1992

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Order Number 9311488

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Iowa State University, 1992

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Palladium-promoted cross-coupling of alkenyl heterocycles with organomercurials, organic halides and triflates

by

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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:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

For the Major Department

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa

1992

DEDICATION

I would like to dedicate this work to the chemist who initiated and stimulated my interest in chemistry. In these many years, his love supported me to pursue this degree. If he could be alive today, he would be very proud to see that his little girl, who was young and naive 16 years ago, now has become a mature and knowledgeable organic chemist. To my father Kaicheng Ding.

TABLE OF CONTENTS

TABLE OF ABBREVIATIONS

aq	Aqueous
Ar	Aryl
br	Broad
bp	Boiling point
Bu	Butyl
cm	Centimetres
d	Doublet
dba	Dibenzylideneacetone
dd	Doublet of doublets
ddd	Double doublet of doublets
ddt	Double doublet of triplets
DMA	*N,N*-Dimethylacetamide
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dt	Doublet of triplets
eq	Equations
equiv.	Equivalents
Et	Ethyl
g	Grams
GC	Gas chromatography
HRMS	High resolution mass spectrometry
IR	Infrared
LDA	Lithium diispropylamide
M	Molar

m	Multiplet
mg	Milligrams
ml	Milliliters
mmHg	Millimetre Mercury
mol	Moles
mmol	Millimoles
mp	Melting point
NMR	Nuclear magnetic resonance
Ph	Phenyl
Pr	Propyl
rt	Room temperature
q	Quartet
s	Singlet
t	Triplet
TBAC	Tetra-*n*-butylammonium chloride
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethyldiamine
Ts	Tolylsulfonyl

GENERAL INTRODUCTION

In the past two decades, the role of organopalladium chemistry in organic synthesis has rapidly expanded. Palladium-promoted nucleophilic and organometallic additions to vinylic epoxides have become extremely versatile and useful synthetic reactions. These reactions produce 1,2- or 1,4-addition products in a highly regio- and stereoselective manner and have been used in the synthesis of a number of natural products. This dissertation focuses on the development of useful synthetic methodologies for palladium-promoted cross-coupling of alkenyl heterocycles with organomercurials, organic halides and triflates.

This dissertation is divided into four parts. Each part is presented with its own introduction, results and discussion, experimental section, conclusion, and references. Following the last part is a general summary.

The first part focuses on the development of palladium-promoted cross-coupling of alkenyl 2-azetidinones with aryl- and vinylmercurials. These reactions are the first observed examples of alkenyl 2-azetidinones reacting with organometallic reagents to afford 3-alkenamides. Procedures employing both stoichiometric and catalytic amounts of a palladium(II) salt have been investigated and will be discussed.

The focus of the second part is on the palladium-catalyzed cross-coupling of alkenyl 2-azetidinones with aryl and vinylic halides. These reactions provide an alternate synthetic route to functionally-substituted 3-alkenamides. A wide variety of aryl and vinylic halides have been employed in the reaction to explore the scope and limitations of this synthetic transformation.

The focus of the third part is on the palladium-catalyzed cross-coupling of vinylic epoxides with organic halides and triflates to afford allylic alcohols. A number of different vinylic epoxides and various organic halides containing electron-donating and withdrawing

groups have been examined. The scope and limitations of this reaction have been determined and will be discussed.

In the final part, the palladium-promoted cross-coupling of vinylic oxetanes with various aryl and vinylic halides has been investigated. The purpose is to determine the scope and limitations of this reaction for producing a variety of homoallylic alcohols.

PART I. PALLADIUM(II)-PROMOTED CROSS-COUPLING OF ALKENYL 2-AZETIDINONES WITH ORGANOMERCURIALS

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 palladium-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.[1-5]

One method of preparing organopalladium compounds involves the transmetallation of organomercurials with palladium(II) salts (eq 1.1).[1,2] Organomercurials are easily

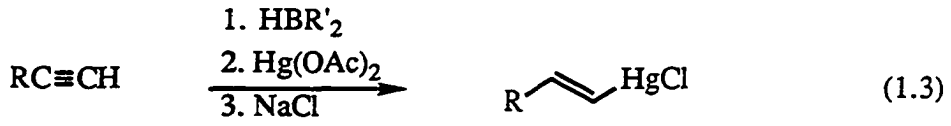
$$RHgX + PdX_2 \longrightarrow RPdX + HgX_2 \qquad (1.1)$$

prepared, can accommodate a wide variety of functionality and are stable precursors to the highly reactive organopalladium compounds. The use of organomercurials as useful synthetic reagents in organic chemistry has been reviewed by Larock.[6,7] The preparation of a wide variety of organomercurials is covered in these reviews and the references cited therein.

Arylmercurials are easily prepared by simple electrophilic aromatic mercuration of the arene of interest (eq 1.2). These reactions generally produce high yields and tolerate a wide variety of functionality. Isomers formed in these reactions can usually be easily separated by recrystallization.

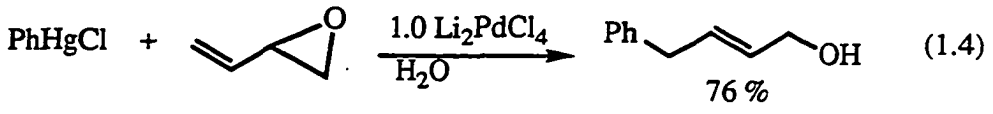
$$ArH + HgX_2 \longrightarrow ArHgX + HX \qquad (1.2)$$

Vinylmercurials can be prepared from the corresponding organomagnesium, -lithium, or -boron reagents. The preparation of vinylmercurials via the first two routes severely restricts the type of functionality that can be present in the molecule. Thus, only the boron reagents are of real synthetic utility. Vinylmercurials can be prepared in high yields using a hydroboration-mercuration procedure (eq 1.3).[8-10]



(1.3)

Larock and Ilkka have reported that vinylic epoxides will react with aryl- and vinylmercurials in the presence of a stoichiometric amount of palladium(II) (eq 1.4).[11] This



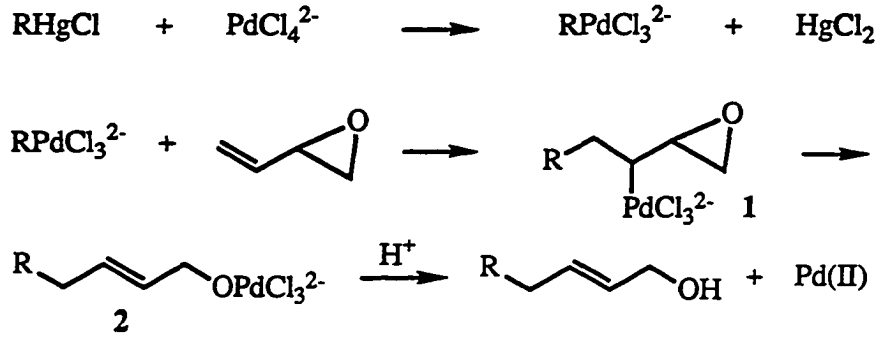
(1.4)

reaction provides an excellent high yielding, regio- and stereoselective route to functionally substituted allylic alcohols.

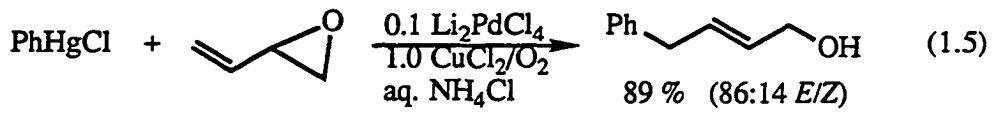
The following mechanism has been proposed to explain how allylic alcohols are formed in these reactions (Scheme 1). The first step of the mechanism involves transmetallation of the arylmercurial with a palladium(II) salt. The organopalladium species then adds across the double bond of the vinylic epoxide. The aryl group becomes attached to the least hindered end of the olefin to form intermediate **1**. Intermediate **1** then undergoes palladium alkoxide elimination to form the alkoxypalladium species **2**. The allylic alcohol can then be formed from intermediate **2** by reaction with a proton source.

Larock and Ilkka have found that the reactions of vinylic epoxides with organomercurials could also be run using a catalytic amount of palladium(II) if cupric

Scheme 1

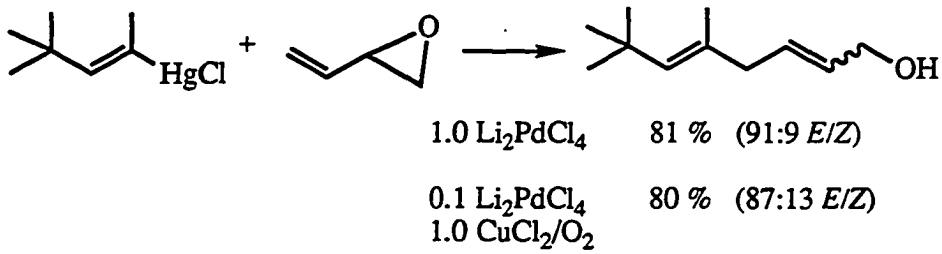


chloride was added to the reaction and the reactions were conducted under an atmosphere of oxygen (eq 1.5). Unfortunately, Larock and Ilkka were unable to find conditions for the catalytic reaction which would yield only the *E*-isomer of the corresponding allylic alcohol.



(1.5)

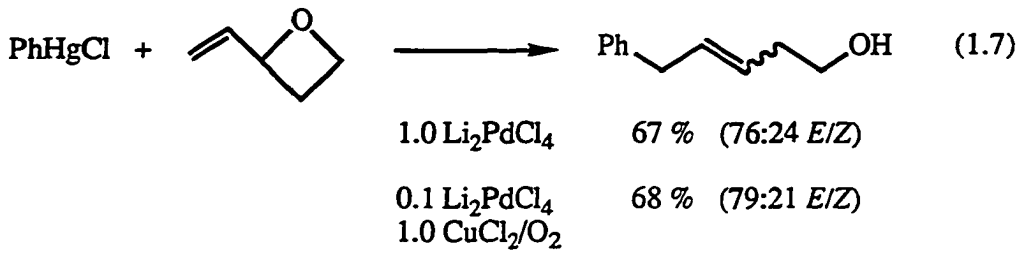
Vinylmercurials also react readily with vinylic epoxides in the presence of palladium (eq 1.6). Using the stoichiometric procedure which proved best for the synthesis of pure *E*



(1.6)

aryl-substituted allylic alcohols, a high yield of anticipated alcohol was observed, but it was a 91:9 *E* and *Z* mixture about the newly generated double bond. Using vinylmercurials and the previously developed procedure employing catalytic palladium, good yields of dienols are afforded, but some loss of stereoselectivity is observed.

In 1988, Larock and Stolz-Dunn reported the first example of organometallic ring-opening of vinylic oxetanes (eq 1.7).[12] In the presence of a stoichiometric amount of



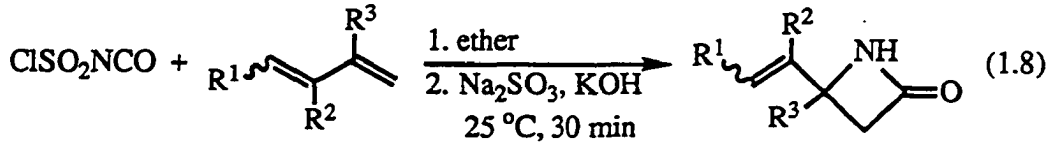
palladium, organomercurials react with vinylic oxetanes to afford good yields of homoallylic alcohols. Unlike the corresponding vinylic epoxide reactions, these reactions show only modest stereoselectivity. When using a catalytic amount of palladium and carrying out the reaction in the presence of cupric chloride and one atmosphere of oxygen, similar results are observed.

As a natural extension of this work, it was thought that the vinylic epoxide or oxetane could be replaced with an alkenyl 2-azetidinone. If this reaction was successful, it would be the first example of the opening of vinylic 2-azetidinones with organometallic reagents to form functionalized 3-alkenamides. In this part, the palladium(II)-promoted cross-coupling of alkenyl 2-azetidinones and organomercurials will be discussed.

Several objectives and goals were set forth before and during the course of this project. First, it was hoped that these reactions would produce 3-alkenamides in high yield with a high degree of stereoselectivity. It was also desirable to use a catalytic amount of palladium in these reactions and still obtain the high yield and stereoselectivity. Finally, in order to develop this reaction into a synthetically useful method, it was necessary to investigate the scope of this reaction with regard to the types of organomercurials and alkenyl 2-azetidinones that would undergo synthetically useful reactions.

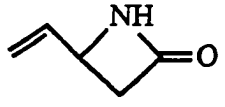
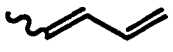
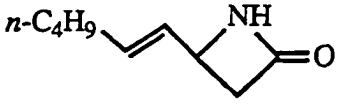
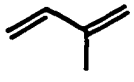
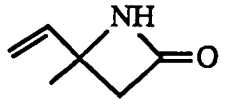
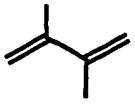
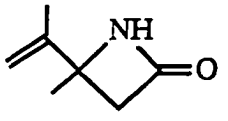
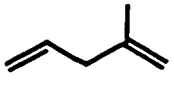
RESULTS AND DISCUSSION

Alkenyl 2-azetidinones were readily prepared from the reaction of chlorosulfonyl isocyanate and the corresponding dienes according to the literature procedures (eq 1.8).[13-15] The results are summarized in Table 1.



(1.8)

Table 1. Preparation of alkenyl 2-azetidinones

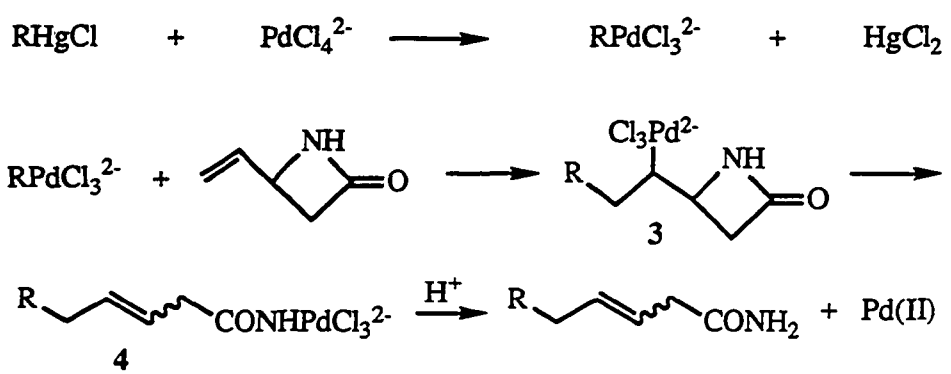
Entry	Diene	Temp (°C)	Time (h)	Product	Yield (%)
1		25	5		30
2[a]		0	3		18
3[b]		0	2.5		25
4		0	1		55
5		0	1		25
6		0	18		54

[a] The product was obtained in an *E*/*Z* ratio of 38:62.

[b] Only the *E* isomer was obtained.

A possible mechanism for the palladium(II)-promoted cross-coupling of alkenyl 2-azetidinones with organomercurials is shown in Scheme 2 to explain how the desired amide is formed in these reactions. While no experiments have been run to attempt to support (or disprove) this mechanism, analogous mechanisms have been proposed to explain how vinylic

Scheme 2



epoxides and oxetanes react with organomercurials in the presence of a palladium(II) salt.[11,12] The first step of the mechanism involves transmetallation of the organomercurial with a palladium(II) salt. The organopalladium species then adds to the double bond of the alkenyl 2-azetidinone to form σ-alkylpalladium species **3**. The organic ligand becomes attached to the least hindered end of the carbon-carbon double bond. This σ-alkylpalladium species then undergoes palladium amide elimination to form amide palladium species **4**. The water or ammonium chloride in the system then protonates the palladium amide species to form the desired product and regenerates palladium(II).

The mechanism shown in Scheme 2 indicates that the reaction between alkenyl 2-azetidinones and organomercurials should be catalytic with respect to palladium(II). When Larock and Ilkka allowed butadiene monoepoxide to react with phenylmercuric chloride using a catalytic amount of palladium(II), they found that they obtained only a 1.8 catalytic turnover

of palladium.[11] Thus, it appears that palladium(II) is being reduced to palladium(0) during the course of the reaction. It was thought that it might be possible to regenerate the palladium(II) using a copper(II) salt in a "Wacker-type" process (eq 1.9).[1] In this process,

$$\text{Pd(0)} + 2\,\text{Cu(II)} \longrightarrow \text{Pd(II)} + 2\,\text{Cu(I)} \xrightarrow{O_2} 2\,\text{Cu(II)} \qquad (1.9)$$

palladium(0) is oxidized to palladium(II), while copper(II) is reduced to copper(I). The copper(II) can then be regenerated, if the reaction is run under an atmosphere of oxygen. Thus, it should be possible to obtain high yields of 3-alkenamides from the reactions of the corresponding alkenyl 2-azetidinones with organomercurials using a catalytic amount of palladium(II), if a copper(II) salt is added to the reaction mixture and the reaction is run under an atmosphere of oxygen.

The stereochemistry of the newly formed carbon-carbon double bond in the 3-alkenamides is also of considerable interest. As discussed previously, the ring-opening of vinylic epoxides in the presence of a stoichiometric amount of dilithium tetrachloropalladate initially afforded a mixture of *E*- and *Z*-allylic alcohols, which was observed to isomerize to the pure *E*-alcohol under the reaction conditions.[11, 16] This isomerization occurs presumably through a process involving palladium(0) insertion into the carbon-oxygen bond of the allylic alcohol, *anti* to *syn* isomerization of the resulting π-allylpalladium species and reductive elimination. When cupric chloride and catalytic amounts of dilithium tetrachloropalladate were used in the reaction, vinylic epoxides afforded mixtures of *E*- and *Z*-allylic alcohols, presumably because any palladium(0) formed was immediately oxidized to palladium(II).

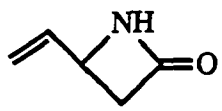
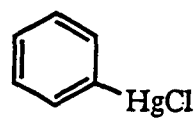
Since there is no longer an allylic carbon-oxygen bond in the amide products, it was expected that the stoichiometric and catalytic reactions would produce 3-alkenamides with roughly the same stereoselectivity. Indeed, this is generally true.

In Table 2 are summarized the results of the palladium(II)-promoted cross-coupling of alkenyl 2-azetidinones and organomercurials. Two different Pd(II) procedures were employed for each reaction: procedure A (1.0 equiv. Li_2PdCl_4 and 20:1 THF / saturated aqueous NH_4Cl at 0 °C for 6 to 12 hours, and then at 25 °C for 0-24 hours), and procedure B (10 mol % Li_2PdCl_4, 1 equiv. cupric iodide, 1 atm. oxygen and 20:1 THF / saturated aqueous NH_4Cl at 0 °C for 0-12 hours, and then at 25 °C for 3-48 hours).

A variety of substituted 2-azetidinones with terminal or internal carbon-carbon double bonds are available from 1,3-dienes and chlorosulfonyl isocyanate, and all azetidinones reacting with arylmercurials generally afford good to excellent yields of ring-opened amide products. As expected, best results are obtained from 2-azetidinones bearing terminal double bonds (entries 1-3 and 10-21), but even reactions with 2-azetidinones containing internal disubstituted double bonds afford respectable yields (entries 4-9). The regioselectivity of the organopalladium addition to internal double bonds is apparently quite high, since none of any products arising from addition of the aryl group next to the nitrogen moiety was observed.

The stereoselectivity of these reactions is dependent on the structure of the alkenyl 2-azetidinones employed. When disubstituted alkene products are formed from 2-azetidinones with terminal double bonds, the *E*-isomer is preferred (entries 1-3). The *E* / *Z* isomer ratio is about 3:1. 2-Azetidinones with internal double bonds give almost exclusively the *E*-disubstituted product (entries 4-9). Trisubstituted alkenyl amides can be obtained in excellent yields using both stoichiometric and catalytic procedures (entries 10 and 11), but there is no stereoselectivity in the formation of these trisubstituted alkenes. Other arylmercurials have also been examined. Both electron-donating and electron-withdrawing groups are readily accommodated in these reactions and give comparable yields (entries 12-19). Tetrasubstituted alkene products can also be formed from these reactions and reasonable stereoselectivity has been observed using the catalytic procedure although the yield is low (entries 20 and 21).

Table 2. Palladium-promoted reaction of alkenyl 2-azetidinones and organomercuric chlorides

Entry	2-Azetidinone (2 equiv)	RHgCl	Procedure[a]
1			A
2			B
3[b]			B
4			A
5			B
6[c]			B
7			A
8			B
9[c]			B
10			A
11			B

[a] See text for explanation of procedures.

[b] 1 Equiv. 2-azetidinone was used.

[c] 2 Equiv. $CuCl_2$ were used.

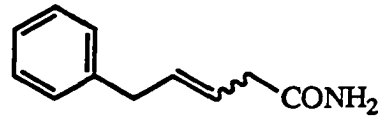
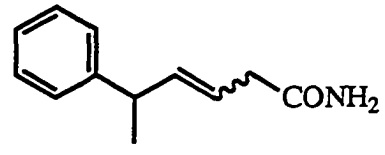
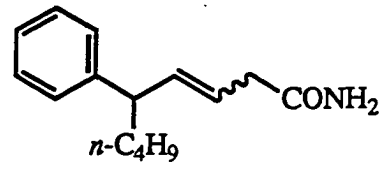
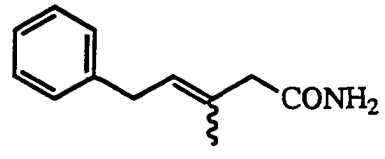
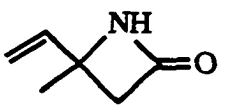
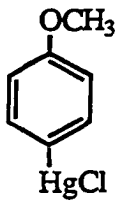
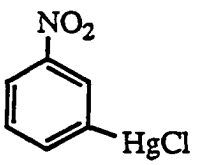
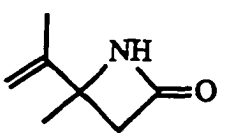
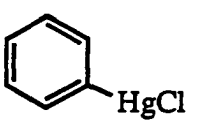
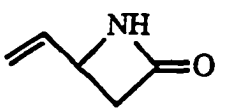
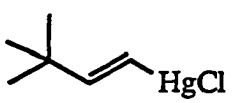
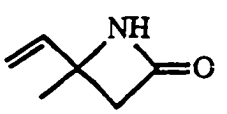
Conditions	Product	*E*/*Z* Ratio	Yield (%)
0 °C, 11 h; 25 °C, 3 h		74:26	60
0 °C, 3 h; 25 °C, 24 h		72:28	50
0 °C, 3 h; 25 °C, 24 h		72:28	57
0 °C, 10 h; 25 °C, 8 h		90:10	51
0 °C, 2 h; 25 °C, 9 h		95:5	32
0 °C, 1 h; 25 °C, 8 h		100:0	38
0 °C, 10 h; 25 °C, 8 h		95:5	55
0 °C, 3 h; 25 °C, 18 h		100:0	26
0 °C, 1 h; 25 °C, 8 h		100:0	42
0 °C, 11 h; 25 °C, 3 h		52:48	90
0 °C, 2 h; 25 °C, 10 h		49:51	91

Table 2. (continued)

Entry	2-Azetidinone (2 equiv)	RHgCl	Procedure[a]
12			A
13[d]			A
14			B
15			B
16			A
17[d]			A
18			B
19[e]			B
20			A
21			B
22			A
23[b]			A
24			A
25[e]			A
26			B

[d] 5 % H_2O was used instead of NH_4Cl.

[e] No NH_4Cl or H_2O was added.

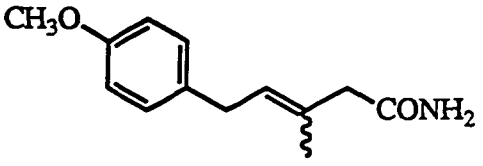
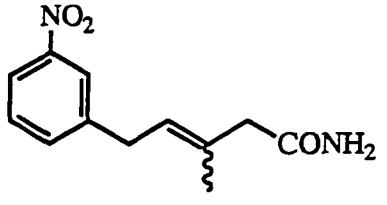
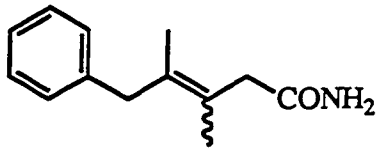
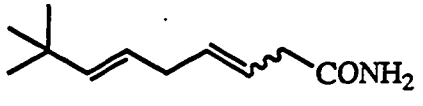
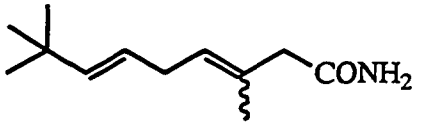
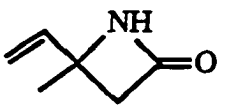
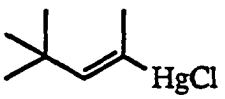
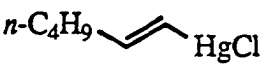
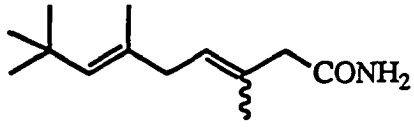
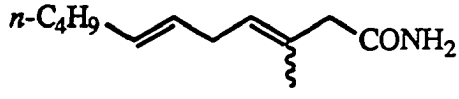
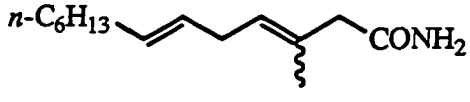
Conditions	Product	*E/Z* Ratio	Yield (%)
0 °C, 10 h; 25 °C, 6 h		47:53	73
0 °C, 6 h		44:56	77
0 °C, 12 h; 25 °C, 3 h		50:50	74
0 °C, 2 h; 25 °C, 28 h		54:46	63
0 °C, 8 h; 25 °C, 7 h		54:46	56
0 °C, 6 h		53:47	79
0 °C, 2 h; 25 °C, 7 h		53:47	32
25 °C, 8 h		48:52	52
0 °C, 12 h; 25 °C, 2 h		52:48	85
0 °C, 3 h; 25 °C, 15 h		83:17	41
0 °C, 11 h; 25 °C, 3 h		-	0
0 °C, 12 h; 25 °C, 3 h		75:25	16
0 °C, 12 h; 25 °C, 3 h		81:19	34
0 °C, 10 h		67:33	21
0 °C, 2 h; 25 °C, 9 h		59:41	18

Table 2. (continued)

Entry	2-Azetidinone (2 equiv)	RHgCl	Procedure[a]
27			A
28[d]			A
29			B
30			B
31			B
32			A

Conditions	Product	*E/Z* Ratio	Yield (%)
0 °C, 11 h; 25 °C, 5 h		68:32	54
0 °C, 12 h		47:53	45
0 °C, 2 h; 25 °C, 8 h		51:49	35
25 °C, 10 h		-	0
25 °C, 48 h		-	0
0 °C, 10 h; 25 °C, 24 h		-	0

Vinylmercurials tend to give significantly lower yields than arylmercurials. Like the corresponding reactions of epoxides and oxetanes, the more sterically hindered the vinylmercurial, the higher the yield of amide product (entries 23-29). No product was even observed when *E*-1-hexenylmercuric chloride and *E*-1-octenylmercuric chloride were employed in the procedure using stoichiometric amounts of palladium (entries 30-32). In general, lower yields were obtained when the catalytic procedure was employed with vinylmercurials. The difficulties are presumably due to the easy dimerization of the less hindered vinylmercurials to 1,3-dienes.[17,18]

4-Methyl-4-(2-propenyl)-2-azetidinone in which the carbon-carbon double bond and the 2-azetidinone are separated by one carbon has also been allowed to react with phenylmercuric chloride using the stoichiometric and catalytic procedures (eq 1.10). An examination of Table 3 shows that none of the desired aryl 3-alkenamide **5** was observed with either procedure. In the presence of a stoichiometric amount of Pd(II) salt, approximately equal amounts of by-products **6** and **7** were obtained (entries 1 and 2). The stereochemical outcome of compound **7** did not seem to change significantly when the reaction conditions were varied.

A mechanism is shown in Scheme 3 which explains how the β-hydride eliminated product **6** and the hydride-reduced product **7** are formed in this reaction (eq 1.10). The first step of the mechanism involves the transmetallation of phenylmercuric chloride with dilithium tetrachloropalladate to form a phenylpalladium species. This phenylpalladium species then adds across the double bond of the alkenyl 2-azetidinone to form σ-alkylpalladium species **8**, followed by the formation of π-palladium species **9**. β-Hydride elimination of the π-palladium species affords product **6** and a palladium hydride species. The palladium hydride species then further reacts with another molecule of the alkenyl 2-azetidinone to form σ-alkylpalladium intermediate **10**. It is followed by palladium hydride elimination and subsequent readdition with the opposite regiochemistry to afford another σ-alkylpalladium

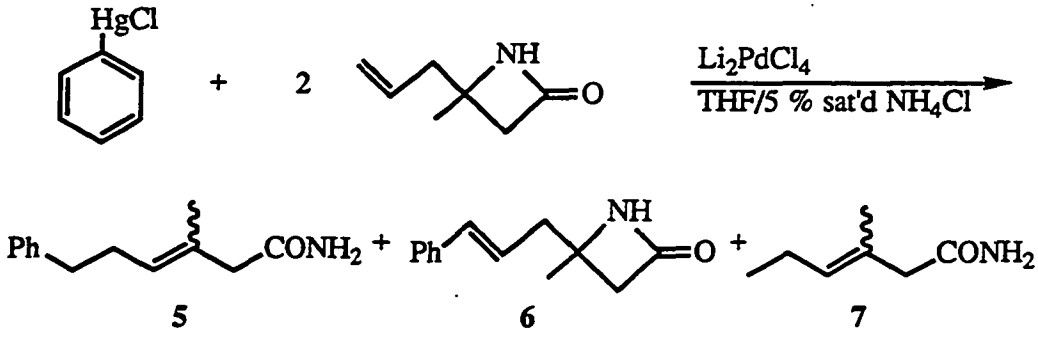


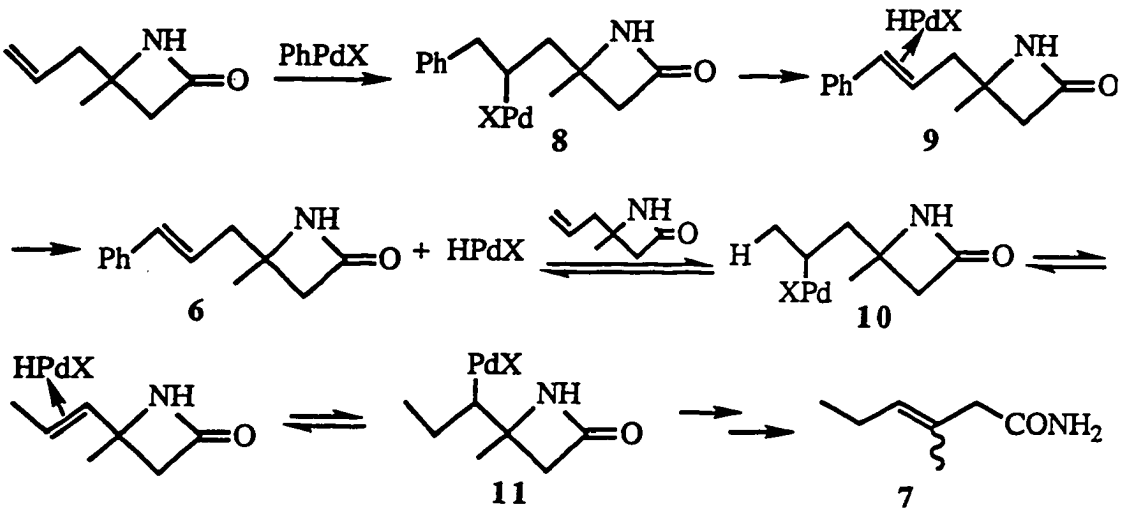
Table 3. Palladium(II)-promoted reaction of 4-methyl-4-(2-propenyl)-2-azetidinone and phenylmercuric chloride

Entry	Procedure[a]	Conditions	Yield (%) 5	Yield (%) 6	Yield (%) 7	E/Z Ratio 7
1	A	0 °C, 12 h; 25 °C, 3 h	0	64	57	45:55
2	A	0 °C, 12 h; 25 °C, 24 h	0	56	46	50:50
3	B	0 °C, 3 h; 25 °C, 8 h	0	0	0	-

[a] See text for explanation of procedures.

species **11**. Finally, product **7** is formed by the ring-opening process and subsequent protonation. If the addition of the palladium hydride species to the double bond of the alkenyl 2-azetidinone is quantitative, equal amounts of products **6** and **7** should be obtained.

Scheme 3



CONCLUSION

The palladium-promoted cross-coupling of alkenyl 2-azetidinones with arylmercurials provides a high yielding route to functionally-substituted 3-alkenamides. The reaction of vinylmercurials generally affords lower yields of the ring-opened products than that of arylmercurials. The 3-alkenamides are isolated as mixtures of *E*- and *Z*-isomers. Catalytic amounts of palladium can be employed in the reaction if cupric chloride and oxygen are used to reoxidize the palladium. These are the first observed examples of alkenyl 2-azetidinones reacting with organometallic reagents to afford 3-alkenamides. Unlike the reactions of the corresponding vinylic epoxides, these reactions exhibit only modest stereoselectivity.

EXPERIMENTAL SECTION

Equipment

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75.5 MHz for carbon nuclei) or a Varian VXR-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75.5 MHz for carbon nuclei). All infrared spectra were recorded on an IBM IR / 98 FT-IR or a Bio-Rad FTS-7. Exact mass spectral analyses were obtained on a Kratos high resolution mass spectrometer. Gas chromatographic analyses were performed on 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 a HP-1 megabore column (HP 5890).

Reagents

All reagents were used directly as obtained commercially unless noted otherwise. Palladium chloride was donated by Kawaken Fine Chemical Co., Inc. Tetrahydrofuran and ethyl ether were distilled from calcium hydride and stored over molecular sieves. Chlorosulfonyl isocyanate was purchased from Aldrich Chemical Company, Inc. and used without further purification. 1,3-Butadiene, 2-methyl-1,3-butadiene, and 2,3-dimethyl-1,3-butadiene were obtained from Aldrich Chemical Company, Inc. (*E*)- and (*Z*)-1,3-Pentadiene, (*E*)- and (*Z*)-1,3-octadiene, and 2-methyl-1,4-pentadiene were puchased from Wiley Organics.

Organomercurials

Phenylmercuric chloride was used as purchased from Fluka. The arylmercurials used were prepared previously by Larock group members, presumably by simple electrophilic mercuration of the corresponding arene.[6] The vinylmercurials used were also synthesized

previously by other Larock group members through a hydroboration-mercuration procedure.[8-10]

General procedure for the preparation of alkenyl 2-azetidinones

The alkenyl 2-azetidinones were prepared by the reaction of the corresponding dienes and chlorosulfonyl isocyanate according to the literature procedures.[13-15] The diene (10 mmol) was added dropwise to a stirred solution of chlorosulfonyl isocyanate (10 mmol) in 6 ml of distilled ether at -10 °C to 0 °C. After maintaining the reaction temperature at 0 °C for an additional hour, the solution was added slowly to a stirred mixture of 25 ml of 25 % aqueous sodium sulfite and 10 ml of ether. The aqueous phase was kept slightly basic by adding 10 % potassium hydroxide solution as the reduction proceeded. After 30 minutes, the layers were separated and the aqueous layer was successively extracted with three 20-ml portions of ether. The combined ether extracts were dried by anhydrous sodium sulfate, filtered, and evaporated. The crude product was purified by flash column chromatography to give the corresponding alkenyl 2-azetidinone as a colorless oil.

4-Vinyl-2-azetidinone (Table 1, entry 1)

Obtained in 30 % isolated yield from the reaction of 1,3-butadiene and chlorosulfonyl isocyanate: ^{1}H NMR ($CDCl_3$) δ 2.65 (ddd, 1 H, J = 14.7 Hz, J = 2.3 Hz, J = 1.2 Hz, CHCO cis to vinyl), 3.15 (ddd, 1 H, J = 14.7 Hz, J = 5.2 Hz, J = 2.0 Hz, CHCO trans to vinyl), 4.08 (m, 1 H, CHN), 5.14 (d, 1 H, J = 10.2 Hz, =CH_2 trans to ring), 5.27 (d, 1 H, J = 16.8 Hz, =CH_2 cis to ring), 5.88 (ddd, 1 H, J = 16.8 Hz, J = 10.2 Hz, J = 6.9 Hz, C<u>H</u>=CH_2), 6.57 (br s, 1 H, NH). The spectroscopic data were identical to those reported for this compound by Moriconi and Meyer.[15]

(*E*)- and (*Z*)-4-Prop-1-enyl-2-azetidinone (Table 1, entry 2)

Obtained in 18 % isolated yield (38:62 *E/Z*) from the reaction of a mixture of (*E*)- and (*Z*)-1,3-pentadiene and chlorosulfonyl isocyanate: ^{1}H NMR ($CDCl_3$) δ 1.66 (d, 3 H, J = 4.8 Hz, CH_3), 2.63 (m, 1 H, CHCO cis to propenyl), 3.15 (m, 1 H, CHCO trans to propenyl), 4.03 and 4.42 (2 m in a ratio of 38:62 respectively, 1 H, CHNH both trans and cis propenyl), 5.40-5.75 (m, 2 H, CH=CH), 6.41(br s, 1 H, NH). The spectroscopic data were identical to those reported for this *E/Z* mixture by Moriconi and Meyer.[15]

(*E*)-4-(1-Hexenyl)-2-azetidinone (Table 1, entry 3)

Obtained in 25 % isolated yield from the reaction of a mixture of (*E*)- and (*Z*)-1,3-hexadiene and chlorosulfonyl isocyanate: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 7.0 Hz, CH_3), 1.29 (m, 4 H, $CH_2CH_2CH_3$), 1.99 (m, 2 H, CH_2Pr), 2.64 (ddd, 1 H, J = 15.0 Hz, J = 2.3 Hz, J = 1.4 Hz, CHCO cis to hexenyl), 3.14 (ddd, 1 H, J = 15.0 Hz, J = 5.2 Hz, J = 2.0 Hz, CHCO trans to hexenyl), 4.08 (m, 1 H, CHN), 5.45 (ddt, 1 H, J = 15.3 Hz, J = 7.6 Hz, J = 1.2 Hz, CH=CHBu), 5.70 (dt, 1 H, J = 15.3 Hz, J = 6.8 Hz, =CHBu), 6.28 (br s, 1 H, NH); IR (neat) 3261, 2995, 2953, 2858, 1767, 1670, 1452, 1414, 1379, 1315, 1267, 1186, 1094, 1053, 1003, 966, 920, 719 cm^{-1}.

(*E*)-4-Methyl-4-vinyl-2-azetidinone (Table 1, entry 4)

Obtained in 55 % isolated yield from the reaction of 2-methyl-1,3-butadiene and chlorosulfonyl isocyanate: ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 3 H, CH_3), 2.80 and 2.81 (2 s, 2 H, CH_2), 5.12 (d, 1 H, J = 10.0 Hz, $=CH_2$ trans to ring), 5.23 (d, 1 H, J = 17.1 Hz, $=CH_2$ cis to ring), 6.03 (dd, 1 H, J = 17.1 Hz, J = 10.0 Hz, $CH=CH_2$), 6.40 (br s, 1 H, NH). The spectroscopic data were identical to those reported for this compound by Moriconi and Meyer.[15]

4-Isopropenyl-4-methyl-2-azetidinone (Table 1, entry 5)

Obtained in 25 % isolated yield from the reaction of 2,3-dimethyl-1,3-butadiene and chlorosulfonyl isocyanate: ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 3 H, CH_3CN), 1.74 (s, 3 H, CH_3C=), 2.71 and 2.80 (2 d, 2 H, J = 14.4 Hz, CH_2CO), 4.82 (s, 1 H, =CH_2 trans to CH_3), 4.89 (s, 1 H, =CH_2 cis to CH_3), 6.80 (br s, 1 H, NH). The spectrocopic data were identical to those reported for this compound by Moriconi and Meyer.[15]

4-Allyl-4-methyl-2-azetidinone (Table 1, entry 6)

Obtained in 54 % isolated yield from the reaction of 2-methyl-1,4-pentadiene and chlorosulfonyl isocyanate: ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3 H, CH_3), 2.39 (m, 2 H, CH_2C=), 2.64 (dd, 1 H, J = 14.6 Hz, J = 1.7 Hz, CHCO trans or cis to methyl), 2.78 (dd, 1 H, J = 14.6 Hz, J = 1.6 Hz, CHCO cis or trans to methyl), 5.13 (d, 1 H, J = 17.5 Hz, =CH_2 cis to methylene), 5.14 (d, 1 H, J = 10.0 Hz, =CH_2 trans to methylene), 5.76 (m, 1 H, C<u>H</u>=CH_2), 6.15 (br s, 1 H, NH); IR (neat) 3225, 3080, 2976, 2930, 1726, 1643, 1454, 1435, 1379, 1296, 1215, 1188, 1154, 1096, 999, 962, 920, 783 cm^{-1}; HRMS: calculated for $C_7H_{12}NO$ (M+H) m/z 126.09189, found 126.09177.

General stoichiometric procedure for the palladium-promoted cross-coupling of alkenyl 2-azetidinones with organomercurials (Procedure A)

The following procedure used for the preparation of a mixture of (*E*)- and (*Z*)-3-methyl-5-phenyl-3-pentenamide is representative of that used for other compounds. To an oven-dried 25 ml round-bottom flask containing a magnetic stirrer were added the following reagents: palladium chloride (88 mg, 0.5 mmol), anhydrous lithium chloride (42 mg, 0.5 mmol), and distilled THF (12 ml). The solution was allowed to stir under nitrogen at room temperature for 4 to 6 hours. The dilithium tetrachloropalladate formed was cooled to 0 °C. To this solution was added sequentially saturated aqueous ammonium chloride (0.6 ml), 2

equiv. 4-methyl-4-vinyl-2-azetidinone (111 mg, 1.0 mmol), and 1 equiv. phenylmercuric chloride (157 mg, 0.5 mmol). The solution mixture was allowed to stir under nitrogen at 0 °C for 11 hours, and then at room temperature for 3 hours. Ether (15 ml) was then added to the reaction mixture. The ether layer was washed with saturated aqueous ammonium chloride (15 ml x 2), and the combined aqueous layers were back extracted with ether (15 ml x 2). The combined ether fractions were dried over anhydrous magnesium sulfate. After removal of the solvents, the residue was purified by flash column chromatography on silica gel using hexane and ethyl acetate as eluants. (*E*)- and (*Z*)-3-Methyl-5-phenyl-3-pentenamide were obtained in 90 % yield (52:48 *E*/*Z*) as a white solid.

General catalytic procedure for the palladium-promoted cross-coupling of alkenyl 2-azetidinones with organomercurials (Procedure B)

The following procedure used for the preparation of a mixture of (*E*)- and (*Z*)-3-methyl-5-phenyl-3-pentenamide is representative of that used for other compounds. To an oven-dried 25 ml round-bottom flask containing a magnetic stirrer were added the following reagents: palladium chloride (8.8 mg, 0.05 mmol), anhydrous lithium chloride (4.2 mg, 0.05 mmol), anhydrous cupric chloride (67 mg, 1.0 mmol) and distilled THF (12 ml). The solution was allowed to stir under nitrogen at room temperature for 4 to 6 hours. The dilithium tetrachloropalladate formed was cooled to 0 °C. To this solution was added sequentially the saturated aqueous ammonium chloride (0.6 ml), 2 equiv. 4-methyl-4-vinyl-2-azetidinone (111 mg, 1.0 mmol), and 1 equiv. phenylmercuric chloride (157 mg, 0.5 mmol). The reaction flask was flushed with oxygen. The solution was allowed to stir at 0 °C for 2 hours, and then at room temperature for 10 hours. Ether (15 ml) was then added to the reaction mixture. The ether layer was washed with saturated aqueous ammonium chloride (15 ml x 2), and the combined aqueous layers were back extracted with ether (15 ml x 2). The combined ether fractions were dried over anhydrous magnesium sulfate. After removal

of the solvent, the residue was purified by flash column chromatography on silica gel using hexane and ethyl acetate as eluants. (*E*)- and (*Z*)-3-Methyl-5-phenyl-3-pentenamide were obtained in 91 % yield (49:51 *E/Z*) as a white solid.

(*E*)- and (*Z*)-5-Phenyl-3-pentenamide (Table 2, entry 1)

Obtained in 60 % isolated yield (74:26 *E/Z*) from the reaction of 4-vinyl-2-azetidinone and phenylmercuric chloride using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 2.97 (d, 2 H, J = 7.1 Hz, CH_2CO), 3.38 (d, 2 H, J = 6.6 Hz, CH_2Ph), 5.40-6.00 (m, 4 H, CH=CH, NH_2), 7.10-7.40 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 33.51, 38.90, 123.94, 126.12, 128.38, 128.44, 134.52, 139.82, 173.73.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 3.14 (d, 2 H, J = 7.5 Hz, CH_2CO); ^{13}C NMR same as the *E*-isomer or not seen, except δ 34.63, 39.82, 122.64, 128.23, 128.54, 132.84.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 76-78 °C; IR (neat) 3362, 3192, 3086, 3063, 1713, 1661, 1630, 1495, 1452, 1404, 1269, 974, 750, 700 cm^{-1}; HRMS: calculated for $C_{11}H_{13}NO$ m/z 175.09972, found 175.09995.

(*E*)- and (*Z*)-5-Phenyl-3-hexenamide (Table 2, entry 4)

Obtained in 51 % isolated yield (90:10 *E/Z*) from the reaction of 4-(1-propenyl)-2-azetidinone and phenylmercuric chloride using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.37 (d, 3 H, J = 7.2 Hz, CH_3), 2.96 (d, 2 H, J = 6.9 Hz, CH_2CO), 3.49 (p, 1 H, J = 6.9 Hz, CHPh), 5.58 (ddt, 1 H, J = 15.5 Hz, J = 6.9 Hz, J = 1.2 Hz, C<u>H</u>CH_2CO), 5.81 (ddt, 1 H, J = 15.5 Hz, J = 6.9 Hz, J = 1.2 Hz, C<u>H</u>CHPh), 5.67 and 6.17 (2 br s, 2 H, NH_2), 7.15-7.32 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 21.03, 39.80, 42.22, 121.86, 126.17, 126.99, 128.41, 140.49, 145.23, 173.99.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 3.17 (d, 2 H, J = 7.5 Hz, CH_2CO); ^{13}C NMR same as the *E*-isomer or not seen, except δ 23.10, 35.62, 119.19.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 59-61 °C; IR (neat) 3356, 3182, 3028, 2964, 1664, 1636, 1452, 1406, 1377, 1279, 1261, 974, 766, 702 cm^{-1}; HRMS: calculated for $C_{12}H_{15}NO$ m/z 189.11537, found 189.11503.

<u>(*E*)-5-Phenyl-3-nonenamide</u> (Table 2, entry 9)

Obtained in 42 % isolated yield from the reaction of (*E*)-4-(1-hexenyl)-2-azetidinone and phenylmercuric chloride using procedure B: ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H, J = 7.0 Hz, CH_3), 1.20-1.35 (m, 4 H, C<u>H$_2$C</u>H$_2$CH$_3$), 1.71 (q, 2 H, J = 7.8 Hz, CH_2Pr), 2.96 (d, 2 H, J = 6.9 Hz, CH_2CO), 3.25 (q, 1 H, J = 7.8 Hz, CHPh), 5.56 (ddt, 1 H, J = 15.6 Hz, J = 6.9 Hz, J = 0.9 Hz, C<u>H</u>CH_2CO), 5.78 (dd, J = 15.6 Hz, J = 7.8 Hz, C<u>H</u>CHPh), 5.51-5.82 (2 br s, 2 H, NH_2), 7.13-7.34 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 13.98, 22.58, 29.76, 35.39, 39.92, 48.85, 122.07, 126.20, 127.41, 128.50, 140.22, 144.39, 173.71; IR (neat) 3333, 3190, 2957, 2930, 1744, 1670, 1603, 1493, 1452, 1400, 972, 750, 700 cm^{-1}; HRMS: calculated for $C_{15}H_{21}NO$ m/z 231.16232, found 231.16258.

(*E*)- and (*Z*)-3-Methyl-5-phenyl-3-pentenamide (Table 2, entry 10)

Obtained in 90 % isolated yield (52:48 *E/Z*) from the reaction of 4-methyl-4-vinyl-2-azetidinone and phenylmercuric chloride using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.83 (s, 3 H, CH_3), 2.97 (s, 2 H, CH_2CO), 3.41 (d, 2 H, *J* = 7.3 Hz, CH_2Ph), 5.40-5.68 (br s, 2 H, NH_2), 5.57 (t, 1 H, *J* = 7.3 Hz, =CH), 7.10-7.30 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 16.25, 34.36, 47.25, 125.92, 128.12, 128.44, 128.70, 130.84, 140.57, 173.74.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 3.11 (s, 2 H, CH_2CO), 3.39 (d, 2 H, *J* = 7.0 Hz, CH_2Ph), 5.64 (t, 1 H, *J* = 7.0 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 25.44, 39.34.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 87-88 °C; IR (neat) 3375, 3194, 3084, 3028, 2905, 2853, 1653, 1603, 1493, 1454, 1410, 1283, 1221, 1198, 1136, 779, 744, 700 cm^{-1}; HRMS: calculated for $C_{12}H_{15}NO$ m/z 189.11537, found 189.11556.

(*E*)- and (*Z*)-3-Methyl-5-(4-methoxyphenyl)-3-pentenamide (Table 2, entry 13)

Obtained in 77 % isolated yield (44:56 *E/Z*) from the reaction of 4-methyl-4-vinyl-2-azetidinone and 4-methoxyphenylmercuric chloride using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.81 (s, 3 H, CCH_3), 2.95 (s, 2 H, CH_2CO), 3.34 (d, 2 H, *J* = 7.2 Hz, CH_2Ar), 3.77 (s, 3 H, OCH_3), 5.53 (t, 1 H, *J* = 7.2 Hz, CH=), 5.72 and 6.15 (2 br s, 2 H, NH_2), 6.83 (d, 2 H, *J* = 8.7 Hz, H's on C3 and C5 of aryl),

7.07 (d, 2 H, J = 8.7 Hz, H's on C2 and C6 of aryl); ^{13}C NMR ($CDCl_3$) δ 16.14, 33.35, 47.17, 55.13, 113.87, 128.43, 129.06, 130.42, 132.60, 157.85, 173.93.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.83 (s, 3 H, CH_3), 3.08 (s, 2 H, CH_2CO), 5.62 (t, 1 H, J = 7.0 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 23.91, 39.37, 128.99, 130.06, 132.39, 157.79, 173.12.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 111-112 °C; IR (neat) 3362, 3192, 2964, 2937, 1661, 1634, 1512, 1412, 1267, 1248, 1175, 1030, 814 cm^{-1}; HRMS: calculated for $C_{13}H_{17}NO_2$ m/z 219.12593, found 219.12577. Anal. calculated for $C_{13}H_{17}NO_2$: C, 71.21, H, 7.81, N, 6.39. Found: C, 71.48, H, 7.78, N, 6.43.

(*E*)- and (*Z*)-3-Methyl-5-(3-nitrophenyl)-3-pentenamide (Table 2, entry 17)

Obtained in 79 % isolated yield (53:47 *E*/*Z*) from the reaction of 4-methyl-4-vinyl-2-azetidinone and 4-methoxyphenylmercuric chloride using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.81 (s, 3 H, CH_3), 2.98 (s, 2 H, CH_2CO), 3.50 (d, 2 H, J = 7.2 Hz, CH_2Ar), 5.53 (t, 1 H, J = 7.2 Hz, CH=), 5.65 and 5.85 (2 br s, 2 H, NH_2), 7.43 (d, 1 H, J = 7.5 Hz, H on C6 of aryl), 7.49 (dd, 1 H, J = 7.8 Hz, J = 7.5 Hz, H on C5 of aryl), 8.01 (s, 1 H, H on C2 of aryl), 8.03 (d, 1 H, J = 7.8 Hz, H on C4 of aryl); ^{13}C NMR ($CDCl_3$) δ 16.25, 33.84, 47.25, 121.13, 123.09, 126.53, 129.32, 131.90, 134.49, 142.48, 148.37, 172.57.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.84 (s, 3 H, CH_3), 3.07 (s, 2 H, CH_2CO), 5.56 (t, 1 H, J = 7.2 Hz, CH=); ^{13}C NMR same as the

E-isomer or not seen, except δ 24.15, 33.99, 39.35, 121.13, 123.01, 126.31, 129.32, 132.61, 134.49, 173.35.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 97.5-98.5 °C; IR (neat) 3379, 3200, 3074, 2910, 1632, 1520, 1477, 1431, 1354, 1273, 1202, 810, 733, 687 cm^{-1}; HRMS: calculated for $C_{12}H_{14}N_2O_3$ m/z 234.10045, found 234.10056.

(*E*)- and (*Z*)-3,4-Dimethyl-5-phenyl-3-pentenamide (Table 2, entry 20)

Obtained in 85% isolated yield (52:48 E/Z) from the reaction of 4-isopropenyl-4-methyl-2-azetidinone and phenylmercuric chloride using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^1H NMR ($CDCl_3$) δ 1.67 (s, 3 H, CH_3CCCO), 1.90 (s, 3 H, CH_3CCPh), 3.09 (s, 2 H, CH_2CO), 3.48 (s, 2 H, CH_2Ph), 5.70 (br s, 2 H, NH_2), 7.10-7.35 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 18.63, 19.48, 40.23, 42.19, 124.46, 126.02, 128.22, 123.44, 132.55, 139.96, 173.64.

The *Z*-isomer: ^1H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.71 (s, 3 H, CH_3CCPh), 1.82 (s, 3 H, CH_3CCCO), 3.14 (s, 2 H, CH_2CO), 3.44 (s, 2 H, CH_2Ph); ^{13}C NMR same as the *E*-isomer or not seen.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 98-99 °C; IR (neat) 3369, 3192, 3084, 3026, 2918, 1661, 1630, 1495, 1452, 1437, 1290, 1256, 1221, 1132, 1092, 733, 698 cm^{-1}; HRMS: calculated for $C_{13}H_{17}NO$ m/z 203.13102, found 203.13126.

(*E,E*)- and (*Z,E*)-3,8,8-Trimethyl-3,6-nonadienamide (Table 2, entry 24)

Obtained in 34 % isolated yield (81:19 *E/Z*) from the reaction of 4-methyl-4-vinyl-2-azetidinone and (*E*)-3,3-dimethyl-1-butenylmercuric chloride using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 9 H, $(CH_3)_3C$), 1.69 (s, 3 H, CH_3C=), 2.73 (t, 2 H, *J* = 6.6 Hz, $C\underline{H}_2CH$=), 2.93 (s, 2 H, CH_2CO), 5.25 (dt, 1 H, *J* = 15.6 Hz, *J* = 6.6 Hz, $C\underline{H}$=CH-*t*-Bu), 5.34 (t, 1 H, *J* = 6.6 Hz, $C\underline{H}$=CCH_3), 5.45 (d, 1 H, *J* = 15.6 Hz, =CH-*t*-Bu), 5.68 (br s, 2 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 16.18, 29.74, 31.38, 32.87, 47.42, 122.10, 128.86, 130.38, 142.42, 173.94.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.79 (s, 3 H, CH_3C=), 2.99 (s, 2 H, CH_2CO); ^{13}C NMR same as the *E*-isomer or not seen.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 112-114 °C; IR (neat) 3371, 3190, 2963, 2907, 1728, 1659, 1462, 1406, 1360, 1288, 970, 908, 733, 648 cm^{-1}; HRMS: calculated for $C_{12}H_{21}NO$ m/z 195.16232, found 195.16251.

(*E, E*)- and (*E,Z*)-3,6,8,8-Tetramethyl-3,6-nonadienamide (Table 2, entry 27)

Obtained in 54 % isolated yield (68:32 *E/Z*) from the reaction of 4-methyl-4-vinyl-2-azetidinone and (*E*)-1,3,3-trimethyl-1-butenylmercuric chloride using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9 H, $(CH_3)_3C$), 1.68 and 1.70 (2 s, 6 H, 2 CH_3C=), 2.66 (d, 2 H, *J* = 7.2 Hz, $C\underline{H}_2CH$=), 2.94 (s, 2 H, CH_2CO), 5.17 (s, 1 H, =CH-*t*-Bu), 5.35 (t, 1 H, *J* = 7.2 Hz, =$C\underline{H}CH_2$), 5.53 and 5.67 (2 br s, 2 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 16.21, 17.28, 31.12, 32.15, 40.30, 47.56, 125.60, 129.12, 132.33, 135.94, 173.64.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.80 (s, 3 H, $C\underline{H}_3CCH_2CO$), 2.64 (d, 2 H, *J* = 7.2 Hz, $C\underline{H}_2CH$=), 3.00 (s, 2 H, CH_2CO), 5.45 (t, 1 H, *J* = 7.2 Hz, =$C\underline{H}CH_2$); ^{13}C NMR same as the *E*-isomer or not seen, except δ 17.43, 24.04, 31.09, 40.21, 173.12.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 80 °C (decomposed); IR (neat) 3377, 3196, 2959, 2910, 1744, 1663, 1630, 1464, 1439, 1406, 1271, 681 cm^{-1}; HRMS: calculated for $C_{13}H_{23}NO$ m/z 209.17797, found 209.17815.

(*E*)- 4-Methyl-4-(3-phenyl-2-propenyl)-2-azetidinone (6) and (*E*)- and (*Z*)-3-methyl-3-hexenamide (7) (Table 3, entry 2)

Obtained in 102 % isolated yield as an inseparable mixture (55:45 **6**/**7**) from the reaction of 4-methyl-4-(2-propenyl)-2-azetidinone and phenylmercuric chloride (limiting reagent) using procedure A. Compound **7** was produced as a 50:50 mixture of stereoisomers. The ratio of compound **6** to compound **7** and the *E*- to *Z*-isomer ratio of compound **7** were determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

Compound **6**: ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 3 H, CH_3), 2.56 (d, 2 H, *J* = 7.8 Hz, CH_2C=), 2.70 and 2.84 (2 d, 2 H, *J* = 15.0 Hz, CH_2CO), 6.13-6.23 (br s, 1 H, NH), 6.18 (dt, 1 H, *J* = 15.6 Hz, *J* = 7.8 Hz, $C\underline{H}$=CHPh), 6.49 (d, 1 H, *J* = 15.6 Hz, =CHPh), 7.15-7.35 (m, 5 H, phenyl).

The *E*-isomer of compound **7**: ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3 H, *J* = 7.5 Hz, $C\underline{H}_3CH_2$), 1.68 (s, 3 H, CH_3C=), 2.06 (p, 2 H, *J* = 7.5 Hz, $C\underline{H}_2CH_3$), 2.91 (s, 2 H, CH_2CO), 5.36 (t, 1 H, *J* = 7.5 Hz, CH=), 5.55 and 5.85 (br s, 2 H, NH_2). The *Z*-isomer of compound **7**: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer of compound **7** or not seen except δ

1.77 (s, 3 H, CH_3C=), 2.03 (p, 2 H, J = 7.5 Hz, $C\underline{H}_2CH_3$), 2.99 (s, 2 H, CH_2CO), 5.41 (t, 1 H, J = 7.5 Hz, CH=).

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PART II. PALLADIUM(0)-PROMOTED CROSS-COUPLING OF ALKENYL 2-AZETIDINONES WITH ORGANIC HALIDES AND TRIFLATES

INTRODUCTION

In recent years organopalladium chemistry has become an important tool for the synthetic organic chemist.[1-3] As mentioned in Part I, one method of preparing organopalladium compounds involves the transmetallation of organomercurials with palladium(II) salts (eq 2.1).[1,2] The use of organomercurials as useful synthetic reagents

$$RHgX + PdX_2 \longrightarrow RPdX + HgX_2 \qquad (2.1)$$

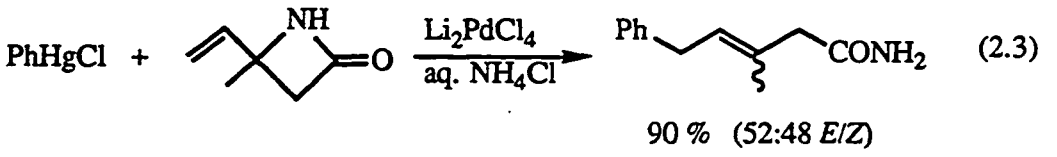
in organic chemistry has been reviewed by Larock.[4,5] The preparation of a wide variety of organomercurials is covered in thise reviews and the references cited therein.

In the last two decades, oxidative addition of organic halides to zerovalent palladium has become a more attractive and important route to prepare reactive organopalladium compounds (eq 2.2).[6-8] This process has recently been employed to carry out palladium-

$$RX + Pd(0) \longrightarrow RPdX \qquad (2.2)$$

catalyzed alkylation,[9-11] annulation,[12-15] migration,[16,17] and many other types of synthetic transformations.[18] Organic halides are easily prepared, can accommodate a wide variety of functionality, and are stable precursors to the highly reactive organopalladium compounds. This catalytic process has circumvented the needs for large amounts of Pd(II) salts and toxic organomercurial starting materials.

Since it has been demonstrated that alkenyl 2-azetidinones can be ring-opened to form substituted 3-alkenamides using organomercurials and palladium(II) salts (eq 2.3),[19] it was



(2.3)

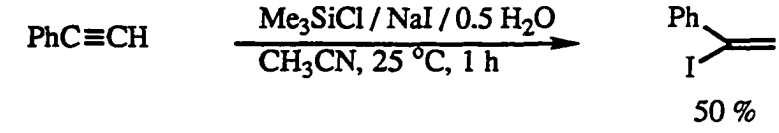
90 % (52:48 *E/Z*)

thought that it might be possible to replace the organomercurial shown in equation 2.3 with organic halides. No such reactions of alkenyl 2-azetidinones have been reported previously. It was hoped that the palladium(0)-catalyzed ring-opening of alkenyl 2-azetidinones would produce 3-alkenamides in good yield with a high degree of regio- and stereoselectivity. It would also be desirable to obtain a high catalytic turnover of palladium. It was also hoped that a number of different organic halides and triflates could be used in the reaction, that the reaction would tolerate a wide variety of functional groups, and that variously substituted alkenyl 2-azetidinones could be utilized in the reaction.

In this part, the palladium(0)-catalyzed cross-coupling of alkenyl 2-azetidinones with various organic halides and triflates will be discussed. It will first cover the palladium(0)-catalyzed reaction of 4-methyl-4-vinyl-2-azetidinone with iodobenzene. And then the reaction of a wide variety of alkenyl 2-azetidinones with organic halides and triflates in the presence of a catalytic amount of palladium(0) will be discussed.

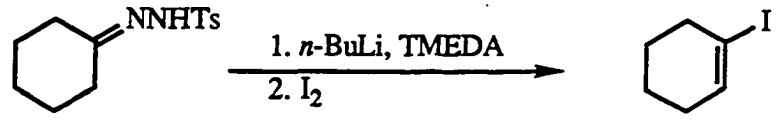
RESULTS AND DISCUSSION

All of the aryl iodides used were commercially available and have been used without further purification. (*E*)-1-Iodo-1-hexene[20] and (*E*)-1-iodo-2-phenylethylene[21] were synthesized by Larock group members according to the literature. 1-Iodo-1-phenylethylene was prepared from phenylacetylene using the published procedure of Kamiya, Chikami, and Ishii (eq 2.4).[22]



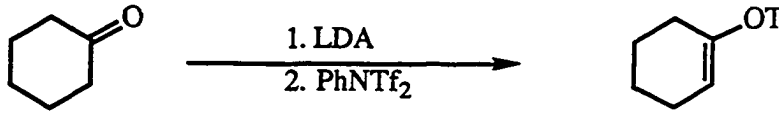
50 % (2.4)

1-Iodo-1-cyclohexene was prepared from the corresponding tosylhydrazone using a procedure developed by Barth and Paquette (eq 2.5).[23] Cyclohexenyl triflate was prepared



14 % (2.5)

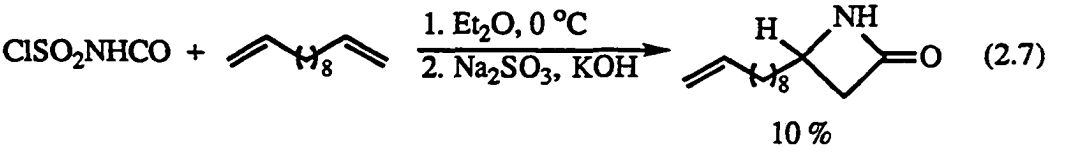
from cyclohexanone using the published procedure of McMurray and Scott (eq 2.6).[24]



40 % (2.6)

Synthesis of most alkenyl 2-azetidinones used was achieved by the reaction of chlorosulfonyl isocyanate and the corresponding dienes according to the literature,[25-27] and

has been reported in Part I. 4-(9-Decenyl)-2-azetidinone was prepared from 1,9-dodecadiene using the procedure of Moricini and Meyer (eq 2.7).[27]

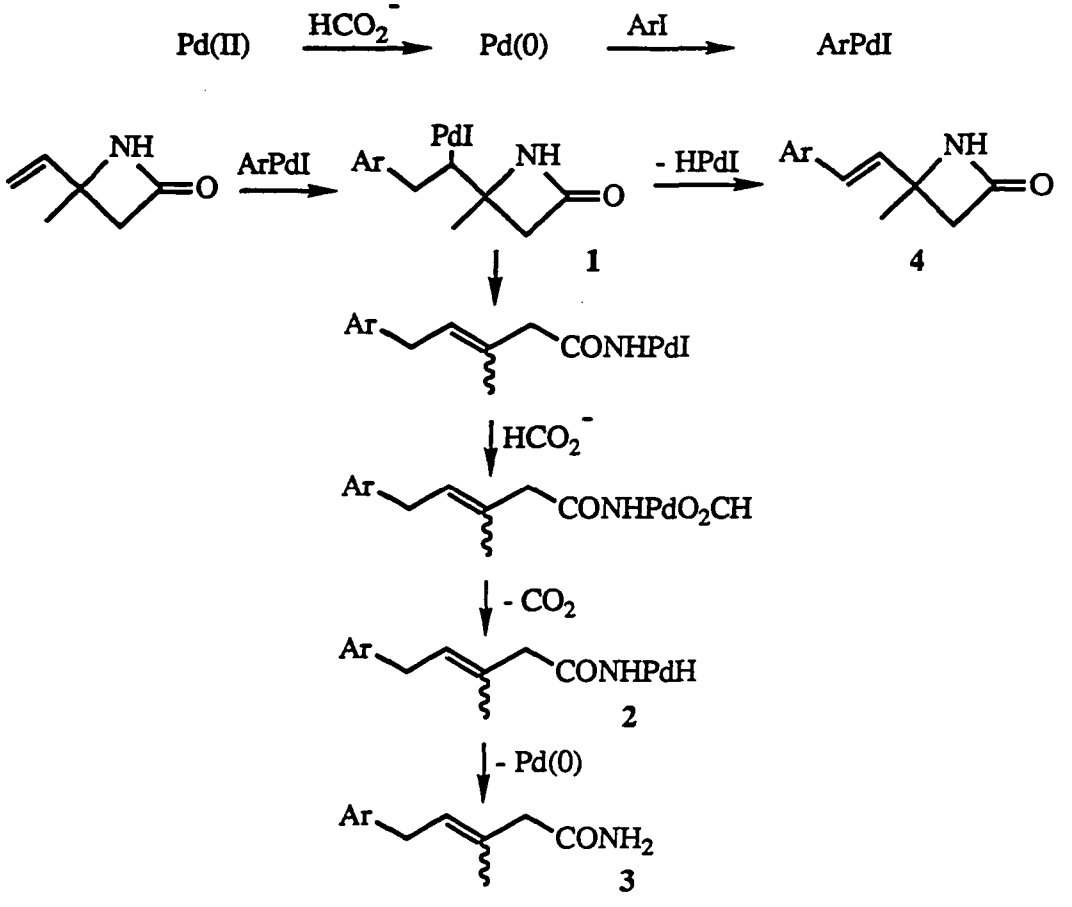


(2.7)

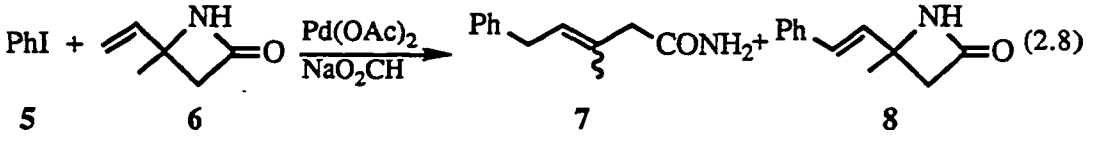
As a first step towards meeting the previously mentioned objectives and establishing this reaction as a new and useful synthetic method, an extensive series of reactions was performed using the reaction of 4-methyl-4-vinyl-2-azetidinone and iodobenzene as a model system. In the reaction of organic halides, palladium(0), and alkenyl 2-azetidinones, the following mechanism accounts for the substituted 3-alkenamides (Scheme 1). Reduction of palladium(II) to palladium(0), followed by oxidative addition of palladium(0) to the organic halide, gives rise to an organopalladium iodide. Olefin coordination and insertion of the organopalladium iodide forms the σ-alkylpalladium species **1**. This σ-alkylpalladium species then undergoes palladium amide elimination, followed by ligand exchange and formate reduction to form amide palladium hydride **2**. Finally, the reductive elimination of palladium(0) produces the desired amide product **3** and regenerates palladium(0). It should be noted that the Heck product **4** was also observed during the study of the reaction. The Heck product **4** is formed by the β-hydride palladium elimination of intermediate **1**.

While no experiments have been run to attempt to support (or disprove) this mechanism, an analogous process has been suggested in the palladium-promoted ring-opening of alkenyl 2-azetidinones by organomercurials.[19] Also, a similar mechanism has been proposed in the palladium-catalyzed cross-coupling of aryl halides and olefinic epoxides in which the carbon-carbon double bond and the epoxide are separated by one or more carbons.[17]

Scheme 1



As a model system, the palladium-catalyzed cross-coupling of 4-methyl-4-vinyl-2-azetidinone and iodobenzene has been extensively studied (eq 2.8). The results are contained in Tables 1-8. Throughout the course of this project, a great many reactions were run in an attempt to see what effect certain solvents, reagents, temperatures, times, and ratios of starting materials would have on the yield and stereochemistry of the reaction.



Most reactions were run in a logical, organized manner; however, as in any research project, a few reactions were run based on hunches or spur of the moment ideas. It is often these reactions which keep the chemists' interest going in their research. While in hindsight many of the reasons behind trying a particular reaction now seem foolish, one can surely say that the information gained from failed experiments is often just as valuable as information from successful ones. No attempt will be made to explain the reasons behind every reaction, nor will a complete correlation between results and reaction conditions be made.

In order to determine the best ratio of starting materials, the model reaction was run using various ratios of starting materials. The results shown in Table 1 indicate that one of

Table 1. Effect of stoichiometry on the reaction of compounds 5 and 6

Entry[a]	Ratio 6/5	Added Reagent	Temp., Time	Yield (%) 8	Yield (%) 7	*E/Z* Ratio 7
1	1:2	3 *i*-Pr_2NEt	80 °C, 1 d	0	94	59:41
2	1:1	3 *i*-Pr_2NEt	80 °C, 1 d	0	49	63:37
3	2:1	3 *i*-Pr_2NEt	80 °C, 1 d	0	75	61:39
4	1:2	0	50 °C, 2 d	0	62	62:38
5	2:1	0	50 °C, 2 d	0	60	65:35
6[b]	1:2	0	25 °C, 4 d	16	65	65:35
7[b]	2:1	0	25 °C, 4 d	17	56	52:48

[a] All reactions were run using 10 mol % $Pd(OAc)_2$, 5 equiv. NaO_2CH, 1 equiv. TBAC, and DMF.

[b] 3 Mol % $Pd(OAc)_2$ and 5 equiv. KO_2CH were used.

the starting materials existing in excess amount was necessary for obtaining a high yield of the desired product **7**. The 1:2 ratio of alkenyl 2-azetidinone **6** to iodobenzene **5** was strongly preferred over the 2:1 ratio at 80 °C (entries 1 and 3), as well as at room temperature (entries 6 and 7), and this value was adopted for subsequent optimization.

The model reaction was also carried out using different amounts of $Pd(OAc)_2$. In Table 2 is listed the correlation of the yield and the percentage of the palladium catalyst. In general, better yields were obtained when 10 mol % of $Pd(OAc)_2$ was used at 80 °C (entry 2) or 50 °C (entry 4). At room temperature, however, 3 mol % of $Pd(OAc)_2$ was the better choice (entry 5).

In order to determine if the yield of compound **7** could be increased when the reducing reagent was varied, the model reaction was run using different formate salts (Table

Table 2. The reaction of compounds **5** and **6** using different percentages of $Pd(OAc)_2$

Entry[a]	Mol % $Pd(OAc)_2$	Equiv. *i*-Pr_2NEt	Temp., Time	Yield (%) **8**	Yield (%) **7**	*E/Z* Ratio **7**
1	3	3	80 °C, 1 d	0	78	59:41
2	10	3	80 °C, 1 d	0	94	59:41
3	3	0	50 °C, 3 d	10	55	68:32
4	10	0	50 °C, 3 d	11	59	65:35
5[b]	3	0	25 °C, 2 d	16	65	65:35
6[b]	10	0	25 °C, 4 d	15	55	54:46

[a] All reactions were run using 5 equiv. NaO_2CH, 1 equiv. TBAC, and DMF.

[b] KO_2CH and DMF/H_2O (9:1) were used instead of NaO_2CH and DMF.

Table 3. Effect of reducing agent on the reaction of compounds **5** and **6**

Entry[a]	Equiv. MO_2CH	Equiv. Base	Temp., Time	Yield (%) **8**	Yield (%) **7**	*E*/*Z* Ratio **7**
1[b]	5 LiO_2CH	3 *i*-Pr_2NEt	80 °C, 24 h	0	83	66:34
2[b]	5 NaO_2CH	3 *i*-Pr_2NEt	80 °C, 24 h	0	94	59:41
3[b]	3 NaO_2CH	3 Et_3N	80 °C, 24 h	0	74	59:41
4[b]	5 NaO_2CH	3 Et_3N	80 °C, 24 h	0	91	58:42
5[b]	5 KO_2CH	3 *i*-Pr_2NEt	80 °C, 24 h	0	78	65:35
6	3 LiO_2CH	0	80 °C, 17 h	4	53	62:38
7	5 LiO_2CH	0	80 °C, 17 h	5	39	52:48
8	3 NaO_2CH	0	80 °C, 17 h	9	45	69:31
9	5 NaO_2CH	0	80 °C, 12 h	10	49	57:43
10	3 KO_2CH	0	80 °C, 12 h	10	50	58:42
11	5 KO_2CH	0	80 °C, 17 h	12	51	58:42
12	5 LiO_2CH	0	50 °C, 3 d	6	52	57:43
13	3 NaO_2CH	0	50 °C, 3 d	10	55	68:32
14	5 KO_2CH	0	50 °C, 4 d	10	47	60:40
15	3 LiO_2CH	0	25 °C, 4 d	3	41	59:41
16	5 NaO_2CH	0	25 °C, 2 d	12	20	63:37
17	3 KO_2CH	0	25 °C, 4 d	15	50	76:24
18	5 CsO_2CH	0	25 °C, 4 d	16	44	49:51

[a] All reactions were run using 3 mol % $Pd(OAc)_2$, 1 equiv. TBAC, and DMF.

[b] 10 Mol % $Pd(OAc)_2$ was used.

3). At 80 °C, the highest yield was obtained when sodium formate was used (entry 2) and the yield tended to decrease in the order of $NaO_2CH > LiO_2CH > KO_2CH$ (entries 1, 2 and 5). Using 5 equiv. formate salt gave better results than using 3 equiv. (entries 3 and 4). At 50 °C, reducing reagent effects seemed to obey the same order as that at 80 °C (entries 12-14). At room temperature, however, potassium formate became the best choice (entry 17).

The effect of base on the yield and stereochemistry of the model reaction was also investigated (Table 4). In terms of the yield, using 3 equiv. an amine largely increased the yield of the desired product **7** and none of the Heck-type product **8** was observed. The role of these amines is not completely understood. Perhaps they promote the olefin insertion of the organopalladium species, as well as the 2-azetidinone ring-opening, in some way. The performance of diisopropylethylamine seemed little better than that of triethylamine. In terms of stereoselectivity, using organic bases had little effect on the *E/Z* isomer ratio of the desired product **7**.

Table 4. Effect of base on the reaction of compounds **5** and **6**

Entry[a]	Mol % $Pd(OAc)_2$	Equiv. Base	Temp., Time	Yield (%) **8**	Yield (%) **7**	*E/Z* Ratio **7**
1	10	0	80 °C, 17 h	3	58	65:35
2	10	3 Et_3N	80 °C, 1d	0	91	58:42
3	10	3 *i*-Pr_2NEt	80 °C, 1d	0	94	59:41
4	3	0	80 °C, 12 h	10	49	57:43
5	3	3 *i*-Pr_2NEt	80 °C, h	0	78	59:41

[a] All reactions were run using 5 equiv. NaO_2CH, 1 equiv. TBAC, and DMF.

The model reaction was run using a variety of solvents to determine what effect different solvents would have on the yield of product **7**. The results presented in Table 5 show that pure *N,N*-dimethylformamide and a 9:1 mixture of *N,N*-dimethylformamide and water were generally good solvents and yields with these two solvents were comparable when no amines were present in the reaction system (entries 4, 5, and 7-10). In the presence

Table 5. Solvent effect on the reaction of compounds **5** and **6**

Entry[a]	MO_2CH	Solvent	Temp., Time	Yield (%) **8**	Yield (%) **7**	*E/Z* Ratio **7**
1	KO_2CH	DMF/NH_4Cl (9:1)	25 °C, 4 d	0	0	-
2	KO_2CH	DMSO	25 °C, 4 d	10	5	60:40
3	KO_2CH	CH_3CN	25 °C, 4 d	29	40	62:38
4	KO_2CH	DMF	25 °C, 4 d	15	50	76:24
5	KO_2CH	DMF/H_2O (9:1)	25 °C, 4 d	16	65	65:35
6	KO_2CH	DMF/NH_4Cl (9:1)	80 °C, 17 h	0	0	-
7	KO_2CH	DMF	80 °C, 17 h	12	51	58:42
8	KO_2CH	DMF/H_2O (9:1)	80 °C, 17 h	19	49	57:43
9	NaO_2CH	DMF	80 °C, 12 h	10	49	57:43
10	NaO_2CH	DMF/H_2O (9:1)	80 °C, 15 h	7	56	56:44
11[b]	NaO_2CH	DMF	80 °C, 24 h	0	88	59:41
12[b]	NaO_2CH	DMF/H_2O (9:1)	80 °C, 24 h	0	34	57:43

[a] All reactions were run using 3 mol % $Pd(OAc)_2$, 1 equiv. TBAC, 5 equiv. formate salt, and 1 ml solvent.

[b] 10 Mol % $Pd(OAc)_2$ and 3 equiv. Et_3N were used.

of triethylamine, the yield with pure *N,N*-dimethylformamide was increased to 88%, while the yield with the 9:1 mixture of *N,N*-dimethylformamide and water was decreased to 34% (entries 11 and 12). Therefore, pure *N,N*-dimethylformamide proved to be the best choice. The performance of other solvents, such as acetonitrile (entry 3), dimethylsulfoxide (entry 2), and a 9:1 mixture of *N,N*-dimethylformamide and saturated aqueous ammonium chloride (entries 1 and 6) ranged from fair to poor. The stereochemical outcome of the reaction seemed little affected by solvents.

The temperature effect was investigated and the results are presented in Table 6. In general, the higher the temperature, the shorter the react time and the higher the yield (entries 1-3). In the presence of diisopropylethylamine, the yield at 80 °C was much higher than that at 50 °C (entries 4 and 5). The *E/Z* isomer ratio of product **7** tended to decrease a little at higher temperatures.

Table 6. Temperature effect on the reaction of compounds **5** and **6**

Entry[a]	Mol % $Pd(OAc)_2$	Equiv. Base	Temp., Time	Yield (%) **8**	Yield (%) **7**	*E/Z* Ratio **7**
1[b]	3	0	25 °C, 2 d	12	20	63:37
2	3	0	50 °C, 2 d	10	43	66:34
3	3	0	80 °C, 12 h	10	49	57:43
4	10	3 *i*-Pr_2NEt	50 °C, 2 d	0	62	62:38
5	10	3 *i*-Pr_2NEt	80 °C, 1 d	0	94	59:41

[a] All reactions were run using 5 equiv. NaO_2CH, 1 equiv. TBAC, and DMF.

[b] The reaction did not go to completion.

The model reaction was also examined when triphenylphosphine and/or sodium halides were added to determine if these added reagents could increase the yield or improve the stereoselectivity of the reaction. The results are listed in Table 7. In general, using triphenylphosphine and/or sodium halides did not significantly affect the yield of the desired product **7** or the stereochemistry of the reaction (entries 1-3). However, the yield of side-product **8** was largely increased when using 3 mol % of triphenyphosphine (entry 2). The role of triphenylphosphine is not clearly understood. Perhaps coordination of the ligand triphenylphosphine to palladium stabilizes and therefore assists the β-hydride palladium elimination.

Table 7. Effect of sodium halides or PPh_3 on the reaction of compounds **5** and **6**

Entry[a]	Equiv. MO_2CH	Added Reagent	Temp., Time	Yield (%) **8**	Yield (%) **7**	*E/Z* Ratio **7**
1	5 NaO_2CH	0	80 °C, 15 h	7	56	56:44
2	5 NaO_2CH	3 % PPh_3	80 °C, 17 h	32	58	57:43
3	5 NaO_2CH	3 % PPh_3 + 1 NaCl	80 °C, 1 d	6	50	57:43
4	5 NaO_2CH	1 NaCl	80 °C, 1 d	9	56	56:44
5	5 NaO_2CH	1 NaBr	80 °C, 1 d	18	49	74:26
6	5 NaO_2CH	1 NaI	80 °C, 1 d	17	50	66:34
7	5 KO_2CH	3 % PPh_3	25 °C, 6 d	8	48	60:40
8	5 KO_2CH	3 % PPh_3 + 1 NaCl	25 °C, 4 d	10	46	57:43
9	5 KO_2CH	1 NaCl	25 °C, 4 d	11	52	62:38

[a] All reactions were run using 3 mol % $Pd(OAc)_2$, 1 equiv. TBAC, and DMF/H_2O (9:1).

The optimization of reaction conditions for the model reaction has been extensively studied. Some excellent procedures were developed and the desired ring-opened product 7 was exclusively afforded in up to 94% yield (Table 1, entry 1). In order to demonstrate the synthetic utility and scope of the palladium-catalyzed cross-coupling of alkenyl 2-azetidinones and organic halides, these excellent procedures were employed for the reactions of a wide variety of alkenyl 2-azetidinones and organic halides. As we will discuss later in this part, however, it was found that these so called best procedures were sensitive to the types of aryl halides and alkenyl 2-azetidinones that were used. Therefore, it became necessary to develop still better procedures which would be more efficient and tolerant with regard to the types of alkenyl 2-azetidinones and organic halides that could be employed.

A few comments on the conditions that have been employed throughout the course of this project seem appropriate. All reactions were run using 1 equiv. of tetra-*n*-butylammonium chloride. Tetra-*n*-butylammonium chloride is an expensive and moisture sensitive compound and it was desirable to replace it with another suitable reagent. The role of tetra-*n*-butylammonium chloride is in this overall synthetic process not completely understood. Perhaps the chloride anions provided by tetra-*n*-butylammonium chloride exchange with iodide anions to form organopalladium chlorides. The chloride anions make palladium more electropositive and therefore help the olefin insertion into the organo-palladium species. If this explanation were correct, it should be possible to replace tetra-*n*-butylammonium chloride with a reagent which could provide the same amount of chloride anions. During optimization, a preliminary experiment indicated that the model reaction also proceeded in high yield when using lithium chloride instead of tetra-*n*-butylammonium chloride. This modification of the reaction conditions is promising, because lithium chloride is a cheap and easily handled reagent. This success encouraged us to further develop the optimal procedure for the model reaction.

In Table 8 is presented data for the model reaction using 10 mol % of palladium acetate, 1 or 2 equiv. lithium chloride, and various other reaction conditions. With regard to the yield and stereochemical outcome of the reaction, several observations can be made. In terms of yield, the best ratio of starting materials was 1:2 of the alkenyl 2-azetidinone to iodobenzene (entry 3). The ratios of 2:1, 1:1 and 1:4 were inferior when compared directly (entries 1-4). In general, the most effective reducing reagent proved to be sodium formate and 5 equiv. were better than 1 or 3 equiv. (entries 3, 5 and 6). The performance of lithium formate (entries 7-9) and potassium formate (entries 10 and 11) were fairly good.

Again, the yield could also be significantly increased by adding 3 equiv. an organic base (entries 3 and 12 - 14) and diisopropylethylamine semmed to be better than triethylamine (entries 3 and 15). The best solvent was *N,N*-dimethylformamide (compare entry 3 with entries 21 - 24). The performance of solvents such as acetonitrile (entry 23), the 9:1 mixture of *N,N*-dimethylformamide to water (entry 21), dichloromethane (entry 22), and dimethylsulfoxide (entry 24) ranged from fair to poor.

The yield could also been affected by the amount of lithium chloride and the reaction time. Comparable yields were obtained when using 1 equiv. lithium chloride and running the reaction for 2 days (entry 18) or using 2 equiv. lithium chloride and running the reaction for 1 day (entry 3). Using 5 equiv. lithium chloride (entry 16) or a longer reaction time (entry 19) did not improve the yield. Changing the reaction temperature from 80 °C (entries 3 and 18) to 50 °C (entries 25 and 26) or 100 °C (entries 27 and 28) slightly decreased the yield of the reaction. Lowering the percentage of catalyst (entry 30) or adding 10 mol % of triphenylphosphine (entry 29) also decreased the yield somewhat.

Similar to the results observed with the reactions using tetra-*n*-butylammonium chloride, the stereochemical outcome of the model reaction seemed little affected by varying conditions which have been employed in Table 8. The desired 3-alkenamide 7 was always produced as a mixture of the *E* and *Z* isomers with a slight preference for formation of the *E*

Table 8. The reaction of compounds **5** and **6** using lithium chloride

Entry[a]	Ratio **6/5**	Equiv. MO_2CH	Equiv. Base	Equiv. LiCl
1	2:1	5 NaO_2CH	3 *i*-Pr_2NEt	2
2	1:1	5 NaO_2CH	3 *i*-Pr_2NEt	2
3	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	2
4	1:4	5 NaO_2CH	3 *i*-Pr_2NEt	2
5	1:2	3 NaO_2CH	3 *i*-Pr_2NEt	2
6	1:2	1 NaO_2CH	3 *i*-Pr_2NEt	2
7	1:2	5 LiO_2CH	3 *i*-Pr_2NEt	2
8	1:2	5 LiO_2CH	3 *i*-Pr_2NEt	1
9	1:2	5 LiO_2CH	3 *i*-Pr_2NEt	1
10	1:2	5 KO_2CH	3 *i*-Pr_2NEt	2
11	1:2	5 KO_2CH	3 *i*-Pr_2NEt	1
12	1:2	5 NaO_2CH	1 *i*-Pr_2NEt	2
13	1:2	5 NaO_2CH	1 *i*-Pr_2NEt	1
14	1:2	5 NaO_2CH	-	1
15	1:2	5 NaO_2CH	3 Et_3N	2
16	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	5
17	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	1
18	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	1
19	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	1
20	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	0

[a] All reactions were run using 10 mol % $Pd(OAc)_2$.

Solvent	Temp. (°C)	Time (day)	Yield (%) **8**	Yield (%) **7**	*E/Z* Ratio **7**
DMF	80	1	4	78	64:36
DMF	80	1	6	67	58:42
DMF	80	1	3	86	62:38
DMF	80	1	6	79	61:39
DMF	80	1	0	75	55:45
DMF	80	1	3	82	61:39
DMF	80	1	2	78	60:40
DMF	80	1	8	65	57:43
DMF	80	2	5	76	57:43
DMF	80	1	6	74	61:39
DMF	80	2	6	77	59:41
DMF	80	2	2	75	61:39
DMF	80	2	5	74	54:46
DMF	80	2	4	24	53:47
DMF	80	2	3	69	64:36
DMF	80	1	0	69	51:49
DMF	80	1	14	70	57:43
DMF	80	2	5	85	55:45
DMF	80	4	5	72	58:42
DMF	80	2	10	62	55:45

Table 8. (Continued)

Entry[a]	Ratio 6/5	Equiv. MO_2CH	Equiv. Base	Equiv. LiCl
21	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	2
22	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	2
23	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	2
24	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	2
25	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	2
26	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	1
27	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	2
28	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	1
29[b]	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	2
30[c]	1:2	5 NaO_2CH	3 *i*-Pr_2NEt	1

[b] 10 Mol % PPh_3 was used.

[c] 3 Mol % $Pd(OAc)_2$ was used.

Solvent	Temp. (°C)	Time (day)	Yield (%) **8**	Yield (%) **7**	*E/Z* Ratio **7**
DMF/H_2O (9:1)	80	2	10	48	56:44
CH_2Cl_2	80	2	3	35	52:48
CH_3CN	80	2	4	76	63:37
DMSO	80	4	4	20	58:42
DMF	50	4	5	76	63:37
DMF	50	1	6	78	58:43
DMF	100	1	2	80	60:40
DMF	100	1	5	72	58:42
DMF	80	1	10	59	61:39
DMF	80	2	5	76	63:37

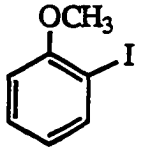
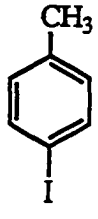
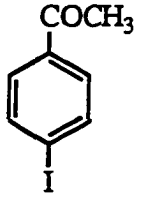
isomer. The *E/Z* isomer ratio varied from 52:48 to 64:36 as determined by proton NMR integration of the protons next to the amide group.

Once the reaction procedures of this model system were thoroughly investigated, 2-azetidinones bearing terminal double bonds, as well as internal double bonds, were studied. A variety of aryl and vinylic halides were employed in this study to determine the scope and limitations of this palladium(0)-catalyzed process. Three different palladium(0) procedures were studied for the reactions of aryl iodides. Procedure A included 1 equiv. alkenyl 2-azetidinone, 2 equiv. aryl iodide, 10 mol % $Pd(OAc)_2$, 2 equiv. LiCl, 3 equiv. *i*-Pr_2NEt, and 2 ml DMF; procedure B was the same as procedure A except 1 equiv. TBAC was used instead of 2 equiv. LiCl; procedure C included 1 equiv. alkenyl 2-azetidinone, 2 equiv. aryl iodide, 3 mol % $Pd(OAc)_2$, 1 equiv. TBAC, and 1 ml DMF/H_2O (9:1). A reducing agent (NaO_2CH, LiO_2CH or KO_2CH) was also employed in each reaction. The amount of reducing agent varied as indicated in Table 9. Initially, all reactions were conducted at 80 °C, and sometimes 25 °C or 100 °C were also employed to see if the reaction gave better results.

The results of this investigation are summarized in Table 9. The following observations have been made in the course of this investigation. In general, the palladium(0)-catalyzed arylation of alkenyl 2-azetidinones produced a mixture of two products. The desired 3-alkenamides were the major product and the Heck-products were minor products. These two products were usually separable by silica gel column chromatography. The desired 3-alkenamides were always obtained as a mixture of *E/Z* isomers. The stereochemistry of the newly formed carbon-carbon double bond depended on the structure of the alkenyl 2-azetidinone and not the substituents present on the aryl iodide.

Using procedure A, all reactions gave the desired aryl 3-alkenamides in good to excellent yields. As expected 4-methyl-4-vinyl-2-azetidinone gave the highest yields in this investigation and excellent yields of 3-alkenamides were generally obtained (entries 1, 2, 11, 13-16, 25 and 26).

Table 9. The palladium(0)-catalyzed reaction of alkenyl 2-azetidinones with organic halides and triflates

Entry	2-Azetidinone	RX	Procedure[a]	Equiv. MO_2CH
1			A	5 NaO_2CH
2			A	5 NaO_2CH
3			B	5 NaO_2CH
4			B	5 LiO_2CH
5			C	5 KO_2CH
6			C	5 NaO_2CH
7[b]			C	5 NaO_2CH
8			C	2 NaO_2CH
9[b]			C	2 NaO_2CH
10[c]			C	2 NaO_2CH
11			A	5 NaO_2CH
12			B	5 NaO_2CH
13			A	5 NaO_2CH
14			A	2 NaO_2CH
15			A	1 NaO_2CH
16			A	5 LiO_2CH
17			B	5 NaO_2CH
18			B	1 NaO_2CH

[a] See text for explanation of procedures.

[b] 3 Mol % PPh_3 was used.

[c] 1.5 Equiv. TBAC were used.

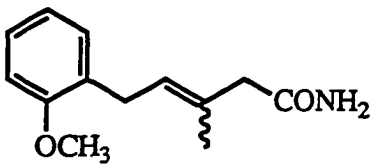
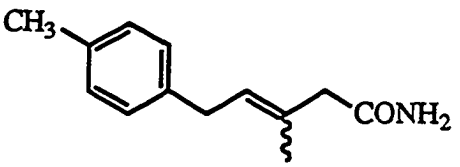
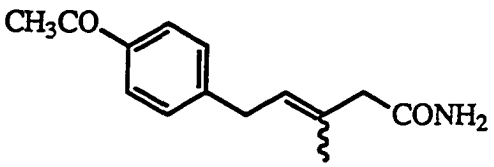
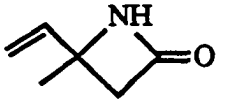
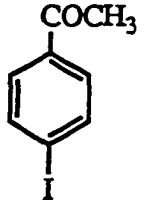
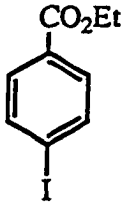
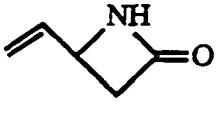
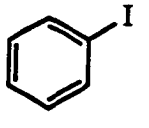
Temp., Time	3-Alkenamide	Yield (%)	*E/Z* Ratio	Heck Prod. (%)
100 °C, 1 d		60	61:39	2
80 °C, 1 d		63	62:38	2
80 °C, 1 d		98	60:40	0
80 °C, 1 d		73	57:43	0
25 °C, 4 d		71	57:43	0
80 °C, 20 h		58	58:42	3
80 °C, 2 d		40	62:38	0
80 °C, 1 d		68	54:46	0
80 °C, 1 d		28	55:45	0
80 °C, 1d		79	53:47	0
80 °C, 1 d		71	63:37	1
80 °C, 1 d		99	66:34	0
80 °C, 1 d		48	64:36	9
100 °C, 2 d		36	64:36	7
80 °C, 2.5 d		52	65:35	5
80 °C, 4 d		41	73:27	0
80 °C, 1 d		49	68:32	0
80 °C, 4 d		57	63:37	4

Table 9. (Continued)

Entry	2-Azetidinone	RX	Procedure[a]	Equiv. MO_2CH
19			C	3 LiO_2CH
20			C	5 NaO_2CH
21			C	3 NaO_2CH
22			C	5 KO_2CH
23			C	5 KO_2CH
24[d]			C	3 KO_2CH
25			A	5 NaO_2CH
26			A	5 NaO_2CH
27			A	1 NaO_2CH
28			B	1 NaO_2CH
29			A	5 NaO_2CH
30[d]			A	5 NaO_2CH
31[e]			A	5 NaO_2CH
32[e]			A	5 NaO_2CH
33			B	5 NaO_2CH
34[f]			B	5 NaO_2CH
35			C	5 NaO_2CH
36			C	5 KO_2CH
37[g]			C	5 NaO_2CH
38[g]			C	5 NaO_2CH

[d] A 2:1 ratio of 2-azetidinone to organic halide was used.

[e] A 3:1 ratio of 2-azetidinone to organic halide was used.

[f] Et_3N was used instead of *i*-Pr_2NEt.

[g] Pure DMF was used as the solvent.

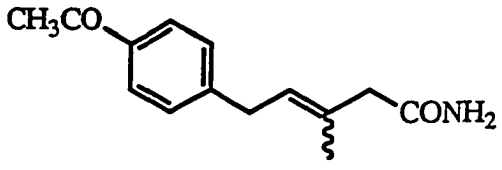
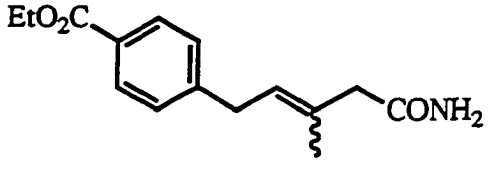
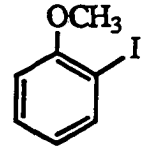
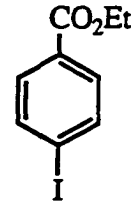
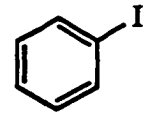
Temp., Time	3-Alkenamide	Yield (%)	*E/Z* Ratio	Heck Prod. (%)
80 °C, 17 h		43	54:46	6
80 °C, 17 h		32	47:53	11
80 °C, 17 h		46	51:49	11
80 °C, 17 h		20	51:49	14
25 °C, 4 d		33	42:58	17
25 °C, 4 d		37	48:52	19
80 °C, 2 d		62	60:40	1
80 °C, 3 d		66	63:37	3
80 °C, 4 d		72	60:40	3
80 °C, 1 d		45	68:32	0
80 °C, 1 d		36	80:20	3
80 °C, 1 d		68	80:20	6
80 °C, 1 d		73	80:20	13
80 °C, 1 d		19	70:30	30
80 °C, 1 d		23	86:14	36
25 °C, 10 d		29	80:20	34
80 °C, 1 d		8	92:8	16
25 °C, 1 d		21	95:5	0
25 °C, 1 d		0	-	5
25 °C, 1 d		25	95:5	0

Table 9. (Continued)

Entry	2-Azetidinone	RX	Procedure[a]	Equiv. MO_2CH
39[d]			A	5 NaO_2CH
40[e]			A	5 NaO_2CH
41[d]			A	1 NaO_2CH
42[e]			A	1 NaO_2CH
43[h]			A	5 NaO_2CH
44[i]			A	5 NaO_2CH
45[d, i]			A	5 NaO_2CH
46[i]			B	5 NaO_2CH
47[e,i]			B	5 NaO_2CH
48			B	5 NaO_2CH
49			B	5 KO_2CH

[h] Pure *E* isomer of the alkenyl 2-azetidinone was used.

[i] A 50:50 *E/Z* isomer mixture of the alkenyl 2-azetidinone was used.

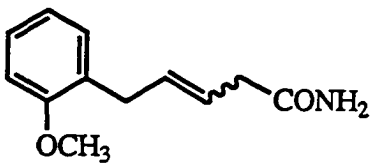
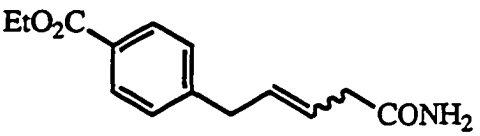
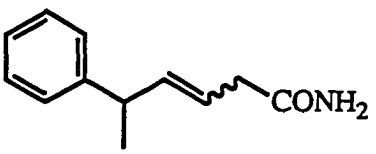
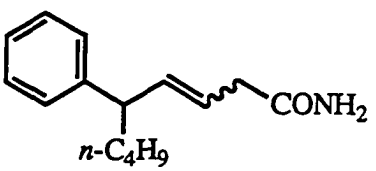
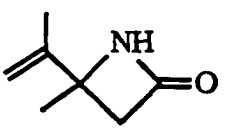
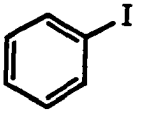
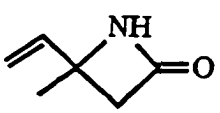
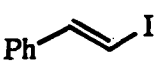
Temp., Time	3-Alkenamide	Yield (%)	*E*/*Z* Ratio	Heck Prod. (%)
80 °C, 1 d		74	83:17	5
80 °C, 1 d		65	80:20	7
80 °C, 3 d		71	85:15	9
80 °C, 3 d		68	90:10	14
80 °C, 7 d		43	91:9	0
80 °C, 7 d		38	89:11	12
80 °C, 7 d		39	89:11	30
80 °C, 1 d		0	-	0
80 °C, 1 d		0	-	0
25 °C, 14 d		28	89:11	0
25 °C, 14 d		10	100:0	0

Table 9. (Continued)

Entry	2-Azetidinone	RX	Procedure[a]	Equiv. MO_2CH
50			A	5 NaO_2CH
51			A	5 NaO_2CH
52[d]			A	5 NaO_2CH
53			B	5 NaO_2CH
54[f]			B	5 NaO_2CH
55			C	5 NaO_2CH
56			C	5 KO_2CH
57[g]			C	5 KO_2CH
58			C	5 KO_2CH
59			A	5 NaO_2CH
60			A	5 LiO_2CH
61			B	5 LiO_2CH
62			B	5 NaO_2CH
63			B	5 NaO_2CH
64			A	5 NaO_2CH
65			A	5 NaO_2CH

[j] A mixture of the Heck-type products was obtained.

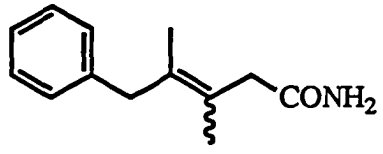
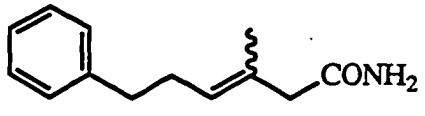
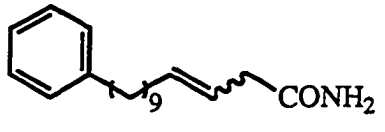
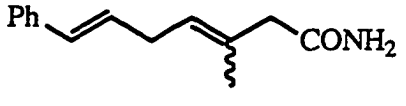
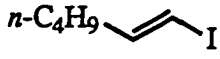
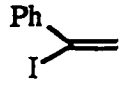
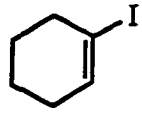
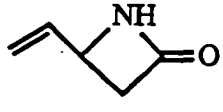
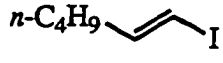
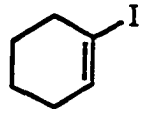
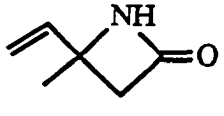
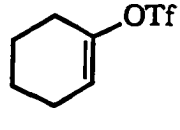
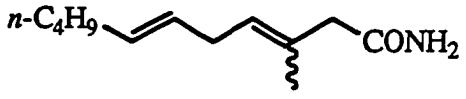
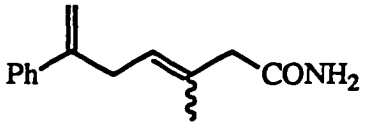
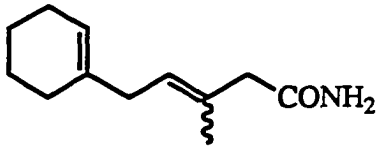
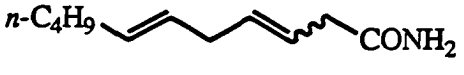
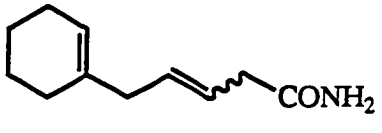
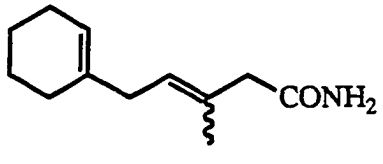
Temp., Time	3-Alkenamide	Yield (%)	*E/Z* Ratio	Heck Prod. (%)
80 °C, 4 d		32	58:42	6
80 °C, 7 d		54	60:40	10
80 °C, 7 d		40	61:39	8
80 °C, 1 d		0	-	0
80 °C, 1 d		0	-	5
25 °C, 14 d		26	70:30	4
25 °C, 4 d		3	62:38	0
25 °C, 6 d		15	81:19	0
80 °C, 2 d		2	85:15	0
80 °C, 1 d		82	57:43	10
80 °C, 1 d		73	59:41	19
80 °C, 1 d		76	58:42	12
80 °C, 1 d		31	50:50	58
80 °C, 1 d		27	60:40	61
80 °C, 2 d		42	82:18	0
80 °C, 1 d		18	65:35	47[j]

Table 9. (Continued)

Entry	2-Azetidinone	RX	Procedure[a]	Equiv. MO_2CH
66			A	5 NaO_2CH
67			A	5 NaO_2CH
68			A	5 NaO_2CH
69			A	5 NaO_2CH
70			A	5 NaO_2CH
71			B	5 NaO_2CH
72			A	5 NaO_2CH
73			B	5 NaO_2CH
74			B	5 NaO_2CH

Temp., Time	3-Alkenamide	Yield (%)	*E/Z* Ratio	Heck Prod. (%)
80 °C, 2 d		13	68:32	0
80 °C, 0.5 d		0	-	0
80 °C, 1 d		4	58:42	0
80 °C, 2 d		2	62:38	0
80 °C, 2 d		23	60:40	0
80 °C, 2 d		31	70:30	25[j]
80 °C, 2 d		0	-	65[j]
80 °C, 2 d		0	-	45[j]
80 °C, 1 d		20	73:27	24[j]

4-Vinyl-2-azetidinone tended to produce the ring-opened product in poor yield when using the standard procedure A (entry 29). However, the same good results as the reactions of 4-methyl-4-vinyl-2-azetidinone were obtained when 2 or 3 equiv. 4-vinyl-2-azetidinone were employed (entries 30, 31, and 39-42). A reasonable explanation is that this simple vinylic 2-azetidinone could directly react with palladium(0) to form a π-allylpalladium species, and then undergo formate reduction or β-hydride elimination. These competitive side reactions appeared to consume the vinylic 2-azetidinone and decreased significantly the yield of the desired product when using only 1 equiv. 4-vinyl-2-azetidinone.

The stereoselectivity of these reactions was virtually identical to that observed in the corresponding organomercurial reactions. Disubstituted alkenamides were formed with an *E/Z* preference of 4 to 1.

Other 2-azetidinones bearing more subtituted terminal or internal carbon-carbon double bonds tended to be less reactive and the yields of the desired 3-alkenamides ranged from only fair to good (entries 43-45, and 50-52). The regioselectivity of the organopalladium addition to the internal carbon-carbon double bonds is apparently quite high, since none of the products arising from addition of the aryl group next to the nitrogen moiety was observed. Similar to the reactions of organomercurials, 2-azetidinones with internal double bonds gave almost exclusively the *E*-isomer.

It is interesting to note that the arylation of alkenyl 2-azetidinones in which the carbon-carbon double bond and the lactam moiety are separated by one or eight carbons also produced 3-alkenamides in good to excellent yields using procedure A (entries 59, 60 and 64). The formation of these products involves a palladium migration process which is similar to the one explained in Scheme 3 of Part I.

Aryl halides bearing electron-donating groups (entries 1, 2, 11, and 39-40), as well as electron-withdrawing groups (entries 13-16, 25-27 and 41-42), were readily accommodated in these reactions and gave good to excellent yields when using procedure A.

However, some slight variations are desirable in the reactions which involve electron-withdrawing groups. In order to prevent reduction of the arylpalladium intermediate by the excess of formate, only 1 equiv. sodium formate was employed. The presence or absence of electron-donating or -withdrawing groups on the aryl halides has little effect on the yield or the stereochemistry of the process.

A variety of vinylic halides has been investigated. Surprisingly, these vinylic halides produced the desired 3-alkenamides in very poor yields and afforded a mixture of the Heck-type side products (entries 65-73). A reasonable explanation is that the oxidative addition of palladium(0) to vinylic halides to form vinylpalladium species was followed by dimerization or formate reduction of the newly formed vinylpalladium species. Another possibility is that alkene insertion, followed by palladium migration, forms a π-allylpalladium intermediate. As shown in the latter discussion and Scheme 2, this π-allylpalladium intermediate might be reduced to give Heck-type products. These side processes apparently occur more rapidly than the olefin insertion and therefore decrease the yield of the desired product. It is also important to note that the stereochemistry of the vinylic halides is retained in these reactions.

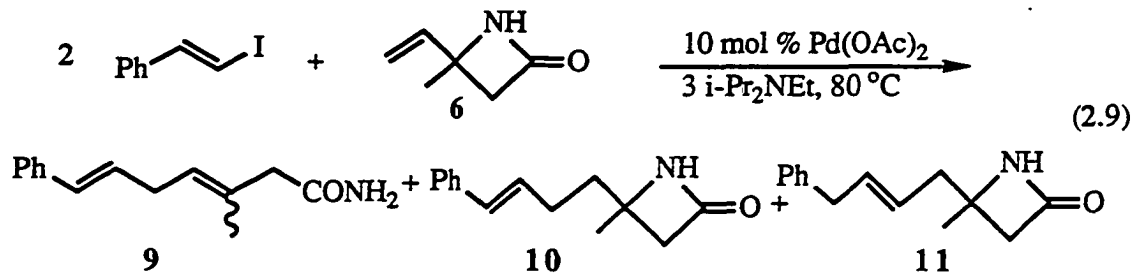
Procedure B solved some of the problems encountered with procedure A. For example, 4-methyl-4-vinyl-2-azetidinone, which always gave a mixture of products when procedure A was employed, reacted smoothly with aryl iodides under the conditions of procedure B to produce the desired 3-alkenamides exclusively in up to 99% yield (entries 3, 12, 17 and 28). In general, procedure B was effective in the reaction of 4-methyl-4-vinyl-2-azetidinone, but ineffective with other alkenyl 2-azetidinones. In some cases, the yields of Heck products increased when procedure B was employed. Currently, there is no good explanation for this observation.

Procedure C was also investigated as an alternative procedure, since it employed only 3 mol % palladium catalyst. Unfortunately, procedure C was ineffective for most of the reactions and gave the desired 3-alkenamides in poor yields. The exceptions appeared to be

entries 5-10 in which the results obtained using procedure C were nearly as good as some of the results obtained using procedures A and B.

A vinylic triflate has also been investigated since such triflate are sometimes easier to prepare than the corresponding iodides. One example of this preliminary study is presented in entry 74. Compared with the corresponding iodide (entry 71), the reaction of cyclohexenyl triflate using procedure B gave similar results with regard to yield and stereochemistry.

Since the palladium(0)-catalyzed reactions of vinylic halides or triflates using procedures A or B gave very poor results, efforts were made to further investigate these reactions. The reaction of 4-methyl-4-vinyl-2-azetidinone (**6**) and *E*-1-iodo-2-phenylethylene was selected as the model system (eq 2.9), because *E*-1-iodo-2-phenylethylene can be easily prepared. Optimization was carried out using various solvents, reagents, times and temperatures, and the results are summarized in Table 10.



(2.9)

With regard to the yield and stereochemical outcome of the reaction, the following observations can be made. In general, the reaction produced a bad mixture of products **9-11**. A mechanism for the formation of these products is presented in Scheme 2. The addition of the vinylpalladium iodide to the alkenyl 2-azetidinone gives rise to σ-alkyl-palladium species **12**. It undergoes β-hydride palladium elimination and subsequent

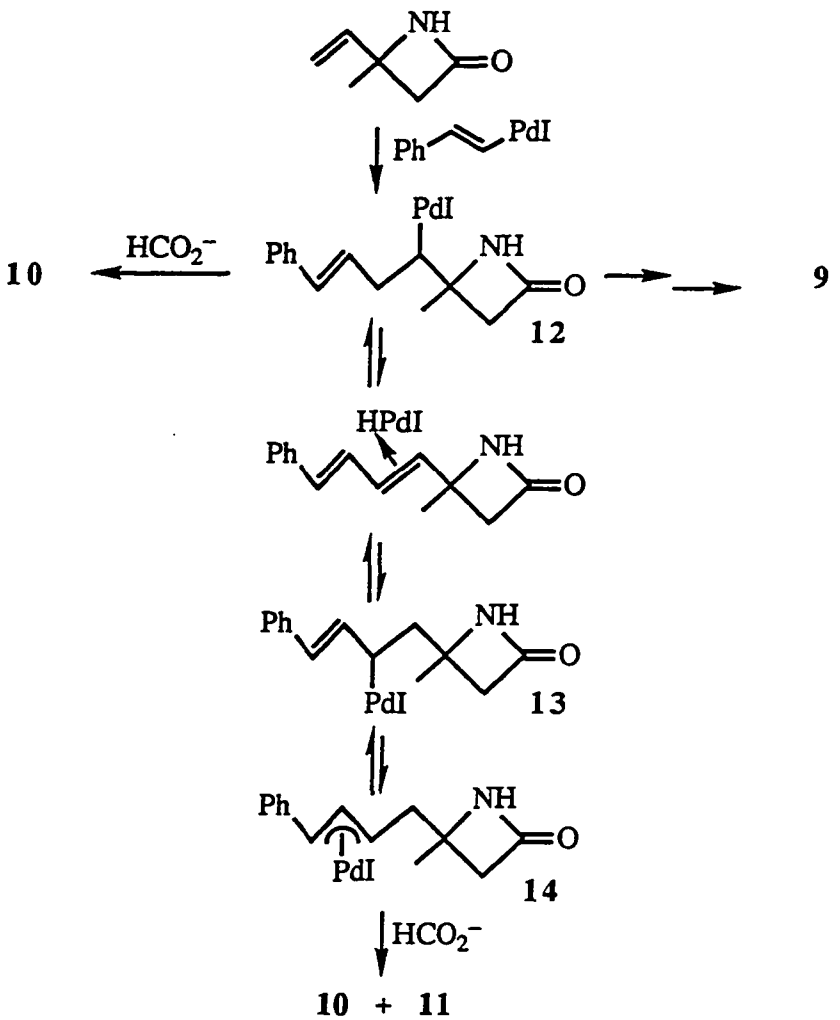
Table 10. The palladium(0)-catalyzed reaction of compound **6** with *E*-1-iodo-2-phenylethylene

Entry	Equiv. MO_2CH	Added Reagent	Solvent	Time (day)	Yield (%) **10 + 11**	Ratio **10/11**	Yield (%) **9**	*E/Z* Ratio **9**
1	5 NaO_2CH	2 LiCl	CH_3CN	1	0	-	19	59:41
2	5 NaO_2CH	2 LiCl	CH_3CN	2	0	-	16	62:38
3	5 NaO_2CH	2 LiCl	CH_3CN	4	0	-	12	64:36
4	5 NaO_2CH	2 LiCl	THF	1	0	-	16	69:31
5	5 NaO_2CH	2 LiCl	DMA	1	62	1.3:1	11	77:23
6	5 NaO_2CH	2 LiCl	DMF	1	47	1.5:1	18	65:35
7	5 NaO_2CH	1 LiCl, 1 TBAC	DMF	1	33	1.5:1	19	67:33
8	5 NaO_2CH	1 TBAC	DMF	1	24	2.0:1	9	65;35
9	1 NaO_2CH	2 LiCl	DMF	1	28	1.4:1	13	60:40
10	5 LiO_2CH	2 LiCl	DMF	1	49	1.2:1	24	63:37
11	5 LiO_2CH	2 LiCl, 10 % PPh_3	DMF	1	41	1.1:1	19	65:35
12[a]	5 LiO_2CH	2 LiCl	DMF	1	64	1.3:1	20	70:30

[a] The ratio of compound **6** to *E*-1-iodo-2-phenylethylene was 2:1.

readdition with the opposite regiochemistry to form allylic σ-alkylpalladium species **13**, which would be expected to rapidly form π-allylpalladium species **14**. The formate reduction of intermediate **14** produces the Heck-type products **10** and **11**. Compound **10** can also be formed by the direct formate reduction of the intermediate **12**.

Scheme 2



When using acetonitrile as the solvent and running the reaction for 1 day, the desired product was produced in 19 % yield with about 50 % of starting material **6** recovered. Even after 4 days, about 30 % of 2-azetidinone **6** still remained in the reaction system while the yield of the product dropped to 12 %. The performance of other solvents, such as tetrahydrofuran (entry 4), *N,N*-dimethylacetamide (entry 5), and *N,N*-dimethylformamide (entry 6) was as bad as that of acetonitrile. Using lithium chloride and/or tetra-*n*-butylammonium chloride seemed to have little effect on the yield (entries 6-8). The yield was also hardly affected by adding 10 mol % triphenylphosphine (entry 11) or reversing the ratio of starting materials (entry 12). Finally, an increase in yield was observed when using 3 equiv. lithium formate. Even so, the desired product **9** was collected in only 24 % yield (entry 10) and a 49 % yield of a mixture of compounds **10** and **11** was also formed.

CONCLUSION

The results presented in this part are the first observed examples of palladium(0)-catalyzed ring-opening of alkenyl 2-azetidinones by organic halides and triflates. The reactions of aryl halides with alkenyl 2-azetidinones in the presence of a catalytic amount of palladium(0) produce the corresponding 3-alkenamides as mixtures of *E* and *Z* isomers in good to excellent yields. The regioselectivity of the reactions is high. The stereoselectivity, however, depends on the structure of the alkenyl 2-azetidinone. The presence or absence of substituents on the aryl moiety seems to have little effect on the stereochemistry of the reactions while electron-withdrawing groups on the aryl halides tend to decrease the yield somewhat. The reactions of vinylic halides with alkenyl 2-azetidinones tend to produce mixtures of 2 or 3 products which contain the desired 3-alkenamides in poor yields (about 20 %). The stereochemistry of the vinylic halide is retained in these reaction processes. A preliminary investigation of a vinylic triflate with an alkenyl 2-azetidinones gave results similar to those observed with vinylic halides.

In conclusion, the palladium(0)-catalyzed cross-coupling of alkenyl 2-azetidinones with organic halides and triflates provides a convenient new synthetic route to 3-alkenamides.

EXPERIMENTAL SECTION

Equipment

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75.5 MHz for carbon nuclei) or a Varian VXR-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75.5 MHz for carbon nuclei). All infrared spectra were recorded on an IBM IR / 98 FT-IR or a Bio-Rad FTS-7. Exact mass spectral analyses were obtained on a Kratos high resolution mass spectrometer. Gas chromatographic analyses were performed on 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 a HP-1 megabore column (HP 5890).

Reagents

Palladium acetate was donated by Johnson Matthey, Inc. Lithium formate, sodium formate, potassium formate, and lithium chloride were purchased from Fisher Scientific Company and oven-dried before use. Tetra-*n*-butylammonium chloride was obtained from Lancaster Synthesis Inc. unless otherwise noted. *N,N*-Dimethyl-formamide, *N,N*-dimethylacetamide, and diisopropylethylamine were purchased from Fisher Scientific and Aldrich Chemical Company, Inc. and stored over molecular sieves. Triethylamine (Kodak) was distilled from calcium hydride and stored over molecular sieves. Iodobenzene and 4-iodotoluene were purchased from Eastman Kodak Company. 2-Iodoanisole was obtained from Aldrich Chemical Company, Inc. 4-Iodoacetophenone was purchased from Pfaltz & Bauer, Inc. Ethyl 4-iodobenzoate and 3-iodonitrobenzene were obtained from Lancaster Synthesis Inc. and used without further purification. (*E*)-1-Iodo-1-hexene[20] and (*E*)-1-iodo-2-phenylethylene[21] were generously supplied by Hoseok Yang and made according to

literature procedures. 4-Vinyl-2-azetidinone, 4-methyl-4-vinyl-2-azetidinone, (*E*)- and (*Z*)-4-(1-propenyl)-2-azetidinone, 4-methyl-4-isopropenyl-2-azetidinone, and 4-methyl-4-(2-propenyl)-2-azetidinone were prepared according to literature procedures[24-26] and their experimental data have been reported in Part I.

1-Iodo-1-phenylethylene[22]

At room temperature in acetonitrile (10 ml) was dissolved NaI (0.90 g, 6.0 mmol) and then Me_3SiCl (0.65 g, 6.0 mmol) was added, followed by H_2O (0.05 g, 3.0 mmol). After 10 minutes, phenylacetylene purchased from Aldrich Chemical Company, Inc. was added to the solution (0.51 g, 5.0 mmol) and allowed to react for 1 hour at ambient temperature. The reaction was quenched by water (5 ml) and extracted with ether (15 ml x 3). Washing with 10 % $Na_2S_2O_3$, drying over $MgSO_4$, evaporating the ether, and purifying the product by flash silica gel column chromatography with hexane as the eluent gave the desired 1-iodo-1-phenylethylene in 50 % yield: ^1H NMR ($CDCl_3$) δ 6.04 (d, 1 H, J = 1.2 Hz, C<u>H</u>H= trans to Ph), 6.47 (d, 1 H, J = 1.2 Hz, C<u>H</u>H= cis to Ph), 7.23-7.49 (m, 5 H, phenyl); IR (neat) 3056, 3029, 1675, 1600, 1442, 1282, 1209, 1054, 1024, 895, 767, 697, 602 cm^{-1}. The spectroscopic data were identical to those reported in the literature.[28]

1-Iodocyclohexene[23]

Cyclohexanone tosylhydrazone (5.86 g, 22.0 mmol) in TMEDA (60 ml) was cooled to -78 °C. To this solution was added 2.0 M *n*-butyllithium in hexane (45 ml) over a period of 30 minutes. The solution was allowed to warm to room temperature and allowed to stir under nitrogen for 3 hours. The solution was then cooled to -78 °C and I_2 (17.7 g, 70 mmol) was added in one portion. The solution was then warmed to room temperature. A vigorous reaction took place after approximately 15 minutes. A solid material was formed in the flask. The solution was allowed to stir at room temperature for 6 hours under

nitrogen and then the reaction was stopped by pouring ice water (50 ml) into the flask. The organic layer was extracted with pentane (50 x 3 ml). The combined pentane layers were washed with water (25 x 2 ml) and brine (25 x 2 ml), and dried over anhydrous $MgSO_4$. The solution was filtered and evaporated to dryness on the rotoevaporator. The residue was purified on a flash silica gel column using hexane as the eluent. The desired 1-iodocyclohexene was obtained in 14 % yield: ^1H NMR ($CDCl_3$) δ 1.67 (m, 4 H, $CH_2CH_2CH_2CH$=), 2.08 (m, 2 H, CH_2CH=), 2.50 (m, 2 H, CH_2Cl=), 6.33 (dd, 1 H, J = 3.9 Hz, J = 1.9 Hz, CH=). The spectroscopic data were identical to those reported in the literature.[29]

Cyclohexenyl triflate[24]

To a -78 °C solution of newly distilled diisopropylamine (1.42 g, 14.2 mmol) in THF (25 ml) was added *n*-butyllithium (7.10 ml, 2.0 M in hexane). The solution was stirred at -78 °C for 30 minutes, 0 °C for 10 minutes, and then cooled back down to -78 °C before freshly distilled cyclohexanone (1.28 g, 13.0 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 (5.00 g, 14.0 mmol) purchased from Aldrich Chemical Company, Inc. in THF (25 ml) was added. The contents were stirred at -78 °C for one hour, 0 °C for two hours, and then at room temperature for three hours. Once analysis by thin-layer chromatography indicated that all of the cyclohexanone had 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), freshly prepared 25 % aqueous $Na_2S_2O_3$ (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 on a flash silica gel column using hexane as the eluent. The desired cyclohexenyl triflate was obtained in 40 % yield: ^1H NMR ($CDCl_3$) δ 1.56 -1.82 (m, 4 H,

CH_2's), 2.17 (m, 2 H, C<u>H</u>$_2$CH=), 2.38 (m, 2 H, CH_2C=), 5.75 (m, 1 H, CH=); ^{13}C NMR ($CDCl_3$) δ 20.93, 22.62, 23.82, 27.53, 118.35, 130.90, 149.34; IR (neat) 2943, 2850, 1684, 1441, 1416, 1206, 1141, 1052, 1031, 980, 881, 832 cm^{-1}; HRMS: calculated for $C_7H_9SO_3F_3$ m/z 230.02245, found 230.02255. The spectroscopic data were identical to those reported in the literature.[24]

<u>4-(9-Decenyl)-2-azetidinone</u>

4-(9-Decenyl)-2-azetidinone was prepared according to the procedure of Moriconi and Meyer.[27] 1,11-Dodecadiene (1.84 g, 11.9 mmol) was added dropwise to a stirred solution of chlorosulfonyl isocyanate purchased from Aldrich Chemical Company, Inc. (1.87 g, 13.2 mmol) in 7 ml of distilled ether at -10 °C to 0 °C. After maintaining the reaction temperature at 0 °C for additional 5 hours, the solution was warmed to room temperature and kept stirring for 4 days. The newly formed *N*-chlorosulfonyl-2-azetidinone was hydrolyzed by adding the reaction mixture slowly to a stirred mixture of 25 ml of 25 % aqueous sodium sulfite and 10 ml of ether. The aqueous phase was kept slightly basic by adding 10 % KOH solution as the reduction proceeded. After 30 minutes, the layers were separated and the aqueous layer was successively extracted with three 20-ml portions of ether. The combined ether extracts were dried by anhydrous Na_2SO_4, filtered, and evaporated. The crude product was purified by flash column chromatography to give the desired 4-(9-decenyl)-2-azetidinone as a colorless oil in 10 % yield: ^{1}H NMR ($CDCl_3$) δ 1.29 (m, 12 H, CH_2's), 1.60 (q, 2 H, *J* = 6.0 Hz, C<u>H</u>$_2$CHNH)), 2.03 (q, 2 H, *J* = 6.9 Hz, CH_2C=), 2.55 (ddd, 1 H, *J* = 14.7 Hz, *J* = 2.1 Hz, *J* = 1.2 Hz, CHCO cis to substituent), 3.04 (ddd, 1 H, *J* = 14.7 Hz, *J* = 4.8 Hz, *J* = 2.1 Hz, CHCO trans to subtituent), 3.60 (m, 1 H, C<u>H</u>NH), 4.93 (d, 1 H, *J* = 10.2 Hz, cis C<u>H</u>H=), 4.99 (d, 1 H, *J* = 16.8 Hz, trans C<u>H</u>H=), 5.81 (ddt, 1 H, *J* = 16.8 Hz, *J* = 10.2 Hz, *J* = 6.9 Hz, CH=), 6.35 (br s, 1 H, NH); ^{13}C NMR

($CDCl_3$) δ 26.14, 28.78, 28.84, 28.95, 29.24, 29.34, 33.68, 35.35, 43.33, 48.14, 114.04, 138.95, 168.49; IR (neat) 3250, 3077, 2919, 2854, 1751, 1642, 1460, 1413, 1375, 1188, 994, 911, 732 cm^{-1}; HRMS: calculated for $C_{13}H_{23}NO$ m/z 209.17796, found 209.17844.

General procedure for the palladium-promoted cross-coupling of alkenyl 2-azetidinones with organic halides and triflates

The following procedure used for the preparation of a mixture of (*E*)- and (*Z*)-3-methyl-5-phenyl-3-pentenamide is representative of procedure A used for other compounds. Procedures B and C were carried out in a similar manner. To an oven-dried 25 ml round-bottom flask containing a magnetic stirrer were added the following reagents: palladium acetate (11.3 mg, 0.05 mmol), sodium formate (170.0 mg, 2.5 mmol), lithium chloride (42.4 mg, 1.0 mmol), diisopropylethylamine (0.26 ml, 1.5 mmol), 4-methyl-4-vinyl-2-azetidinone (55.6 mg, 0.5 mmol), iodobenzene (205.0 mg, 1.0 mmol), and *N,N*-dimethylformamide (2.0 ml). The solution was stirred at 80 °C for 1 day. Ether (15 ml) was then added to the reaction mixture. The ether layer was washed with saturated aqueous ammonium chloride (15 ml x 3), and the combined aqueous layers were back extracted with ether (15 ml x 2). The combined ether fractions were dried over anhydrous magnesium sulfate. After removal of the solvents, the residue was purified by flash column chromatography on silica gel using a 1:2.5 mixture of hexane to ethyl acetate as eluent. The desired substituted 3-alkenamide was obtained as white crystals.

(*E*)- and (*Z*)-5-Phenyl-3-pentenamide, (*E*)- and (*Z*)-5-phenyl-3-hexenamide, (*E*)- and (*Z*)-5-phenyl-3-nonenamide, (*E*)- and (*Z*)-3-methyl-5-phenyl-3-pentenamide, and (*E*)- and (*Z*)-3,4-dimethyl-5-phenyl-3-pentenamide were synthesized and characterized in Part I.

(*E*)- and (*Z*)-5-(2-Methoxyphenyl)-3-methyl-3-pentenamide (Table 9, entry 3)

Obtained in 98 % isolated yield (60:40 *E/Z*) from the reaction of 4-methyl-4-vinyl-2-azetidinone and 2-iodoanisole using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.80 (s, 3 H, CH_3C=), 2.93 (s, 2 H, CH_2CO), 3.40 (d, 2 H, J = 7.2 Hz, CHAr), 3.81 (s, 3 H, OCH_3), 5.47 (t, 1 H, J = 7.2 Hz, CH=), 5.94 and 6.27 (2 br s, 2 H, NH_2), 6.82-6.92 and 7.10-7.20 (2 m, 4 H, aryl); ^{13}C NMR ($CDCl_3$) δ 16.31, 29.36, 47.46, 55.32, 110.38, 120.63, 127.40, 127.91, 128.82, 129.57, 130.56, 157.09, 173.54.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.79 (s, 3 H, CH_3C=), 3.12 (s, 2 H, CH_2CO), 3.36 (d, 2 H, J = 6.9 Hz, CH_2Ar), 3.80 (s, 3 H, OCH_3), 5.54 (t, 1 H, J = 6.9 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 23.86, 29.75, 39.75, 55.31, 110.47, 120.74, 127.49, 129.60, 130.24, 157.27, 174.24.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 105-106 °C; IR (neat) 3396, 3200, 3180, 2986, 2907, 2831, 2783, 1736, 1662, 1629, 1585, 1491, 1458, 1408, 1386, 1285, 1242, 1179, 1107, 1076, 1048, 1027, 874, 783, 750, 747 cm^{-1}; HRMS: calculated for $C_{13}H_{17}NO$ m/z 219.12593, found 219.12574.

The Heck product (*E*)-4-methyl-4-(2-(2-methoxyphenyl)vinyl)-2-azetidinone was also observed, but was not separable from the starting alkenyl 2-azetidinone: ^{1}H NMR ($CDCl_3$) δ 1.66 (s, 3 H, CCH_3), 2.93 (s, 2 H, CH_2), 3.85 (s, 3 H, CH_3O), 6.12 (br s, 1 H, NH), 6.40 (d, 1 H, J = 16.2 Hz, CCH=), 6.87 (d, 1 H, J = 16.2 Hz, =CHAr), 6.95 (m, 2 H, H's on C5 and C6 of aryl), 7.26 (m, 1 H, H on C4 of aryl group), 7.40 (m, 1 H, H on C3 of aryl).

(*E*)- and (*Z*)-3-Methyl-5-(4-methylphenyl)-3-pentenamide (Table 9, entry 12)

Obtained in 99 % isolated yield (66:34 *E/Z*) from the reaction of 4-methyl-4-vinyl-2-azetidinone and 4-iodotoluene using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.81 (s, 3 H, CH_3C=), 2.31 (s, 3 H, CH_3Ar), 2.95 (s, 2 H, CH_2CO), 3.37 (d, 2 H, J = 7.2 Hz, CH_2Ar), 5.54 (t, 1 H, J = 7.2 Hz, CH=), 5.73 and 6.15 (2 br s, 2 H, NH_2), 7.08 (m, 4 H, aryl); ^{13}C NMR ($CDCl_3$) δ 16.28, 20.96, 33.96, 47.36, 128.10, 128.54, 129.24, 130.32, 135.64, 137.34, 173.18.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.82 (s, 3 H, CH_3C=), 3.09 (s, 2 H, CH_2CO), 3.34, (d, 2 H, J =7.2 Hz, CH_2Ar), 5.63 (t, 1 H, J = 7.2 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 24.04, 39.53, 129.28, 130.65, 135.53, 137.58, 173.99.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 104.5-105.5 °C; IR (neat) 3362, 3359, 3190, 3185, 1658, 1632, 1412, 1372, 908, 802, 731 cm^{-1}; HRMS: calculated for $C_{13}H_{17}NO$ m/z 203.13101, found 203.13124.

The Heck product (*E*)-4-methyl-4-(2-(4-methylphenyl)vinyl)-2-azetidinone was also observed, but was not separable from the starting alkenyl 2-azetidinone: ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3Ar), 2.93 (s, 2 H, CH_2), 6.15 (br s, 1 H, NH), 6.33 (d, 1 H, J = 16.1 Hz, CCH=), 6.56 (d, 1 H, J = 16.1 Hz, ArCH=), 7.07-7.26 (m, 4 H, aryl).

(*E*)- and (*Z*)-3-Methyl-5-(4-acetylphenyl)-3-pentenamide (Table 9, entry 15)

Obtained in 52 % isolated yield (65:35 *E/Z*) from the reaction of 4-methyl-4-vinyl-2-azetidinone and 4-iodoacetophenone using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.83 (s, 3 H, CH_3C=), 2.58 (s, 3 H, CH_3CO), 2.99 (s, 2 H, CH_2CO), 3.47 (d, 2 H, J = 7.2 Hz, CH_2Ar), 5.54 (t, 1 H, J = 7.2 Hz, CH=), 5.70 and 5.90 (2 br s, 2 H, NH_2), 7.27 (d, 2 H, J = 8.2 Hz, H's on C2 and C6 of aryl), 7.89 (d, 2 H, J = 8.2 Hz, H's on C3 and C5 of aryl); ^{13}C NMR ($CDCl_3$) δ 16.34, 26.51, 34.30, 47.07, 127.32, 128.41, 128.64, 131.80, 137.52, 146.43, 173.77, 197.83.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.86 (s, 3 H, CH_3C=), 3.10 (s, 2 H, CH_2CO), 5.62 (t, 1 H, J = 7.4 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 16.34, 26.51, 34.30, 47.07, 127.32, 128.41, 128.61, 131.80, 137.52, 146.43, 173.77, 197.83.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 109-110 °C; IR (neat) 3383, 3375, 3189, 3184, 2909, 2779, 1673, 1631, 1569, 1407, 1358, 1302, 1269, 1198, 1180, 1112, 1073, 1014, 958, 870, 832, 819, 778, 698, 668 cm^{-1}; HRMS: calculated for $C_{14}H_{17}NO_2$ m/z 231.12593, found 231.12561.

The Heck product (*E*)-4-methyl-4-(2-(4-acetylphenyl)vinyl)-2-azetidinone was also observed and was not separable from the starting alkenyl 2-azetidinone: ^{1}H NMR ($CDCl_3$) δ 1.68 (s, 3 H, CH_3C), 2.66 (s, 3 H, CH_3CO), 2.97 (s, 2 H, CH_2), 6.24 (br s, 1 H, NH), 6.53 (d, 2 H, J = 16.2 Hz, CCH=), 6.65 (d, 2 H, J = 16.2 Hz, ArCH=), 7.46 (d, 2 H, J = 8.4 Hz, H's on C2 and C6 of aryl), 7.93 (d, 2 H, J = 8.4 Hz, H's on C3 and C5 of aryl).

(*E*)- and (*Z*)-5-(4-Ethoxycarbonylphenyl)-3-methyl-3-pentenamide (Table 9, entry 27)

Obtained in 72 % isolated yield (60:40 *E*/*Z*) from the reaction of 4-methyl-4-vinyl-2-azetidinone and ethyl 4-iodobenzoate using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3 H, *J* = 7.2 Hz, $CH_2\underline{CH_3}$), 1.82 (s, 3 H, CH_3C=), 2.98 (s, 2 H, CH_2CO), 3.46 (d, 2 H, *J* = 7.2 Hz, CH_2Ar), 4.36 (q, 2 H, *J* = 7.2 Hz, $C\underline{H_2}CH_3$), 5.54 (t, 1 H, *J* = 7.2 Hz, CH=), 5.67 and 5.82 (2 br s, 2 H, NH_2), 7.24 (d, 2 H, *J* = 8.1 Hz, H's on C2 and C6 of aryl), 7.96 (d, 2 H, *J* = 8.1 Hz, H's on C3 and C5 of aryl); ^{13}C NMR ($CDCl_3$) δ 14.35, 16.41, 34.43, 47.24, 60.87, 127.76, 128.24, 128.42, 129.87, 131.79, 146.01, 166.57, 173.54.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.85 (s, 3 H, CH_3C=), 3.10 (s, 2 H, CH_2CO), 5.62 (t, 1 H, *J* = 7.2 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 24.11, 34.39, 39.44, 127.17, 128.21, 128.75, 129.83, 131.29, 145.76, 166.52, 172.89.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 112-113 °C; IR (neat) 3366, 3188, 2978, 2909, 1713, 1652, 1635, 1608, 1408, 1366, 1309, 1278, 1176, 1121, 1099, 1021, 878, 761, 707 cm^{-1}; HRMS: calculated for $C_{15}H_{19}NO_3$ m/z 261.13649, found 261.13630.

The Heck product (*E*)-4-(2-(4-ethoxycarbonylphenyl)vinyl)-4-methyl-2-azetidinone was also observed and was not separable from the starting alkenyl 2-azetidinone: ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3 H, *J* = 7.2 Hz, $CH_2\underline{CH_3}$), 1.67 (s, 3 H, CH_3C), 2.96 (s, 2 H, CH_2CO), 4.38 (q, 2 H, *J* = 7.2 Hz, $C\underline{H_2}CH_3$), 6.19 (br s, 1 H, NH), 6.51 (d, 1 H, *J* = 15.9 Hz, CCH=), 6.64 (d, 1 H, *J* = 15.9 Hz, ArCH=), 7.43 (d, 2 H, *J* = 8.4 Hz, H's on C2 and C6 of aryl), 8.00 (d, 2 H, *J* = 8.4 Hz, H's on C3 and C5 of aryl).

<u>(*E*)- and (*Z*)-5-(2-Methoxyphenyl)-3-pentenamide</u> (Table 9, entry 39)

Obtained in 74 % isolated yield (83:17 *E*/*Z*) from the reaction of 4-vinyl-2-azetidinone and 2-iodoanisole using procedure A. The *E*- to *Z*-isomer ratio was determined

by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 2.94 (d, 2 H, J = 7.2 Hz, CH_2CO), 3.37 (d, 2 H, J = 6.6 Hz, CH_2Ar), 3.81 (s, 3 H, CH_3O), 5.59 (dt, 1 H, J = 15.3 Hz, J = 7.2 Hz, =C<u>H</u>CH_2CO), 5.76 (dt, 1 H, J = 15.3 Hz, J = 6.6 Hz, =C<u>H</u>CH_2Ar), 5.93 and 6.25 (2 br s, 2 H, NH_2), 6.84-6.92 (m, 2 H, H's on C5 and C6 of aryl), 7.10-7.12 (m, 1 H, H on C4 of aryl), 7.18-7.23 (m, 1 H, H on C3 of aryl); ^{13}C NMR ($CDCl_3$) δ 33.54, 39.93, 55.35, 110.47, 120.68, 123.36, 127.59, 127.63, 129.88, 134.66, 157.22, 174.17.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 3.15 (d, 2 H, J = 7.2 Hz, CH_2CO); ^{13}C NMR same as the *E*-isomer or not seen, except δ 28.27, 122.30, 128.22, 129.57, 130.03, 132.89.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 97.5-98.5 °C; IR (neat) 3325, 3188, 2939, 2835, 1670, 1601, 1493, 1464, 1396, 1319, 1290, 1244, 1177, 1113, 1049, 1028, 972, 754 cm^{-1}; HRMS: calculated for $C_{12}H_{15}NO_2$ m/z 205.11028, found 205.11021.

The Heck product (*E*)-4-(2-(2-methoxyphenyl)vinyl)-2-azetidinone was also observed, but was not separable from the starting alkenyl 2-azetidinone: ^{1}H NMR ($CDCl_3$) δ 2.81 (ddd, 1 H, J = 14.7 Hz, J = 2.4 Hz, J = 1.2 Hz, CHCO cis to C=C), 3.28 (ddd, 1 H, J = 14.7 Hz, J = 5.4 Hz, J = 2.1 Hz, CHCO trans to C=C), 4.32 (m, 1 H, CHN), 6.26 (dd, 1 H, J = 15.9 Hz, J = 7.8 Hz, CCH=), 6.56 (br s, 1 H, NH), 6.87-6.96 (m, 2 H, H's on C5 and C6 of aryl), 7.22-7.28 (m, 1 H, H on C4 of aryl), 7.39-7.42 (m, 1 H, H on C3 of aryl), the peak corresponding to the vinyl proton nearer the aryl proton is buried under the amide proton peak.

(*E*)- and (*Z*)-5-(4-Ethoxycarbonylphenyl)-3-pentenamide (Table 9, entry 41)

Obtained in 71% isolated yield (85:15 *E*/*Z*) from the reaction of 4-vinyl-2-azetidinone and ethyl 4-iodobenzoate using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3 H, J = 7.2 Hz, $CH_2\underline{CH_3}$), 3.00 (d, 2 H, J = 6.3 Hz, CH_2CO), 3.43 (d, 2 H, J = 6.0 Hz, CH_2Ar), 4.36 (q, 2 H, J = 7.2 Hz, $\underline{CH_2}CH_3$), 5.64 (dt, 1 H, J = 15.6 Hz, J = 6.3 Hz, $=\underline{CH}CH_2CO$), 5.76 (dt, 1 H, J = 15.6 Hz, J = 6.0 Hz, $=\underline{CH}CH_2Ar$), 5.95 and 6.27 (2 br s, 2 H, NH_2), 7.23 (d, 2 H, J = 8.1 Hz, H's on C2 and C6 of aryl), 7.95 (d, 2 H, J = 8.1 Hz, H's on C3 and C5 of aryl); ^{13}C NMR ($CDCl_3$) δ 14.33, 38.87, 39.71, 60.87, 124.71, 128.28, 128.46, 129.81, 133.42, 145.19, 166.56, 173.74.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 3.14 (d, 2 H, J = 6.0 Hz, CH_2CO), 3.47 (d, 2 H, J = 6.3 Hz, CH_2Ar); ^{13}C NMR same as the *E*-isomer or not seen, except δ 33.52, 34.57, 61.08, 123.36, 126.83, 128.53, 129.87, 131.82.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 93-94 °C; IR (neat) 3408, 3202, 2984, 2907, 1707, 1651, 12610, 1576, 1477, 1404, 1367, 1313, 1279, 1198, 1123, 1105, 1024, 968, 766 cm^{-1}; HRMS: calculated for $C_{14}H_{17}NO_3$ m/z 247.12084, found 247.12125.

The Heck product (*E*)-4-(2-(4-ethoxycarbonylphenyl)vinyl)-2-azetidinone was also observed, but was not separable from the starting alkenyl 2-azetidinone: ^{1}H NMR ($CDCl_3$) δ 1.45 (t, 3 H, J = 7.2 Hz, $CH_2\underline{CH_3}$), 2.82 (d, 1 H, J = 14.8 Hz, CHCO cis to C=C), 3.37 (m, 1 H, CHCO trans to C=C), 4.36 (m, 3 H, CHN and $\underline{CH_2}CH_3$), 6.40 (dd, 1 H, J = 15.9 Hz, J = 7.2 Hz, CCH=), 6.66 (d, 1 H, J = 15.9 Hz, =CHAr), 7.43 (d, 2 H, J = 8.1 Hz, H's on C2 and C6 of aryl), 8.01 (d, 2 H, J = 8.1 Hz, H's on C3 and C5 of aryl).

(*E*)- and (*Z*)-3-Methyl-6-phenyl-3-hexenamide (Table 9, entry 59)

Obtained in 82 % isolated yield (57:43 *E/Z*) from the reaction of 4-allyl-4-methyl-2-azetidinone and iodobenzene using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 3 H, CH_3), 2.40 (q, 2 H, J = 7.5 Hz, CH_2CH=), 2.71 (t, 2 H, J = 7.5 Hz, CH_2Ph), 2.86 (s, 2 H, CH_2CO), 5.34 (t, 1 H, J = 6.6 Hz, CH=), 5.54 and 5.78 (2 br s, 2 H, NH_2), 7.15-7.29 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 16.16, 29.61, 35.45, 47.44, 125.97, 128.40, 128.47, 129.60, 130.95, 141.69, 173.84.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.59 (s, 3 H, CH_3), 2.87 (s, 2 H, CH_2CO), 5.43 (t, 1 H, J = 6.6 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 23.86, 30.27, 35.67, 39.40, 125.99, 128.56, 128.79, 130.40, 141.56, 173.31.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 90.5-91.5 °C; IR (neat) 3455, 3329, 3322, 3187, 2959, 2920, 2851, 1660, 1602, 1493, 1451, 1382, 1272, 1075, 765, 698 cm^{-1}; HRMS: calculated for $C_{13}H_{17}NO$ m/z 203.13101, found 203.13115.

The Heck product 4-methyl-4-(3-phenyl-2-propyl)-2-azetidinone was also observed and has been characterized in Part I.

(*E*)- and (*Z*)-13-Phenyl-3-tridecenamide (Table 9, entry 64)

Obtained in 42 % isolated yield (82:18 *E/Z*) from the reaction of 4-(9-decenyl)-2-azetidinone and iodobenzene using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.24 (m, 10 H, CH_2's), 1.60 (m, 4 H, CH_2's), 2.03 (q, 2 H, J = 6.3 Hz, $C\underline{H}_2CH$=), 2.59 (t, 2 H, J = 6.9 Hz, CH_2Ar), 2.95 (d, 2 H, J = 6.3 Hz, CH_2CO), 5.49-5.68 (m, 4 H, CH=CH and NH_2), 7.12-7.29 (m, 5 H, aryl).

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 2.56 (t, 2 H, J = 7.2 Hz, CH_2Ar), 3.09 (d, 2 H, J = 6.3 Hz, CH_2CO).

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: mp 57-58 °C; ^{13}C NMR ($CDCl_3$) δ 22.39, 23.42, 27.73, 29.19, 29.22, 29.36, 29.48, 29.54, 31.56, 32.56, 32.58, 36.02, 38.45, 39.98, 40.04, 44.09, 48.42, 122.34, 125.58, 125.78, 127.01, 128.25, 128.28, 128.43, 135.41, 136.76, 142.95, 174.04; IR (neat) 3401, 3202, 2917, 2847, 1649, 1462, 1412, 1383, 1258, 968, 740, 696 cm^{-1}; HRMS: calculated for $C_{19}H_{29}NO$ m/z 287.22491, found 287.22565.

(E,E)- and *(Z,E)*-3-Methyl-7-phenyl-3,6-heptadienamide (Table 9, entry 65)

Obtained in 18 % isolated yield (65:35 *E,E/Z,E*) from the reaction of 4-methyl-4-vinyl-2-azetidinone and (*E*)-1-iodo-2-phenylethylene using procedure A. The *E,E*- to *Z,E* isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E,E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3 H, CH_3), 2.98 (m, 4 H, CH_2's), 5.46 (t, 1 H, J = 7.2 Hz, CH=C), 5.53-5.69 (br s, 2 H, NH_2), 6.18 (dt, 1 H, J = 15.9 Hz, J = 6.6 Hz, CH=CHPh), 6.40 (d, 1 H, J = 15.9 Hz, =CHPh), 7.21-7.35 (m, 5 H, aryl).

The *Z,E*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E,E*-isomer or not seen, except δ 1.84 (s, 3 H, CH_3), 2.92, (m, 2 H, $C\underline{H}_2CH$=), 3.06 (s, 2 H, CH_2CO). This compound decomposed while waiting for further characterization.

The Heck-type products (*E*)-4-methyl-4-(4-phenyl-3-butenyl)-2-azetidinone (**10**) and (*E*)-4-methyl-4-(4-phenyl-2-butenyl)-2-azetidinone (**11**) were also obtained in 47 %

isolated yield as an inseparable mixture (60:40 **10/11**). The ratio of compound **6** to compound **7** was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

Compound **10**: ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 3 H, CH_3), 1.86 (t, 2 H, J = 7.2 Hz, $C\underline{H}_2CH_2C$=), 2.30 (m, 2 H, CH_2C=), 2.71 and 2.80 (2 s, 2 H, CH_2CO), 6.22 (dt, 1 H, J = 15.9 Hz, J = 6.9 Hz, C$\underline{H}$=CHPh), 6.40 (br s, 1 H, NH), 6.42 (d, 1 H, J = 15.9 Hz, C=CHPh), 7.30 (m, 5 H, aryl).

Compound **11**: ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3 H, CH_3), 2.38 (d, 2 H, J = 5.4 Hz, CH_2C=), 2.66 and 2.76 (2 s, 2 H, CH_2CO), 3.39 (d, 2 H, J = 6.3 Hz, CH_2Ph), 5.51 and 5.70 (2 m, 2 H, CH=CH), 7.20 (m, 5 H, aryl).

(*E,E*)- and (*Z,E*)-3-Methyl-3,6-undecadienamide (Table 9, entry 66)

Obtained in 13 % isolated yield (68:32 *E,E*/*Z,E*) from the reaction of 4-methyl-4-vinyl-2-azetidinone and (*E*)-1-iodo-1-hexene using procedure A. The *E,E*- to *Z,E*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E,E*-isomer: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 6.9 Hz, $C\underline{H}_3CH_2$), 1.39 (m, 4 H, $C\underline{H}_2C\underline{H}_2CH_3$), 1.70 (s, 3 H, CH_3C), 1.99 (q, 2 H, J = 6.0 Hz, CH_2Pr), 2.75 (t, 2 H, J = 6.6 Hz, =CHC$\underline{H}_2$CH=), 2.94 (s, 2 H, CH_2CO), 5.40 (m, 3 H, vinyl H's), 5.76 and 5.97 (2 br s, 2 H, NH_2).

The *Z,E*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E,E*-isomer or not seen, except δ 1.84 (s, 3 H, CH_3), 2.92, (m, 2 H, $C\underline{H}_2$CH=), 3.06 (s, 2 H, CH_2CO). The amount of compound was insufficient to obtain further spectral data.

(E,E)- and *(Z,E)*-3-Methyl-6-phenyl-3,6-heptadienamide (Table 9, entry 68)

Obtained in 4 % isolated yield (58:42 *E/Z)* from the reaction of 4-methyl-4-vinyl-2-azetidinone and 1-iodo-1-phenylethylene using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3 H, CH_3), 2.90 (s, 2 H, CH_2CO), 3.29 (d, 2 H, J = 6.0 Hz, CH_2CPh), 5.12 and 5.35 (2 s, 2H, $=CH_2$), 5.40 (t, 1 H, J = 6.0 Hz, =CH), 5.50 (br s, 2 H, NH_2), 7.26-7.41 (m, 5 H, aryl).

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 3.02 (s, 2 H, CH_2CO). The amount of compound was insufficient to obtain further spectral data.

(E,E)- and *(Z,E)*-3-Methyl-6-phenyl-3,6-heptadienamide (Table 9, entry 71)

Obtained in 31 % isolated yield (70:30 *E/Z*) from the reaction of 4-methyl-4-vinyl-2-azetidinone and 1- iodocyclohexene using procedure A. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the amide group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.54 (m, 4 H, $C\underline{H_2}C\underline{H_2}CH_2C=$), 1.71 (s, 3 H, CH_3), 1.91 and 1.98 (2 m, 4 H, $CH_2C=CCH_2$), 2.67 (d, 2 H, J = 6.9 Hz, $C=CCH_2C=C$), 2.95 (s, 2 H, CH_2CO), 5.41 (m, 2 H, vinyl H's), 5.76 and 6.01 (2 br s, 2 H, NH_2).

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.81 (s, 3 H, CH_3), 3.01 (s, 2 H, CH_2CO). This compound decomposed while waiting for further characterization.

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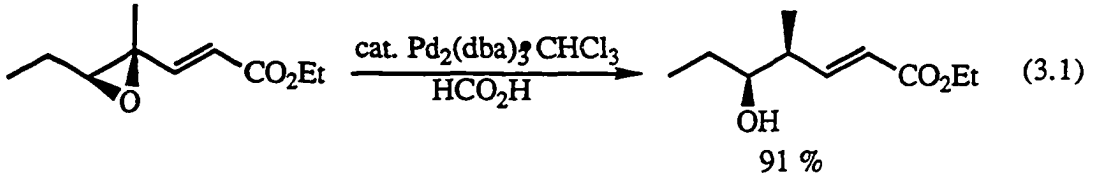
PART III. PALLADIUM(0)-PROMOTED CROSS-COUPLING OF VINYLIC EPOXIDES WITH ORGANIC HALIDES AND TRIFLATES

INTRODUCTION

In the past two decades, the role of organopalladium chemistry in organic synthesis has rapidly expanded. Palladium-promoted nucleophilic and organometallic additions to vinylic epoxides have become extremely versatile and useful synthetic reactions. These reactions produce 1,2- or 1,4-addition products in a highly regio- and stereoselective manner and have been used in the synthesis of a number of natural products. The palladium(0)-promoted reaction of vinylic epoxides has been well reviewed[1,2] and this introduction will focus on the progress that has been achieved in this field in recent years.

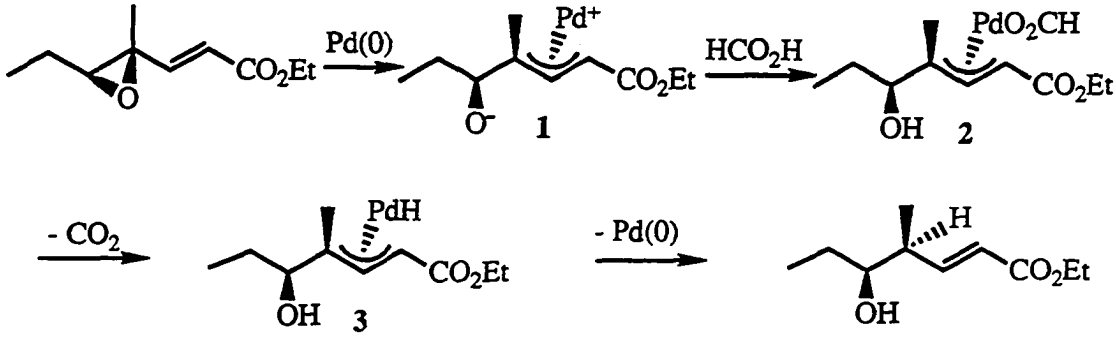
Oshima and co-workers have recently reported that the palladium(0)-catalyzed selective hydrogenolysis of chiral vinylic epoxides with formic acid gives optically active homoallylic alcohols (eq 3.1).[3] The stereoselectivity of the reaction depends on the nature and the amount of the phosphine ligand employed.



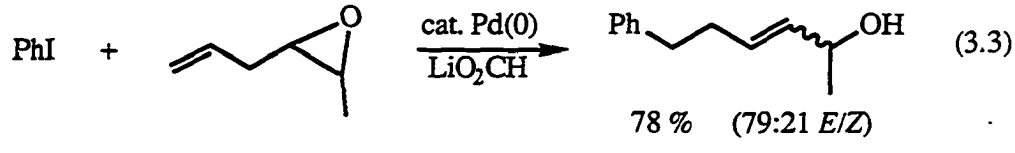
91 % (3.1)

The following mechanism has been proposed to explain how homoallylic alcohols are formed in this reaction (Scheme 1). At first, the palladium(0)-phosphine complex coordinating to the vinylic epoxide displaces the oxide with inversion to form the π-allylpalladium alkoxide complex **1**. Then formic acid reacts with the palladium alkoxide complex **1** to give the π-allylpalladium formate **2** which undergoes decarboxylation to form the π-allylpalladium hydride complex **3**. Finally, reductive elimination of palladium by internal attack of the hydride to the more substituted carbon of the π-allylpalladium species **3** gives the homoallylic alcohol and regenerates the palladium(0).

Scheme 1

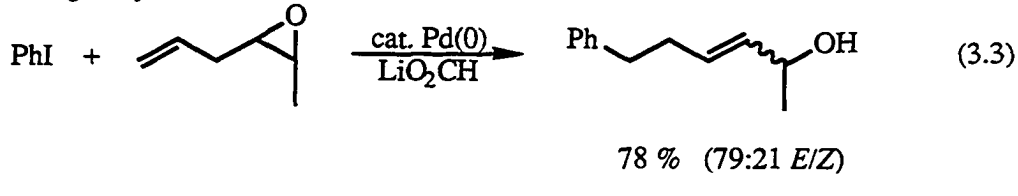


More recently, Oshima and co-workers have reported the chiral synthesis of (-)-serricornin in which the palladium(0)-catalyzed stereoselective hydrogenolysis of a vinylic epoxide with formic acid was employed as a key step (eq 3.2).[4]



(3.3)

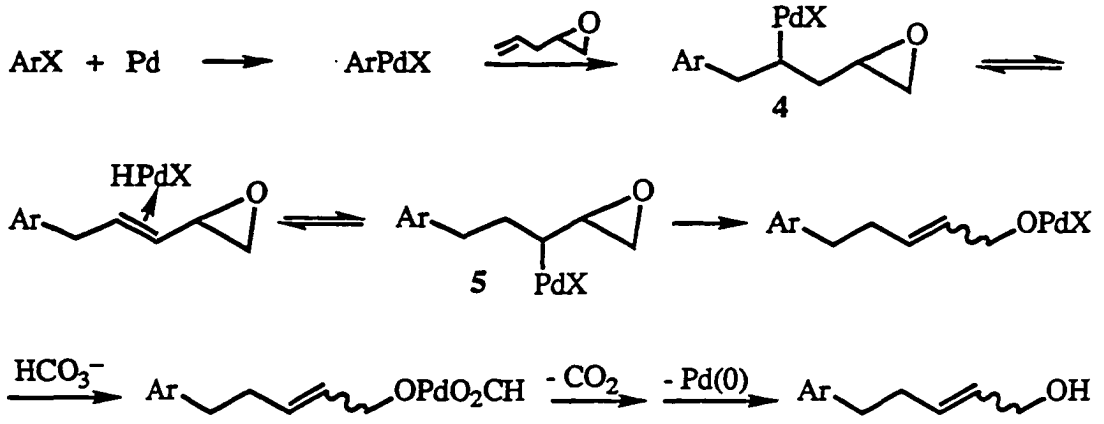
Larock and Leung have investigated the palladium(0)-catalyzed cross-coupling of aryl halides and olefinic epoxides bearing one to ten carbons between the two functional groups (eq 3.3).[5] The arylated allylic alcohols were afforded as a mixture of *E* and *Z* isomers in good yields.



(3.3)

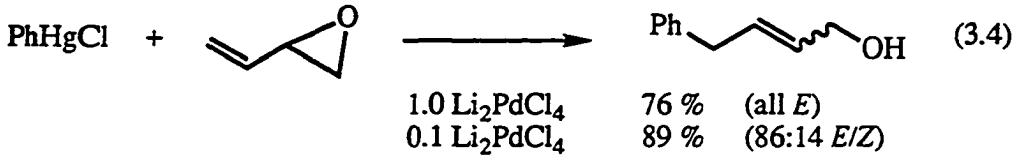
Larock and Leung have proposed the following mechanism to explain how allylic alcohols are produced from the above reaction (Scheme 2). The reaction process first

Scheme 2



involves the oxidative addition of the aryl halide to palladium(0) and subsequent olefin insertion to form σ-alkylpalladium species **4**. This is followed by a palladium migration process in which the palladium hydride eliminates and subsequently readds to the carbon-carbon double bond with the opposite regiochemistry. Finally, the newly formed σ-alkyl-palladium species **5** undergoes ring-opening and subsequent formate reduction to form the arylated allylic alcohol and simultaneously regenerate palladium(0).

Larock and Ilkka have reported that vinylic epoxides react with aryl- and vinyl-mercurials in the presence of a stoichiometric amount of palladium(II) (eq 3.4).[6]

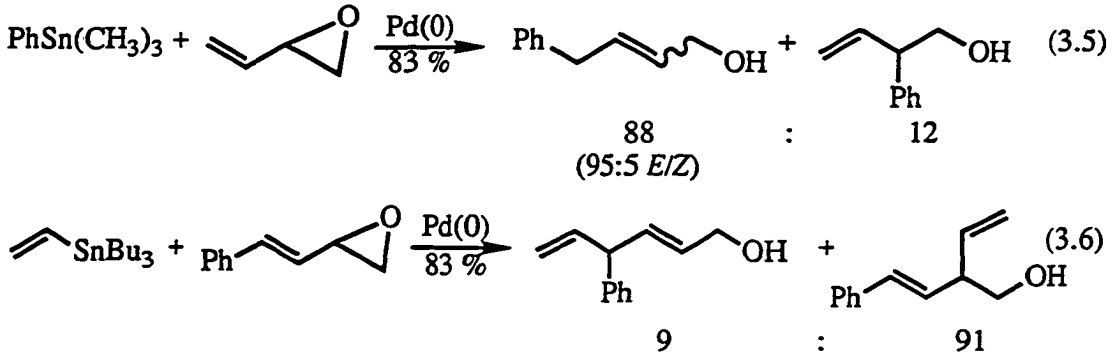


(3.4)

These reactions provided an excellent high yielding, regio- and stereoselective route to functionally-substituted allylic alcohols. Larock and Ilkka have also found that the reactions of vinylic epoxides with organomercurials can be run using a catalytic amount of palladium(II), if cupric chloride is added to the reaction and the reactions are conducted

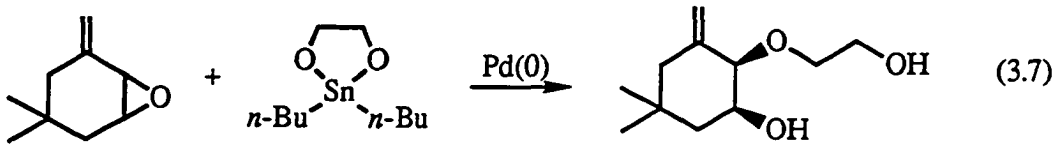
under an atmosphere of oxygen. However, under these conditions the allylic alcohols are obtained as mixtures of *E* and *Z* isomers.

Stille and co-workers have shown that the palladium(0)-catalyzed coupling of vinylic epoxides with organostannanes yield the desired products as a mixture of regio- and stereoisomers (eqs 3.5 and 3.6).[7,8] The regioselectivity of the reaction is affected by



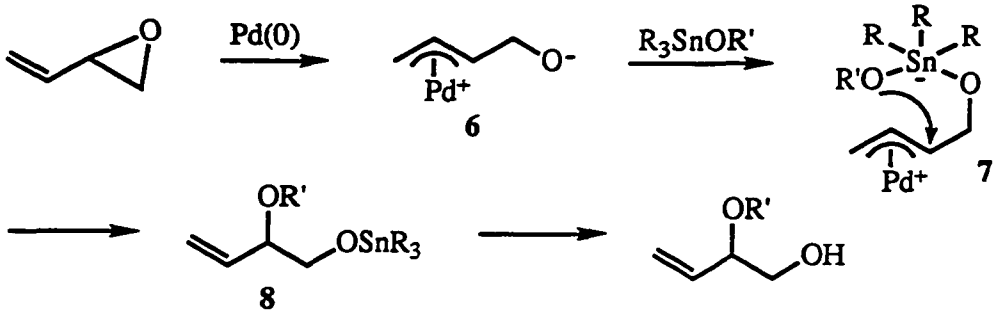
the substitution pattern of the vinylic epoxide. It was determined that vinyl, phenyl, and styryl groups were rapidly transferred, and that trimethyl- and tri-*n*-butylstannanes participate equally well in the transmetallation reaction.

Trost and Tenaglia have recently investigated the palladium(0)-catalyzed coupling of vinylic epoxides with cyclic stannyl ethers (eq 3.7).[9] It was found that only substitution proximal to the oxygen occurs.



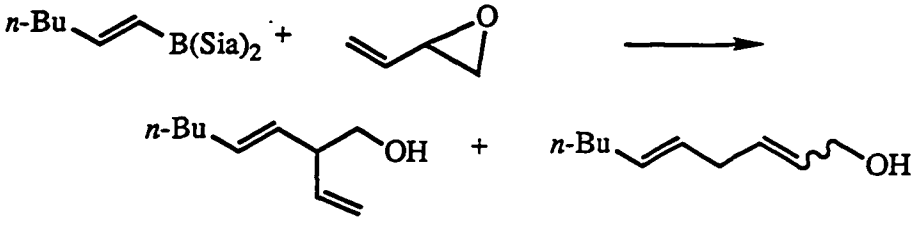
The following mechanism was proposed for the palladium(0)-catalyzed coupling of vinylic epoxides with stannyl ethers (Scheme 3). As seen previously, the first step of the mechanism involves formation of cationic π-allylpalladium species **6**. The alkoxide ion,

Scheme 3



thus formed, attacks the stannyl ether to form intermediate **7**. The oxygen nucleophile is tethered in this complex to affect its internal delivery to produce compound **8**. The tin-oxygen bond is then cleaved to produce the corresponding unsymmetrical ethylene glycol derivative.

Miyaura and co-workers have reported that vinylic epoxides react with alkenylboranes in the presence of a catalytic amount of a palladium or nickel complex (eq 3.8).[10] The regioselectivity observed in the reaction is dependent on the nature of the catalyst used and the structure of the alkenylborane.

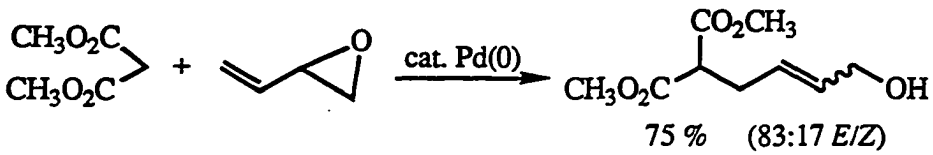


(3.8)

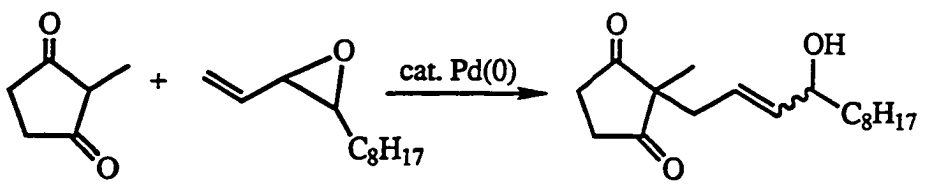
$Pd(dba)_2$	92 % (74:26)
$PdCl_2(PhCN)_2$	51 % (22:78)

In the last 10 years, the palladium-catalyzed reaction of vinylic epoxides with stabilized carbon nucleophiles has been extensively studied. In 1981, Trost[11] and Tsuji[12] independently reported that vinylic epoxides react with carbon nucleophiles in the presence

of a catalytic amount of palladium(0) to produce allylic alcohols in good yields (eqs 3.9 and 3.10). These reactions were generally highly regio- and stereoselective. However, the reaction produces a mixture of stereoisomers when butadiene monoepoxide is used or a trisubstituted allylic alcohol is formed.

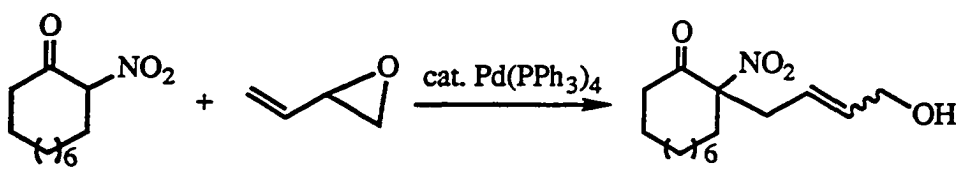


75 % (83:17 *E/Z*) (3.9)



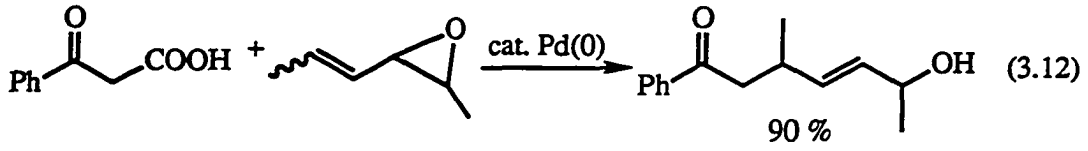
91 % (98:2 *E/Z*) (3.10)

Hesse and co-worker have demonstrated that nitrocycloalkanones can be used in the palladium(0)-catalyzed nucleophilic ring-opening of vinylic epoxides (eq 3.11).[13]



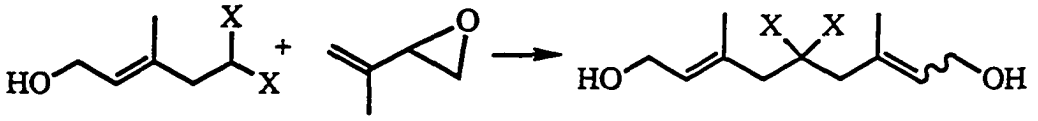
89 % (90:10 *E/Z*) (3.11)

Tsuda and co-workers have shown that β-keto acids can be used in the reaction to afford keto allylic alcohols in good yields (eq 3.12).[14] Again, these reactions are highly regio- and stereoselective, except the reaction of butadiene monoepoxide in which a 4.5:1 mixture of *E* to *Z* isomers is obtained.



(3.12)

Trost and Granja have recently reported the palladium(0)-catalyzed allylic alkylation of vinylic epoxides using a bis(sulfone) as a carbon nucleophile (eq 3.13).[15] Either the *E,E*- or *E,Z*-diene could be selectively synthesized and the stereoselectivity of the reaction depends on the nature of the palladium catalyst used.



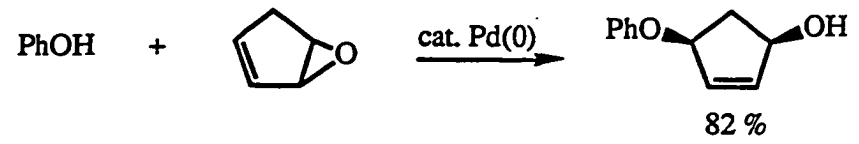
$X = SO_2Ph$

cat. $Pd_2(dba)_3 \cdot CHCl_3$ 91 % (81:19 *E,E*/*E,Z*)
cat. $Pd(OAc)_2$ 85 % (all *E,Z*)

(3.13)

A number of variously substituted vinylic epoxides have also been allowed to react with stabilized carbon nucleophiles in the presence of a palladium(0) catalyst to form the corresponding allylic alcohol.[16-18] Since the palladium(0)-catalyzed nucleophilic additions of vinylic epoxides with carbon nucleophiles show a high degree of regio- and stereoselectivity, they have been utilized considerably in the synthesis of natural products.[19-25]

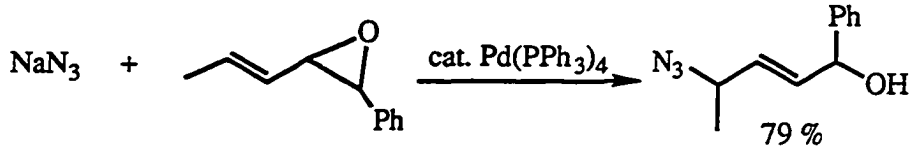
In addition to carbon nucleophiles, heteroatom nucleophiles have also been employed in the palladium(0)-catalyzed nucleophilic ring-opening of vinylic epoxides. The reactions of nitrogen[12,26-28] and sulfur[29] nucleophiles generally proceed in a highly regio- and stereoselective manner. Oxygen nucleophiles have been used in the palladium(0)-catalyzed allylic alkylation of cyclopentadiene monoepoxide, as reported by Deardorff and co-workers (eq 3.14).[30] *cis*-1,4-Addition products are selectively formed in these reactions.



(3.14)

Deardorff has also demonstrated that silyl-protected alcohols can be prepared from the reaction when using silyl phenoxides or silyl carboxylates as nucleophiles.[31]

Tenaglia and Waegell have found that azide can be used for the palladium(0)-catalyzed nucleophilic ring-opening of vinylic epoxides (eq 3.15).[32] When acyclic vinylic

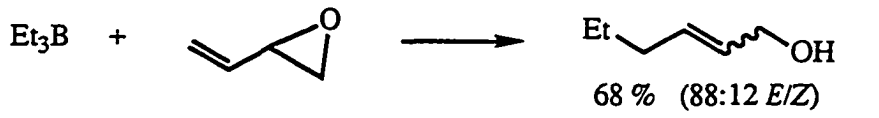


(3.15)

epoxides are used, the corresponding allylic alcohols are produced with a high degree of regio- and stereoselectivity. When cyclohexadiene monoepoxide is used, however, none of the desired product is observed.

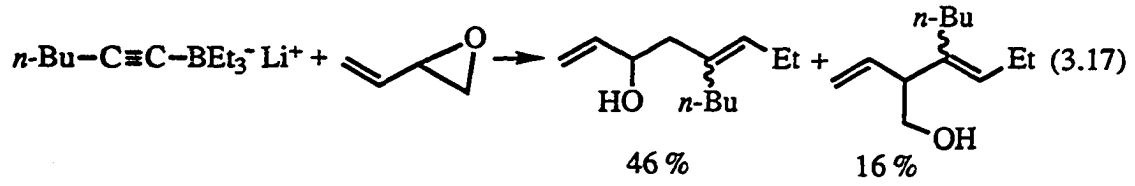
The cross-coupling of vinylic epoxides and stoichiometric amounts of organoboron, -magnesium, -lithium and -copper compounds also provides an important route to allylic alcohols. These reactions have been well studied and comprehensively reviewed.[1,2,33,34]

It has been shown that the reaction of vinylic epoxides with organoboranes generally produces 1,4-addition products (eq 3.16).[35] This reaction is believed to occur via a free-radical chain mechanism. Trialkylboranes also undergo additions to ethynyl epoxides to produce the corresponding allenic alcohols.[36]



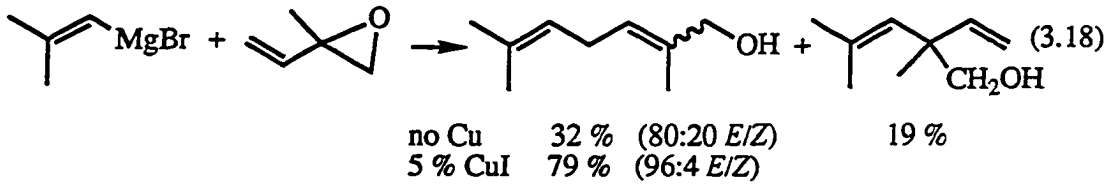
(3.16)

Gore and co-workers have reported that the reaction of vinylic epoxides with lithium trialkynylborates affords a mixture of regio- and stereoisomers (eq 3.17).[37]



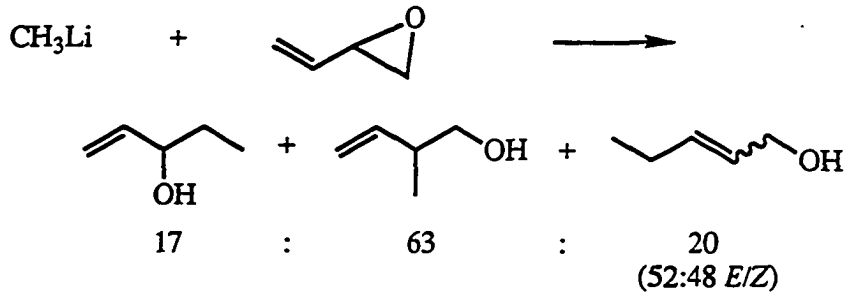
(3.17)

Organomagnesium compounds react with vinylic epoxides to produce a mixture of 1,2- and 1,4-addition products (eq 3.18).[38,39] The ratio of products is dependent on the Grignard reagent. When a catalytic amount of copper iodide is used, however, the 1,4-addition product is solely formed with a high degree of stereoselectivity.



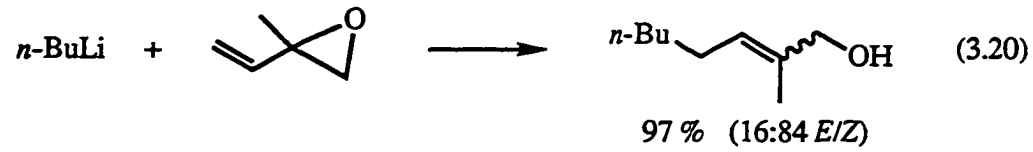
(3.18)

When butadiene monoepoxide is reacted with organolithium reagents, a mixture of 1,2- and 1,4-addition products are obtained (eq 3.19).[40,41] The ratio of products depends on the organolithium reagent and the procedure used to run the reaction.



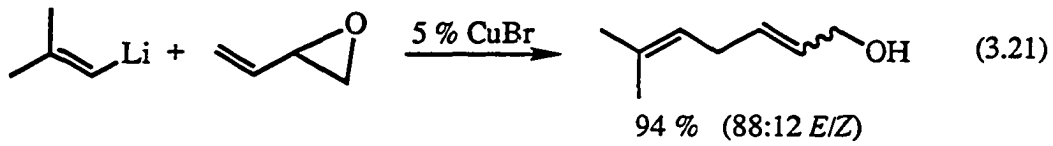
(3.19)

It was found that the reaction of 3,4-epoxy-3-methyl-1-butene with organolithium reagents predominately affords the 1,4-addition product as a mixture of stereoisomers (eq 3.20).[37,42]



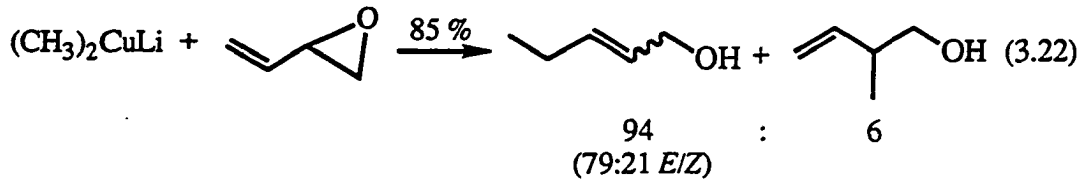
(3.20)

Similar to the reaction of organomagnesium reagents, the reaction of organolithium reagents produces predominately the *E*-isomer of allylic alcohols when using a catalytic amount of copper iodide (eq 3.21).[38]



(3.21)

Organocuprate reagents have proven to be superior reagents for the formation of allylic alcohols from vinylic epoxides.[34] In general, the nucleophilic reactions of vinylic epoxides with organocuprate reagents proceeds predominately in a 1,4-fashion to yield the corresponding *E*-allylic alcohols with a high degree of stereoselectivity (eq 3.22).[40,43]



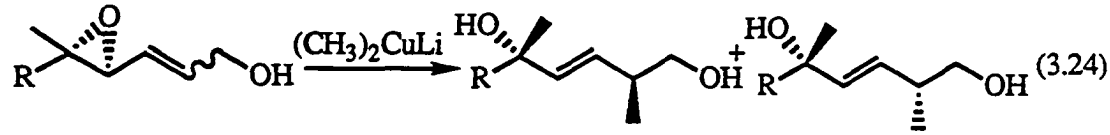
(3.22)

Alexakis and co-workers reported that the regio- and stereoselectivity of the reaction could be controlled when 3,4-epoxy-3-methyl-1-butene is reacted with alkylcopper reagents.[44,45] In the presence of one equivalent of boron trifluoride etherate, the *E*-isomer of the allylic alcohols is formed quantitatively.

Normant and co-workers have investigated the reactions of vinylic epoxides with vinylcopper derivatives (eq 3.23).[38,46] These reactions produce excellent yields of the corresponding 1,4-dienols in a highly stereospecific manner.

(3.23)

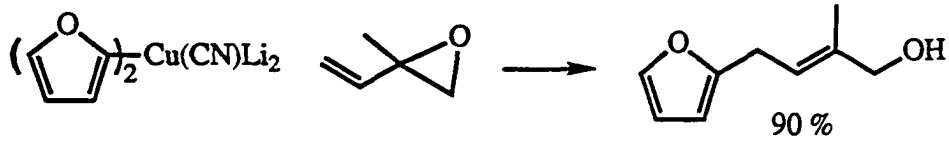
Marshall and co-workers have studied the reactions of optically active acyclic vinylic epoxides with organocuprate reagents (eq 3.24).[47,48] They found that the reaction proceeds predominately in an anti S_N2' fashion to afford the *E*-allylic alcohols.



(3.24)

E-isomer	81 %	84	:	16
Z-isomer	75 %	3	:	97

Campbell and co-workers have investigated the reaction of vinylic epoxides with cyanocuprates (eq 3.25).[49] The *E*-isomer of the allylic alcohol is exclusively produced by the regiospecific S_N2' ring-opening of 3,4-epoxy-3-methyl-1-butene.



(3.25)

In conclusion, there have been a large number of nucleophilic additions to vinylic epoxides reported in the literature. While organomagnesium and -lithium reagents are easy to prepare, their reactions with vinylic epoxides are not regioselective. On the other hand, organocuprates are superior reagents for forming allylic alcohols regio- and stereoselectively from the corresponding vinylic epoxides. The range of functionality accommodated by organolithium, -magnesium, and -copper reagents, however, is severely restricted because of their reactive nature. Additions of organoboranes to vinylic epoxides

have received less attention and seem to offer few advantages except for the range of functionality one might incorporate.

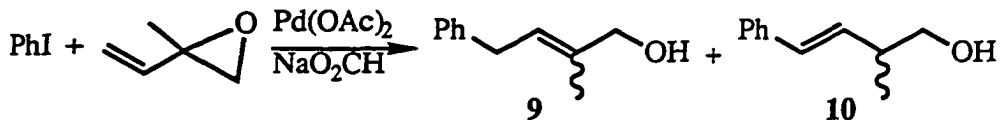
The palladium-catalyzed nucleophilic and organometallic additions of vinylic epoxides have also been well studied. These reactions form allylic alcohols with a high degree of regio- and stereoselectivity. The palladium-catalyzed nucleophilic ring-opening of vinylic epoxides has recently been used in the synthesis of a number of natural compounds.

In this part, the palladium(0)-catalyzed cross-coupling of vinylic epoxides with various organic halides and triflates will be discussed. It will cover the palladium(0)-catalyzed reaction of 3-methyl-3,4-epoxy-1-butene with iodobenzene. The reaction of a wide variety of vinylic epoxides with organic halides and triflates in the presence of a catalytic amount of palladium(0) will also be discussed.

RESULTS AND DISCUSSION

Most of the aryl halides used were commercially available and used without further purification. Vinylic halides and vinylic epoxides were synthesized by Larock group members. The preparation of 1-iodo-1-cyclohexene and cyclohexenyl triflate was carried out using published procedures and has been reported in Part II.

As a first step towards meeting the previously mentioned objectives and establishing this reaction as a new and useful synthetic method, an extensive series of reactions was performed using the reaction of 3,4-epoxy-3-methyl-1-butene and iodobenzene as a model system (eq 3.26). In addition to the desired product **9**, a ring-opened side product **10** was

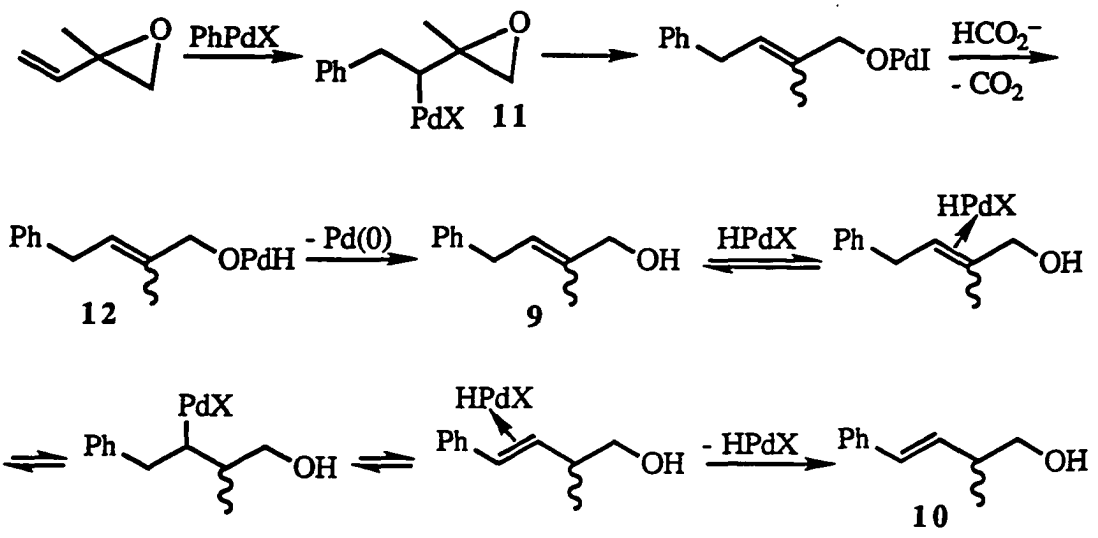


9 **10** (3.26)

also observed during the optimization of reaction conditions.

The following mechanism explains how the desired allylic alcohol **9** and the side product **10** are formed in this reaction (Scheme 4). In the first step of the mechanism, phenylpalladium iodide, formed by the oxidative addition of palladium(0) to iodobenzene, adds to the carbon-carbon double bond of the vinylic epoxide to form σ-alkylpalladium species **11.** The organic ligand becomes attached to the least hindered end of the olefin. This σ-alkylpalladium species then undergoes palladium alkoxide elimination, followed by ligand exchange and carbon dioxide elimination to form alkoxypalladium hydride **12.** The reductive elimination of palladium(0) produces the desired allylic alcohol **9** and regenerates palladium(0). The side product **10** is produced by the addition of palladium hydride to the carbon-carbon double bond of product **9**, followed by elimination of the palladium hydride towards the phenyl group.

Scheme 4



As a model system, the palladium(0)-catalyzed cross-coupling of 3,4-epoxy-3-methyl-1-butene and iodobenzene has been extensively studied and the results are summarized in Table 1. Throughout the course of this project, a great many reactions were run in an attempt to see what effect certain solvents, reagents, temperatures, and ratios of starting materials would have on the yield and stereochemistry of the reaction. Efforts were also made to maximize the yield of the desired compound **9** and to minimize the formation of the side product **10**.

By examining the results in Table 1, the following observations can be made. In terms of the yield of the desired product, the most effective solvent was *N,N*-dimethylacetamide (entries 4, 8, and 10-25). Although acetonitrile gave comparable yields (compare entries 3 and 4, and entries 7 and 8), a much longer reaction time was needed for acetonitrile. Yields with dimethyl sulfoxide (entry 1), tetrahydrofuran (entry 2), *N*-methylacetamide (entry 5), and *N,N*-dimethylformamide (entries 6 and 9), were generally inferior when compared directly although the results varied with temperature. In general,

Table 1. The palladium(0)-catalyzed reaction of 3,4-epoxy-3-methyl-1-butene and PhI

Entry[a]	PhI/Epoxide	Equiv. MO_2CH	Equiv. Base	Equiv. MCl
1	1:3	5 NaO_2CH	3 *i*-Pr_2NEt	2 LiCl
2	1:3	5 NaO_2CH	3 *i*-Pr_2NEt	2 LiCl
3	1:3	5 NaO_2CH	3 *i*-Pr_2NEt	2 LiCl
4	1:3	5 NaO_2CH	3 *i*-Pr_2NEt	2 LiCl
5	1:3	5 NaO_2CH	3 *i*-Pr_2NEt	2 LiCl
6	1:3	5 NaO_2CH	3 *i*-Pr_2NEt	2 LiCl
7	1:3	5 NaO_2CH	3 *i*-Pr_2NEt	1 TBAC
8	1:3	5 NaO_2CH	3 *i*-Pr_2NEt	1 TBAC
9	1:3	5 NaO_2CH	3 *i*-Pr_2NEt	1 TBAC
10	1:3	5 NaO_2CH	0	1 TBAC
11	1:3	5 KO_2CH	3 $C_6H_{11}N$	1 TBAC
12	1:3	5 NaO_2CH	3 C_5H_5N	1 TBAC
13	1:3	5 NaO_2CH	3 Et_3N	1 TBAC
14	1:3	5 NaO_2CH	3 $KHCO_3$	1 TBAC
15	1:3	5 NaO_2CH	3 K_2CO_3	1 TBAC
16	1:3	5 NaO_2CH	3 KOAc	1 TBAC
17	1:5	5 NaO_2CH	3 *i*-Pr_2NEt	1 TBAC
18[b]	1:5	5 NaO_2CH	3 *i*-Pr_2NEt	1 TBAC

[a] All reactions were run using 10 mol % $Pd(OAc)_2$.

[b] TBAC purchased from Chemical Dynamics Company was used.

Solvent	Temp. (°C)	Time (day)	Yield (%) **9+10**	**9/10**	*E/Z* Ratio **9**
DMSO	80	1	13	1:1.5	55:45
THF	80	1	15	1:0	59:41
CH_3CN	80	3	23	1:0	31:69
DMA	80	1	24	4:1	40:60
CH_3NHAc	80	1	28	1.4:1	50:50
DMF	80	1	34	2:1	59:41
CH_3CN	80	3	50	14:1	54:46
DMA	80	1	48	1:0	58:42
DMF	80	1	30	6:1	57:43
DMA	80	1	25	7:1	50:50
DMA	80	1	0	-	-
DMA	80	1	8	3:1	57:43
DMA	80	1	13	1:0	57:43
DMA	80	1	16	1:0	46:54
DMA	80	1	19	5:1	46:54
DMA	80	1	21	3.4:1	55:45
DMA	80	2	60	1:0	61:39
DMA	80	1	46	1:0	59:41

Table 8. (Continued)

Entry[a]	PhI/Epoxide	Equiv. MO_2CH	Equiv. Base	Equiv. MCl
19	1:5	5 NaO_2CH	3 *i*-Pr_2NEt	2 TBAC
20	1:5	3 NaO_2CH	3 *i*-Pr_2NEt	2 TBAC
21	1:5	1 NaO_2CH	3 *i*-Pr_2NEt	2 TBAC
22[c]	1:5	5 NaO_2CH	3 *i*-Pr_2NEt	1 TBAC
23[d]	1:3	5 NaO_2CH	3 *i*-Pr_2NEt	1 TBAC
24[e]	1:3	5 NaO_2CH	3 *i*-Pr_2NEt	1 TBAC
25	1:5	3 LiO_2CH	3 *i*-Pr_2NEt	1 LiCl + 1 TBAC
26	1:5	3 LiO_2CH	3 *i*-Pr_2NEt	1 LiCl + 1 TBAC
27	1:5	3 LiO_2CH	3 *i*-Pr_2NEt	1 LiCl + 1 TBAC

[c] 5 Mol % PPh_3 was added.

[d] 10 Mol % PPh_3 was added.

[e] 30 Mol % PPh_3 was added.

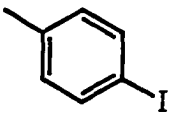
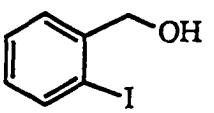
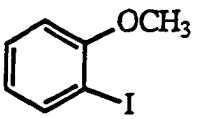
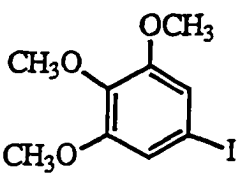
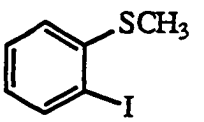
Solvent	Temp. (°C)	Time (day)	Yield (%) **9+10**	**9/10**	*E/Z* Ratio **9**
DMA	80	1	71	1:0	63:37
DMA	80	1	50	1:0	63:37
DMA	80	1	7	1:0	59:41
DMA	80	1	54	1:0	60:40
DMA	80	1	35	1:0	59:41
DMA	80	1	0	-	-
DMA	80	2	22	1:0	52:48
DMF	80	2	26	1:0	41:59
DMF	50	3	5	1:0	55:45

the best base proved to be diisopropylethylamine (entries 1-9 and 17-27). The performance of bases such as piperidine (entry 11), pyridine (entry 12), triethylamine (entry 13), potassium bicarbonate (entry 14), potassium carbonate (entry 15), and potassium acetate (entry 16) ranged from fair to poor. Increasing the amount of epoxide increased the yield of the desired product significantly (compare entries 8 and 17). Tetra-*n*-butylammonium chloride tended to give a higher yield and a better ratio of **9** to **10** than lithium chloride (compare entries 8 and 4). Doubling the amount of tetra-*n*-butylammonium chloride increased the yield significantly (entry 19). The source of tetra-*n*-butylammonium chloride was also important. The tetra-*n*-butylammonium chloride purchased from Chemical Dynamics Company proved less effective for this reaction (entry 18) than that from Lancaster Synthesis Inc. The yield decreased when decreasing the amount of sodium formate (entries 19-21) or adding 5-30 mol % triphenylphosphine (entries 22-24). Finally, the best procedure developed for the reaction of aryl halides and epoxides bearing remote carbon-carbon double bonds was also employed for this model system (entries 25-27).[5] However, the yield dropped significantly.

The stereochemistry of the reaction seemed little affected by solvents, bases, or other conditions. Like the corresponding 2-azetidinone reactions, the model vinylic epoxide reaction always afforded an *E* and *Z* mixture of allylic alcohol.

Once the reaction conditions for this model system were thoroughly investigated, epoxides bearing terminal double bonds as well as internal double bonds were studied. A variety of aryl and vinylic halides were employed in this study to determine the scope and limitations of this palladium(0)-catalyzed process. All of the reactions were run using the best procedure arising from the optimization of the model system, which included 1 equiv. of organic halide or triflate, 5 equiv. vinylic epoxide, 10 mol % of $Pd(OAc)_2$, 1 or 2 equiv. TBAC, 3 equiv. *i*-Pr_2NEt, and 2 ml of DMA at 80 °C for 1 day. The results of this investigation are summarized in Table 2.

Table 2. Palladium(0)-catalyzed reaction of vinylic epoxides with organic halides and triflates

Entry	Epoxide	RX	Equiv. TBAC
1			1
2			2
3			2
4			1
5			2
6			2
7			2
8[a]			2

[a] A 40 % yield of thioanisole was also isolated.

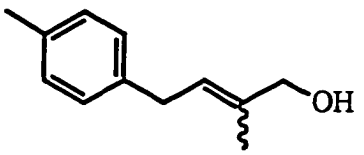
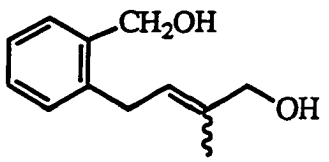
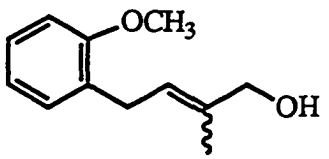
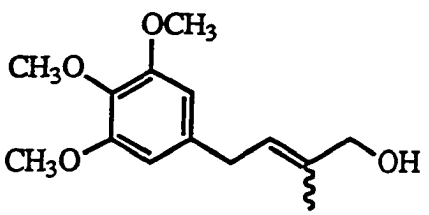
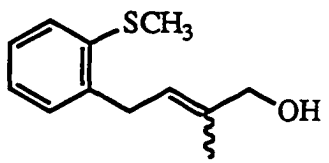
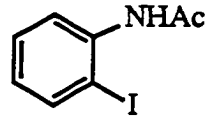
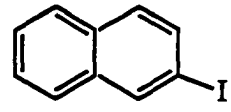
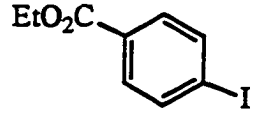
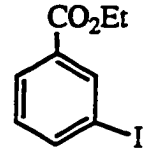
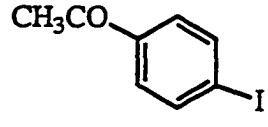
Time (day)	Product	Yield (%)	E/Z Ratio
1		65	57:43
1		77	62:38
1		70	69:31
1		62	57:43
1		75	60:40
1		94	50:50
3		73	61:39
1		56	66:34

Table 2. (Continued)

Entry	Epoxide	RX	Equiv. TBAC
9[b]			2
10[c]			2
11			2
12			1
13[c]			1
14[c]			2
15[c,d]			2
16[c]			2
17[c]			2

[b] A 73 % yield of *N*-phenylacetamide was also isolated.

[c] 1 Equiv. NaO_2CH was used.

[d] DMF was used instead of DMA.

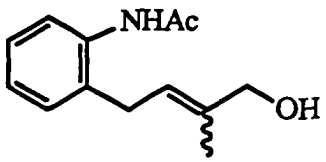
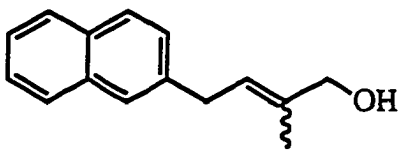
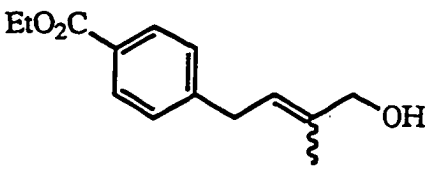
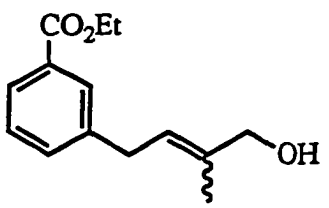
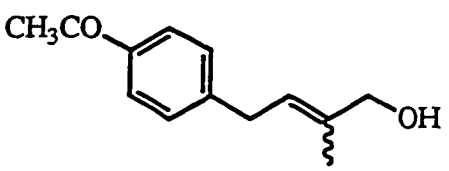
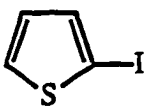
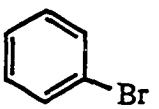
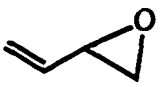
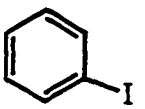
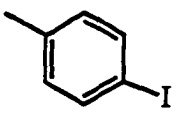
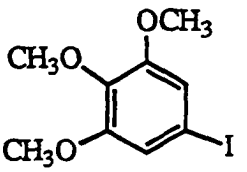
Time (day)	Product	Yield (%)	E/Z Ratio
1		0	-
1		<5	55:45
1		65	59:41
1		37	59:41
1		36	53:47
1		41	63:37
1		43	53:47
1		32	54:46
1		34	66:34

Table 2. (Continued)

Entry	Epoxide	RX	Equiv. TBAC
18			2
19			2
20			1
21			2
22[e]			2
23			2
24			2

[e] A 1:10 ratio of organic halide to vinylic epoxide was used.

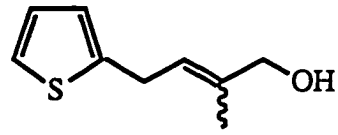
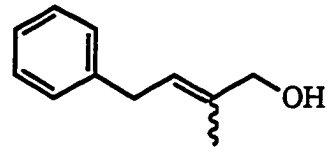
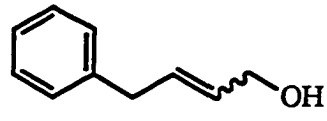
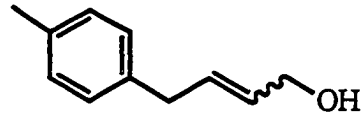
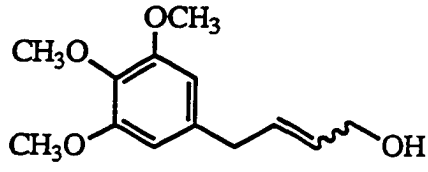
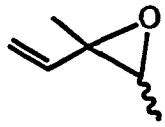
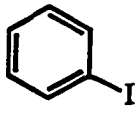
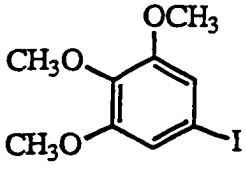
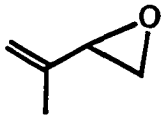
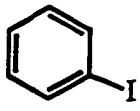
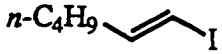
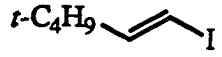
Time (day)	Product	Yield (%)	E/Z Ratio
1		18	61:39
1		5	53:47
1		38	70:30
1		33	63:37
1		30	73:27
1		40	73:27
1		51	73:27

Table 2. (Continued)

Entry	Epoxide	RX	Equiv. TBAC
25			2
26			2
27			2
28			2
29			2
30			2

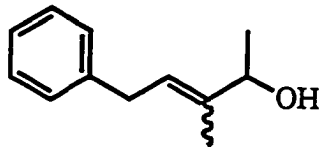
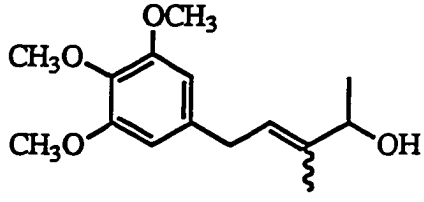
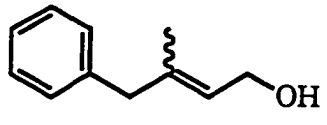
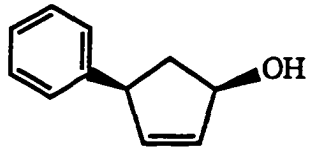
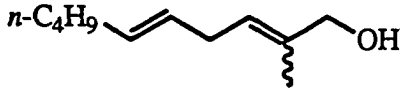
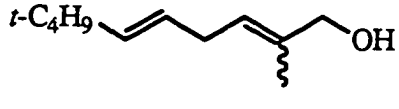
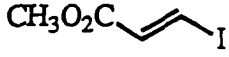
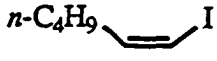
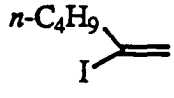
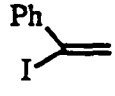
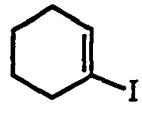
Time (day)	Product	Yield (%)	E/Z Ratio
1		38	50:50
1		72	52:48
1		24	41:59
1		0	-
1		82	50:50
2		85	50:50

Table 2. (Continued)

Entry	Epoxide	RX	Equiv. TBAC
31			1
32			2
33			2
34			2
35			2
36			2
37[f]			2

[f] TBAC was purchased from Chemical Dynamics Company.

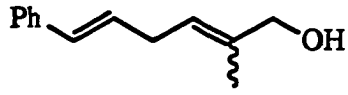
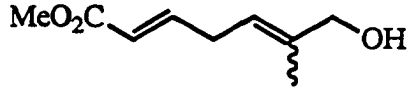
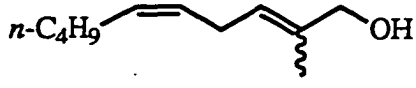
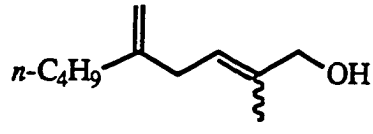
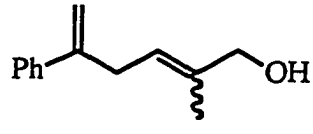
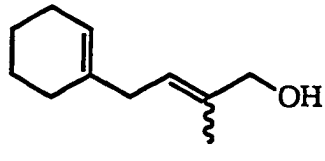
Time (day)	Product	Yield (%)	E/Z Ratio
1		42	57:43
1		58	59:41
1		0	-
2		50	55:45
1		37	64:46
1		31	55:45
2		62	55:45

Table 2. (Continued)

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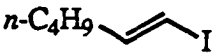
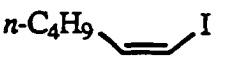
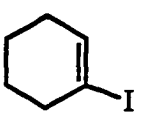
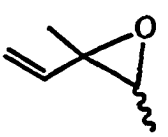
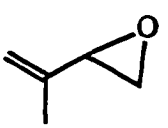
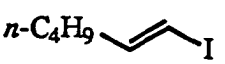
38			2
39			2
40			2
41[g]			1
42[f,g]			1
43			2
44[f]			2

[g] A 1:3 ratio of organic halide to vinylic epoxide was used.

[h] The product was contaminated by an inseparable unknown compound (1:1 product to unknown).

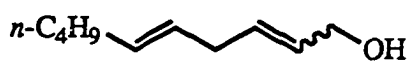
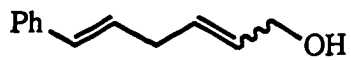
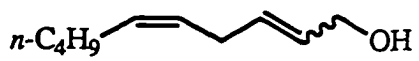
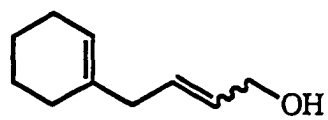
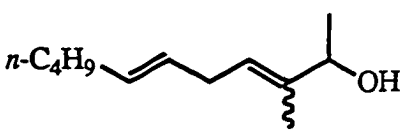
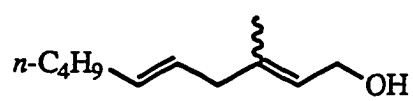
Time (day)	Product	Yield (%)	E/Z Ratio
1		91	72:27
1		77	77:23
1		61	72:28
2		52[h]	70:30
2		51[h]	70:30
1		71	50:50
1		0	0

Table 2. (Continued)

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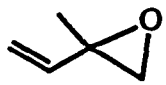
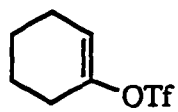
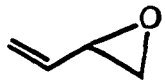
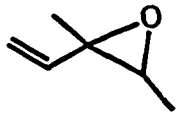
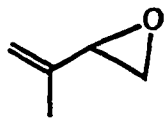
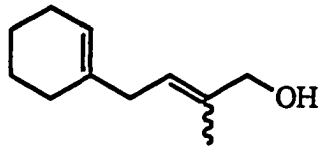
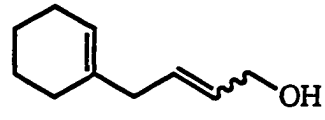
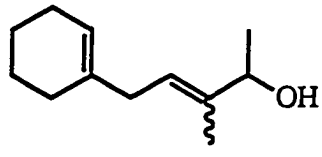
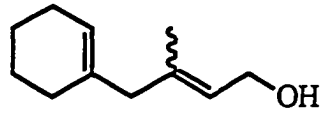
45			1
46			2
47[d]			2
48			2
49[d]			1
50[d]			1

Time (day)	Product	Yield (%)	E/Z Ratio
1		38	66:38
1		34	54:46
1		29	51:49
1		45	78:22
1		41[h]	70:30
1		0	-

The following observations have been made in the course of this investigation. In general, the palladium(0)-catalyzed cross-coupling of vinylic epoxides with aryl and vinylic halides proceeded smoothly and the desired allylic alcohols were isolated in good to excellent yield as mixtures of *E* and *Z* isomers. The stereochemistry of the newly formed carbon-carbon double bond depends on the structure of the vinylic epoxide and not the substituents present in the organic triflate or halide.

As expected 3,4-epoxy-3-methyl-1-butene was the vinylic epoxide which generally gave the highest yield in most reactions and excellent yields of trisubstituted allylic alcohols were generally obtained when reacting it with a variety of aryl halides (entries 1-19), as well as vinylic halides (entries 29-37) and a vinylic triflate (45-47). 3,4-Epoxy-1-butene (entries 20-24) and 3,4-epoxy-3-methyl-1-pentene (entries 25 and 26) tended to produce the desired aryl allylic alcohols in lower yield when using aryl halides. However, excellent yields were obtained when they reacted with vinylic halides (entries 38-43) and a triflate (entries 48 and 49). Other epoxides with more substituted double bonds, such as 3,4-epoxy-2-methyl-1-butene (entries 27 and 50) and 3,4-epoxy-1-cyclopentene (entry 28), seemed less reactive and the yields of the desired allylic alcohols were poor.

The regioselectivity of the organopalladium addition to the carbon-carbon double bonds of the vinylic epoxides is apparently quite high, since none of the products arising from addition of the aryl or vinylic group to the internal carbon of the double bond was observed.

The stereoselectivity of these reactions was virtually identical to that observed in the corresponding alkenyl 2-azetidinone reactions. Disubstituted allylic alcohols were formed with an *E/Z* preference of approximately 4 to 1. Trisubstituted allylic alcohols were also produced as mixtures of *E* and *Z* isomers with the *E* isomer usually in only slight preference.

Aryl halides bearing electron-donating groups were readily accommodated in these reactions and give excellent yields (entries 1-11, 23, 24 and 26). However, aryl halides bearing electron-withdrawing groups tend to give lower yields (entries 12-17) and biaryl product was also isolated in one case (entry 12). One possible explanation for this is that arylpalladium halides bearing electron-withdrawing groups are formed more rapidly than those bearing electron-donating groups, and therefore, can be more easily dimerized before adding to the carbon-carbon double bond. Another possible explanation is that the arylpalladium intermediates can be readily reduced by the excess of formate. In order to decrease the possibility of formate reduction, generally only 1 equiv. sodium formate was employed, although there is no firm evidence that this indeed improved the yields. The presence or absence of electron-donating or -withdrawing groups on the aryl halides has little effect on the stereochemistry of the process. 2-Iodothiophene (entry 18) and bromobenzene (entry 19) were also investigated and seemed unreactive under the current reaction conditions.

A variety of vinylic halides has been investigated and the desired allylic alcohols were generally produced from these reactions in good to excellent yield (entries 29-44). The only exception is methyl (*E*)-3-iodopropenoate in which the vinylic halide bearing an electron-withdrawing group did not react at all (entry 33). (*E*)-1-Iodoalkenes (entries 29-32, 38 and 39) gave better yields in these reactions than (*Z*)-1-iodoalkenes (entries 34 and 40) and both (*E*)- and (*Z*)-1-iodoalkenes tended to give higher yields than 2-iodoalkenes (entries 35 and 36). It is also important to note that the stereochemistry of the vinylic halides is retained in these reactions.

A vinylic triflate was also investigated since triflates are sometimes easier to prepare than the corresponding iodides. Compared with the corresponding iodide reactions, the reaction of cyclohexenyl triflate gave similar results with regard to the stereochemistry, but lower yields were obtained (entries 45-50).

CONCLUSION

The palladium(0)-catalyzed cross-coupling of vinylic epoxides with organic halides and triflates has been investigated. The arylation of vinylic epoxides produces the corresponding aryl allylic alcohols as mixtures of *E* and *Z* isomers in good to excellent yields. The regioselectivity of the reactions is high. The stereoselectivity, however, depends on the structure of the vinylic epoxide. The presence or absence of substituents on the aryl moiety seems to have little effect on the stereochemistry of the reaction, although electron-withdrawing groups on the aryl halide tend to decrease the yield. The reaction of vinylic halides with vinylic epoxides also produces allylic alcohols in good to excellent yield and gives results similar to the reactions of aryl halides with regard to the stereoselectivity. The stereochemistry of the vinylic halide is retained in this reaction. The results of a preliminary investigation of the reaction of one vinylic triflate with vinylic epoxides are similar to those observed in the reactions of vinylic halides, though the yields are somewhat lower.

In conclusion, the palladium(0)-catalyzed cross-coupling of vinylic epoxides with organic halides and triflates provides a convenient new synthetic route to aryl-substituted allylic alcohols and dienols.

EXPERIMENTAL SECTION

Equipment

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75.5 MHz for carbon nuclei) or a Varian VXR-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75.5 MHz for carbon nuclei). All infrared spectra were recorded on an IBM IR / 98 FT-IR or a Bio-Rad FTS-7. Exact mass spectral analyses were obtained on a Kratos high resolution mass spectrometer. Gas chromatographic analyses were performed on 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 a HP-1 megabore column (HP 5890).

Reagents

Palladium acetate was donated by Johnson Matthey, Inc. Lithium formate, sodium formate, and lithium chloride were purchased from Fisher Scientific Company and oven-dried before use. Tetra-*n*-butylammonium chloride was obtained from Lancaster Synthesis Inc. unless otherwise noted. *N,N*-Dimethylformamide, *N,N*-dimethylacetamide, and diisopropylethylamine were purchased from Fisher or Aldrich and stored over molecular sieves. Triethylamine (Kodak) was distilled from calcium hydride and stored over molecular sieves. Iodobenzene, bromobenzene, and 4-iodotoluene were purchased from Eastman Kodak Company. 2-Iodobenzyl alcohol, 2-iodoanisole, 2-iodothioanisole, and 2-iodothiophene were obtained from Aldrich Chemical Company, Inc. Ethyl 3-iodobenzoate and ethyl 4-iodobenzoate were purchased from Lancaster Synthesis Inc. 4-Iodoacetophenone was obtained from Pfaltz & Bauer, Inc. and used without further purification. (*E*)-1-Iodo-1-hexene, (*E*)-1-iodo-3,3-dimethyl-1-butene, (*E*)-1-iodo-2-phenylethylene, (*Z*)-1-

iodo-1-hexene, 2-iodo-1-hexene, 5-iodo-1,2,3-trimethoxybenzene, methyl (*E*)-3-iodopropenoate, *N*-acetyl-2-iodoaniline, 3,4-epoxy-3-methyl-1-butene, 3,4-epoxy-1-butene, 3,4-epoxy-3-methyl-1-pentene, 3,4-epoxy-1-cyclopentene, and 2-methyl-3,4-epoxy-1-butene were generously supplied by Larock group members. The preparation of 1-iodostyrene, 1-iodo-1-cyclohexene and cyclohexenyl triflate was carried out according to literature procedures as reported in Part II.

General procedure for the palladium-promoted cross-coupling of vinylic epoxides with organic halides and triflates

The following procedure used for the preparation of (*E*)- and (*Z*)-2-methyl-4-phenyl-2-buten-1-ol is representative of that used for other compounds. To an oven-dried 25 ml round-bottom flask containing a magnetic stirrer were added the following reagents: palladium acetate (11.3 mg, 0.05 mmol), sodium formate (170 mg, 2.5 mmol), tetra-*n*-butylammonium chloride (277 mg, 1.0 mmol), diisopropylethylamine (0.26 ml, 1.5 mmol), iodobenzene (102 mg, 0.5 mmol), 3,4-epoxy-3-methyl-1-butene (210 mg, 2.5 mmol), and *N*,*N*-dimethylacetamide (2.0 ml). The solution was stirred at 80 °C for 1 day. Ether (15 ml) was then added to the reaction mixture. The ether layer was washed with saturated aqueous ammonium chloride (15 ml x 2), and the combined aqueous layers were back extracted with ether (15 ml x 2). The combined ether fractions were dried over anhydrous magnesium sulfate. After removal of the solvents, the residue was purified by flash column chromatography on silica gel using a 10:1 mixture of hexane to ethyl acetate as eluents. (*E*)- and (*Z*)-2-Methyl-4-phenyl-2-buten-1-ol were obtained in 71 % yield as a colorless liquid.

(*E*)- and (*Z*)-2-Methyl-4-phenyl-2-buten-1-ol (Table 1, entry 19)

Obtained in 71 % isolated yield (63:37 *E/Z*) from the reaction of iodobenzene and 3,4-epoxy-3-methyl-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.58 (br s, 1 H, OH), 1.78 (s, 3 H, CH_3), 3.39 (d, 2 H, J = 7.2 Hz, CH_2Ph), 4.09 (s, 2 H, $C\underline{H}_2OH$), 5.61 (t, 1 H, J = 7.2 Hz, CH=), 7.15-7.40 (m, 5 H, phenyl).

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.84 (s, 3 H, CH_3), 3.41 (d, 2 H, J = 7.8 Hz, CH_2Ph), 4.23 (s, 2 H, $C\underline{H}_2OH$), 5.36 (t, 1 H, J = 7.2 Hz, CH=). The spectral data were identical to those reported for this compound by Ilkka.[1]

(*E*)- and (*Z*)-2-Methyl-4-(4-methylphenyl)-2-buten-1-ol (Table 2, entry 2)

Obtained in 77 % isolated yield (62:38 *E/Z*) from the reaction of 4-iodotoluene and 3,4-epoxy-3-methyl-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.74 (s, 1 H, OH), 1.77 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3Ar), 3.35 (d, 2 H, J = 7.2 Hz, CH_2Ar), 4.02 (s, 2 H, $C\underline{H}_2OH$), 5.59 (t, 1 H, J = 7.2 Hz, CH=), 7.08 (m, 4 H, aryl); ^{13}C NMR ($CDCl_3$) δ 21.04, 33.54, 68.91, 125.09, 127.19, 128.13, 128.25, 129.20, 129.25 (one carbon was missing).

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.83 (s, 3 H, CH_3), 3.37 (d, 2 H, J = 6.6 Hz, CH_2Ar), 4.22 (s, 2 H, $C\underline{H}_2OH$), 5.49 (t, 1 H, J = 6.6 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 21.41, 33.43, 61.70, 128.16.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3362, 2922, 2860, 1680, 1609, 1514, 1450, 1379, 1273, 1020, 804 cm^{-1}; HRMS: calculated for $C_{12}H_{16}O$ m/z 176.12012, found 176.11975.

(*E*)- and (*Z*)-4-(2-Hydroxymethylphenyl)-2-methyl-2-buten-1-ol (Table 2, entry 3)

Obtained in 70 % isolated yield (69:31 *E*/*Z*) from the reaction of 2-iodobenzyl alcohol and 3,4-epoxy-3-methyl-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^1H NMR ($CDCl_3$) δ 1.74 (s, 3 H, CH_3), 2.60 (br s, 2 H, OH's), 3.41 (d, 2 H, J = 7.2 Hz, CH_2Ar), 3.94 (s, 2 H, =CC$\underline{H_2}$OH), 4.61 (s, 2 H, ArC$\underline{H_2}$OH), 5.48 (t, 1 H, J = 7.2 Hz, CH=), 7.20-7.40 (m, 4 H, aryl); ^{13}C NMR ($CDCl_3$) δ 13.81, 30.94, 62.54, 68.07, 124.09, 126.32, 127.82, 128.24, 129.30, 135.40, 138.48, 138.91.

The *Z*-isomer: ^1H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.78 (s, 3 H, CH_3), 3.47 (d, 2 H, J = 7.2 Hz, CH_2Ar), 4.20 (s, 2 H, =CC$\underline{H_2}$OH), 5.36 (t, 1 H, J = 7.2 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 21.55, 31.14, 61.02, 63.04, 126.29, 126.51, 128.11, 128.94, 129.57, 134.99, 138.25, 139.47.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3353, 3332, 2965, 2916, 2871, 1602, 1488, 1451, 1376, 1210, 1100, 1037, 1003, 924, 751 cm^{-1}; HRMS: calculated for $C_{12}H_{16}O_2$ m/z 174.10447, found 174.10415.

(*E*)- and (*Z*)-2-Methyl-4-(2-methoxyphenyl)-2-buten-1-ol (Table 2, entry 5)

Obtained in 75 % isolated yield (60:40 *E*/*Z*) from the reaction of 2-iodoanisole and 3,4-epoxy-3-methyl-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3 H, CH_3C), 2.10 (br s, 1 H, OH), 3.36 (d, 2 H, J = 7.2 Hz, CH_2Ar), 3.78 (s, 3 H, OCH_3), 3.98 (s, 2 H, $C\underline{H_2}OH$), 5.59 (t, 1 H, J = 7.2 Hz, CH=), 6.81-6.91 and 7.10-7.19 (2 m, 4 H, aryl); ^{13}C NMR ($CDCl_3$) δ 13.74, 28.25, 55.33, 69.03, 110.28, 120.84, 124.37, 126.57, 127.19, 129.44, 129.70, 157.00.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.80 (s, 3 H, CH_3C), 3.37 (d, 2 H, J = 7.5 Hz, CH_2Ar), 4.19 (s, 2 H, $C\underline{H_2}OH$), 5.41 (t, 1 H, J = 7.5 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 21.78, 28.67, 55.43, 61.77, 110.58, 120.49, 127.37.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3396, 2937, 2837, 1601, 1587, 1493, 1464, 1379, 1323, 1290, 1244, 1177, 1111, 1051, 1030, 910, 752 cm^{-1}; HRMS: calculated for $C_{12}H_{16}O_2$ m/z 192.11503, found 192.11489.

(*E*)- and (*Z*)-2-Methyl-4-(3,4,5-trimethoxyphenyl)-2-buten-1-ol (Table 2, entry 6)

Obtained in 94 % isolated yield (50:50 *E*/*Z*) from the reaction of 5-iodo-1,2,3-trimethoxybenzene and 3,4-epoxy-3-methyl-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.68 (br s, 1 H, OH), 1.78 (s, 3 H, CCH_3), 3.34 (d, 2 H, J = 7.2 Hz, CH_2Ar), 3.81 (s, 3 H, OCH_3), 3.84 (s, 6 H, OCH_3's), 4.06 (s, 2 H, $C\underline{H_2}OH$), 5.60 (t, 1 H, J = 7.2 Hz, CH=), 6.40 (s, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 13.60, 34.01, 55.83, 60.59, 68.12, 105.04, 123.91, 135.41, 135.65, 136.71, 152.93.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.86 (s, 3 H, CCH_3), 3.36 (d, 2 H, J = 7.2 Hz, CH_2Ar), 4.24 (s, 2 H, $C\underline{H_2}OH$), 5.29 (t, 1 H, J = 7.2

Hz, HC=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 21.15, 33.84, 61.07, 105.01, 126.08, 135.88, 136.67, 152.91.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3481, 3421, 2959, 2937, 2836, 1589, 1506, 1457, 1419, 1330, 1237, 1182, 1126, 1007, 948, 850, 822, 779, 669 cm^{-1}; HRMS: calculated for $C_{14}H_{20}O_4$ m/z 252.13616, found 252.13642.

(*E*)- and (*Z*)- 2-Methyl-4-(2-thioanisyl)-2-buten-1-ol (Table 2, entry 8)

Obtained in 56 % isolated yield (66:34 *E*/*Z*) from the reaction of 2-iodothioanisole and 3,4-epoxy-3-methyl-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^1H NMR ($CDCl_3$) δ 1.54 (br s, 1 H, OH), 1.79 (s, 3 H, CCH_3), 2.46 (s, 3 H, SCH_3), 3.46 (d, 2 H, J = 7.2 Hz, CH_2Ar), 4.04 (s, 2 H, $C\underline{H_2}OH$), 5.57 (t, 1 H, J = 7.2 Hz, CH=), 7.06-7.20 (m, 4 H, aryl); ^{13}C NMR ($CDCl_3$) δ 13.95, 15.78, 31.91, 68.80, 123.45, 124.99, 125.38, 126.84, 128.80, 136.32, 137.29, 138.67.

The *Z*-isomer: ^1H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.84 (s, 3 H, CCH_3), 4.26 (s, 2 H, $C\underline{H_2}OH$), 5.41 (t, 1 H, J = 7.2 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 21.45, 61.70, 125.21, 125.58, 128.86.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3372, 3347, 3055, 3003, 2970, 2918, 2858, 1586, 1466, 1437, 1064, 999, 953, 920, 870, 746 cm^{-1}; HRMS: calculated for $C_{12}H_{16}OS$ m/z 208.09204, found 208.09219.

(*E*)- and (*Z*)-2-Methyl-4-(2-naphthyl)-2-buten-1-ol (Table 2, entry 11)

Obtained in 65 % isolated yield (59:41 *E/Z*) from the reaction of 2-iodonaphthalene and 3,4-epoxy-3-methyl-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3 H, CH_3), 1.85 (br s, 1 H, OH), 3.52 (d, 2 H, J = 7.2 Hz, $ArCH_2$), 4.02 (s, 2 H, CH_2OH), 5.65 (t, 1 H, J = 7.2 Hz, HC=), 7.24-7.30 (m, 1 H, H on C3 of naphthyl), 7.35-7.44 (m, 2 H, H's on C6 and C7 of naphthyl), 7.59 (d, 1 H, J = 5.7 Hz, H on C1 of naphthyl), 7.72-7.77 (3 s, 3 H, H's on C4, C5, and C8 of naphthyl); ^{13}C NMR ($CDCl_3$) δ 13.83, 33.91, 68.56, 124.27, 125.18, 125.95, 126.19, 127.23, 127.41, 127.58, 127.99, 131.99, 133.61, 135.89, 138.44.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.84 (s, 3 H, CH_3), 4.23 (s, 2 H, CH_2OH), 5.54 (t, 1 H, J = 7.2 Hz, HC=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 21.36, 34.03, 61.47, 125.23, 125.93, 126.15, 126.45, 127.14, 127.40, 128.03, 135.53.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3345, 3051, 2968, 2914, 2868, 1632, 1600, 1057, 1448, 1435, 1376, 2363, 1213, 1124, 1084, 1017, 1000, 934, 889, 853, 815, 745 cm^{-1}; HRMS: calculated for $C_{15}H_{16}O$ m/z 212.12012, found 212.12017.

(*E*)- and (*Z*)-4-(4-Ethoxycarbonylphenyl)-2-methyl-2-buten-1-ol (Table 2, entry 14)

Obtained in 41% isolated yield (63:37 *E/Z*) from the reaction of ethyl 4-iodobenzoate and 3,4-epoxy-3-methyl-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3 H, *J* = 7.2 Hz, $CH_2\underline{CH_3}$), 1.60 (br s, 1 H, OH), 1.77 (s, 3 H, CCH_3), 3.44 (d, 2 H, *J* = 6.6 Hz, CH_2Ar), 4.06 (s, 2 H, $\underline{CH_2}OH$), 4.36 (q, 2 H, *J* = 7.2 Hz, $\underline{CH_2}CH_3$), 5.60 (t, 1 H, *J* = 6.6 Hz, HC=), 7.24 (d, 2 H, *J* = 8.1 Hz, H's on C2 and C6 of aryl), 7.96 (d, 2 H, *J* = 8.1 Hz, H's on C3 and C5 of aryl); ^{13}C NMR ($CDCl_3$) δ 13.86, 14.35, 33.93, 60.92, 68.49, 123.32, 128.32, 129.78, 129.87, 136.53, 146.39, 166.67.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.86 (s, 3 H, CCH_3), , 3.47 (d, 2 H, *J* = 6.9 Hz, $ArCH_2$), 4.24 (s, 2 H, $\underline{CH_2}OH$), 5.47 (t, 1 H, *J* = 6.9 Hz, HC=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 21.38, 33.84, 60.85, 61.54, 125.61, 128.27, 129.81, 146.35, 166.64.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3414, 3032, 2973, 2924, 2869, 2729, 1808, 1716, 1699, 1608, 1574, 1506, 1463, 1415, 1366, 1309, 1275, 1176, 1106, 1020, 927, 873, 850, 759, 703 cm^{-1}; HRMS: calculated for $C_{14}H_{18}O_3$ m/z 234.12559, found 234.12525.

<u>(*E*)- and (*Z*)-4-(3-Ethoxycarbonylphenyl)-2-methyl-2-buten-1-ol</u> (Table 2, entry 16)

Obtained in 32 % isolated yield (54:46 *E/Z*) from the reaction of ethyl 3-iodobenzoate and 3,4-epoxy-3-methyl-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3 H, *J* = 7.2 Hz, $CH_2\underline{CH_3}$), 1.63 (br s, 1 H, OH), 1.78 (s, 3 H, CCH_3), , 3.45 (d, 2 H, *J* = 6.6 Hz, CH_2Ar), 4.06 (s, 2 H, $\underline{CH_2}OH$), 4.37 (q, 2 H, *J* = 7.2 Hz, $\underline{CH_2}CH_3$), 5.61 (t, 1 H, *J* = 6.6 Hz, HC=), 7.36 (m, 2 H, H's on C5 and C6 of aryl), 7.85 (m, 2 H, H's on C2 and C4 of aryl); ^{13}C NMR ($CDCl_3$) δ 13.90,

14.38, 33.72, 61.00, 68.63, 123.87, 127.30, 128.53, 129.47, 130.70, 132.92, 136.33, 141.33, 166.81.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.86 (s, 3 H, CCH_3), , 3.47 (d, 2 H, J = 6.6 Hz, CH_2Ar), 4.25 (s, 2 H, $C\underline{H_2}OH$), 5.49 (t, 1 H, J = 6.6 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 21.40, 33.64, 61.64, 126.13, 127.23, 128.48, 129.40, 130.66, 132.86, 135.91, 141.30, 166.78.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3416, 2978, 2931, 2870, 1711, 1649, 1604, 1586, 1460, 1390, 1367, 1276, 1193, 1104, 1021, 943, 904, 864, 816, 749, 694 cm^{-1}; HRMS: calculated for $C_{14}H_{18}O_3$ m/z 234.12559, found 234.12518.

(*E*)- and (*Z*)-4-(4-Acetylphenyl)-2-methyl-2-buten-1-ol (Table 2, entry 17)

Obtained in 34 % isolated yield (66:34 *E*/*Z*) from the reaction of 4-iodoacetophenone and 3,4-epoxy-3-methyl-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 1 H, OH), 1.77 (s, 3 H, CH_3C), 2.57 (s, 3 H, CH_3CO), 3.45 (d, 2 H, J = 7.2 Hz, CH_2Ar), 4.08 (s, 2 H, $C\underline{H_2}OH$), 5.56 (t, 1 H, J = 7.2 Hz, CH=), 7.28 (d, 2 H, J = 8.1 Hz, H's on C2 and C6 of aryl), 7.88 (d, 2 H, J = 8.1 Hz, H's on C3 and C5 of aryl); ^{13}C NMR ($CDCl_3$) δ 13.90, 26.01, 33.94, 68.53, 123.20, 125.55, 128.58, 128.68, 136.26, 146.81 (the carbonyl peak was not seen).

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.86 (s, 3 H, CCH_3), , 3.48 (d, 2 H, J = 7.2 Hz, CH_2Ar), 4.24 (s, 2 H, $C\underline{H_2}OH$), 5.42 (t, 1 H, J = 7.2 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen except δ 21.42, 33.87, 61.62, 128.53, 128.71, 135.19, 146.76.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3418, 2924, 2856, 1680, 1607, 1570, 1414, 1360, 1271, 1182, 1016, 959, 822 cm^{-1}; HRMS: calculated for $C_{13}H_{16}O_2$ m/z 204.11503, found 204.11472.

(*E*)- and (*Z*)-2-Methyl-4-(2-thienyl)-2-buten-1-ol (Table 2, entry 18)

Obtained in 18 % isolated yield (61:39 *E/Z*) from the reaction of 2-iodothiophene and 3,4-epoxy-3-methyl-1-butene and was inseparable from the side product 2-methyl-3-butene-1,2-diol carbonate. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^1H NMR ($CDCl_3$) δ 1.78 (s, 3 H, CH_3), 3.58 (d, 2 H, *J* = 6.9 Hz, CH_2), 4.04 (s, 2 H, $C\underline{H_2}OH$), 5.66 (t, 1 H, *J* = 6.9 Hz, CH=), 6.79 (m, 1 H, H on C3 of thiophene), 6.92 (dd, 1 H, H on C4 of thiophene), 7.11 (m, 1 H, H on C5 of thiophene), the hydroxy proton peak was buried under the methyl proton peak.

The *Z*-isomer: ^1H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.86 (s, 3 H, CH_3), 3.60 (d, 2 H, *J* = 7.2 Hz, CH_2), 4.22 (s, 2 H, $C\underline{H_2}OH$), 5.54 (t, 1 H, *J* = 6.9 Hz, CH=).

(*E*)- and (*Z*)-4-Phenyl-2-buten-1-ol (Table 2, entry 20)

Obtained in 38 % isolated yield (70:30 *E/Z*) from the reaction of iodobenzene and 3,4-epoxy-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^1H NMR ($CDCl_3$) δ 1.60 (br s, 1 H, OH), 3.39 (d, 2 H, *J* = 6.6 Hz, CH_2Ph), 4.10 (d, 2 H, *J* = 4.8 Hz, $C\underline{H_2}OH$), 5.72 (dt, 1 H, *J* = 15.3 Hz, *J* = 4.8 Hz,

$HOCH_2C\underline{H}$=), 5.85 (dt, 1 H, 1 H, J = 15.3 Hz, J = 6.6 Hz, $PhCH_2C\underline{H}$=), 7.15-7.30 (m, 5 H, phenyl).

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 3.34 (d, 2 H, J = 5.4 Hz, CH_2Ph), 4.31 (d, 2 H, J = 4.8 Hz, $C\underline{H}_2OH$).

The spectral data were identical to those reported for this compound by Ilkka.[1]

(*E*)- and (*Z*)-4-(4-Methylphenyl)-2-buten-1-ol (Table 2, entry 23)

Obtained in 40 % isolated yield (73:27 *E*/*Z*) from the reaction of 4-iodotoluene and 3,4-epoxy-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.75 (br s, 1 H, OH), 2.31 (s, 3 H, CH_3Ar), 3.33 (d, 2 H, J = 6.6 Hz, CH_2Ar), 4.10 (d, 2 H, J = 6.0 Hz, $C\underline{H}_2OH$), 5.70 and 5.80 (2 m, 2 H, HC=CH), 7.06 and 7.10 (2 d, 4 H, J = 8.1 Hz, aryl); ^{13}C NMR ($CDCl_3$) δ 21.04, 38.25, 63.63, 128.20, 128.47, 129.20, 130.04, 132.04, 135.69.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 3.39 (d, 2 H, J = 5.1 Hz, CH_2Ar), 4.29 (d, 2 H, J = 4.8 Hz, $C\underline{H}_2OH$); ^{13}C NMR same as the *E*-isomer or not seen, except δ 33.20, 58.60, 129.27, 130.23.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3375, 3020, 2924, 1690, 1610, 1514, 1433, 1379, 1273, 1180, 1042, 974, 841 cm^{-1}; HRMS: calculated for $C_{11}H_{14}O$ m/z 162.10447, found 162.10438.

(*E*)- and (*Z*)-4-(3,4,5-Trimethoxyphenyl)-2-buten-1-ol (Table 2, entry 24)

Obtained in 51 % isolated yield (73:27 *E*/*Z*) from the reaction of 5-iodo-1,2,3-trimethoxybenzene and 3,4-epoxy-1-butene. The *E*- to *Z*-isomer ratio was determined by

integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.62 (br s, 1 H, OH), 3.32 (d, 2 H, J = 6.3 Hz, CH_2Ar), 3.82 (s, 3 H, CH_3O), 3.84 (s, 6 H, 2 CH_3O), 4.14 (d, 2 H, J = 5.7 Hz, $C\underline{H}_2OH$), 5.74 (m, 1 H, =$C\underline{H}CH_2OH$), 5.82 (m, 1 H, $ArCH_2C\underline{H}$=), 6.40 (s, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 39.04, 56.10, 58.53, 63.46, 105.47, 129.50, 130.37, 131.31, 135.79, 153.21.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 3.39 (d, 2 H, J = 6.0 Hz, CH_2Ar), 4.31 (d, 2 H, J = 5.1 Hz, $C\underline{H}_2OH$); ^{13}C NMR same as the *E*-isomer or not seen, except δ 33.87, 60.87, 130.96, 153.26.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3477, 2939, 2839, 1672, 1591, 1508, 1462, 1421, 1335, 1240, 1184, 1126, 1009, 972, 827, 781, 735, 671 cm^{-1}; HRMS: calculated for $C_{13}H_{18}O_4$ m/z 238.12051, found 238.12012.

(*E*)- and (*Z*)-3-Methyl-5-phenyl-3-penten-2-ol (Table 2, entry 25)

Obtained in 38 % isolated yield (50:50 *E*/*Z*) from the reaction of iodobenzene and 3,4-epoxy-3-methyl-1-pentene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.28 (d, 3 H, J = 6.3 Hz, $CHC\underline{H}_3$), 1.62 (br s, 1 H, OH), 1.74 (s, 3 H, CCH_3), 3.41 (d, 2 H, J = 7.2 Hz, CH_2Ar), 4.24 (q, 1 H, J = 6.3 Hz, $C\underline{H}OH$), 5.60 (t, 1 H, J = 7.2 Hz, CH=), 7.15-7.30 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 11.56, 21.52, 33.69, 73.11, 123.42, 125.78, 128.21, 128.33, 139.45, 143.05.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.29 (d, 3 H, J = 6.6 Hz, $CHC\underline{H}_3$), 1.76 (s, 3 H, CCH_3), 3.37 (d, 2 H, J = 7.2 Hz, CH_2Ar), 4.90 (q, 1 H, J = 6.6 Hz, $C\underline{H}OH$), 5.39 (t, 1 H, J = 7.2 Hz, CH=); ^{13}C NMR same as the *E*-isomer

or not seen, except δ 17.10, 21.19, 33.25, 65.53, 124.81, 125.83, 128.14, 128.38, 138.72, 140.95.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3325, 3084, 3061, 2916, 1668, 1601, 1495, 1452, 1377, 1242, 1155, 1072, 999, 733, 698 cm^{-1}; HRMS: calculated for $C_{12}H_{16}O$ m/z 176.12012, found 176.11980.

(*E*)- and (*Z*)-3-Methyl-5-(3,4,5-trimethoxyphenyl)-3-penten-2-ol (Table 2, entry 26)

Obtained in 72 % isolated yield (52:48 *E/Z*) from the reaction of 5-iodo-1,2,3-trimethoxybenzene and 3,4-epoxy-3-methyl-1-pentene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *Z*-isomer: ^1H NMR ($CDCl_3$) δ 1.31 (d, 3 H, J = 6.6 Hz, $CHC\underline{H}_3$), 1.42 (br s, 1 H, OH), 1.78 (d, 3 H, J = 0.9 Hz, CCH_3), 3.32 (d, 2 H, J = 6.9 Hz, CH_2Ar), 3.82 (s, 3 H, CH_3O on C4 of aryl), 3.85 (s, 6 H, CH_3O's on C3 and C5 of aryl), 4.90 (q, 1 H, J = 6.6 Hz, $C\underline{H}OH$), 5.39 (t, 1 H, J = 6.9 Hz, CH=), 6.39 (s, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 17.29, 21.48, 33.70, 56.12, 60.90, 65.73, 105.18, 123.38, 124.87, 136.83, 139.07, 153.23.

The *E*-isomer: ^1H NMR ($CDCl_3$) same as the *Z*-isomer or not seen, except δ 1.30 (d, 3 H, J = 6.6 Hz, $CHC\underline{H}_3$), 3.37 (d, 2 H, J = 6.9 Hz, CH_2Ar), 4.27 (q, 1 H, J = 6.6 Hz, $C\underline{H}OH$), 5.60 (t, 1 H, J = 6.9 Hz, CH=); ^{13}C NMR same as the *Z*-isomer or not seen, except δ 11.81, 21.82, 34.13, 56.19, 73.21.

The following spectral data were taken from a mixture of the *Z*- and *E*-isomers: IR (neat) 3437, 2970, 2837, 1589, 1506, 1456, 1420, 1331, 1238, 1182, 1126, 1034, 1009, 893, 824, 779 cm^{-1}; HRMS: calculated for $C_{15}H_{22}O_4$ m/z 266.15181, found 266.15133.

(*E*)- and (*Z*)-3-Methyl-4-phenyl-2-buten-1-ol (Table 2, entry 27)

Obtained in 24 % isolated yield (41:59 *E/Z*) from the reaction of iodobenzene and 3,4-epoxy-2-methyl-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.36 (br s, 1 H, OH), 1.62 (s, 3 H, CH_3), 3.32 (s, 2 H, CH_2Ar), 4.19 (d, 2 H, *J* = 6.9 Hz, $C\underline{H}_2OH$), 5.49 (t, 1 H, *J* = 6.9 Hz, CH=), 7.14-7.31 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 16.18, 46.06, 59.49, 125.27, 126.23, 128.36, 128.98, 139.02, 139.43.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.68 (s, 3 H, CH_3), 3.42 (s, 2 H, CH_2Ar), 4.28 (d, 2 H, *J* = 6.9 Hz, $C\underline{H}_2OH$), 5.59 (t, 1 H, *J* = 6.9 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 23.51, 38.03, 59.38, 125.33, 126.17, 128.50, 128.55, 138.73, 139.40.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3325, 3084, 3061, 2916, 1668, 1601, 1495, 1452, 1377, 1242, 1155, 1072, 999, 733, 698 cm^{-1}; HRMS: calculated for $C_{11}H_{14}O$ m/z 162.10447, found 162.10413.

(*E,E*)- and (*Z,E*)-2-Methyl-2,5-decadien-1-ol (Table 2, entry 29)

Obtained in 82 % isolated yield (50:50 *E,E/Z,E)* from the reaction of *E*-1-iodo-1-hexene and 3,4-epoxy-3-methyl-1-butene. The *E,E*- to *Z,E*- isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *Z,E*-isomer: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, *J* = 6.9 Hz, $CH_2C\underline{H}_3$), 1.31 (m, 4 H, $C\underline{H}_2C\underline{H}_2CH_3$), 1.49 (s, 1 H, OH), 1.81 (s, 3 H, CCH_3), 1.98 (q, 2 H, *J* = 6.6 Hz, CH_2Pr), 2.74 (t, 2 H, *J* = 5.9 Hz, $=CCH_2C=$), 4.13 (s, 2 H, $C\underline{H}_2OH$), 5.38 (m, 3 H, vinyl); ^{13}C NMR ($CDCl_3$) δ 13.99, 21.39, 22.27, 30.89, 31.71, 32.25, 61.65, 126.59, 128.37, 131.09, 137.89.

The *E,E*-isomer: ^{1}H NMR ($CDCl_3$) same as the *Z,E*-isomer or not seen, except δ 1.67 (s, 3 H, CCH_3), 4.02 (s, 2 H, $C\underline{H}_2OH$); ^{13}C NMR same as the *Z,E*-isomer or not seen, except δ 14.08, 30.89, 31.74, 32.78, 68.97, 121.13, 124.43, 127.79, 135.00.

The following spectral data were taken from a mixture of the *Z,E*- and *E,E*-isomers: IR (neat) 3331, 2959, 2926, 1801, 1456, 1379, 1248, 1178, 1096, 1063, 1007, 968, 773 cm^{-1}; HRMS: calculated for $C_{11}H_{20}O$ m/z 168.15142, found 168.15123.

(*E,E*)- and (*Z,E*)-2,7,7-Trimethyl-2,5-octadien-1-ol (Table 2, entry 30)

Obtained in 85 % isolated yield (50:50 *E,E*/*Z,E*) from the reaction of *E*-1-iodo-4,4-dimethyl-1-butene and 3,4-epoxy-3-methyl-1-butene. The *E,E*- to *Z,E*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *Z,E*-isomer: ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 9 H, CH_3's), 1.29 (br s, 1 H, OH), 1.82 (s, 3 H, CH_3), 2.75 (t, 2 H, *J* = 6.3 Hz, $C\underline{H}_2CH$=), 4.13 (s, 2 H, $C\underline{H}_2OH$), 5.27 (dt, 1 H, *J* = 6.3 Hz, *J* = 15.3 Hz, $C\underline{H}$=CH-*t*-Bu), 5.45 (d, 1 H, *J* = 15.3 Hz, CH=$C\underline{H}$-*t*-Bu), the peak corresponding to the proton on C3 was buried under the other vinylic proton peaks; ^{13}C NMR ($CDCl_3$) δ 21.43, 29.75, 30.86, 32.90, 61.67, 123.12, 126.79, 135.00, 142.09.

The *E,E*-isomer: ^{1}H NMR ($CDCl_3$) same as the *Z,E*-isomer or not seen except δ 1.67 (s, 3 H, CH_3), 4.02 (s, 2 H, $C\underline{H}_2OH$), 5.46 (d, 1 H, *J* = 15.3 Hz, CH=$C\underline{H}$-*t*-Bu); ^{13}C NMR same as the *Z,E*-isomer or not seen, except δ 13.69, 29.78, 30.97, 68.96, 122.49, 124.63, 142.07.

The following spectral data were taken from a mixture of the *E,E*- and *Z,E*-isomers: IR (neat) 3341, 3024, 2961, 2866, 1670, 1628, 1593, 1475, 1462, 1391, 1321, 1269, 1242, 1003, 970, 854, 750 cm^{-1}; HRMS: calculated for $C_{11}H_{20}O$ m/z 168.15142, found 168.15126.

(*E*)- and (*Z*)-2-Methyl-6-phenyl-2,5-hexadien-1-ol (Table 2, entry 32)

Obtained in 58 % isolated yield (59:41 *E,E/Z,E*) from the reaction of (*E*)-1-iodo-2-phenylethylene and 3,4-epoxy-3-methyl-1-butene. This compound was inseparable from the side product 2-methyl-3-butene-1,2-diol carbonate. The *E,E*- to *Z,E*-somer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E,E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 3 H, CH_3), 1.80 (s, 1H, OH), 2.97 (t, 2 H, J = 6.6 Hz, $C\underline{H}_2CH$=), 4.04 (s, 2 H, $C\underline{H}_2OH$), 5.42 (m, 1 H, CH=C), 6.17 (dt, 1 H, J = 15.9 Hz, J = 6.6 Hz, $C\underline{H}$=CHPh), 6.37 (d, 1 H, J = 15.9 Hz, CHPh), 7.32 (m, 5 H, phenyl).

The *Z,E*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E,E*-isomer or not seen, except δ 1.85 (s, 3 H, CH_3), 4.18 (s, 2 H, $C\underline{H}_2OH$), 6.19 (dt, 1 H, J = 15.9 Hz, J = 6.3 Hz, $C\underline{H}$=CHPh), 6.39 (d, 1 H, J = 15.9 Hz, CHPh).

(*E,Z*)- and (*Z,Z*)-2-Methyl-2,5-decadien-1-ol (Table 2, entry 34)

Obtained in 50 % isolated yield (55:45 *E,Z/Z,Z*) from the reaction of *Z*-1-iodo-1-hexene and 3,4-epoxy-3-methyl-1-butene. The *E,Z*- to *Z,Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E,Z*-isomer: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 6.6 Hz, $CH_2C\underline{H}_3$), 1.33 (m, 3 H, $C\underline{H}_2CH_3$ and OH), 1.41 (m, 2 H, CH_2Et), 1.69 (s, 3 H, CCH_3), 2.06 (m, 2 H, CH_2Pr), 2.78 (t, 2 H, J = 6.6 Hz, $C\underline{H}_2CH$=), 4.01 (s, 2 H, $C\underline{H}_2OH$), 5.36 (m, 3 H, vinyl H's); ^{13}C NMR ($CDCl_3$) δ 13.71, 14.02, 21.32, 25.99, 26.99, 31.89, 68.95, 124.80, 127.42, 130.48, 134.55.

The *Z,Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E,Z*-isomer or not seen, except δ 1.80 (s, 3 H, CCH_3), 2.81 (t, 2 H, J = 6.6 Hz, $C\underline{H}_2CH$=), 4.16 (s, 2 H, $C\underline{H}_2OH$); ^{13}C NMR

same as the *E,Z*-isomer or not seen, except δ 18.08, 22.39, 25.93, 31.84, 61.66, 126.91, 127.72, 130.47, 134.90.

The following spectral data were taken from a mixture of the *E,Z*- and *Z,Z*-isomers: IR (neat) 3340, 3333, 3007, 3956, 3936, 3858, 1463, 1377, 1131, 1084, 1001, 962, 838 cm^{-1}; HRMS: calculated for $C_{11}H_{20}O$ m/z 168.15142, found 168.15154.

(*E*)- and (*Z*)-5-*n*-Butyl-2-methyl-2,5-hexadien-1-ol (Table 2, entry 35)

Obtained in 37 % isolated yield (64:36 *E/Z*) from the reaction of 2-iodo-1-hexene and 3,4-epoxy-3-methyl-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^1H NMR ($CDCl_3$) δ 0.91 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.30 (m, 5 H, $C\underline{H}_2C\underline{H}_2CH_3$ and OH), 1.68 (s, 3 H, CCH_3), 2.02 (t, 2 H, J = 6.9 Hz, CH_2Pr), 2.74 (d, 2 H, J = 7.2 Hz, $C\underline{H}_2CH$=), 4.04 (s, 2 H, $C\underline{H}_2OH$), 4.71 (s, 1 H, one of CH_2=), 4.72 (s, 1 H, one of CH_2=), 5.48 (t, 1 H, J = 7.2 Hz, $CH_2C\underline{H}$=); ^{13}C NMR ($CDCl_3$) δ 13.65, 14.04, 22.49, 29.95, 34.39, 36.01, 68.94, 109.26, 123.76, 136.07, 148.68.

The *Z*-isomer: ^1H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.84 (s, 3 H, CCH_3), 4.13 (s, 2 H, $C\underline{H}_2OH$), 5.38 (t, 1 H, J = 7.2 Hz, $CH_2C\underline{H}$=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 61.95, 109.23.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3329, 3322, 3075, 2956, 2927, 2859, 1644, 1463, 1436, 1362, 1062, 1015, 950, 888, 775, 667 cm^{-1}; HRMS: calculated for $C_{11}H_{20}O$ m/z 168.15142, found 168.15112.

(*E*)- and (*Z*)-2-Methyl-5-phenyl-2,5-hexadien-1-ol (Table 2, entry 36)

Obtained in 31 % isolated yield (55:45 *E/Z*) from the reaction of 1-iodo -2-phenylethylene and 3,4-epoxy-3-methyl-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 3 H, CCH_3), 3.24 (d, 2 H, J = 6.9 Hz, $C\underline{H}_2CH$=), 4.02 (s, 2 H, $C\underline{H}_2OH$), 5.08 (d, 1 H, J = 1.5 Hz, $\underline{H}CH$= trans to phenyl), 5.35 (d, 1 H, J = 1.5 Hz, $\underline{H}CH$= cis to phenyl), 5.51 (tq, 1 H, J = 6.9 Hz, 1.2 Hz, HC=), 7.33 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 13.80, 33.52, 68.81, 112.63, 123.52, 126.02. 127.59, 128.32, 136.42, 141.13, 146.68.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.82 (s, 3 H, CCH_3), 4.15 (s, 2 H, $C\underline{H}_2OH$), 5.06 (d, 1 H, J = 1.5 Hz, $\underline{H}CH$= trans to phenyl), 5.32 (d, 1 H, J = 1.5 Hz, $\underline{H}CH$= cis to phenyl), 5.41 (q, 1 H, J = 6.9 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 21.41, 33.47, 61.68, 112.74, 125.40, 126.68, 127.51, 128.36, 136.18, 141.11, 147.27.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3329, 3322, 3075, 2956, 2927, 2859, 1644, 1463, 1436, 1362, 1062, 1015, 950, 888, 775, 667 cm^{-1}; HRMS: calculated for $C_{13}H_{16}O$ m/z 188.12012, found 188.11975.

(*E*)- and (*Z*)-2-Methyl-4-(1-cyclohexenyl)-2-buten-1-ol (Table 2, entry 37)

Obtained in 62 % isolated yield (55:45 *E/Z*) from the reaction of 1-iodo-1-cyclohexene and 3,4-epoxy-3-methyl-1-butene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.50-1.66 (m, 5 H, OH and CH_2's of cyclohexenyl), 1.68 (s, 3 H, CH_3), 1.85-2.00 (m, 4 H, allylic CH_2's of cyclohexenyl), 2.65 (d, 2

H, J = 7.2 Hz, $CC\underline{H}_2CH$=), 4.02 (s, 2 H, $C\underline{H}_2OH$), 5.34 (t, 1 H, J = 7.2 Hz, $C\underline{H}$=CCH_2OH), 5.43 (m, 1 H, $C\underline{H}$=CCH_2); ^{13}C NMR ($CDCl_3$) δ 13.70, 22.51, 23.00, 25.29, 28.62, 36.18, 69.02, 121.39, 126.24, 135.60, 137.08.

The *Z*-isomer: ^1H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.83 (s, 3 H, CH_3), 4.13 (s, 2 H, $C\underline{H}_2OH$); ^{13}C NMR same as the *E*-isomer or not seen, except δ 21.46, 22.50, 22.97, 25.28, 28.57, 36.04, 121.33, 124.19, 135.43, 136.61.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3375, 2933, 2862, 1959, 1799, 1676, 1625, 1448, 1379, 1261, 1058, 873, 802 cm^{-1}; HRMS: calculated for $C_{11}H_{18}O$ m/z 166.13577, found 166.13544.

(*E,E*)- and (*Z,E*)-2,5-Decadien-1-ol (Table 2, entry 38)

Obtained in 91 % isolated yield (72:28 *E,E*/*Z,E*) from the reaction of *E*-1-iodo-1-hexene and 3,4-epoxy-1-butene. The *E,E*- to *Z,E*-isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E,E*-isomer: ^1H NMR ($CDCl_3$) δ 0.89 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.32 (m, 4 H, $C\underline{H}_2C\underline{H}_2CH_3$), 1.89 (br s, 1 H, OH), 2.06 (q, 2 H, *J* = 6.9 Hz, CH_2Pr), 2.74 (t, 2 H, *J* = 5.1 Hz, =$CHC\underline{H}_2CH$=), 4.01 (d, 2 H, *J* = 4.8 Hz, $C\underline{H}_2OH$), 5.42 (m, 2 H, CH=CHBu), 5.67 (m, 2 H, $C\underline{H}$=$C\underline{H}CH_2OH$); ^{13}C NMR ($CDCl_3$) δ 13.98, 22.25, 31.67, 32.26, 35.24, 63.73, 127.38, 129.33, 131.81, 131.96.

The *Z,E*-isomer: ^1H NMR ($CDCl_3$) same as the *E,E*-isomer or not seen, except δ 2.77 (t, 2 H, *J* = 5.7 Hz, =$CHC\underline{H}_2CH$=), 4.20 (d, 2 H, *J* = 6.0 Hz, $C\underline{H}_2OH$); ^{13}C NMR same as the *E,E*-isomer or not seen, except δ 22.26, 30.59, 31.64, 32.22, 58.26, 127.53, 128.80, 131.09, 131.53.

The following spectral data were taken from a mixture of the *E,E*- and *Z,E*-isomers: IR (neat) 3333, 3020, 2957, 2872, 1796, 1672, 1466, 1433, 1379, 1173, 1092, 1005, 968 cm^{-1}; HRMS: calculated for $C_{10}H_{18}O$ m/z 154.13577, found 154.13555.

(*E*)- and (*Z*)-6-Phenyl-2,5-hexadien-1-ol (Table 2, entry 39)

Obtained in 77 % isolated yield (77:23 *E,E/Z,E)* from the reaction of *E*-1-iodo-2-phenylethylene and 3,4-epoxy-1-butene. The *E,E*- to *Z,E*-isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E,E*-isomer: ^1H NMR ($CDCl_3$) δ 1.61 (br s, 1 H, OH), 2.95 (t, 2 H, *J* = 6.6 Hz, $C\underline{H}_2CH$=), 4.12 (d, 1 H, *J* = 4.5 Hz, $C\underline{H}_2OH$), 5.74 (m, 2 H, $C\underline{H}$=$C\underline{H}CH_2OH$), 6.21 (dt, 1 H, *J* = 15.6 Hz, *J* = 6.6 Hz, $C\underline{H}$=CHPh), 6.40 (d, 1 H, *J* =15.6 Hz, =CHPh), 7.33 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 35.50, 63.57, 126.03, 127.09, 128.05, 128.51, 129.74, 130.48, 130.93, 137.49.

The *Z,E*-isomer: ^1H NMR ($CDCl_3$) same as the *E,E*-isomer or not seen, except δ 4.23 (d, 2 H, *J* = 6.6 Hz, $C\underline{H}_2OH$) ; ^{13}C NMR same as the *E,E*-isomer or not seen, except δ 30.87, 58.52, 128.07, 128.61, 129.79, 130.26, 130.53, 137.42.

The following spectral data were taken from a mixture of the *E,E*- and *Z,E*-isomers: IR (neat) 3329, 3082, 3059, 2924, 1598, 1499, 1448, 1425, 1308, 1175, 1090, 1072, 968, 910, 735, 694 cm^{-1}; HRMS: calculated for $C_{12}H_{14}O$ m/z 174.10447, found 174.10414.

(*E,Z*)- and (*Z,Z*)-2,5-Decadien-1-ol (Table 2, entry 40)

Obtained in 61 % isolated yield (72:28 *E,Z/Z,Z*) from the reaction of *Z*-1-iodo-1-hexene and 3,4-epoxy-1-butene. The *E,Z*- to *Z,Z*-isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E,Z*-isomer: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 6.9 Hz, CH_3), 1.31 - 1.37 (m, 5 H, $C\underline{H_2}C\underline{H_2}CH_3$ and OH), 2.05 (m, 2 H, CH_2Pr), 2.81 (m, 2 H, CH_2), 4.10 (d, 2 H, J = 3.9 Hz, $C\underline{H_2}OH$), 5.35 - 5.69 (m, 4 H, vinyl); ^{13}C NMR ($CDCl_3$) δ 14.03, 22.38, 26.91, 30.84, 31.84, 63.79, 126.53, 129.22, 131.30, 131.52.

The *Z,Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E,Z*-isomer or not seen, except δ 4.23 (d, 2 H, J = 6.9 Hz, $C\underline{H_2}OH$); ^{13}C NMR same as the *E,Z*-isomer or not seen, except δ 25.85, 27.00, 31.80, 58.65, 127.01, 128.57, 130.95, 131.38.

The following spectral data were taken from a mixture of the *E,Z*- and *Z,Z*-isomers: IR (neat) 3321, 3013, 2959, 2927, 2874, 1668, 1466, 1400, 1379, 1094, 1005, 970 cm^{-1}; HRMS: calculated for $C_{10}H_{18}O$ m/z 154.13577, found 154.13610.

(*E*)- and (*Z*)-4-(1-Cyclohexenyl)-2-buten-1-ol (Table 2, entry 41)

Obtained in 52 % isolated yield (70:30 *E/Z*) from the reaction of 1-iodo-1-cyclohexene and 3,4-epoxy-1-butene. The compound was contaminated by an unknown compound (1:1). The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.50-1.68 (m, 5 H, OH and H's on C4 and C5 of cyclohexenyl), 1.91-1.99 (m, 4 H, H's on C3 and C6 of cyclohexenyl), 2.68 (d, 2 H, J = 3.9 Hz, $=CC\underline{H_2}CH=$), 4.11 (d, 2 H, J = 4.2 Hz, $C\underline{H_2}OH$), 5.43 (m, 1 H, vinyl H of cyclohexenyl), 5.66 (m, 2 H, CH=CH).

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 4.20 (d, 2 H, J = 6.3 Hz, $C\underline{H_2}OH$).

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: HRMS: calculated for $C_{10}H_{16}O$ m/z 152.12012, found 152.11981. The ^{1}H NMR spectral data were identical to those reported for this compound by Ilkka.[1]

(*E,E*)- and (*Z,E*)-3-Methyl-3,6-undecadien-2-ol (Table 2, entry 43)

Obtained in 71 % isolated yield (50:50 *E,E*/*Z,E*) from the reaction of *E*-1-iodo-1-hexene and 3,4-epoxy-3-methyl-1-pentene. The *E,E*- to *Z,E*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E,E*-isomer: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, *J* = 6.9 Hz, $CH_2C\underline{H}_3$), 1.24 (d, 3 H, *J* = 6.3 Hz, $CHC\underline{H}_3$), 1.31 (m, 4 H, $C\underline{H}_2C\underline{H}_2CH_3$), 1.43 (br s, 1 H, OH), 1.63 (s, 3 H, CCH_3), 1.97 (q, 2 H, *J* = 6.3 Hz, CH_2Pr), 2.70 (t, 2 H, *J* = 6.0 Hz, $=CCH_2C=$), 4.22 (q, 1 H, *J* = 6.3 Hz, C<u>H</u>OH), 5.40 (m, 3 H, vinyl); ^{13}C NMR ($CDCl_3$) δ 11.44, 13.08, 21.60, 22.26, 30.77, 31.73, 32.26, 73.36, 123.21, 127.87, 130.97, 137.05.

The *Z,E*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E,E*-isomer or not seen, except δ 1.26 (d, 3 H, *J* = 6.3 Hz, $CHC\underline{H}_3$), 1.72 (s, 3 H, CCH_3), 4.79 (q, 1 H, *J* = 6.3 Hz, C<u>H</u>OH); ^{13}C NMR same as the *E,E*-isomer or not seen, except δ 17.17, 21.15, 30.39, 32.24, 65.60, 124.69, 128.37, 130.99, 138.45.

The following spectral data were taken from a mixture of the *E,E*- and *Z,E*-isomers: IR (neat) 3364, 2959, 1662, 1454, 1377, 1285, 1171, 1082, 1034, 966, 893, 851, 777, 729 cm^{-1}; HRMS: calculated for $C_{12}H_{22}O$ m/z 182.16707, found 182.16668.

(*E*)- and (*Z*)-5-(1-Cyclohexenyl)-3-methyl-3-penten-2-ol (Table 2, entry 49)

Obtained in 41 % isolated yield (70:30 *E*/*Z*) from the reaction of 1-iodo-1-cyclohexene and 3,4-epoxy-3-methyl-1-pentene. The compound was contaminated by an unknown compound (95:5 ratio of product to unknown). The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.24 (d, 3 H, J = 6.6 Hz, $C\underline{H}_3CHOH$), 1.59-1.64 (m, 5 H, OH and H's on C4 and C5 of cyclohexenyl), 1.73 (s, 3 H, CH_3C), 1.90-1.98 (2 m, 4 H, H's on C3 and C6 of cyclohexenyl), 2.63 (d, 2 H, J = 6.6 Hz, $=CC\underline{H}_2CH=$), 4.22 (q, 1 H, J = 6.6 Hz, $C\underline{H}OH$), 5.39 (m, 2 H, vinyl).

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.25 (d, 3 H, J = 6.6 Hz, $C\underline{H}_3CHOH$), 4.78 (d, 2 H, J = 6.6 Hz, $C\underline{H}OH$).

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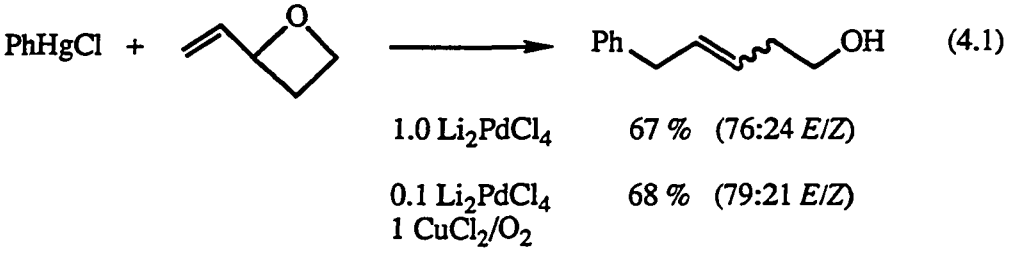
PART IV. PALLADIUM(0)-PROMOTED CROSS-COUPLING OF VINYLIC OXETANES WITH ORGANIC HALIDES AND TRIFLATES

INTRODUCTION

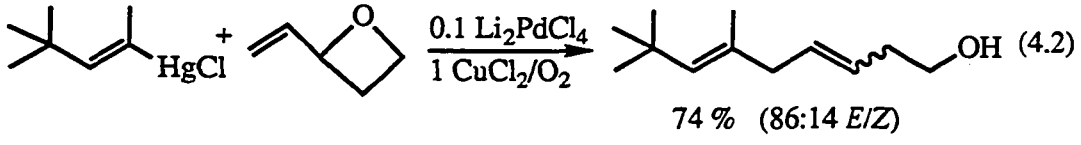
In the last two decades, reactions involving nucleophilic and organometallic displacement of allylic compounds have been well studied and reviewed.[1,2] These reactions are synthetically useful when the regio- and stereochemistry of the product can be controlled.

Larock and Stolz-Dunn reported that homoallylic alcohols could be prepared in good to excellent yield when vinylic oxetanes were allowed to react with arylmercurials in the presence of a stoichiometric amount of palladium(II) (eq 4.1).[3] The reaction proceeded



(4.1)

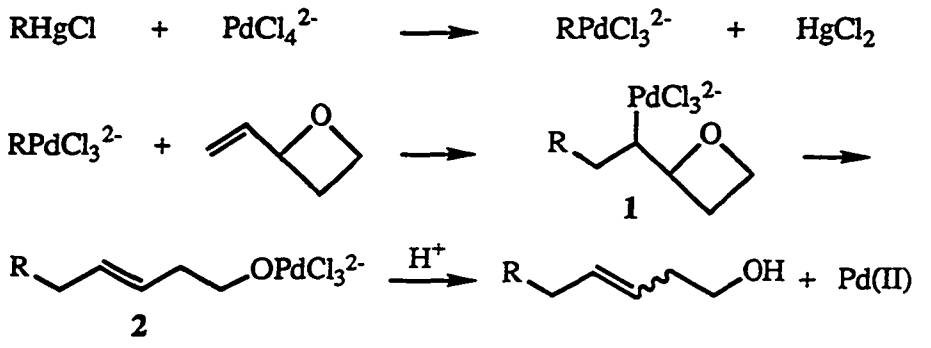
with a high degree of regioselectivity and modest stereoselectivity. It has also been shown that the reactions could be run using catalytic amounts of palladium(II) if cupric chloride was added to the reaction and the reactions were carried out under an atmosphere of oxygen. Vinylmercurials could be readily used in the reactions to produce the corresponding homoallylic alcohols in good yields (eq 4.2).



(4.2)

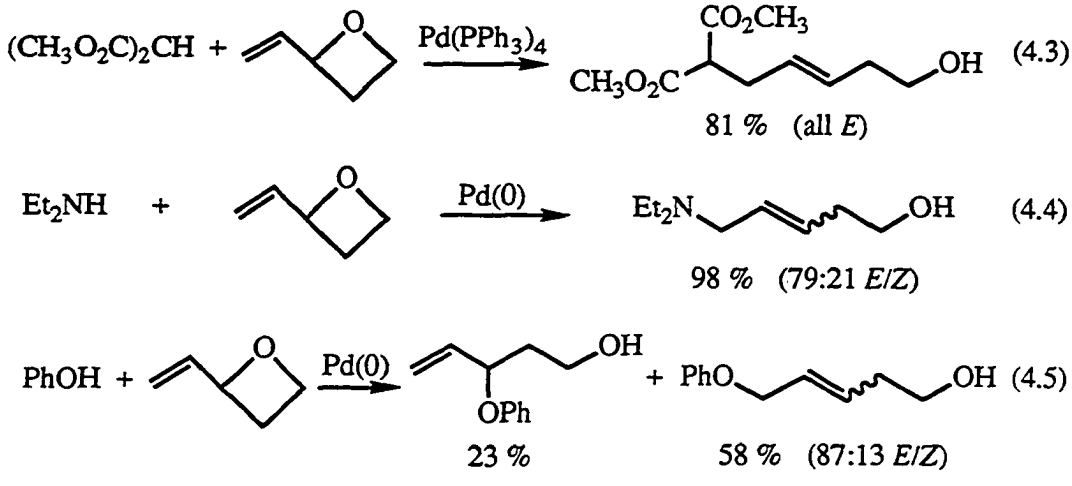
The following mechanism has been proposed to explain how homoallylic alcohols are formed in these reactions (Scheme 1). The first step of the mechanism involves

Scheme 1

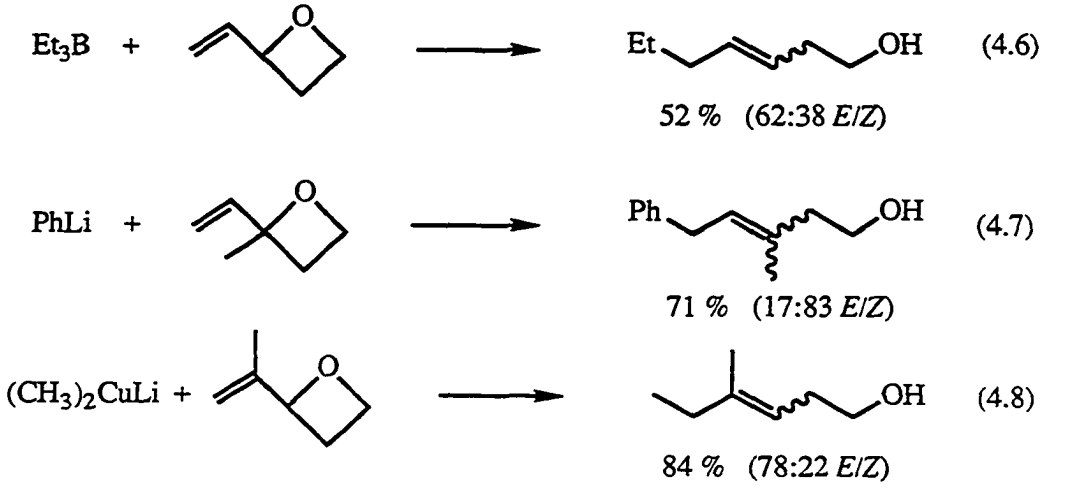


transmetallation of the aryl- or vinylmercurials with a palladium(II) salt. The organopalladium species then adds across the carbon-carbon double bond of the vinylic oxetane. The aryl or vinyl group becomes attached to the less hindered end of the olefin to form intermediate **1**. Intermediate **1** then undergoes palladium alkoxide elimination to form alkoxypalladium species **2**. The homoallylic alcohols are then formed by protonation of intermediate **2**.

Larock and Stolz-Dunn have also investigated the palladium(0)-catalyzed nucleophilic ring opening of vinylic oxetanes (eqs 4.3-4.5).[4] These were the first examples of the palladium(0)-catalyzed S_N2' ring opening of vinylic oxetanes. A number of stabilized carbon or heteroatom nucleophiles, such as acidic hydrocarbons, a β-keto acid, phenol, benzoic acid, and diethylamine, were employed in the reaction. The reactions of carbon nucleophiles were highly regio- and stereoselective. The amine reacted in a regio- but not stereoselective manner, while the oxygen nucleophiles afforded regio- and stereochemical mixtures. These reactions provide a convenient new synthetic route to homoallylic alcohols.



It has also been shown that homoallylic alcohols can be prepared with a high degree of regioselectivity when vinylic oxetanes are allowed to react with organolithium, -boron, and -copper reagents (eqs 4.6-4.8).[5] In general, alkylcopper and -boron reagents react



in a completely regioselective fashion with vinylic oxetanes, with preference for formation of the *E*-isomer. Allylcopper reactions proceed by S_N2' attack, but the *E:Z* ratio is generally only about 2:1. Regioselectivity is a problem with vinyl- and phenylcopper reagents when direct oxygen displacement is not hindered. Reactions with organolithium

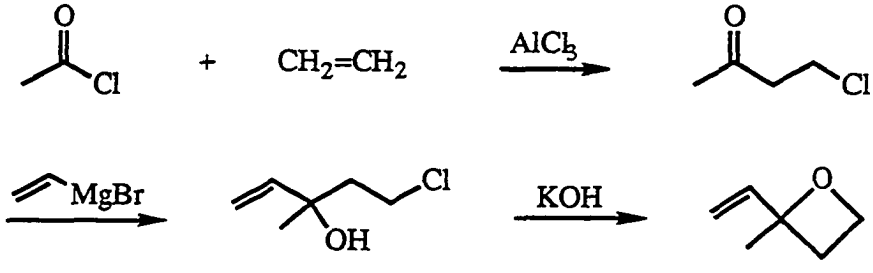
reagents often proceed in low yield and the regio- and stereoselectivity vary with the oxetane used, usually favoring the *Z*-isomer.

Since it has been demonstrated that vinylic oxetanes can be ring-opened to form substituted homoallylic alcohols using organomercurials and palladium(II) salts (eq 4.1), it was thought that it might be possible to replace the organomercurial shown in equation 4.1 with an organic halide. No such reactions of vinylic oxetanes have been reported previously. It was hoped that the palladium(0)-catalyzed ring-opening of vinylic oxetanes would produce homoallylic alcohols in good yield with a high degree of regio- and stereoselectivity. It is also desirable that it be possible to use variously substituted vinylic oxetanes in the reaction and that the reaction tolerate a number of different organic halides and triflates.

In this part of the thesis, the palladium(0)-catalyzed cross-coupling of vinylic oxetanes with various organic halides and triflates will be discussed. The palladium(0)-catalyzed reaction of 3-methyl-3,5-epoxy-1-pentene with iodobenzene will be covered in some detail. This will be followed by a discussion of the reaction of a variety of vinylic oxetanes with organic halides and triflates in the presence of a catalytic amount of palladium(0).

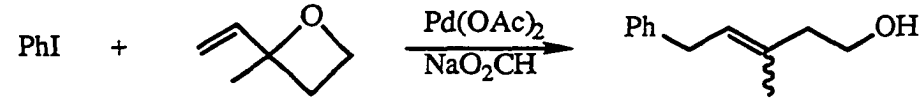
RESULTS AND DISCUSSION

Sources of organic halides and triflates were indicated in Part III and they were used directly without further purification. 3,5-Epoxy-3-methyl-1-pentene was prepared from the condensation of acetyl chloride and ethylene followed by vinylation and ring closure using the literature procedures (eq 4.9).[6,7] Other vinylic oxetanes were synthesized by Larock group members using the procedure reported by Portnyagin and Pak.[7]



(4.9)

As a first step towards meeting the previously mentioned objectives and establishing this reaction as a new and useful synthetic method, a number of reactions was performed using the reaction of 3,5-epoxy-3-methyl-1-pentene and iodobenzene as a model system (eq 4.10). The reaction afforded homoallylic alcohol **5**. The formation of the desired product



3 **4** **5** (4.10)

involved a palladium(0)-catalyzed process which is similar to the one explained in Scheme 4 of Part III . The results of this investigation are summarized in Table 1 and the following observations can be made.

Table 1. The palladium(0)-catalyzed reaction of compounds **3** and **4**

Entry[a]	Ratio **3/4**	Equiv. MCl	Added Reagent	Yield (%) **5**	*E*/*Z* Ratio
1	1:3	2 TBAC	-	57	54:46
2	1:5	2 TBAC	-	76	59:41
3	1:5	1 TBAC	-	45	59:41
4	1:5	2 LiCl	-	76	62:38
5	1:5	2 TBAC	10 % CuI	47	55:45

[a] All reactions were run using 10 mol % of $Pd(OAc)_2$, 5 equiv. NaO_2CH, 3 equiv. *i*-Pr_2NEt, and 2 ml DMA at 80 °C for 1 day.

All reactions gave the desired homoallylic alcohol **5** in good to excellent yield. Examining the stoichiometry of the starting materials for this model system, a 1:5 ratio of iodobenzene to the vinylic oxetane seemed the better choice (compare entries 1 and 2). Lowering the amount of the oxetane decreased the yield somewhat (entry 1). Using 1 equiv. tetra-*n*-butylammonium chloride afforded only a modest yield of the product (entry 3). Doubling the amount of tetra-*n*-butylammonium chloride increased the yield significantly (entry 2). Lithium chloride could also be used in the reaction and proved to be as good as tetra-*n*-butylammonium chloride (entry 4). Finally, this model reaction was also carried out using 10 mol % copper iodide, but the yield of the homoallylic alcohol decreased.

The stereochemistry of the reaction seemed little affected by stoichiometry, added reagents, or other conditions. Like the corresponding epoxide reactions, the vinylic oxetane model reaction always afforded an *E* and *Z* mixture of homoallylic alcohols.

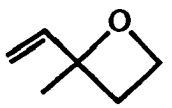
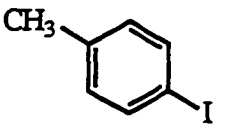
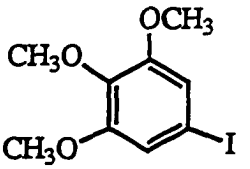
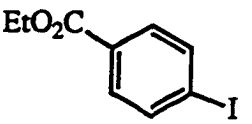
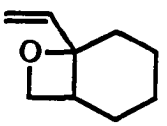
Once the reaction procedure for this model system was optimized, vinylic oxetanes bearing terminal double bonds, as well as internal double bonds, were studied. A variety of aryl and vinylic halides were employed in this study to determine the scope and limitations of this palladium(0)-catalyzed process. All of the reactions were run using the best procedure arising from the model system, which included 1 equiv. organic halide, 5 equiv. vinylic oxetane, 10 mol % of $Pd(OAc)_2$, 5 equiv. NaO_2CH, 3 equiv. *i*-Pr_2NEt, 2 equiv. TBAC or LiCl, and 2 ml of DMA at 80 °C for 1 day. The results of this investigation are summarized in Table 2.

The following observations have been made in the course of this investigation. Among the vinylic oxetanes examined, 3,5-epoxy-3-methyl-1-pentene gave the best results and good yields of the desired homoallylic alcohols were obtained from the arylation reactions (entries 1-3). The arylation of 1-vinyl-8-oxabicyclo[4.2.0]octane also gave a good yield of the desired product (entry 4). 3,5 -Epoxy-2,3-dimethyl-1-pentene and 4,6-epoxy-4-methyl-2-hexene, which bear more substituted carbon-carbon double bonds, gave poor yields when reacting with 1-iodo-3,4,5-trimethoxybenzene (entries 6-8). The significant decrease in yield is presumably due to the greater steric hindrance to addition of the arylpalladium halide to the more substituted carbon-carbon double bonds.

Aryl halides bearing electron-donating groups (entries 1 and 2), as well as an electron-withdrawing group (entry 3), were readily accommodated in these reactions. The yields, however, decreased somewhat is going from the former to the latter. The presence or absence of electron-donating or -withdrawing groups on the aryl halides appears to have some minor effect on the stereochemistry of the process.

Vinylic halides have also been investigated. They produced the desired homoallylic alcohols in poor to good yields (entries 9-12). A reasonable explanation for the poor yields is that the oxidative addition of the vinylic halide to palladium(0) to form a vinylpalladium

Table 2. Palladium(0)-catalyzed reaction of vinylic oxetanes with organic halides

Entry	Oxetane	RI	Chloride source
1			TBAC
2			TBAC
3			TBAC
4			TBAC

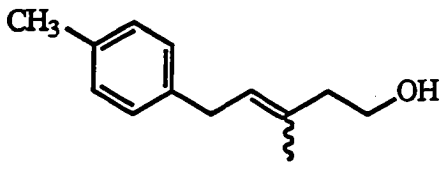
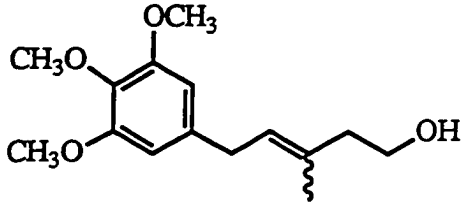
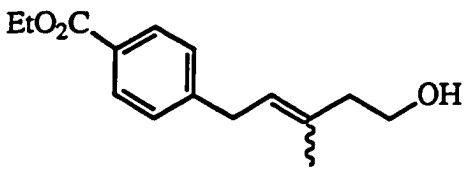
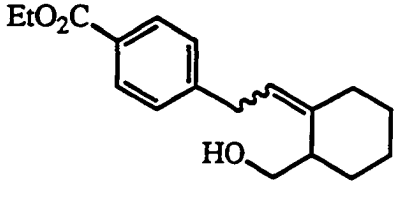
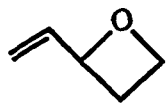
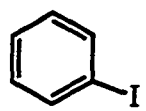
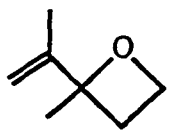
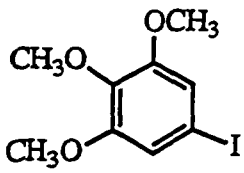
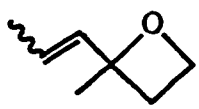
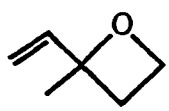
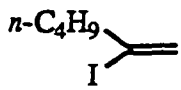
Product	Yield (%)	E/Z Ratio
	70	56:44
	62	56:44
	57	68:32
	55	67:33

Table 2. (Continued)

Entry	Oxetane	RI	Chloride source
5			TBAC
6 7			TBAC LiCl
8			TBAC
9			TBAC

[a] The product was inseparable from an unknown compound (2:1 ratio of product to unknown).

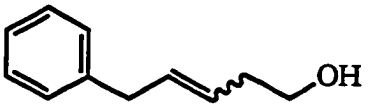
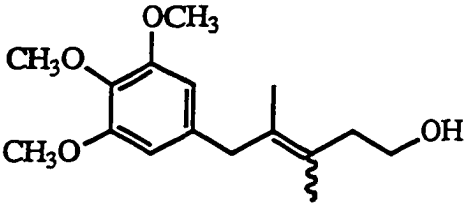
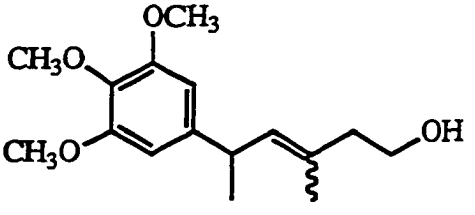
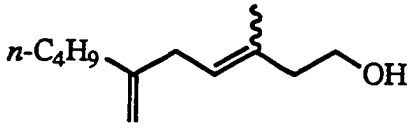
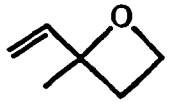
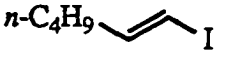
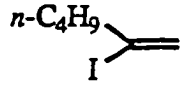
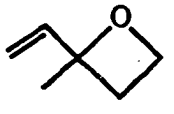
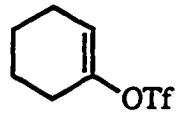
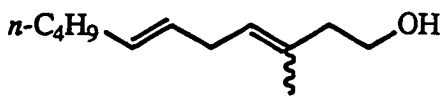
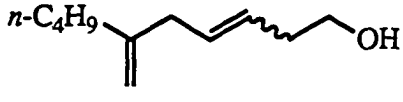
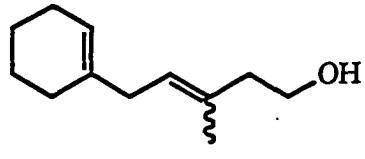
Product	Yield (%)	E/Z Ratio
	41[a]	80:20
	13 15	66:34 64:36
	11	70:30
	25	62:38

Table 2. (Continued)

Entry	Oxetane	RI	Chloride source
10 11			TBAC LiCl
12			TBAC
13			TBAC

[b] The product was inseparable from the side-product 3-methyl-3-penten-1-ol (37:63 ratio of product to side product).

Product	Yield (%)	E/Z Ratio
	40[b] 8	- 66:34
	60	82:18
	44	67:33

iodide is followed by dimerization or formate reduction of the newly formed vinyl-palladium species. These side processes apparently occur more rapidly than the olefin insertion and therefore decreased the yield of the desired product.

The reaction of 3,5-epoxy-3-methyl-1-pentene and cyclohexenyl triflate was also examined. A modest yield of the desired homoallylic alcohols was obtained. The stereochemistry of the reaction was similar to that of vinyl halides.

CONCLUSION

The palladium(0)-catalyzed cross-coupling of vinylic oxetanes with organic halides and triflates has been investigated. The arylation of vinylic oxetanes bearing mono-substituted carbon-carbon double bonds produces the corresponding aryl homoallylic alcohols as mixtures of *E*- and *Z*-isomers in good yields. The regioselectivity of the reactions is high. Substituents on the carbon-carbon double bond of the vinylic oxetane significantly decrease the yield of the homoallylic alcohol. The presence or absence of substituents on the aryl moiety seems to have little effect on the stereochemistry of the reactions or the yield. The reaction of vinylic halides and triflates with vinylic oxetanes affords homoallylic alcohols in poor to good yields.

EXPERIMENTAL SECTION

Equipment

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75.5 MHz for carbon nuclei) or a Varian VXR-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75.5 MHz for carbon nuclei). All infrared spectra were recorded on an IBM IR / 98 FT-IR or a Bio-Rad FTS-7. Exact mass spectral analyses were obtained on a Kratos high resolution mass spectrometer. Gas chromatographic analyses were performed on 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 a HP-1 megabore column (HP 5890).

Reagents

Palladium acetate was donated by Johnson Matthey Inc. Sodium formate and lithium chloride were purchased from Fisher Scientific Company and oven-dried before use. Tetra-*n*-buthylammonium chloride and ethyl 4-iodobenzoate were obtained from Lancaster Synthesis Inc. Diisopropylethylamine was purchased from Aldrich Chemical Company, Inc. and stored over molecular sieves. Iodobenzene and 4-iodotoluene were purchased from Eastman Kodak Company. (*E*)-1-Iodo-1-hexene, 2-iodo-1-hexene, 5-iodo-1,2,3-trimethoxybenzene, 3,5-epoxy-2,3-dimethyl-1-pentene, (*E*)- and (*Z*)-4,6-epoxy-4-methyl-2-hexene, and 1-vinyl-8-oxabicyclo[4.2.0]octane were generously supplied by Larock group members.

3,5-Epoxy-3-methyl-1-pentene[6,7]

Freshly distilled acetyl chloride (78.5 g, 1.0 mol) was added during 20 minutes to a solution of aluminum chloride (140.0 g, 1.05 mol) in 300 ml of dried chloroform at 0 °C. Ethylene was allowed to bubble through the stirred mixture for 2.5 hours. The reaction mixture was then poured into a mixture of 150 ml of concentrated hydrochloric acid and 1000 g of ice. The organic layer was washed with dilute hydrochloric acid (100 ml x 3), a 10 % aqueous solution of sodium bicarbonate (100 ml x 3), water (100 ml x 3), and dried with $MgSO_4$. Solvents were removed by vaccum distillation (25 °C / 110 mmHg) and the residue was distilled to give a 37 % yield of 4-chloro-2-butanone (43-44 °C / 15 mmHg).

Vinylmagnesium bromide purchased from Aldrich (410 ml, 1.0 M in THF) was placed in a 1000 ml three-neck round bottom flask equipped with a magnetic stirrer. The flask was cooled to -10 °C in an ice-acetone bath. To this flask was slowly added 4-chloro-2-butanone (35.0 g, 0.33 mol). During the addition, the temperature of the reaction mixture was kept at 0-10 °C. The reaction mixture was then allowed to stir overnight under nitrogen at room temperature. The flask was cooled to 0 °C and the reaction mixture was slowly added to saturated aqueous ammonium chloride at 0 °C. The solution was filtered through glass wool and the organic layer was separated. The aqueous layer was extracted with ether (50 ml x 3) and the combined organic layers were washed with saturated aqueous sodium bicarbonate (100 ml x 2), followed by water (100 ml x 2) and then dried over Na_2SO_4. Solvents were removed by rota-evaporation. 5-Chloro-3-methyl-1-penten-3-ol was obtained in 78 % yield.

Potassium hydroxide (105 g) was added to 100 ml of water and was heated to a boil. To this solution was rapidly added 5-chloro-3-methyl-1-penten-3-ol (34.6 g, 0.26 mol) With vigorous stirring, the product was distilled off through a fractionating column. The distillate was saturated with sodium chloride. The organic layer was separated and dried

with $MgSO_4$, and then distilled. The desired 3,5-epoxy-3-methyl-1-pentene was obtained as a colorless liquid in 41 % yield: bp 94-96 °C / 760 mm; ^1H NMR ($CDCl_3$) δ 1.50 (s, 3 H, CH_3), 2.52 (m, 2 H, CH_2C), 4.48 (m, 2 H, CH_2O), 5.11 (d, 1 H, J = 10.8 Hz, C<u>H</u>H= trans to ring), 5.33 (d, 1 H, J = 17.1 Hz, C<u>H</u>H= cis to ring), 6.06 (dd, 1 H, J = 17.1 Hz, J = 10.8 Hz, CH=); IR (neat) 3090, 2972, 2883, 1643, 1445, 1404, 1369, 1273, 1182, 1136, 1097, 995, 966, 924, 872, 689 cm^{-1}.

<u>General procedure for the palladium-promoted cross-coupling of vinylic oxetanes with organic halides</u>

The following procedure used for the preparation of (*E*)- and (*Z*)-3-methyl-5-phenyl-3-penten-1-ol is representative of that used for other compounds. To an oven-dried 25 ml round-bottom flask containing a magnetic stirrer were added the following reagents: palladium acetate (11.3 mg, 0.05 mmol), sodium formate (170 mg, 2.5 mmol), tetra-*n*-butylammonium chloride (277 mg, 1.0 mmol), diisopropylethylamine (0.26 ml, 1.5 mmol), iodobenzene (102 mg, 0.5 mmol), 3,5-epoxy-3-methyl-1-pentene (245 mg, 2.5 mmol), and *N*,*N*-dimethylacetamide (2.0 ml). The solution was stirred at 80 °C for 1 day. Ether (15 ml) was then added to the reaction mixture. The ether layer was washed with saturated aqueous ammonium chloride (15 ml x 2), and the combined aqueous layers were back extracted with ether (15 ml x 2). The combined ether fractions were dried over anhydrous magnesium sulfate. After removal of the solvents, the residue was purified by flash column chromatography on silica gel using a 20:1 mixture of hexane to ethyl acetate as eluents. (*E*)- and (*Z*)-3-Methyl-5-phenyl-3-penten-1-ol were obtained in 76 % yield as a colorless liquid.

(*E*)- and (*Z*)-3-Methyl-5-phenyl-3-penten-1-ol (Table 1, entry 2)

Obtained in 76 % isolated yield (59:41 *E/Z*) from the reaction of iodobenzene and 3,5-epoxy-3-methyl-1-pentene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens nearer the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.43 (br s, 1 H, OH), 1.67 (s, 3 H, CH_3), 2.23 (t, 2 H, J = 6.3 Hz, CH_2C=), 3.31 (d, 2 H, J = 7.2 Hz, CH_2Ph), 3.62 (t, 2 H, J = 6.3 Hz, $C\underline{H}_2OH$), 5.38 (t, 1 H, J = 7.2 Hz, CH=), 7.08-7.22 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$) δ 15.99, 34.18, 42.72, 60.31, 125.90, 126.46, 128.29, 128.48, 132.47, 141.28.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.70 (s, 3 H, CH_3), 2.36 (t, 2 H, J = 6.6 Hz, CH_2C=), 5.44 (t, 1 H, J = 7.2 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 23.50, 34.36, 35.15, 60.72, 126.93, 128.31, 132.29, 141.39.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3379, 3084, 3063, 2928, 1603, 1493, 1452, 1379, 1182, 1094, 1054, 1005, 868, 789, 741, 703 cm^{-1}; HRMS: calculated for $C_{12}H_{16}O$ m/z 176.12012, found 176.12053. All spectral data were identical to those reported for this compound by Stolz-Dunn.[8]

(*E*)- and (*Z*)-3-Methyl-5-(4-methylphenyl)-3-penten-1-ol (Table 2, entry 1)

Obtained in 70 % isolated yield (56:44 *E/Z*) from the reaction of 4-iodotoluene and 3,5-epoxy-3-methyl-1-pentene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens nearer the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.74 (s, 3 H, CH_3), 2.29 (t, 2 H, J = 6.6 Hz, CH_2C=), 2.31 (s, 3 H, CH_3Ar), 3.35 (d, 2 H, J = 7.2 Hz, CH_2Ar), 3.70 (t, 2 H, J = 6.6 Hz, $C\underline{H}_2OH$), 5.44 (t, 1 H, J = 7.2 Hz, CH=), 7.08 (m, 5 H, phenyl), the proton of the hydroxyl

group was not seen; ^{13}C NMR ($CDCl_3$) δ 15.94, 20.99, 33.73, 42.70, 60.29, 126.73, 127.19, 128.14, 129.16, 132.17, 135.34.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.76 (s, 3 H, CH_3), 2.42 (t, 2 H, J = 6.6 Hz, CH_2C=), 5.51 (t, 1 H, J = 7.2 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 23.49, 33.89, 35.12, 60.70, 128.16, 131.98, 138.20.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3366, 2924, 1664, 1514, 1447, 1379, 1094, 1043, 868, 847 cm^{-1}; HRMS: calculated for $C_{13}H_{18}O$ m/z 190.13577, found 190.13589.

(*E*)- and (*Z*)-5-(3,4,5-Trimethoxyphenyl)-3-methyl-3-penten-1-ol (Table 2, entry 2)

Obtained in 62 % isolated yield (56:44 *E*/*Z*) from the reaction of 1-iodo-3,4,5-trimethoxybenzene and 3,5-epoxy-3-methyl-1-pentene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens nearer the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.76 (s, 3 H, CCH_3), 2.33 (t, 2 H, J = 6.3 Hz, CH_2C=), 3.34 (d, 2 H, J = 7.2 Hz, CH_2Ar), 3.72 (t, 2 H, J = 6.3 Hz, $C\underline{H_2}OH$), 3.82 (s, 3 H, CH_3O on C4 of aryl), 3.84 (s, 6 H, CH_3O's on C3 and C5 of aryl), 5.45 (t, 1 H, J = 7.2 Hz, CH=), 6.40 (s, 2 H, aryl), the proton of the hydroxyl group was not seen ; ^{13}C NMR ($CDCl_3$) δ 15.83, 34.33, 42.55, 55.81, 60.17, 60.48, 104.96, 126.55, 132.34, 135.98, 136.85, 153.04.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.79 (s, 3 H, CCH_3), 2.44 (t, 2 H, J = 6.6 Hz, CH_2C=), 3.74 (t, 2 H, J = 6.6 Hz, $C\underline{H_2}OH$), 5.51 (t, 1 H, J = 7.2 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 23.30, 34.39, 34.96, 60.70, 105.02, 126.03, 132.67, 137.00.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3466, 2939, 2839, 1591, 1508, 1458, 1421, 1331, 1238, 1182, 1126, 1043, 1009, 824, 779 cm^{-1}; HRMS: calculated for $C_{15}H_{22}O_4$ m/z 266.15181, found 266.15157.

(*E*)- and (*Z*)-5-(4-Ethoxycarbonylphenyl)-3-methyl-3-penten-1-ol (Table 2, entry 3)

Obtained in 57 % isolated yield (68:32 *E/Z*) from the reaction of ethyl 4-iodobenzoate and 3,5-epoxy-3-methyl-1-pentene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens nearer the hydroxy group.

The *E*-isomer: ^1H NMR ($CDCl_3$) δ 1.38 (t, 3 H, *J* = 7.2 Hz, $CH_2\underline{CH_3}$), 1.60 (br s, 1 H, OH), 1.75 (s, 3 H, CCH_3), 2.32 (t, 2 H, *J* = 6.3 Hz, CH_2C=), 3.43 (d, 2 H, *J* = 7.2 Hz, CH_2Ar), 3.73 (t, 2 H, *J* = 6.3 Hz, $\underline{CH_2}OH$), 4.36 (q, 2 H, *J* = 7.2 Hz, $\underline{CH_2}CH_3$), 5.44 (t, 1 H, *J* = 7.2 Hz, CH=), 7.23 (d, 2 H, *J* = 8.4 Hz, H's on C3 and C5 of aryl), 7.96 (d, 2 H, *J* = 8.4 Hz, H's on C2 and C6 of aryl); ^{13}C NMR ($CDCl_3$) δ 14.36, 16.06, 34.19, 42.68, 60.36, 60.83, 125.21, 125.70, 128.25, 129.79, 133.47, 146.68, 166.67.

The *Z*-isomer: ^1H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.79 (s, 3 H, CCH_3), 2.43 (t, 2 H, *J* = 6.6 Hz, CH_2C=), 3.44 (d, 2 H, *J* = 6.9 Hz, CH_2Ar), 3.71 (t, 2 H, *J* = 6.6 Hz, $\underline{CH_2}OH$), 5.49 (t, 1 H, *J* = 6.9 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 23.50, 34.35, 35.16, 60.65, 128.27, 129.77, 133.28, 146.79.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3418, 3034, 2934, 1717, 1610, 1576, 1416, 1367, 1310, 1278, 1171, 1107, 1045, 1022, 851, 760, 704 cm^{-1}; HRMS: calculated for $C_{15}H_{20}O_3$ m/z 248.14124, found 248.14150.

(*E*)- and (*Z*)-2-Hydroxymethyl-1-(2-(4-ethoxycarbonylphenyl)ethylidene)cyclohexane (Table 2, entry 4)

Obtained in 55 % isolated yield (67:33 *E/Z*) from the reaction of ethyl 4-iodobenzoate and 1-vinyl-8-oxabicyclo[4.2.0]octane. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the vinylic hydrogen.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 3 H, J = 7.2 Hz, CH_3), 1.40-1.89 (m, 7 H, 3 CH_2's of cyclohexane ring and OH), 2.28 (m, 3 H, CHC= and CH_2C=), 3.45 (m, 2 H, CH_2Ar), 3.76 (m, 2 H, $C\underline{H}_2OH$), 4.35 (q, 2 H, J = 7.2 Hz, $C\underline{H}_2CH_3$), 5.35 (t, 1 H, J = 7.5 Hz, CH=), 7.23 (d, 2 H, J = 8.1 Hz, H's on C2 and C6 of aryl), 7.95 (d, 2 H, J = 8.1 Hz, H's on C3 and C5 of aryl); ^{13}C NMR ($CDCl_3$) δ 14.31, 23.60, 26.62, 27.70, 30.05, 33.44, 46.92, 60.77, 63.68, 120.52, 123.37, 128.22, 129.34, 140.89, 146.94, 166.64.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 5.48 (t, 1 H, J = 6.9 Hz, CH=); ^{13}C NMR δ 21.68, 28.12, 33.14, 33.32, 38.87, 63.16, 125.84, 128.25, 129.82, 139.99.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3410, 2928, 2856, 1717, 1610, 1576, 1447, 1416, 1367, 1312, 1278, 1177, 1107, 1022, 852, 758, 704 cm^{-1}; HRMS: calculated for $C_{18}H_{24}O_3$ m/z 288.1725, found 288.17189.

(*E*)- and (*Z*)-5-Phenyl-3-penten-1-ol (Table 2, entry 5)

Obtained in 41 % isolated yield (80:20 *E/Z*) from the reaction of iodobenzene and 3,5-epoxy-1-pentene. The product was contaminated by an unknown compound (2:1 ratio of product to unknown). The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens next to the phenyl group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 2.30 (q, 2 H, *J* = 6.6 Hz, $C\underline{H}_2CH_2OH$), 3.37 (d, 2 H, *J* = 6.6 Hz, CH_2Ph), 3.63 (t, 2 H, *J* = 6.6 Hz, $C\underline{H}_2OH$), 5.49 (dt, 1 H, *J* = 15.3 Hz, J = 6.6 Hz, $=C\underline{H}CH_2CH_2$), 5.72 (dt, 1 H, *J* = 15.3 Hz, *J* = 6.6 Hz, $=C\underline{H}CH_2Ph$), 7.20-7.18 (m, 5 H, phenyl), the peak of hydroxy group was buried under peaks of the unknown compound.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 3.44 (δ, 2 H, *J* = 6.9 Hz, CH_2Ph).

The following spectral data were taken from a mixture of (*E*) and (*Z*)-5-phenyl-3-penten-1-ol and the unknown compound: IR (neat) 3400, 3063, 3028, 2930, 1713, 1603, 1495, 1432, 1373, 1180, 1126, 1049, 970, 700 cm^{-1}.

(*E*)- and (*Z*)-5-(3,4,5-Trimethoxyphenyl)-3,4-dimethyl-3-penten-1-ol (Table 2, entry 7)

Obtained in 15 % isolated yield (64:36 *E*/*Z*) from the reaction of 1-iodo-3,4,5-trimethoxybenzene and 3,5-epoxy-2,3-dimethyl-1-pentene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the protons of the vinylic methyl groups.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 1.64 and 1.77 (2 s, 6 H, $CH_3C=CCH_3$), 1.92 (s, 1 H, OH), 2.45 (t, 2 H, *J* = 6.9 Hz, $C\underline{H}_2CH_2OH$), 3.39 (s, 2 H, CH_2Ar), 3.72 (t, 2 H, *J* = 6.9 Hz, $C\underline{H}_2OH$), 3.83 (s, 6 H, CH_3O's on C3 and C5 of aryl), 3.86 (s, 3 H, CH_3O on C4 of aryl), 6.38 (s, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 18.53, 18.65, 37.78, 40.51, 56.07, 60.86, 61.06, 105.36, 122.40, 126.18, 130.04, 136.30, 153.09.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.78 and 1.82 (2 s, 6 H, $CH_3C=CCH_3$), 2.47 (t, 2 H, *J* = 6.6 Hz, $C\underline{H}_2CH_2OH$), 3.36 (s, 2 H, CH_2Ar), 3.75 (t, 2 H, *J* = 6.6 Hz, $C\underline{H}_2OH$); ^{13}C NMR same as the *E*-isomer or not seen, except δ 18.51, 18.70, 37.63, 40.04, 56.02, 60.98, 105.10, 130.27, 136.10, 153.13.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3452, 2939, 1589, 1506, 1458, 1420, 1331, 1236, 1182, 1126, 1042, 1009, 825, 781 cm^{-1}; HRMS: calculated for $C_{16}H_{24}O_4$ m/z 280.16746, found 280.16705.

(*E*)- and (*Z*)-5-(3,4,5-Trimethoxyphenyl)-3-methyl-3-hexen-1-ol (Table 2, entry 8)

Obtained in 11 % isolated yield (70:30 *E/Z*) from the reaction of 1-iodo-3,4,5-trimethoxybenzene and 4,6-epoxy-4-methyl-2-hexene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens nearer the hydroxy group. This compound was contaminated by *N,N*-dimethylacetamide.

The *E*-isomer: ^1H NMR ($CDCl_3$) δ 1.36 (d, 3 H, J = 7.2 Hz, CH_3CH), 1.60 (s, 1 H, OH), 1.71 (s, 3 H, CCH_3), 2.28 (t, 2 H, J = 6.3 Hz, CH_2C=), 3.68 (m, 1 H, CHAr), 3.81 (t, 2 H, J = 6.3 Hz, CH_2OH), 3.82 (s, 3 H, CH_3O on C4 of aryl), 3.85 (s, 6 H, CH_3O's on C3 and C5 of aryl), 5.48 (d, 1 H, J = 7.5 Hz, CH=), 6.44 (s, 2 H, aryl).

The *Z*-isomer: ^1H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.75 (s, 3 H, CCH_3), 2.41 (t, 2 H, J = 6.6 Hz, CH_2C=).

The following spectral data were taken from a mixture of (*E*)- and (*Z*)-5-(3,4,5-trimethoxyphenyl)-3-methyl-3-hexen-1-ol and *N,N*-dimethylacetamide: IR (neat) 3450, 2964, 2839, 1815, 1630, 1589, 1508, 1462, 1418, 1371, 1329, 1238, 1182, 1128, 1051, 1009, 833, 777, 663 cm^{-1}; HRMS: calculated for $C_{12}H_{22}O$ m/z 182.16707, found 182.16703.

(*E*)- and (*Z*)-6-Butyl-3-methyl-3,6-heptadien-1-ol (Table 2, entry 9)

Obtained in 25 % isolated yield (62:38 *E/Z*) from the reaction of 2-iodo-1-hexene and 3,5-epoxy-3-methyl-1-pentene. The *E*- to *Z*-isomer ratio was determined by integration

of the 300 MHz ^{1}H NMR spectral peaks corresponding to the protons of the 3-methyl group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3 H, *J* = 7.2 Hz, $C\underline{H}_3CH_2$), 1.26-1.42 (m, 5 H, $CH_2C\underline{H}_2CH_3$ and OH), 1.65 (s, 3 H, CCH_3), 2.01 (t, 2 H, *J* = 7.2 Hz, CH_2Pr), 2.29 (t, 2 H, *J* = 6.3 Hz, CH_2C=), 2.73 (d, 2 H, *J* = 7.2 Hz, $C\underline{H}_2CH$=), 3.67 (t, 2 H, *J* = 6.3 Hz, $C\underline{H}_2OH$), 4.71 (s, 2 H, CH_2=), 5.30 (t, 1 H, *J* = 7.2 Hz, CH=); ^{13}C NMR ($CDCl_3$) δ 14.03, 15.75, 22.49, 29.99, 34.56, 36.12, 42.78, 60.29, 109.09, 125.51, 132.68, 149.74.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.76 (s, 3 H, CCH_3), 2.33 (t, 2 H, *J* = 6.6 Hz, CH_2C=), 5.40 (t, 1 H, *J* = 7.2 Hz, CH=); ^{13}C NMR same as the *E*-isomer or not seen, except δ 23.52, 34.83, 34.99, 36.00, 60.63, 108.96, 125.77, 148.90.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3360, 3078, 2959, 2930, 1645, 1445, 1379, 1267, 1232, 1184, 1045, 1005, 889 cm^{-1}; HRMS: calculated for $C_{12}H_{22}O$ m/z 182.16707, found 182.16686.

<u>(*E,E*)- and (*Z,E*)-3-Methyl-3,6-undecadien-1-ol and (*E*)- and (*Z*)-3-methyl-3-penten-1-ol</u> (Table 2, entry 10)

Obtained in 40 % isolated yield as an inseparable mixture from the reaction of (*E*)-1-iodo-1-hexene and 3,5-epoxy-3-methyl-1-pentene. The ratio of 3-methyl-3,6-undecadien-1-ol to 3-methyl-3-penten-1-ol is 37:63. The *E,E*- to *Z,E*-isomer ratio of 3-methyl-3,6-undecadien-1-ol was unable to be determined by ^{1}H NMR spectral data.

The *E,E*-isomer of 3-methyl-3,6-undecadien-1-ol: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H, *J* = 7.2 Hz, $C\underline{H}_3CH_2$), 1.32 (m, 4 H, $C\underline{H}_2C\underline{H}_2CH_3$), 1.38 (br s, 1 H, OH), 1.72 (s, 3 H, CCH_3), 1.98 (m, 2 H, CH_2Pr), 2.72 (t, 2 H, *J* = 6.9 Hz, =$CHC\underline{H}_2CH$=), peaks of vinylic and homoallylic protons buried under 3-methyl-3-penten-1-ol.

The *Z,E*-isomer of 3-methyl-3,6-undecadien-1-ol: ^{1}H NMR ($CDCl_3$) same as the *E,E*-isomer or buried under 3-methyl-3-penten-1-ol.

The *E*-isomer of 3-methyl-3-penten-1-ol: ^{1}H NMR ($CDCl_3$) δ 1.47 (br s, 1 H, OH), 1.61 (d, 3 H, J = 7.2 Hz, $CHC\underline{H}_3$), 1.63 (s, 3 H, CCH_3), 2.25 (t, 2 H, J = 6.3 Hz, CH_2C=), 3.66 (t, 2 H, J = 6.3 Hz, $C\underline{H}_2OH$), 5.33 (q, 1 H, J = 7.2 Hz, CH=).

The *Z*-isomer of 3-methyl-3-penten-1-ol: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.72 (s, 3 H, CCH_3), 2.34 (t, 2 H, J = 6.9 Hz, CH_2C=), 5.42 (q, 1 H, J = 6.9 Hz, CH=).

The following spectral data were taken from a mixture of (*E,E*)- and (*Z,E*)-3-methyl-3,6-undecadien-1-ol and (*E*)- and (*Z*)-3-methyl-3-penten-1-ol: IR (neat) 3358, 2959, 2928, 1663, 1456, 1379, 1096, 1045, 966 cm^{-1}.

(*E*)- and (*Z*)-6-Butyl-3,6-heptadien-1-ol (Table 2, entry 12)

Obtained in 60 % isolated yield (82:18 *E/Z*) from the reaction of 2-iodo-1-hexene and 3,5-epoxy-1-pentene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^{1}H NMR spectral peaks corresponding to the allylic hydrogens nearer the hydroxy group.

The *E*-isomer: ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3 H, J = 7.2 Hz, CH_3), 1.29-1.42 (m, 4 H, $C\underline{H}_2C\underline{H}_2CH_3$), 1.57 (br s, 1 H, OH), 2.01 (t, 2 H, J = 7.2 Hz, CH_2Pr), 2.30 (q, 2 H, J = 6.3 Hz, $C\underline{H}_2CH_2OH$), 2.72 (d, 2 H, J = 6.6 Hz,=$CC\underline{H}_2CH$=),4.72 and 4.73 (2 s, 2 H, CH_2=), 5.43 (dt, 1 H, J = 15.3 Hz, J = 6.3 Hz, =$C\underline{H}CH_2CH_2$), 5.57 (dt, 1 H, J = 15.3 Hz, J = 6.6 Hz, =$C\underline{H}CH_2C$=); ^{13}C NMR ($CDCl_3$) δ 14.01, 22.45, 29.86, 35.71, 35.97, 39.56, 62.07, 109.52, 127.63, 131.55, 148.89.

The *Z*-isomer: ^{1}H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 2.78 (d, 2 H, J = 6.9 Hz, =$CC\underline{H}_2CH$=); ^{13}C NMR same as the *E*-isomer or not seen.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3371, 3078, 2930, 1645, 1456, 1433, 1379, 1232, 1164, 1128, 1047, 970, 889, 731, 696 cm^{-1}; HRMS: calculated for $C_{11}H_{20}O$ m/z 168.15163, found 168.15142.

(*E*)- and (*Z*)-5-(1-Cyclohexenyl)-3-methyl-3-penten-1-ol (Table 2, entry 13)

Obtained in 44 % isolated yield (67:33 *E*/*Z*) from the reaction of 1-cyclohexenyl triflate and 3,5-epoxy-3-methyl-1-pentene. The *E*- to *Z*-isomer ratio was determined by integration of the 300 MHz ^1H NMR spectral peaks corresponding to the allylic hydrogens nearer the hydroxy group.

The *E*-isomer: ^1H NMR ($CDCl_3$) δ 1.45 (br s, 1 H, OH), 1.55-1.63 (m, 4 H, H's on C4 and C5 of cyclohexenyl), 1.65 (s, 3 H, CH_3), 1.91 and 1.98 (2 m, 4 H, H's on C3 and C6 of cyclohexenyl), 2.28 (t, 2 H, J = 6.3 Hz, $C\underline{H}_2CH_2OH$), 2.65 (d, 2 H, J = 7.2 Hz, $=CC\underline{H}_2CH=$), 3.67 (t, 2 H, J = 6.3 Hz, $C\underline{H}_2OH$), 5.27 (t, 1 H, J = 7.2 Hz, $C\underline{H}=CCH_3$); ^{13}C NMR ($CDCl_3$) δ 15.77, 22.55, 23.01, 25.28, 28.61, 36.63, 42.81, 60.21, 121.15, 125.91, 132.19, 136.79.

The *Z*-isomer: ^1H NMR ($CDCl_3$) same as the *E*-isomer or not seen, except δ 1.75 (s, 3 H, CH_3), 2.34 (t, 2 H, J = 6.6 Hz, $C\underline{H}_2CH_2OH$); ^{13}C NMR same as the *E*-isomer or not seen, except δ 23.52, 25.31, 28.74, 35.00, 36.29, 60.66, 121.09, 126.17, 132.21, 137.50.

The following spectral data were taken from a mixture of the *E*- and *Z*-isomers: IR (neat) 3360, 2928, 2835, 1670, 1439, 1379, 1267, 1132, 1045, 920, 870, 856, 800 cm^{-1}; HRMS: calculated for $C_{12}H_{20}O$ m/z 180.15135, found 180.15142.

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GENERAL SUMMARY

In this dissertation, the palladium-promoted cross-coupling of alkenyl heterocycles with organomercurials, organic halides and triflates has been demonstrated.

In the first part of this thesis, the development of the palladium(II)-promoted cross-coupling of alkenyl 2-azetidinones with aryl- and vinylmercurials was discussed. Functionally-substituted 3-alkenamides were isolated as mixtures of *E*- and *Z*-isomers in good to high yields. Catalytic amounts of palladium could be employed in the reaction if cupric chloride and oxygen were used to reoxidize the palladium. These reactions are the first observed examples of alkenyl 2-azetidinones reacting with organometallic reagents to afford 3-alkenamides.

In the second part of this thesis, the palladium(0)-catalyzed cross-coupling of alkenyl 2-azetidinones with aryl and vinylic halides was explored. The arylation of alkenyl 2-azetidinones proceeded in high yield and was both regio- and stereoselective. The vinylation of alkenyl 2-azetidinones, however, afforded the corresponding substituted 3-alkenamides in low yield.

In the third part of this thesis, the palladium(0)-catalyzed reaction of vinylic epoxides with various aryl and vinylic halides and triflates was discussed. The allylic alcohols were isolated in good to high yields as mixtures of stereoisomers with preference for the formation of *E*-isomers.

In the final part of this thesis, the palladium-promoted cross-coupling of vinylic oxetanes with various aryl and vinylic halides and triflates was also investigated. The arylation of vinylic oxetanes bearing unsubstituted carbon-carbon double bonds proceeded in good yield. The vinylation of vinylic oxetanes, however, afforded the corresponding homoallylic alcohols in only low yields.

ACKNOWLEDGEMENTS

I would like to thank my major professor, Richard C. Larock, for his guidance, kindness, understanding, patience, and financial support during the course of this work.

I would like to thank Chi Tu, Lisa Hasvold, and Mark Doty for the valuable time they spent helping me type and correct this dissertation and other paperwork during these years. I would like to thank Hoseok Yang, Dr. Sandi Stolz-Dunn, and Dr. William Gong for providing chemicals which made the course of this work much easier and faster. I would like to thank the following people for their helpful and stimulating discussions and for their friendship: Dr. William Leong, Dr. Mann-yan Kuo, Tim Hightower, Kelvin Sham, Liangqin Guo, Yao Wang, and John Zenner.

I would like to thank my husband, Ping, who encouraged and supported me to pursue this degree and all of my dreams. I would like to thank my two and a half year-old son, Kevin, who always waved bye-bye while smiling and never did heart-breaking crying, for his cooperation and understanding while his mother could not spend a little more time with him. Finally, I would like to express my deepest thanks to my mother, who spent the last two and a half years taking care of my son for days and nights. Without her help, this work would not have been possible.