl_3$) δ 2.01 (s, 3 H, C=C-CH_3), 3.07 (s, 3 H, SO_2CH_3), 4.84 (s, 2 H, C=C-CH_2), 6.28 (s, 1 H, HC=C).

(*Z*)-1,3-Diiodo-2-methyl-1-propene (41)

In a dry 50 mL round bottom flask equipped with a stirring bar were placed the crude mesylate, reagent grade acetone (20 mL), and NaI (1.38 g, 9.15 mmol). The mixture was stirred at room temperature for two hours. The mixture was diluted with water (25 mL) and ether (25 mL). The aqueous layer was removed, and the organic layer was washed with water (50 mL), and freshly prepared 10 % $Na_2S_2O_3$ (50 mL), and then dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and columned over silica gel using

hexane to afford the desired compound in 68 % overall yield. ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3 H, CH_3), 4.00 (s, 2 H, CH_2), 6.15 (s, 1 H, ICH=); IR (neat) 3055, 2982, 2939, 1603, 1431, 1373, 1279, 1161, 1148, 1024 1009, 773, 671 cm^{-1}.

Diethyl 3-cyclohexenylmalonate

In a dry 50 mL round bottom flask containing a stirring bar was placed NaH (50 % in mineral oil, 0.552 g, 11.5 mmol). The flask was sealed and the contents were flushed with N_2 and a N_2 atmosphere was maintained. DMF (6.6 mL) was injected, followed by diethyl malonate (1.54 g, 1.46 mL, 9.60 mmol), which was injected slowly since quite a bit of hydrogen and heat evolved. The reaction was allowed to stir for 45 minutes at room temperature at which time the solution was a clear yellow liquid. 3-Bromo-1-cyclohexene (1.28 g, 0.92 mL, 8.00 mmol) dissolved in THF (3.40 mL) was slowly injected into the reaction mixture. A white precipitate, sodium bromide, formed almost immediately and the mixture was allowed to stir overnight at room temperature. The reaction mixture was poured into a separatory funnel containing water (30 mL) and ether (30 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 x 25 mL). The combined ether layers were washed with saturated solutions of NaCl, twice with NH_4Cl, and water. The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated in vacuo to afford a residue, and columned over silica gel using hexane / EtOAc (6 : 1) to afford the desired malonate in 100 % yield. ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 6 H, J = 7.2 Hz, CH_3), 1.29 - 1.36 (m, 1 H, C<u>H</u>H), 1.45 - 1.52 (m, 1 H, CH<u>H</u>), 1.62 - 1.74 (m, 2 H, CH_2), 1.91 - 1.96 (m, 2 H, C=C-CH_2), 2.77 - 2.86 (m, 1 H, EtO_2C-CH-C<u>H</u>-C=C), 3.16 (d, 1 H, J = 7.5 Hz, EtO_2C-CH-CO_2Et), 4.12 (q, 4 H, J = 7.2 Hz, CH_2's), 5.50 (dd, 1 H, J = 10.2 Hz, J = 2.7 Hz, C<u>H</u>=CH), 5.65 - 5.71 (m, 1 H, CH=C<u>H</u>); ^{13}C

NMR ($CDCl_3$) δ 13.09, 20.79, 24.77, 26.45, 35.08, 56.93, 60.98, 127.40, 129.09, 168.20; IR (neat) 3024, 2980, 2864, 1735, 1734, 1463, 1446, 1367, 1329, 1296, 1229, 1177, 1096, 1030, 976, 721 cm^{-1}; HRMS: calcd for $C_{13}H_{20}O_4$ m/z 240.13616, found m/z 240.13583.

Dienyl iodide 31

A dry 50 mL round bottom flask containing a stirring bar was flushed with N_2 and a positive N_2 atmosphere was maintained. THF (5 mL) and diisopropylamine (0.541 g, 0.75 mL, 5.35 mmol) were sequentially injected. After the solution was cooled to -78 °C, *n*-butyllithium (2.62 mL, 5.87 mmol , 2.24 *M*) was injected. The solution was allowed to stir and steadily warm up to -20 °C over a period of one hour. After the solution was cooled back down to -78 °C, the solution was stirred for 10 minutes before HMPA (0.958 g, 0.93 mL, 5.35 mmol) was injected. This solution was stirred for 30 minutes before 1-cyano-1-cyclohexene (0.514 g, 5.35 mmol) was injected, and 30 minutes later (Z)-1,4-diiodo-1-butene (2.14 g, 6.94 mmol) was injected. The solution was then allowed to warm up to room temperature over a period of two hours. The reaction was quenched with water and combined with hexane. The organic layer was isolated and washed consecutively with aqueous HCl (10 %), saturated NH_4Cl, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and columned over silica gel using hexane / EtOAc (10 : 1) to afford the desired vinylic iodide in 78 % yield. ^1H NMR ($CDCl_3$) δ 1.55 - 1.85 (m, 4 H, CH_2's), 1.90 - 2.15 (m, 4 H, CH_2's), 2.35 (dd, 2 H, *J* = 6.9 Hz, *J* = 6.9 Hz, C=C-CH_2), 5.56 - 5.61 (m, 1 H, C<u>H</u>=CH-CCN)), 5.94 (ddd, 1 H, *J* = 9.6 Hz, *J* = 4.2 Hz, *J* = 3 Hz, CH=C<u>H</u>-CCN), 6.22 (ddd, 1 H, *J* = 7.5 Hz, *J* = 6.9 Hz, *J* = 6.9 Hz, ICH=C<u>H</u>), 6.29 (d, 1 H, *J* = 7.5 Hz, IC<u>H</u>=CH); ^{13}C NMR ($CDCl_3$) δ 19.18,

24.49, 30.15, 32.59, 36.72, 37.47, 83.99, 122.85, 125.96, 131.55, 139.14; IR (neat) 3068, 3028, 1229, 1018 cm^{-1}; HRMS: calcd for $C_{11}H_{14}IN$ m/z 287.01710, found m/z 287.01736.

Dienyl iodide 32

In a flame-dried 25 mL round bottom flask containing a stirring bar and a nitrogen atmosphere was injected THF (2.5 mL). The flask was cooled to -78 °C and diisopropylamine (0.216 g, 0.300 mL, 2.14 mmol) was injected. After the amine solution was stirred for 10 minutes, *n*-butyllithium (1.03 mL, 2.57 mmol, 2.5 *M*) was injected. The solution was slowly warmed to -20 °C over a period of one hour, cooled back down to -78 °C, stirred for 10 minutes, and then HMPA (0.383 g, 0.400 mL, 2.14 mmol) was injected. The solution was allowed to stir for 30 minutes before 1-carboethoxy-1-cyclohexene (0.330 g, 2.14 mmol) dissolved in THF (2.5 mL) was injected, the solution was stirred for one hour, and then (Z)-1,4-diiodo-1-butene (1.12 g, 3.64 mmol) dissolved in THF (2.5 mL) was injected. The solution was stirred and allowed to come to room temperature overnight. The reaction mixture was combined with water (50 mL) and hexane (50 mL). The organic layer was separated, washed with 5% HCl (2 x 50 mL), saturated Na_2CO_3, 5 % $Na_2S_2O_3$, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and columned over silica gel using hexane / EtOAc (10 : 1) to afford the desired compound in 88 % yield. ^1H NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 6 Hz, CH_3), 1.58 - 1.80 (m, 6 H, CH_2's), 2.00 (br s, 2 H, CH_2), 2.07 - 2.22 (m, 2 H, CH_2's), 4.10 - 4.21 (m, 2 H, OCH_2), 5.72 (d, 1 H, J = 10.2 Hz, CH=C<u>H</u>CO_2Et), 5.81 (dt, 1 H, J = 3.3 Hz, J = 10.2 Hz, C<u>H</u>=CHCO_2Et), 6.10 - 6.20 (m, 2 H, ICH=CH); ^{13}C NMR ($CDCl_3$) δ 14.33, 19.57, 24.85, 30.10, 37.78, 46.37, 60.49, 82.71, 128.74, 129.26 (2 peaks),

140.32, 175.46; IR(neat) 3068, 3026, 2979, 1726, 1448, 1388, 1304, 1274, 1207, 1028, 729 cm^{-1}; HRMS calcd for $C_{13}H_{19}IO_2$ m/z 206.13068, found 206.13057.

Dienyl iodide 33

This dienyl iodide was synthesize by a procedure identical to the one used for the synthesis of compound **31**. After the crude product was columned over silica gel by using hexane / EtOAc / CH_2Cl_2 (17 : 1 : 1) the desired product was provided in 63 % yield. ^1H NMR ($CDCl_3$) δ 1.70 - 2.09 (m, 6 H, CH_2's), 2.12 (d, 3 H, J = 1.2 Hz, ICH=CC<u>H</u>$_3$), 2.58 (d, 1 H, J = 13.8 Hz, C(<u>H</u>)H-CCN), 2.70 (d, 1 H, J = 13.8 Hz, C(H)<u>H</u>-CCN), 5.56 - 5.61 (m, 1 H, CH=C<u>H</u>-CCN), 5.94 (dt, 1 H, J = 9.9 Hz, J = 3.9 Hz, C<u>H</u>=CH-CCN), 6.21 (d, 1 H, J = 1.2 Hz, IC<u>H</u>=); ^{13}C NMR ($CDCl_3$) δ 18.71, 23.91, 24.15, 32.09, 35.07, 46.65, 80.33, 122.78, 125.57, 130.85, 141.91; IR (neat) 3005, 2945, 2864, 2100, 1445, 1178, 781, 735 cm^{-1}; HRMS: calcd for $C_{11}H_{14}IN$ m/z 287.01710, found m/z 287.01695.

Dienyl iodide 34

In a dry 50 mL round bottom flask containing a stirring bar was placed sodium hydride (50 % in mineral oil, 0.256 g, 5.34 mmol). The flask was sealed and the contents were flushed with nitrogen and a positive nitrogen atmosphere was maintained. DMF (3.3 mL) was injected, and diethyl 3-cyclohexenylmalonate (1.07 g, 4.45 mmol) dissolved in DMF (1 mL) was slowly added. The reaction was allowed to stir at room temperature for 45 minutes and at this time the solution was a clear yellow liquid. (Z)-1,3-Diiodo-2-methyl-1-propene (1.78 g, 5.79 mmol) dissolved in THF (1.7 mL) was slowly injected into the reaction mixture. A white precipitate, sodium bromide, formed almost

immediately, and the mixture was allowed to stir overnight at room temperature. The reaction mixture was poured into a separatory funnel containing water (30 mL) and ether (30 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 x 35 mL). The combined ether layers were washed with saturated solutions of NaCl, twice with NH_4Cl, and then water. The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and columned over silica gel using hexane / EtOAc (7 : 1) to afford the desired dienyl iodide in 67 % yield. ^1H NMR ($CDCl_3$) δ 1.18 (t, 3 H, J = 7.2 Hz, CH_3), 1.19 (t, 3 H, J = 7.2 Hz, CH_3), 1.72 - 1.96 (m, 9 H, CH_2's and CH), 2.88 (d, 3 H, J = 5.7 Hz, $C{=}CCH_3$), 4.09 (q, 2 H, J = 7.2 Hz, CH_2), 4.10 (q, 2 H, J = 7.2 Hz, CH_2), 5.68 - 5.87 (m, 2 H, CH=CH), 5.90 (t, 1 H, J = 1.2 Hz, $CH{=}CCH_3$); ^{13}C NMR ($CDCl_3$) δ 19.95, 22.99, 24.20, 24.53, 24.88, 41.09, 41.96, 60.55, 60.96, 61.03, 78.03, 127.92 (two peaks), 128.57, 144.84, 170.02, 170.17; IR (neat) 3033, 2980, 2934, 1730, 1445, 1367, 1298, 1238, 1225, 1146, 1094, 1055 cm^{-1}; HRMS: calcd for $C_{17}H_{25}IO_4$ m/z 420.07977, found m/z 420.07993.

Dienyl iodide 35

In a dry 25 mL round bottom flask equipped with a stirring bar was placed sodium hydride (0.200 g, 50 % in oil, 4.17 mmol). Immediately afterwards, the flask was sealed, flushed with nitrogen, and a positive nitrogen atmosphere was maintained with a bubbler. 2-Cyclopenten-1-ol (0.234 g, 2.78 mmol) dissolved in THF (5 mL) was injected and hydrogen gas immediately evolved. After the contents were stirred at room temperature for 20 minutes, a reflux condenser was attached, and (*Z*)-1,3-diiodo-2-methyl-1-propene (1.28 g, 4.17 mmol) dissolved in THF was injected. The flask was heated to 80 °C for two hours. The contents were poured into a separatory funnel containing water (50 mL)

and ether (25 mL). The layers were separated and the aqueous layer was washed with ether (2 x 25 mL). The combined ether layers were washed with saturated NaCl, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and columned over silica gel using hexane / EtOAc (30 : 1) to afford the desired compound in 100 % yield. ^1H NMR ($CDCl_3$) δ 1.69 - 1.79 (m, 1 H, C<u>H</u>H), 1.86 (d, 3 H, J = 1.5 Hz, CH_3), 2.04 - 2.25 (m, 2 H, C=CCH_2), 2.39 - 2.49 (m, 1 H, CH<u>H</u>), 4.04 (s, 2 H, C=CCH_2), 4.47 - 4.52 (m, 1 H, CH-O), 5.78 - 5.82 (m, 1 H, C<u>H</u>=CH), 5.94 - 5.97 (m, 2H, CH=C<u>H</u> and IC<u>H</u>=); ^{13}C NMR ($CDCl_3$) δ 29.80, 31.03, 31.55, 73.08, 75.56, 84.03, 130.64, 135.78, 144.76; IR (neat) 3055, 1616, 1437, 1080 cm^{-1}; HRMS: calcd for $C_9H_{13}IO$ m/z 264.00112, found m/z 264.00099.

Dienyl iodide 36

The procedure for the preparation of this compound was identical to the procedure above to prepare **35**, except 2-cyclohexen-1-ol was employed. The ether was columned over silica gel using hexane / EtOAc (15 : 1) to afford the desired product in 100 % yield. ^1H NMR ($CDCl_3$) δ 1.49 - 1.83 (m, 4 H, CH_2's), 1.91 (d, 3 H, J = 1.2 Hz, CH_3), 1.95 - 2.07 (m, 2 H, C=CCH_2), 3.80 - 3.82 (m, 1 H, C=CCH-O), 4.12 (s, 2 H, C=CCH_2), 5.73 - 5.77 (m, 1 H, C<u>H</u>=CH), 5.81 - 5.87 (m, 1 H, CH=C<u>H</u>), 5.98 (s, 1 H, IC<u>H</u>=); ^{13}C NMR ($CDCl_3$) δ 21.94, 25.16, 28.26, 71.83, 72.64, 75.63, 127.44, 131.02 (two peaks), 144.82; IR (neat) 3026, 2928, 2860, 1448, 1437, 1319, 1283, 1084, 1051, 1022, 727, 667 cm^{-1}; HRMS: calcd for $C_{10}H_{15}IO$ m/z 278.01677, found m/z 278.01671.

Dienyl bromide 37

In a 50 mL round bottom flask were placed 2-bromopropenoic acid (0.825 g, 5.50 mmol), ether (8 mL), and DEAD (1.2 g, 1.0 mL, 6.6 mmol), and the contents were rapidly stirred at room temperature. In a separate flask were placed PPh_3 (1.56 g, 6.00 mmol) and 2-cyclohexen-1-ol (0.82 g, 0.83 mL, 8.4 mmol), and ether (8 mL). This latter solution was slowly added dropwise via syringe to the former solution. After the addition was complete, the solution was allowed to stir at room temperature for 24 hours. The mixture was diluted with ether, washed with saturated NaCl, and water. The organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and columned over silica gel using hexane / EtOAc (10 : 1) to afford the desired ester in 100 % yield. ^1H NMR ($CDCl_3$) δ 1.20 - 1.63 (m, 4 H, CH_2's), 1.96 - 2.16 (m, 2 H, C=C-CH_2), 5.32 (br s, 1 H, C=C-CH-O), 5.74 - 5.78 (m, 1 H, C<u>H</u>=CH), 5.97 - 6.03 (m, 1 H, CH=C<u>H</u>), 6.26 (d, 1 H, J = 1.5 Hz, CH=CBr), 6.94 (d, 1 H, J = 1.5 Hz, CH=CBr); ^{13}C NMR ($CDCl_3$) δ 18.48, 24.67, 27.91, 70.39, 121.87, 124.56, 129.92, 133.26, 161.15; IR (neat) 3034, 2937, 2870, 1720, 1610, 1385, 1259, 1099, 1049, 1007, 933, 908, 795, 731 cm^{-1}; HRMS: calcd for $C_9H_{11}BrO_2$ m/z 229.99424, found m/z 229.99418.

Dienyl iodide 38

This dienyl iodide was synthesized with a procedure identical to the one used for the synthesis of compound **37**. The crude product after purification through silica gel using hexane / EtOAc (10 : 1) afforded the desired product in 56 % yield. ^1H NMR ($CDCl_3$) δ 1.62 - 2.10 (m, 6 H, CH_2's), 5.39 - 5.58 (m, 1 H, C=CCH-O), 5.74 - 5.80 (m, 1 H, CH=C<u>H</u>CH-O), 5.99 (dt, 1 H, J = 10.2 Hz, J = 3.6 Hz, C<u>H</u>=CH-C-O), 6.89 (d, 1 H, J = 8.7 Hz, ICH=C<u>H</u>-CO_2), 7.42 (d, 1 H, J = 8.7 Hz, IC<u>H</u>=CH-CO_2); ^{13}C NMR

($CDCl_3$) δ 18.48, 24.56, 27.90, 68.23, 94.28, 124.95, 129.84, 132.64, 163.70; IR (neat) 3062, 3033, 2941, 2867, 1718, 1650, 1251, 1193, 1097, 1050, 1010, 808, 765 cm^{-1}; HRMS: calcd for $C_9H_{11}IO_2$ m/z 277.98038, found m/z 277.98037.

Dienyl iodide 39

In a flame - dried 25 mL round bottom flask containing a stirring bar was placed sodium hydride (50 % in mineral oil, 0.264 g, 5.50 mmol). The flask was sealed, flushed with N_2, and a N_2 atmosphere was maintained. THF (1.5 mL) was injected and the contents were cooled to 0 °C. (*Z*)-3-Iodo-2-methyl-2-propen-1-ol (0.99 g, 5.0 mmol) dissolved in THF (4.5 mL) was injected and the reaction mixture was allowed to stir and warm from 0 °C to room temperature over a period of one hour. The solution was cooled back down to 0 °C before 2-(3-cyclopentenyl)-1-iodoethane (1.3 g, 6.0 mmol) in THF (3.0 mL) was added dropwise. The reaction was allowed to warm to room temperature overnight. The mixture was poured into a separatory funnel containing water (25 mL) and ether (25 mL). The aqueous layer was removed and the organic layer was sequentially washed with saturated solutions of NaCl, NH_4Cl, and water. The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and columned over silica gel using hexane / EtOAc (12 : 1) to afford the desired product in 20 % yield. ^1H NMR ($CDCl_3$) δ 1.30 - 1.41 (m, 1 H, C<u>H</u>H), 1.44 - 1.53 (m, 1 H, CH<u>H</u>), 1.58 - 1.67 (m, 1 H, C<u>H</u>H), 1.85 (d, 3 H, *J* = 1.2 Hz, CH_3), 1.83 - 2.03 (m, 1 H, CH<u>H</u>), 2.18 - 2.29 (m, 2 H, C=C-CH_2), 2.66 - 2.72 (m, 1 H, C=C-CH), 3.38 (t, 2 H, *J* = 6.9 Hz, $CH_2C\underline{H_2}$-O), 4.01 (s, 2 H, CH_2-O), 5.59 - 5.67 (m, 2 H, CH=CH), 5.95 (t, 1 H, *J* = 1.2 Hz, C<u>H</u>=CCH_3); ^{13}C NMR ($CDCl_3$) δ 29.89, 31.87, 35.84, 42.46, 68.05, 75.22, 75.55, 108.87, 130.36, 134.73, 144.46; IR (neat) 3044, 2928, 2851, 1614, 1431, 1371, 1348,

1281, 1138, 1103, 1053, 1020, 719, 667 cm^{-1}; HRMS: calcd for $C_{11}H_{17}IO$ m/z 292.03242, found m/z 292.03264.

Procedure A

In a 10 mL round bottom flask equipped with a stirring bar were weighed $Pd(OAc)_2$ (0.006 g, 2.5 mol %), TBAC (0.294 g, 1.0 mmol), KOAc (0.294 g, 3.0 mmol), and the dienyl halide (1.0 mmol). The flask was sealed with a septum, and the contents were flushed with N_2. After DMF (2.0 mL) was injected, the contents were allowed to stir at 80 °C for the time specified in Table 1. After GC analysis had indicated that all of the dienyl halide had been consumed, the reaction was diluted with ether (10 mL), and the mixture was poured into a separatory funnel containing ether (25 mL) and saturated NH_4Cl (50 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and the residue was columned over silica gel using hexane / EtOAc as the eluent.

Procedure B

In a 25 mL round bottom flask equipped with a side arm and a stirring bar were placed $Pd(OAc)_2$ (0.007 g, 3.0 mol %), PPh_3 (0.024 g, 9.0 mol %), Ag_2CO_3 (0.552 g, 2.0 mmol), and dienyl iodide (1.0 mmol). The flask was affixed with a reflux condenser and the entire apparatus was sealed with a septum. The contents were flushed with N_2 and a N_2 atmosphere was maintained with a bubbler. After CH_3CN (12 mL) was injected, the mixture was stirred at 80 °C for the time specified in Table 1. After GC analysis of the mixture indicated that all of the starting material had been consumed, the mixture was diluted with ether (10 mL) and filtered through a plug of Celite to remove the AgI. The

solids were washed several times with ether, and the filtrate was added to a separatory funnel containing saturated NH_4Cl (50 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and columned over silica gel to afford the desired product. Note: all cyclic 1,4-dienes reported in the following were prepared using procedure B.

Diene 43

This diene was columned over silica gel using hexane / EtOAc (10 : 1). ^1H NMR ($CDCl_3$) δ 1.12 - 1.63 (m, 2 H, CH_2), 1.65 - 2.41 (m, 6 H, CH_2's), 3.00 (br s, 1 H, C=C-CH-C=C), 5.50 - 5.54 (m, 2 H, CH=C-C-C=CH), 5.65 - 5.71 (m, 2 H, C=CH-C-CH=C); ^{13}C NMR ($CDCl_3$) δ 21.50, 27.96, 33.95, 39.07, 54.02, 124.69, 126.40; IR (neat) 3030, 2946, 2229, 1437, 1261, 1094, 793 cm^{-1}; HRMS calcd for $C_{11}H_{13}N$ m/z 159.10480, found m/z 159.10516.

Diene 44

The crude product was purified over silica gel using hexane / EtOAc (8 : 1) to afford the diene. ^1H NMR ($CDCl_3$) δ 1.24 (t, 3 H, J = 7.2 Hz, CH_3), 1.75 - 1.79 (m, 4 H, CH_2's), 2.03 - 2.07 (m, 4 H, C=C-CH_2's), 3.29 (br s, 1 H, C=CCHC=C), 4.14 (q, 2 H, J = 7.2 Hz, OCH_2), 5.60 (br s, 4 H, CH=CHCCH=CH); ^{13}C NMR ($CDCl_3$) δ 14.13, 22.13, 27.76, 36.95, 43.70, 60.27, 124.11, 128.77, 176.92; HRMS calcd for $C_{13}H_{18}O_2$ m/z 206.2068, found m/z 206.13057.

Diene 45

The crude product was purified over silica gel using hexane / EtOAc (10 : 1) to afford the diene. ^{1}H NMR ($CDCl_3$) δ 1.65 (d, 3 H, J = 0.9 Hz, CH=CC<u>H</u>$_3$), 1.76 - 1.80 (m, 2 H, CH_2), 1.99 - 2.01 (m, 1 H, C<u>H</u>H), 2.23 - 2.28 (d and m, 2 H, J = 15.3 Hz, CH<u>H</u> and C(<u>H</u>)H-CCN), 2.88 (d, 1 H, J = 15.3 Hz, C(H)<u>H</u>-CCN), 3.43 (br s, 1 H, C=C-CH-C=C), 5.15 (s, 1 H, C<u>H</u>=CCH$_3$), 5.64 - 5.80 (m, 2 H, CH=CH-CCN); ^{13}C NMR ($CDCl_3$) δ 16.16, 21.52, 29.17, 38.05, 48.33, 50.45, 124.60, 125.44, 125.49, 126.54, 136.09; IR (neat) 3030, 2900, 2847, 2233, 1443, 733 cm^{-1}; HRMS: calcd for $C_{11}H_{13}N$ m/z 159.10480, found m/z 159.10501.

Diene 46

This diene was purified over silica gel using hexane / EtOAc (8 : 1). ^{1}H NMR ($CDCl_3$) δ 1.12 - 1.20 (m, 6 H, CH_3's), 1.61 (s, 3 H, CH_3), 1.95 - 1.99 (m, 2 H, C=C-CH_2), 2.41 (br s, 1 H, C<u>H</u>H), 2.45 (br s, 1 H, CH<u>H</u>), 2.58 - 2.63 (m, 3 H, C=C-CH_2 and CH), 2.95 - 2.97 (m, 1 H, C=C-CH-C=C), 4.09 (dt, 2 H, J = 2.4 Hz, J = 7.2 Hz, OCH_2), 4.12 (q, 2 H, J = 7.2 Hz, OCH_2), 5.07 (s, 1 H, C<u>H</u>=CCH$_3$), 5.53 - 5.65 (m, 2 H, CH=CH); ^{13}C NMR ($CDCl_3$) δ 13.95, 14.62, 19.33, 23.33 (two peaks), 25.40, 30.64, 34.95, 36.61, 58.23, 61.18, 61.25, 121.97, 128.22, 129.17, 170.37, 170.57; IR (neat) 3020, 2964, 2933, 1734, 1445, 1259, 1231, 1182, 1123, 1084, 1030, 875, 833 cm^{-1}; HRMS calcd for $C_{17}H_{24}O_4$ m/z 292.16747, found m/z 292.16793

Diene 47

This product was columned over silica gel using hexane / EtOAc (30 : 1) as the eluent to afford the desired product. ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 3 H, CH_3), 2.44 (d, 1 H, J =

18.3 Hz, C=C-CHH), 2.61 - 2.70 (m, 1 H, C=C-CHH), 2.93 (br s, 1 H, C=C-CH-C=C), 3.84 (d, 1 H, J = 15.3 Hz, CHH-O), 3.95 (d, 1 H, J = 15.3 Hz, CHH-O), 4.20 (dd, 1 H, J = 5.1 Hz, J = 5.1 Hz, CHO), 5.62 - 5.64 (m, 2 H, CH=CH), 5.74 - 5.77 (m, 1 H, CH_3C=CH); ^{13}C NMR ($CDCl_3$) δ 19.24, 40.04, 45.83, 66.74, 75.12, 118.99, 127.62, 131.67, 133.73; IR(neat) 3057, 3020, 2932, 1429, 1117, 1097, 982, 847, 825 cm^{-1}; HRMS: calcd for $C_9H_{12}O$ m/z 136.08882, found m/z 136.08904.

Diene 48

This diene was purified over silca gel using hexane / EtOAc (15 : 1). ^1H NMR ($CDCl_3$) δ 1.62 (s, 3 H, CH_3), 1.66 - 1.74 (m, 1 H, CHH), 1.90 - 2.05 (m, 2 H, C=C-CH_2), 2.17 - 2.23 (m, 1 H, CHH), 2.59 - 2.62 (m, 1 H, C=C-CH-C=C), 3.82 (br s, 1 H, CH-O), 4.00 (d, 1 H, J = 15.9 Hz, CHH-O), 4.08 (d, 1 H, J = 15.9 Hz, CHH-O), 5.46 - 5.49 (m, 2 H, CH=CH and CH_3C=CH), 5.69 - 5.74 (m, 1 H, CH=CH); ^{13}C NMR ($CDCl_3$) δ 18.69, 20.19, 26.71, 35.19, 68.28, 70.12, 121.33, 125.17, 126.63, 132.87; IR(neat) 3020, 2968, 2856, 1443, 1366, 1175, 1109, 1030, 837, 654 cm^{-1}; HRMS: calcd for $C_{10}H_{14}O$ m/z 150.10447, found m/z 150.1044.

REFERENCES

1. Heck, R. F. *Org. React.* **1982**, *27*, 345.
2. Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1980**, *45*, 2938.
3. Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L.S. *J. Org. Chem.* **1980**, *45*, 2709.
4. Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4133.
5. Mori, M.; Ban, Y. *Tetrahedron Lett.* **1979**, 1133.
6. Mori, M; Chiba, K.; Ban, Y. *Tetrahedron Lett.* **1977**, 1037.
7. Hegedus, L.S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800.
8. Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328.
9. Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett.* **1988**, *29*, 2918.
10. Terpko, M. O.; Heck, R. F. *J. Am. Chem. Soc.* **1979**, *101*, 5281.
11. Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1697.
12. Kasahara, A.; Izumi, T.; Murakami, S.; Yanai, H. Yakatori, M. *Bull .Chem. Soc. Jpn.* **1986**, *59*, 927.
13. Ziegler, F. E.; Chakaborty, U. R.; Weisenfeld, R. B. *Tetrahedron* **1981**, *37*, 4035.
14. Narula, C. K.; Mak, K. T.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 2702.
15. Shi, L.; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 3894.
16. Negishi, E.-I.; Miller, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 6761.
17. Tour, J. M.; Negishi, E.-I. *J. Am. Chem. Soc.* **1985**, *107*, 8289.
18. Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1073.
19. Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron* **1988**, *44*, 2033.

20. Jeffrey, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287.

21. Jeffrey, T. *Tetrahedron Lett.* **1985**, *26*, 2667.

22. Jeffrey, T. *Synthesis* **1987**, 70.

23. Negishi, E.-I.; Zhang, Y.; O'Connor, B. *Tetrahedron Lett.* **1988**, *29*, 2915.

24. O'Connor, B.; Zhang, Y.; Negishi, E.-I.; Luo, F.-T.; Cheng, J.-W. *Tetrahedron Lett* . **1988**, *29*, 3903.

25. Zhang, Y.; O'Connor, B.; Negishi, E.-I. *J. Org. Chem.* **1988**, *53*, 5588.

26. Sato, Y.; Mikiko, S.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738.

27. Kagan, H. B. "Asymmetric Synthesis"; Morrison, J.D., Ed.; Academic Press, Inc.: New York, 1985, vol. 6., p 1.

28. Tsuji, T. "Organic Synthesis with Palladium Compounds"; Springer Verlag: New York, 1980.

29. Oppolzer, W.; Gaudin, J.-M. *Helv. Chim. Acta* **1987**, *70*, 1477.

30. Baker, B. E., Ph.D. Dissertation, Iowa State University, 1988.

31. Krishnamurthy S.; Brown, H. C. *J. Org. Chem.* **1975**, *40*, 1864.

32. Song, H. C., Ph.D. Dissertation, Iowa State University, 1988.

33. Ruzicka, L.; Brugger, W. *Helv. Chim. Acta* **1926**, *9*, 319.

34. Vogel, A. "Vogel's Textbook of Practical Organic Chemistry", 4th ed.; Longman Group Limited: London, 1978, pp 513 - 514.

GENERAL SUMMARY

In this dissertation, the versatility of organopalladium chemistry in organic synthesis was demonstrated. In Part One of this work, the development of an improved procedure for intermolecular allylic arylation was discussed. Previous procedures (A and B) were ineffective in promoting the desired cross-coupling of cyclic alkenes and some aryl iodides containing certain organic functional groups. Procedure C, which is a simple modification of procedure A, was effective in circumventing these functional group difficulties found when procedures A and B were used, and it provided 3-arylcycloalkenes in high yields generally within 24 hours.

In Part Two of this work, the power of procedure C was exploited in the development of a three-step synthesis of *trans*-2,5-diaryltetrahydrofurans, which are known to be potent inhibitors of platelet activating factor. Indeed, when an aryl iodide was allowed to react with 2,3-dihydrofuran under the conditions of procedure C, 2-aryl-2,3-dihydrofurans were produced along with only a trace amount of the allylic isomer. Taking advantage of the selectivity procedure C provided, this procedure was then used as the key step in this three-step synthetic process to provide only the biologically active *trans* isomer. This process represents the only process available today for producing only the *trans* isomer.

In Part Three, the intermolecular vinylation of cyclic alkenes was explored. Procedures A, B, and C were employed, and a general method for preparing 1,4-dienes was established. Vinylic iodides containing simple alkyl groups, as well as electron-withdrawing groups, were examined. Cycloalkenes of ring sizes 5 through 8, and vinylic ethers such as 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran were explored. In general,

procedure A was effective in providing the desired 1,4-diene when vinylic iodides containing simple alkyl groups and cyclopentene were cross - coupled. Unfortunately, cycloheptene, 2,3-dihydrofuran, and 3,4-dihydro-2*H*-pyran all provided mixtures of 1,4- and 1,5-dienes, and cyclohexene and cyclooctene proved to be inert under the reaction conditions of procedure A. Procedure B was effective in suppressing the formation of 1,5-dienes providing only the 1,4-dienes in all cases where procedure A failed. Moreover, procedure B was also successful in the vinylation of cyclohexene. Unfortunately, cyclooctene remained inert when using procedure B. Vinylic iodides containing electron-withdrawing groups were found to be problematic as they provided bad regioisomeric mixtures of products when using procedure A. Procedures B and C afforded only symmetrical dimers corresponding to the starting material.

In Part Four, the use of procedures A, B, and C in the intramolecular vinylation of cyclic alkenes was explored. Procedure A's major limitation was the tendency to generate a large amount of homoallylic side product. Procedure B was effective in providing only the desired bicyclic 1,4-diene in good to excellent yields. Procedure C proved to be problematical as it tends to produce mixtures of many unidentifiable organic products. The limitations of both procedures A and B appear to be their incompatibility with dienyl iodides containing an allylic ester.

ACKNOWLEDGEMENTS

I wish to thank my major professor, Richard C. Larock, for his experience, kindness, understanding, patience, financial support, and for teaching me to be an effective researcher. I wish to thank Yong de-Lu, Drs. Bruce Baker, Norman Berrios-Pena, Hanchul Song, Colleen Fried, Mann-yan Kuo, and William Leong for their valuable time and helpful discussions. I wish to thank my wife, Melinda, who tolerated my late night studying, and the many evenings that I wasn't home with her. I would like to thank my parents, especially my mother, who, without their faith in me and a loan for the purchase of this computer, this work would not have been possible. I would like to thank my father and mother-in-law, Myron and Lovell Lee, for all of their support (financial and otherwise) and for understanding what their daughter had to endure. I would like to thank my other "parents", Jack and Jan Husak, for all of their help, love, and encouragement. I would like to thank my best friend, Jeff Husak, who encouraged me to pursue this degree and all of my dreams. With deepest appreciation and affection, I wish to thank my pastor, Tom Nesbitt, and my family at GABC who supported me with their prayers and friendship. Finally, I thank the Lord for the promises He's kept and for the wonderful friends He's provided (Psalm 37 : 4, Phil. 4 : 13, and Romans 8 : 28).