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Synthesis of allylic and homoallylic alcohols via organometallic ring-opening of vinylic epoxides and oxetanes

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Stolz-Dunn, Sandra K., Ph.D.

Iowa State University, 1989

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Synthesis of allylic and homoallylic alcohols via organometallic ring-opening of vinylic epoxides and oxetanes

by

Sandra K. Stolz-Dunn

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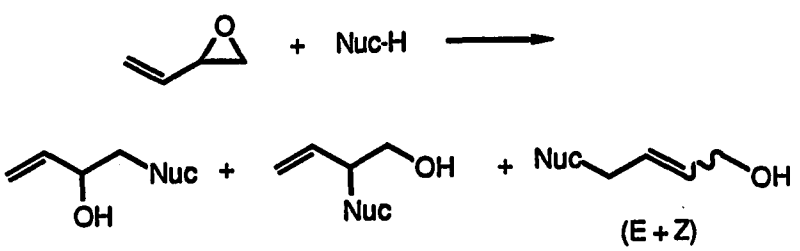
ABBREVIATIONS

Ar	aryl
Bu	butyl
dba	dibenzylideneacetone
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
Et	ethyl
HMPA	hexamethylphosphoramide
IR	infrared
LDA	lithium diisopropyl amide
m-CPBA	m-chloroperoxybenzoic acid
Me	methyl
NMR	nuclear magnetic resonance
Ph	phenyl
TBAA	tribenzylideneacetylacetone
THF	tetrahydrofuran
TLC	thin layer chromatography

CHAPTER I. LITERATURE REVIEW

Introduction

Over the past several decades, reactions involving nucleophilic and organometallic displacements of allylic compounds have been well studied and reviewed.[1] Nucleophilic and organometallic additions to vinyl epoxides have become useful synthetic reactions, when the regio- and stereochemistry of the product can be controlled. However, many times these reactions are not regioselective; mixtures of 1,2- and 1,4-addition products are formed. The 1,4-addition product is also generally produced as a mixture of E- and Z-isomers. The E/Z ratio, however, is generally greater than 80:20 (eq. 1.1).



(1.1)

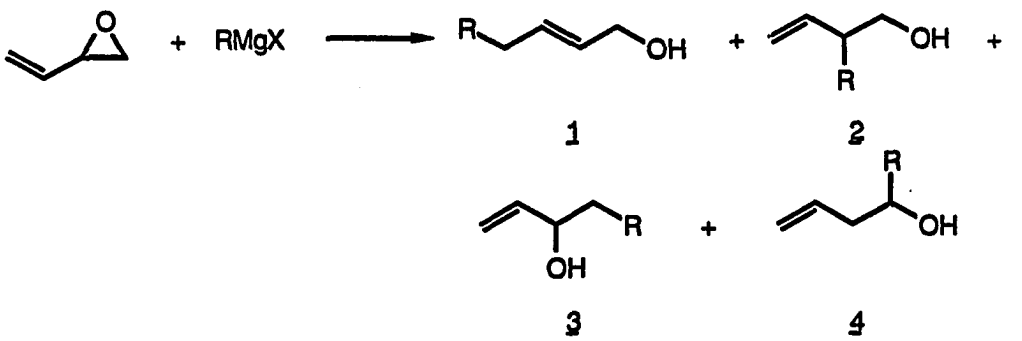
In the first part of this chapter, the reactions of vinylic epoxides with organometallic nucleophiles will be discussed. Included in this class of nucleophiles are organomagnesium, -lithium, -copper, and -boron reagents. Next, the palladium(0)-catalyzed nucleophilic ring-opening of vinylic epoxides will be examined. The nucleophiles are divided into three classes: carbon, heteroatom and other

nucleophiles. Finally, the palladium-mediated coupling of vinylic epoxides with organostannanes, -mercurials and -boranes will be reviewed.

Additions of Organometallic Nucleophiles to Vinylic Epoxides

Organomagnesium reagents

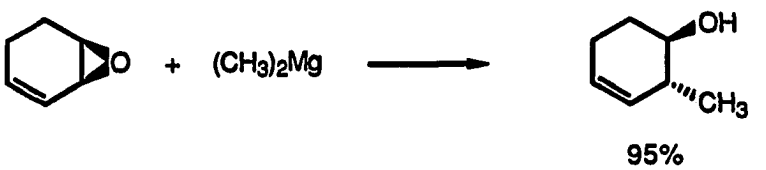
Alkyl and aryl Grignard reagents were the first organometallic nucleophiles reported to react with butadiene monoepoxide (eq. 1.2).[2-4] It was initially reported that the



1 2 3 4 (1.2)

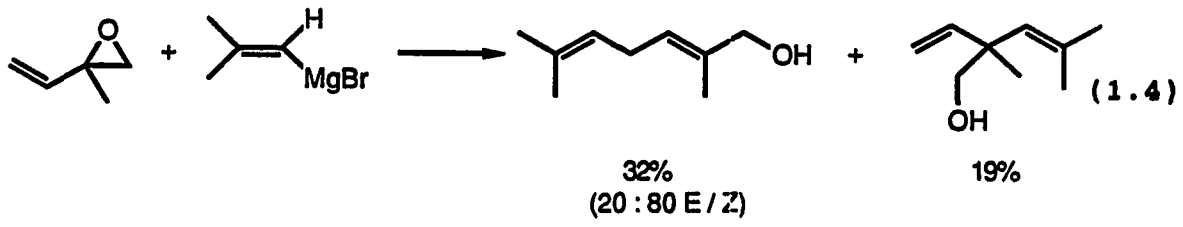
reaction yielded solely 1,4-addition product 1, but closer examination of the reaction revealed that mixtures of alcohols 1-4 are obtained.[5-12] The ratio of products is dependent upon the Grignard reagent.

A single alkylation product was obtained, however, when cyclohexadiene monoepoxide was allowed to react with dimethylmagnesium (eq. 1.3).[13]



95% (1.3)

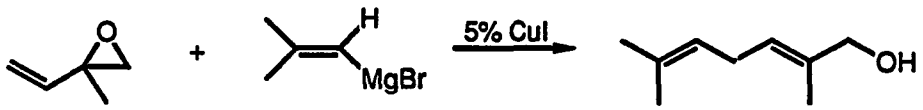
Excellent results are also obtained when vinylic epoxides are allowed to react with Grignard reagents in the presence of a catalytic amount of copper iodide (eqs. 1.4 and 1.5).[14,15]



32%
(20 : 80 E / Z)

19%

(1.4)



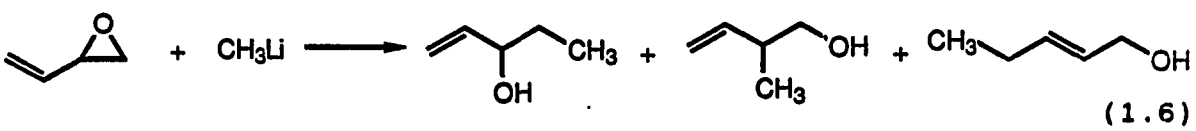
79%
(96 : 4 E / Z)

(1.5)

This reaction has recently been used in the synthesis of chiloscyphone[16] and co-enzyme Q_{10}.[17]

Organolithium reagents

When butadiene monoepoxide was treated with organolithium reagents, mixtures of products were obtained (eq. 1.6).[10,11]



17 : 63 : 20
(1.1 : 1 E/Z)

(1.6)

The ratio of products depended upon the organolithium reagent and the procedure used to run the reaction.

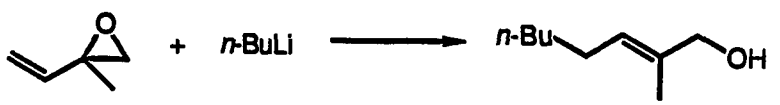
Similar results were obtained when cyclic vinylic epoxides were used in the reaction.[13,18] Saddler and Fuchs found, however, when they treated a cyclic epoxy vinyl sulfone with methyllithium that the regio- and stereochemistry of the

product could be controlled if lithium perchlorate was added to the reaction (eq. 1.7).[19]

81%
(95 : 5 cis / trans)

(1.7)

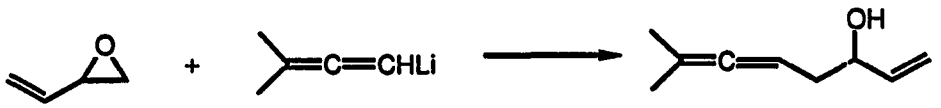
If 3-methyl-3,4-epoxy-1-butene was allowed to react with organolithium reagents, the 1,4-addition product was formed exclusively or predominantly, as a mixture of stereoisomers (eq. 1.8).[12,20,21]



97%
(16 : 84 E / Z)

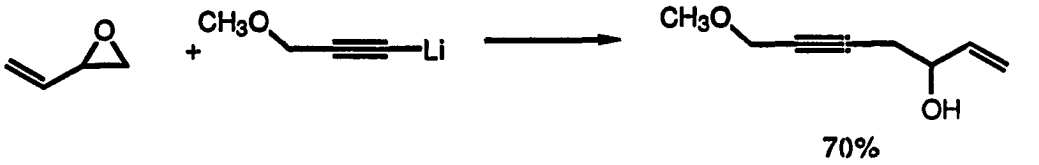
(1.8)

Blame et al.[22,23] and Doutheau et al.[24] have found that the reactions of allenyl- or alkynyllithium compounds with butadiene monoepoxide will generally give rise to products resulting from attack of the organolithium species on the unsubstituted carbon of the vinylic epoxide (eqs. 1.9 and 1.10). When cyclic vinylic epoxides were treated with



77%

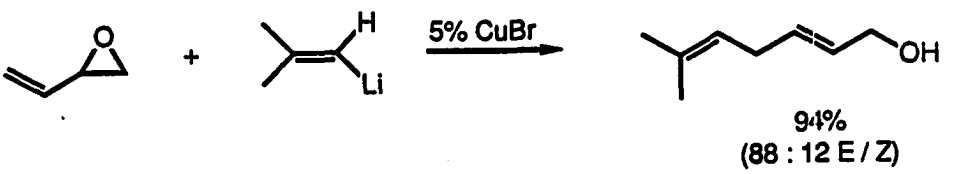
(1.9)



70% (1.10)

alkynyllithium reagents, however, only the 1,2-addition product was obtained.[25] The product of this reaction has been used to synthesize a prostaglandin intermediate.

Just as with organomagnesium reagents, reactions between vinylic epoxides and organolithium compounds catalyzed by copper produced allylic alcohols as predominantly the E-isomer (eq. 1.11).[14]



94% (88 : 12 E / Z) (1.11)

Tamura and co-workers have reported that allylic alcohols of Z-configuration can be prepared with a high degree of regio- and stereoselectivity, if acyclic vinylic epoxides were allowed to react with alkyllithium reagents in the presence of a base, such as a tertiary amine or lithium alkoxide (eq. 1.12).[26,27] This reaction has been used to prepare

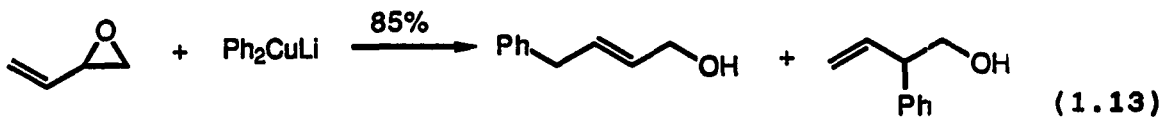
(1.12)

no base	76%	(88 : 12 E / Z)
1 *n*-BuOLi	73%	(97 : 3 E / Z)

α-santalol, which is one of the main constituents in East Indian sandalwood oil.[26,27]

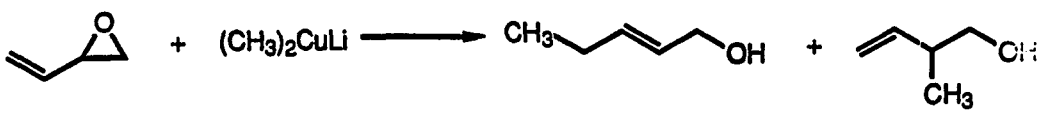
Organocopper reagents

Organocuprate reagents have proven to be superior reagents for the formation of allylic alcohols from vinylic epoxides. Since it was known that copper(I) salts promoted the conjugate addition of Grignard reagents to α,β-unsaturated ketones,[28,29] early researchers extended this reaction to include vinylic epoxides. It was found that organocuprate reagents would add to vinylic epoxides predominantly in a 1,4-fashion to yield the corresponding E-allylic alcohols with a high degree of stereoselectivity (eqs. 1.13 and 1.14).[9,10] Mechanistic aspects of these



85 : 15 (1.13)

(90 : 10 E/Z)



94 : 6 (1.14)

(3.8 : 1 E/Z)

reactions have been studied recently.[30]

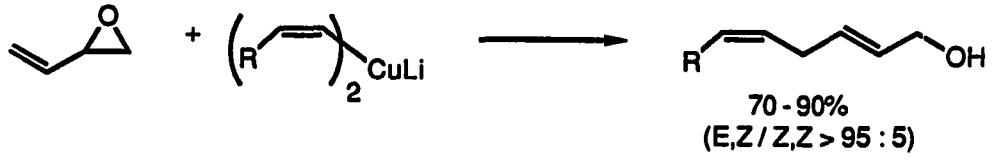
Lipshutz and co-workers have found that nearly the same results as those shown in equations 1.13 and 1.14 could be obtained, if 3-methyl-3,4-epoxy-1-butene was allowed to react with organocuprates of the type $[R_2Cu(CN)Li_2]$.[31,32]

Ghribi et al.[33] and Alexakis et al.[34] have found that they were able to control the regio- and stereoselectivity of

the reaction of 3-methyl-3,4-epoxy-1-butene with alkylcopper reagents. If the reactions were run in the presence of one equivalent of boron trifluoride etherate, the E-isomer of the allylic alcohol was formed quantitatively.

In the reactions shown in equations 1.13 and 1.14, only one of the alkyl groups of the organocuprate can react with a vinylic epoxide; the other is sacrificed. In order to overcome this drawback, Johnson and Dhanoa have studied the reactions of vinylic epoxides with organocuprates of the type $[(CH_3SOCH_2CuR)Li]$.[35] They found that allylic alcohols were obtained exclusively as the E-isomer from these reactions.

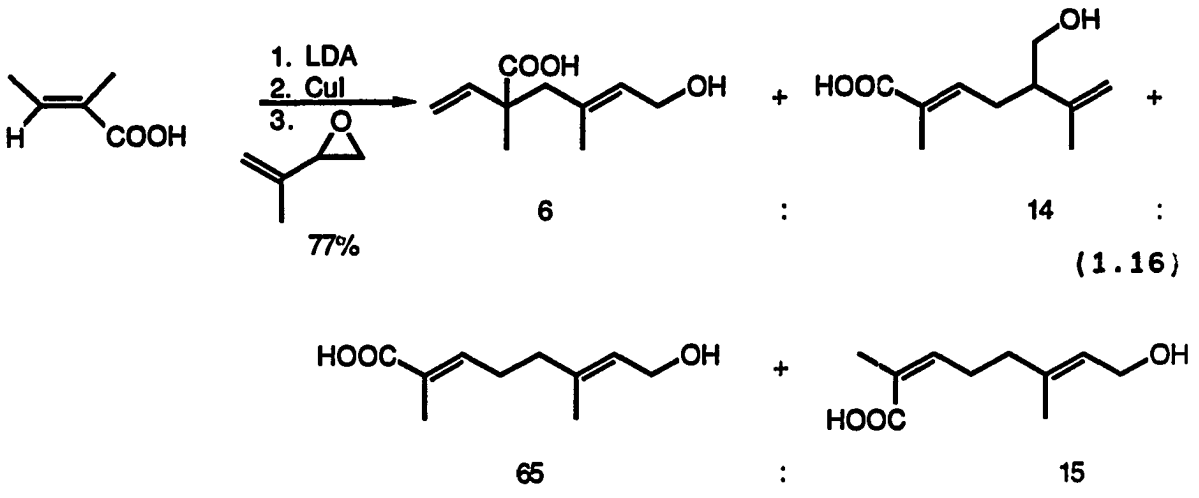
It has been reported that acyclic vinylic epoxides will react with vinylcopper derivatives (eq. 1.15).[14,36]



(1.15)

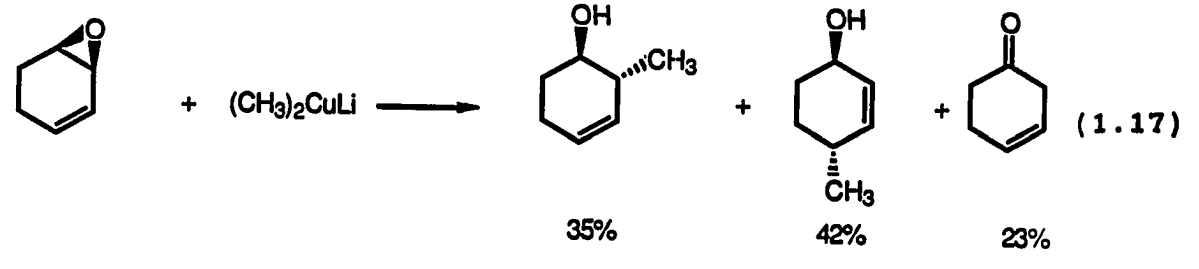
These reactions produced excellent yields of the corresponding 1,4-dienols in a highly stereospecific manner. This methodology has been used to prepare the sex pheromone of the potato tuberworm moth.[15]

It has been found that copper dienolates, derived from α,β-unsaturated acids, will react with acyclic vinylic epoxides to form mixtures of regio- and stereoisomers (eq. 1.16).[37] The mixture of regioisomers arises because



vinylic epoxides can react with organocopper reagents in either an S_N2 or S_N2' fashion and because copper dienolates can be alkylated at either the α or γ carbon. The ratio of products formed depended both upon the α,β-unsaturated acid used and the structure of the initial vinylic epoxide.

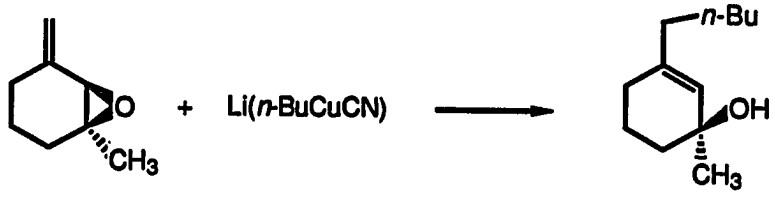
Unlike the additions of organocuprate reagents to acyclic vinylic epoxides, the reactions with cyclic vinylic epoxides yielded a significant amount of the 1,2-addition product (eq. 1.17).[13,17,38-40] Similar results were obtained when



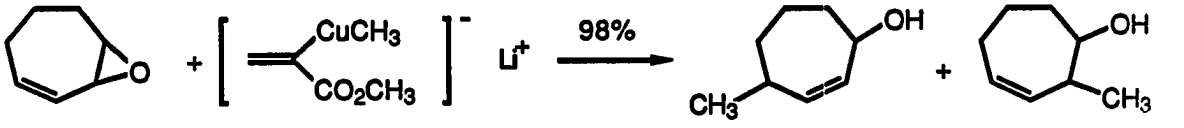
cyclohexadiene monoepoxide was allowed to react with dilithium pentamethyltricuprate.[41]

Marino and co-workers have allowed mixed cyano- and

acrylatecuprates to react with cyclic vinylic epoxides with good success (eqs. 1.18 and 1.19).[42,43] Here they observe



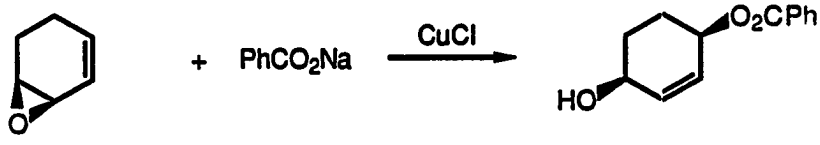
85% (1.18)



97 : 3 (1.19)

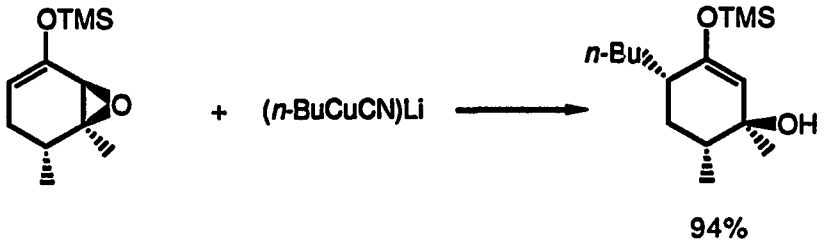
that the amount of 1,2-addition product was greatly reduced or non-existent.

Marino and Jaen have found a mild method for the 1,4-syn opening of certain cyclic vinylic epoxides, using sodium carboxylates in the presence of cuprous chloride (eq. 1.20).[44]



83% (1.20)

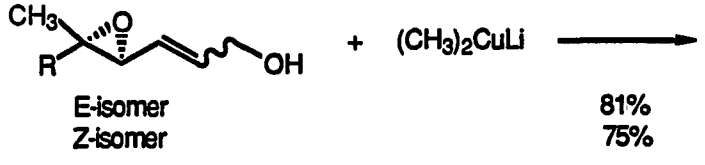
It has been reported in the literature that enol ethers of 2,3-epoxycycloalkenones will react with alkyl- and phenylcopper reagents in a regio- and stereoselective manner to yield, in most cases, the 1,4-trans adducts (eq. 1.21).[45-48] Vinylic cuprates show a regioselectivity that



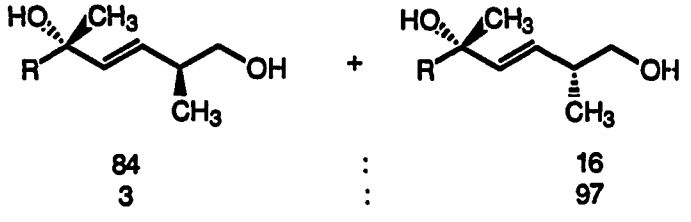
(1.21)

is dependent on the substitution pattern of each particular substrate. The 1,2-addition products are obtained, however, if organolithium or -magnesium reagents are used in the reaction.[48]

Marshall and Trometer have studied the reactions of optically active acyclic vinylic epoxides with organocuprate reagents (eq. 1.22).[49] They found that the reaction proceeded



(1.22)



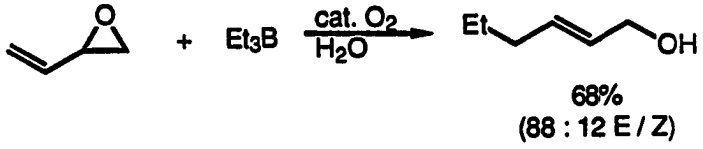
predominantly in an anti S_N2' fashion to afford the E-allylic alcohols.

Saddler and Fuchs have reported that optically active cyclic epoxy vinyl sulfones will react with organocuprates in the presence of trimethylaluminum to yield the cis-1,4-addition product.[19]

Since the reactions of vinylic epoxides with organocopper reagents can proceed with a high degree of regio- and stereoselectivity, these reactions have been used to synthesize a number of complex molecules and natural products. These reactions have been used to prepare trans-cycloalkenes,[50] pheromones,[15] steroids,[51] and prostaglandins.[52]

Organoboron reagents

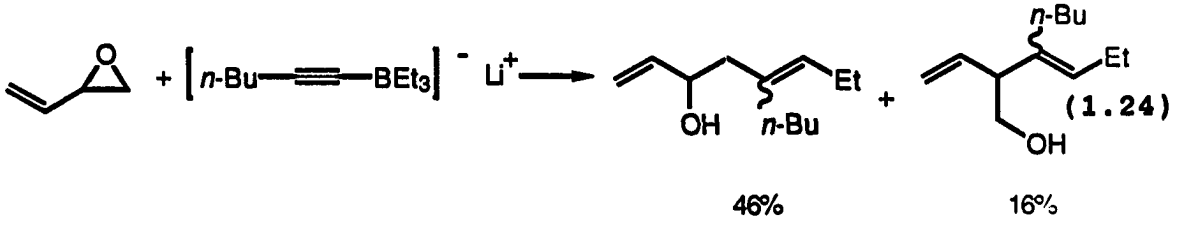
It has been shown that alkylboranes will undergo 1,4-additions to butadiene monoepoxide (eq. 1.23).[53] This



(1.23)

reaction is believed to occur via a free-radical chain mechanism. Trialkylboranes will also undergo additions to ethynyl epoxides to produce the corresponding allenic alcohols.[54]

Mas and co-workers have found that vinylic epoxides will react with lithium trialkylalkynylborates (eq. 1.24).[55]



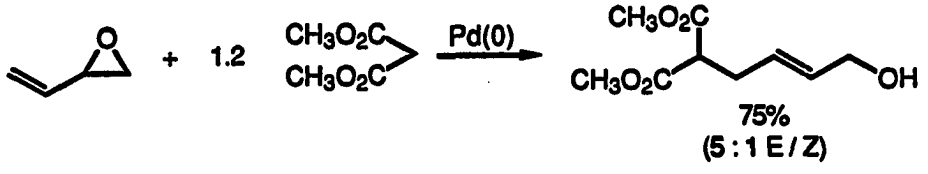
(1.24)

Unfortunately, the products of these reactions were isolated as mixtures of regio- and stereoisomers.

Palladium(0)-Catalyzed Nucleophilic Ring-Opening of Vinylic Epoxides

Carbon nucleophiles

In 1981 Trost and Molander[56] and Tsuji et al.[57] independently reported that vinylic epoxides will react with stabilized carbon nucleophiles in the presence of a catalytic amount of palladium(0) to produce allylic alcohols in good yields (eqs. 1.25-1.28). These reactions are generally highly



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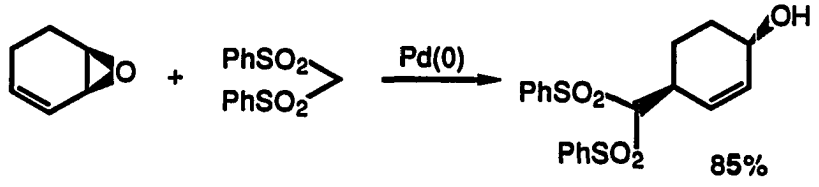

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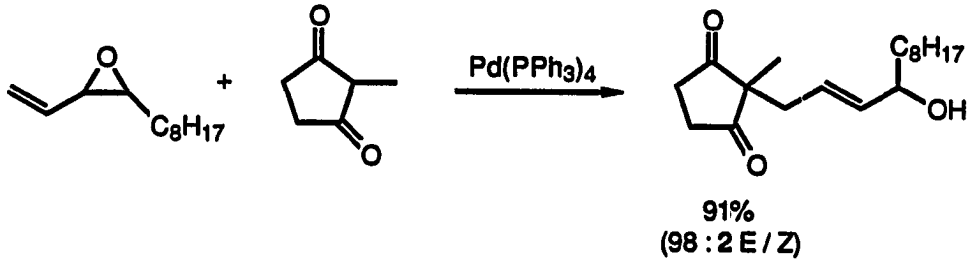

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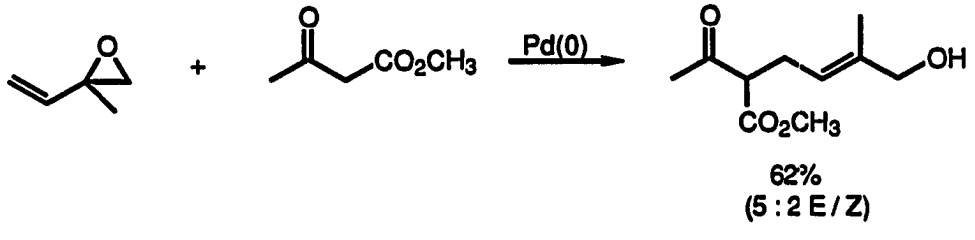


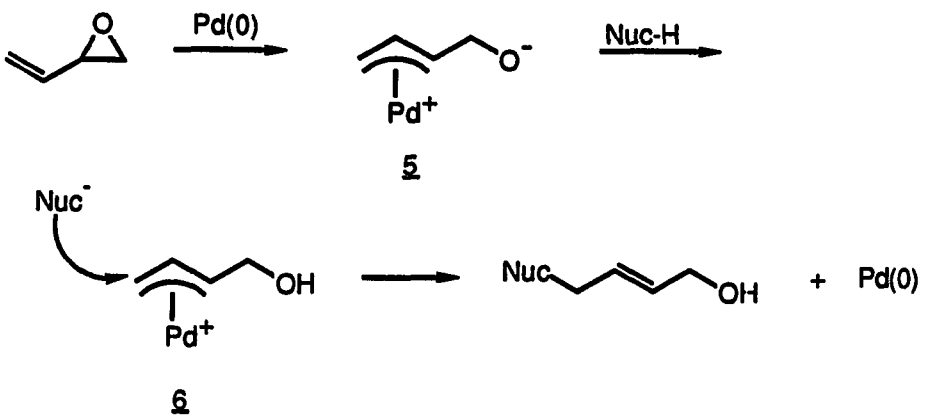
(1.28)

regio- and stereoselective. If butadiene monoepoxide is used in the reaction or a trisubstituted allylic alcohol is formed, however, a mixture of stereoisomers is produced.

Since the palladium-catalyzed reactions of vinylic epoxides with stabilized carbon nucleophiles show a high degree of regio- and stereoselectivity, they have recently found considerable utility in the synthesis of natural products. These reactions have been used in the synthesis of steroids,[58] vitamin D_3,[59] prostaglandins,[60] digitoxigenin,[61] and punctaporonin B.[62] Trost and co-workers have also used this methodology to prepare macrocycles[63] and α-dienyl-ω-allyl acetates.[64]

The following mechanism has been proposed to explain how allylic alcohols are produced from the reactions illustrated in equations 1.25-1.28 (Scheme 1.1).[56,57] In the first step

Scheme 1.1.



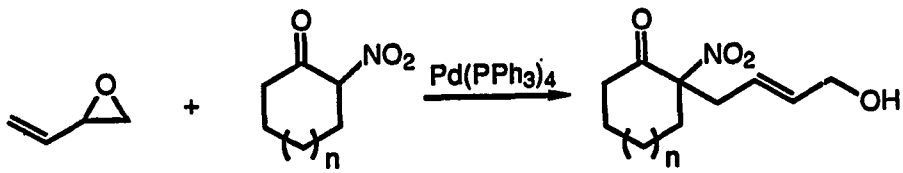
5

6

of the mechanism, the palladium(0)-catalyst oxidatively adds to the vinylic epoxide, forming (π-allyl)palladium

intermediate 5. The alkoxide ion, thus formed, abstracts the acidic proton of the nucleophile. The nucleophile then attacks the least hindered end of cationic (π-allyl)palladium complex 6, yielding the allylic alcohol and regenerating the palladium(0)-catalyst.

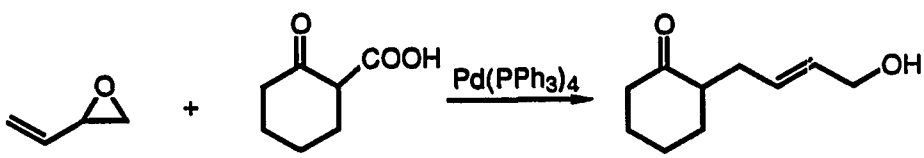
In addition to the nucleophiles used in equations 1.25-1.28, it has been found that nitrocycloalkanones can be used in the palladium(0)-catalyzed nucleophilic ring-opening of vinylic epoxides (eq. 1.29).[65]



n=6
89%
(9:1 E/Z)

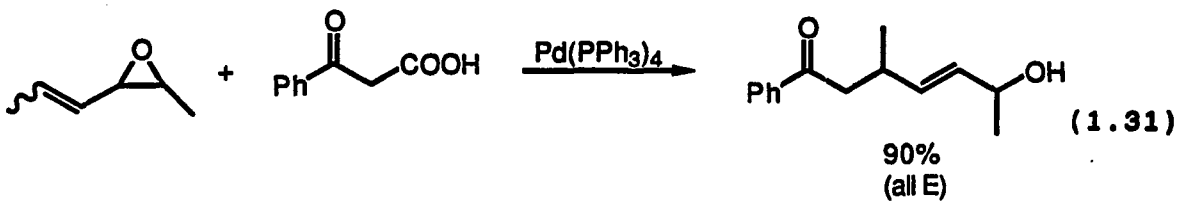
(1.29)

Tsuda and co-workers have reported that vinylic epoxides will react with β-keto acids in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0), with quantitative evolution of carbon dioxide, to produce keto allylic alcohols in good yields.[66] The reactions shown in



88%
(4.5:1 E/Z)

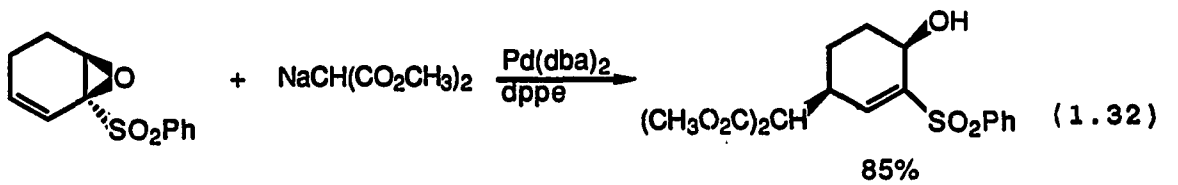
(1.30)



(1.31)

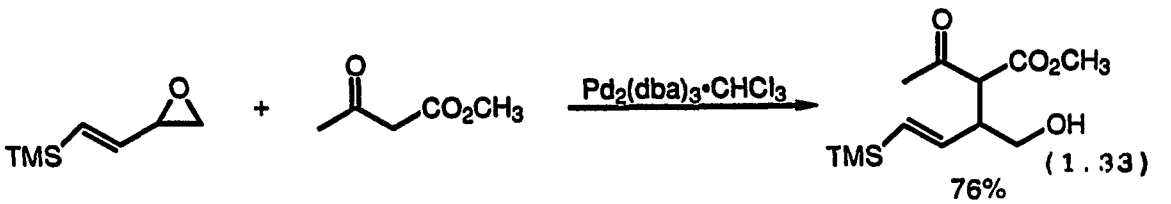
equations 1.30 and 1.31 once again demonstrate a high degree of regio- and stereoselectivity, except when butadiene monoepoxide is used in the reaction.

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 alcohols. Backvall and Juntunen have found that 1,2-epoxy-2-(phenylsulfonyl)-3-alkenes will participate in the reaction (eq. 1.32).[67]



(1.32)

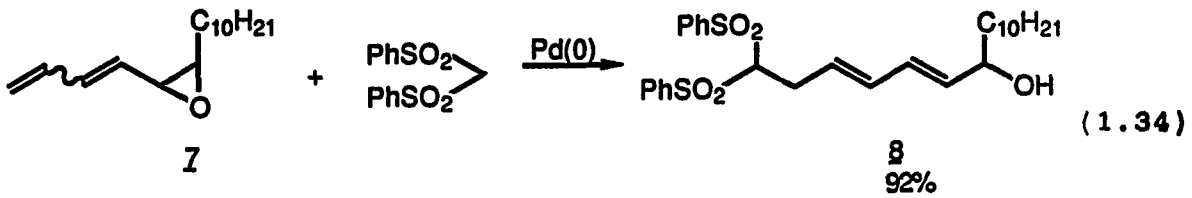
Tsuji and co-workers have found that γ-trimethylsilylated vinylic epoxides will react with stabilized carbon nucleophiles in the presence of a catalytic amount of palladium(0) to yield exclusively the 1,2-addition product (eq. 1.33).[68] This unusual regioselectivity was attributed



(1.33)

to electronic rather than steric factors.

Trost and co-workers have reported that dienyl epoxides can also react with stabilized carbon nucleophiles in the presence of a palladium(0) catalyst (eq. 1.34).[69] When

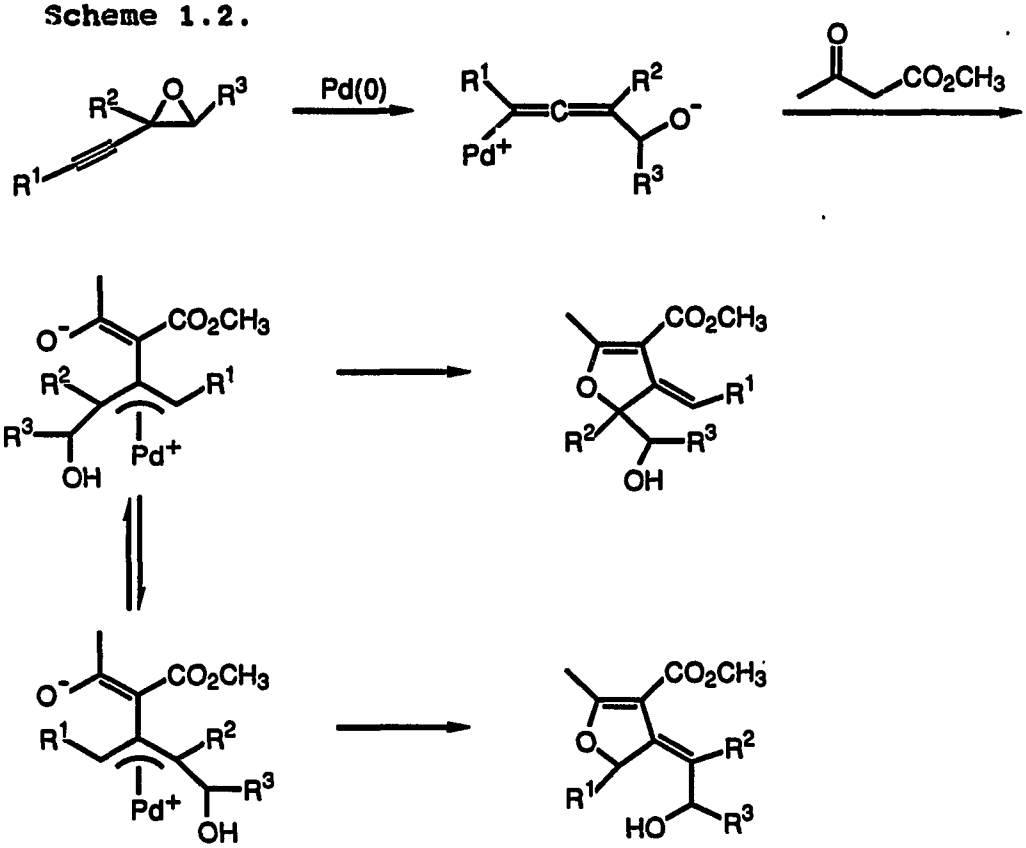


7 8 92% (1.34)

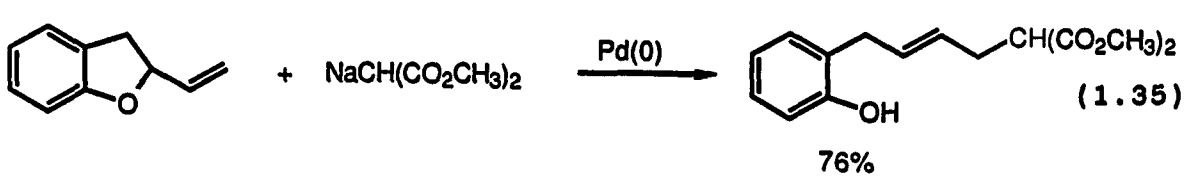
compound 7 was used in the reaction, it was found that the nucleophile attacked only the terminal end of the dienyl epoxide. The regioselectivity of the reaction shown in equation 1.34, however, is dependent upon the substituents present on the dienyl epoxide.

Minami and co-workers have found that 3-alkylidene-2,3-dihydrofuran-4-carboxylates can be formed in high yields from the reactions of α-alkynyl epoxides with β-keto esters in the presence of a catalytic amount of palladium(0) (Scheme 1.2).[70] It was found that the regioselectivity of these reactions depended upon substituents, R_1-R_3.

Scheme 1.2.

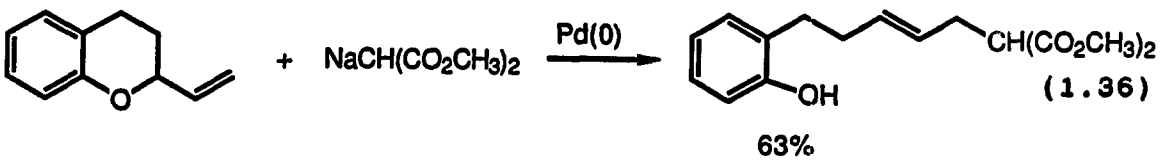


Other cyclic allyl ethers have also been found to be ring-opened by a palladium(0) catalyst. The intermediate (π-allyl)palladium complexes can then react with stabilized carbon nucleophiles. Hosokawa and co-workers have found that 2-vinyl-2,3-dihydrobenzofurans and 2-vinylchroman will participate in the palladium(0)-catalyzed nucleophilic ring-opening reactions, to yield the corresponding phenols (eqs. 1.35 and 1.36).[71]



(1.35)

76%

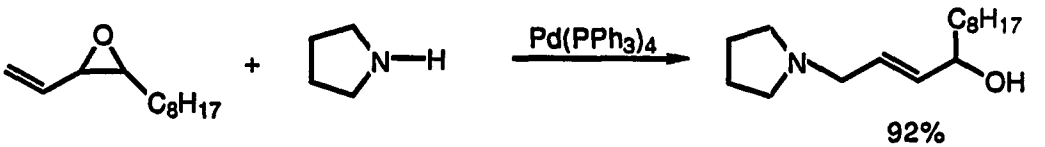


63% (1.36)

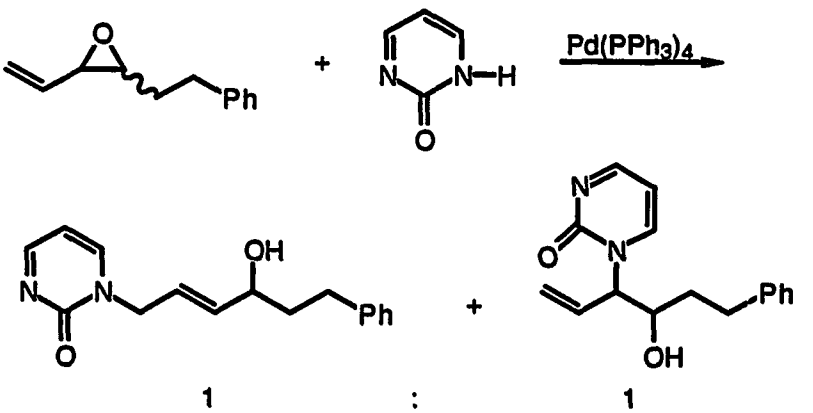
Heteroatom nucleophiles

In addition to stabilized carbon nucleophiles, heteroatom nucleophiles have also been observed to react with vinylic epoxides in the presence of a catalytic amount of palladium(0). The reactions of vinylic epoxides with nitrogen, oxygen, sulfur and azide nucleophiles will be discussed.

Trost et al.[72,73] and Tsuji et al.[57] have both reported that amines could be used in the palladium(0)-catalyzed nucleophilic ring-opening of vinylic epoxides. As one can see from the results given in equations 1.37 and 1.38, amines will



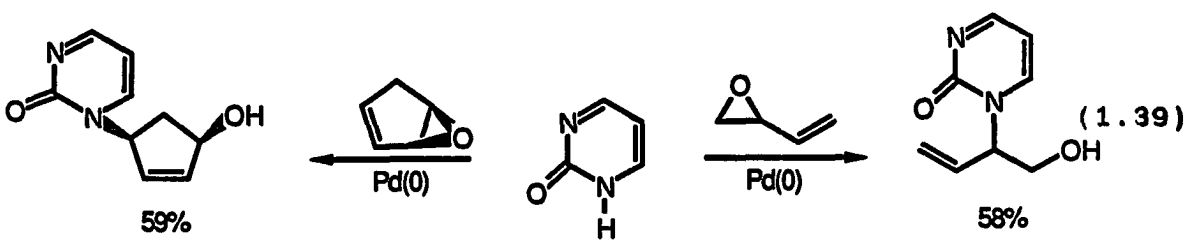
92% (1.37)



1 : 1 (1.38)

add to vinylic epoxides in the presence of a palladium(0) catalyst in both a 1,2- and 1,4-manner. The 1,4-addition product, formed by distal attack of the amine on the intermediate (π-allyl)palladium species, is produced as only the E-isomer.

Trost and co-workers have found that the choice of vinylic epoxide may play a role in the regioselectivity of this reaction. They found that amines will attack cyclic vinylic epoxides in the presence of palladium(0) to form exclusively the 1,4-addition product (eq. 1.39).[73] However,



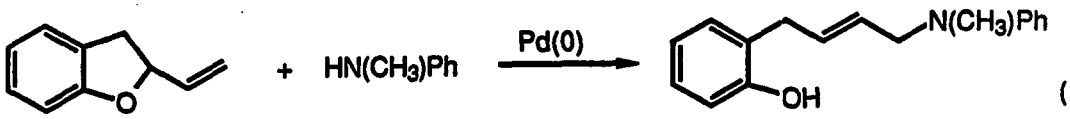
(1.39)

when acyclic vinylic epoxides are used in the reaction, only the 1,2-addition product is isolated.

Trost and co-workers have used the reactions of vinylic epoxides with amines and a palladium catalyst to prepare aristeromycin and 2',3'-diepi-aristeromycin.[73] The reaction has also been used in the synthesis of optically active isoquinuclidines.[74]

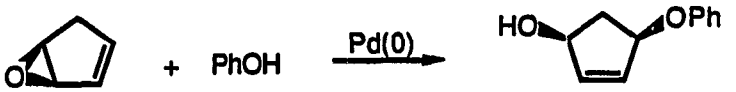
Hosokawa and co-workers have demonstrated that N-methylaniline will react with 2-vinyl-2,3-dihydrobenzofuran

in the presence of a catalytic amount of palladium(0), to yield the corresponding phenol (eq. 1.40).[71]

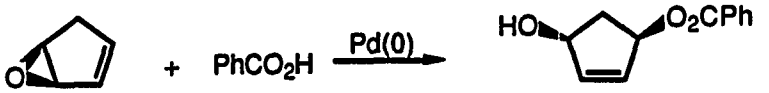


46% (1.40)

Oxygen nucleophiles have also been found to participate in the palladium(0)-catalyzed nucleophilic ring-opening of vinylic epoxides. Deardorff and co-workers have found that cyclopentadiene monoepoxide will react with phenol and carboxylic acids in the presence of palladium(0).[75] From the results given in equations 1.41 and 1.42, one can see that



82% (1.41)



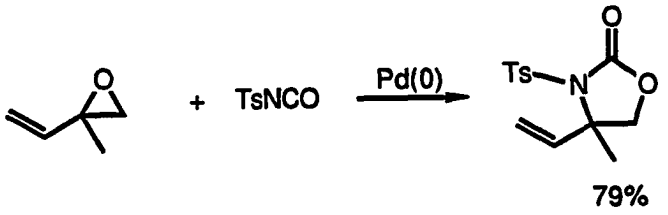
87% (1.42)

<u>cis</u>-1,4-addition products are formed selectively in these reactions.

Deardorff and co-workers have also demonstrated that silyl-protected alcohols can be prepared from the palladium(0)-catalyzed reactions of cyclopentadiene monoepoxide with silyl phenoxides or silyl carboxylates.[76]

Isocyanates have also been shown to participate in the palladium(0)-catalyzed nucleophilic ring-opening of vinylic

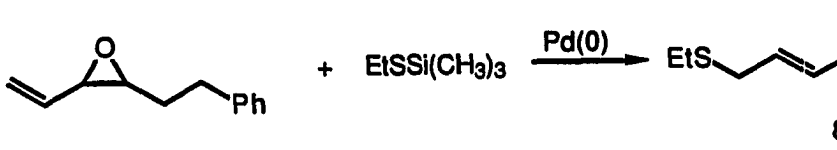
epoxides. Trost and Sudhakar allowed vinylic epoxides to react with various isocyanates in the presence of a palladium(0) catalyst (eq. 1.43).[77] It was found that



(1.43)

isocyanates will react with the intermediate (π-allyl)-palladium species, formed by the reaction of a vinylic epoxide with palladium(0), to yield only the N-alkylated product. None of the corresponding O-alklated product was ever produced in these reactions.

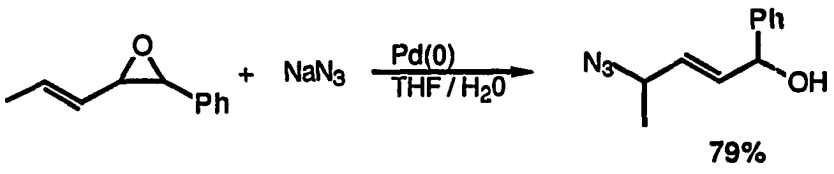
Trost and Scanlan have reported that allyl sulfides could be prepared in a highly regio- and stereoselective manner if the palladium(0)-catalyzed nucleophilic ring-opening of vinylic epoxides was run using alkylthiotrimethylsilanes as the nucleophiles (eq. 1.44).[78] The silyl group is cleaved at



(1.44)

the end of the reaction to form the corresponding allylic alcohol. If thiols were used directly in this reaction, the desired allyl sulfides were formed in irreproducible yields due to poisoning of the palladium catalyst.

Tenaglia and Waegell have studied the palladium-catalyzed reactions of vinylic epoxides with sodium azide (eq. 1.45).[79]



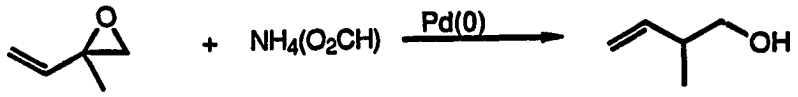
79% (1.45)

When acyclic vinylic epoxides were used, the reactions were totally regio- and stereoselective. When cyclohexadiene monoepoxide was used in the reaction, however, none of the desired allylic alcohol was formed.

Other nucleophiles

Besides the carbon and heteroatom nucleophiles discussed in the previous two sections, other nucleophiles have been used in the palladium(0)-catalyzed ring-opening of vinylic epoxides. This section will cover the use of ammonium formate and carbon dioxide in these reactions.

Tsuji and co-workers have found that vinylic epoxides will react with ammonium formate in the presence of a catalytic amount of palladium(0) (1.46).[80] The reaction

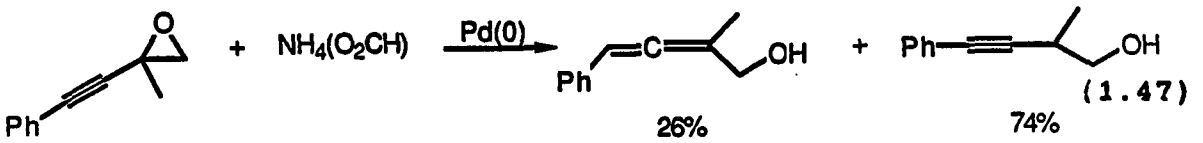


97% (1.46)

proceeds, with quantitative evolution of carbon dioxide, to produce 1-olefins regioselectively in good yields.

Tsuji and co-workers have reported that α-alkynyl

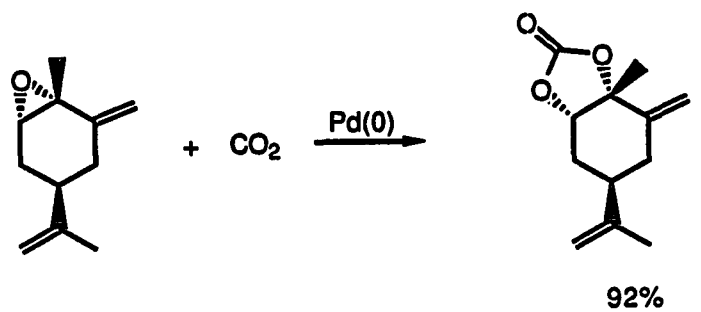
epoxides will also react with sodium formate in the presence of a catalytic amount of palladium(0) (eq. 1.47).[81] The



(1.47)

products isolated from these reactions were mixtures of the corresponding allenic and propargylic alcohols.

The palladium-catalyzed reactions of vinylic epoxides with carbon dioxide have also been studied (eq. 1.48).[82]



(1.48)

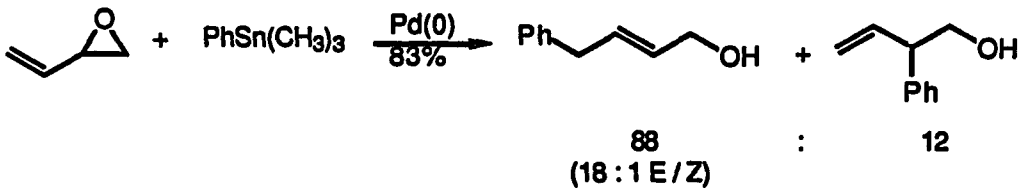
These reactions have been found to exhibit high chemo-, regio-, and diastereoselectivity, when both cyclic and acyclic vinylic epoxides were used. Trost and co-workers have recently used this reaction in a formal synthesis of (+)-citreoviral.[83]

Palladium-Mediated Coupling of Vinylic Epoxides with Organometallic Reagents

Organostannanes

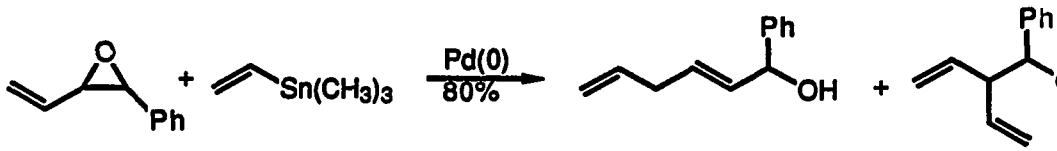
Echavarren and co-workers have recently reported that vinylic epoxides will react with organostannanes in the

presence of a catalytic amount of palladium(0) to yield the desired product as a mixture of regio- and stereoisomers (eqs. 1.49 and 1.50).[84] The regioselectivity of this reaction was



88 : 12
(18 : 1 E/Z)

(1.49)

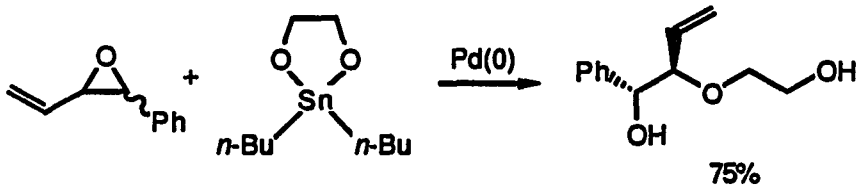


98 : 2
(> 10 : 1 E/Z)

(1.50)

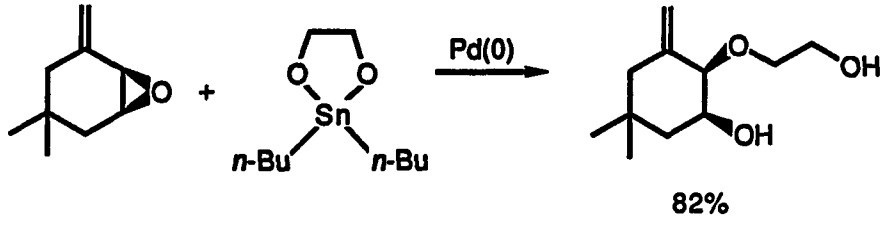
affected by the substitution pattern of the vinylic epoxide. It was determined that vinyl, phenyl and styryl groups were readily transferred and that trimethyl- and tri-n-butylstannanes participated equally well in the transmetallation reaction.

Trost and Tenaglia have shown that vinylic epoxides will react with cyclic stannyl ethers in the presence of a catalytic amount of palladium(0) (eqs. 1.51 and 1.52).[85]



75%
(6.7 : 1 threo / erythro)

(1.51)

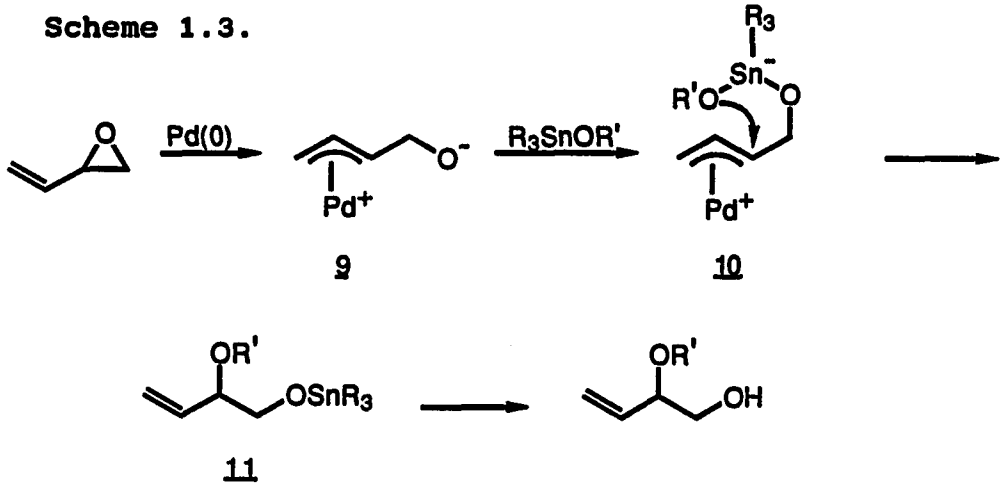


82% (1.52)

In each case studied, it was found that only substitution proximal to the oxygen had occurred. When acyclic vinylic epoxides were used in the reaction, the same diastereomeric mixture of products was obtained regardless of whether the starting material was enriched in the trans or cis epoxide.

The palladium-catalyzed coupling of vinylic epoxides with stannyl ethers is postulated to proceed by the following mechanism (Scheme 1.3). As seen previously, the first

Scheme 1.3.



9 10

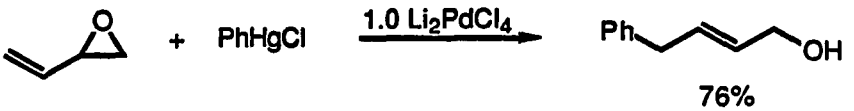
11

step of the mechanism involves formation of cationic (π-allyl)palladium species 9. The alkoxide ion, thus formed, attacks the stannyl ether to form intermediate 10. The oxygen nucleophile is tethered, in this complex, to effect its internal delivery to produce compound 11. The tin-oxygen bond

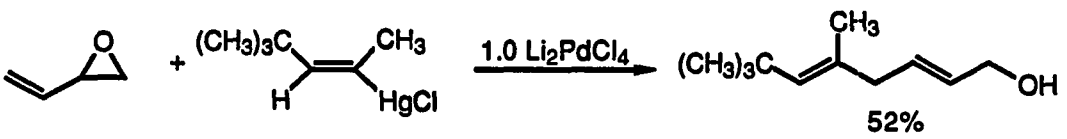
is then cleaved to produce the corresponding unsymmetrical ethylene glycol analogs.

Organomercurials

Larock and Ilkka have reported that vinylic epoxides will react with aryl- and vinylmercurials in the presence of a stoichiometric amount of palladium(II) (eqs. 1.53 and 1.54).[86]



(1.53)

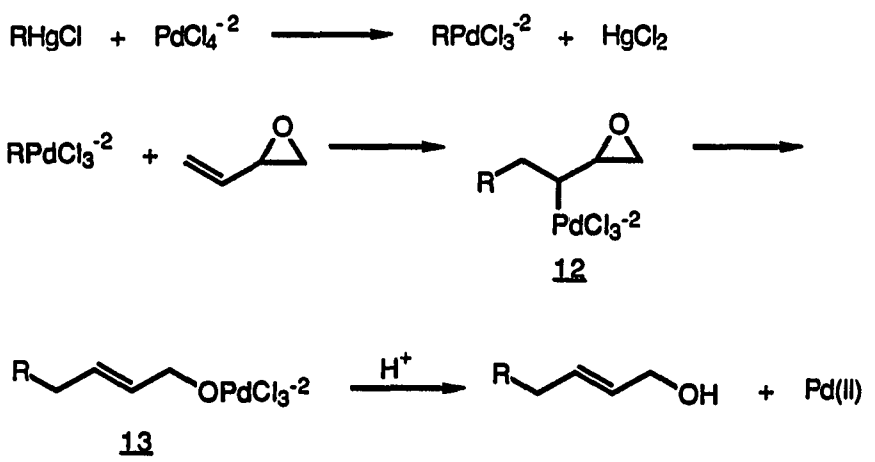


(1.54)

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

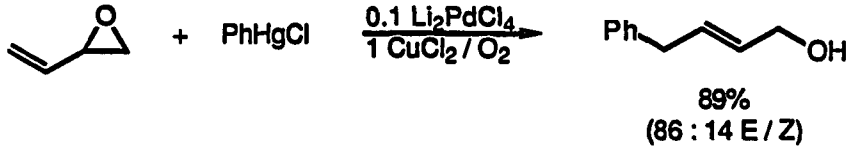
The following mechanism has been proposed to explain how allylic alcohols are formed in these reactions (Scheme 1.4).

Scheme 1.4.



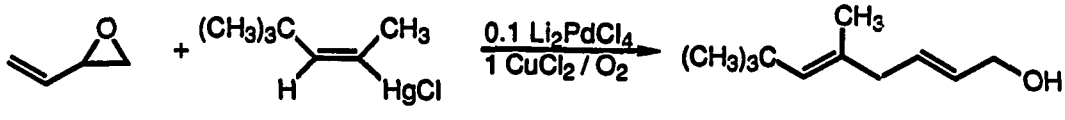
The first step of the mechanism involves transmetallation of the aryl- or vinylmercurial with a palladium(II) salt. The organopalladium species then adds across the double bond of the vinylic epoxide. The aryl or vinyl group becomes attached to the least hindered end of the olefin to form intermediate 12. Intermediate 12 then undergoes palladium alkoxide elimination to form alkoxy palladium species 13. The allylic alcohol can then be formed from intermediate 13 by treating it 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 chloride was added to the reaction and the reactions were conducted under an atmosphere of oxygen (eqs. 1.55 and 1.56). Unfortunately,



89%
(86 : 14 E / Z)

(1.55)



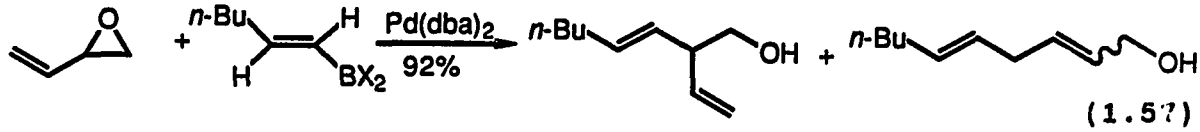
(1.56)

80%
(91 : 9 E / Z)

they were unable to find conditions for the catalytic reaction, which would yield only the E-isomer of the corresponding allylic alcohol.

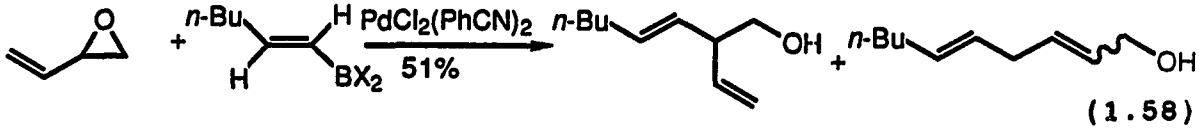
Organoboranes

It has been demonstrated by Miyaura and co-workers that butadiene monoepoxide will react with alkenylboranes in the presence of a catalytic amount of a palladium or nickel complex (eqs. 1.57 and 1.58).[87] The regioselectivity observed



(1.57)

74 : 26



(1.58)

22 : 78

X_2 = bis(1,2-dimethylpropyl)

in the reaction was dependent on the nature of the catalyst used and the structure of the alkenylborane.

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 reactions of vinylic epoxides with carbon, heteroatom and other nucleophiles have also been well studied. These reactions form allylic alcohols in a highly regio- and stereoselective manner. The palladium-catalyzed nucleophilic ring-opening of vinylic epoxides has recently been used in the synthesis of a number of natural products.

Finally, the palladium-mediated coupling of vinylic epoxides with organometallic reagents have also been examined. Several of these reactions will produce the desired product regio- and stereoselectively. Since most of these reactions have been reported during the last three years, they will probably be studied more extensively in the future.

CHAPTER II. ORGANOPALLADIUM ADDITIONS TO VINYLIC OXETANES

Introduction

In recent years organopalladium chemistry has become an important tool for the synthetic organic chemist.[88-91] One method of preparing organopalladium compounds involves the transmetallation of organomercurials with palladium(II) salts (eq. 2.1).[88,90] Organomercurials are easily prepared, can

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

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.[92,93] The preparation of a wide variety of organomercurials is covered in these reviews and the references cited therein.

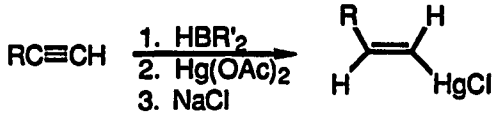
Arylmercurials are easily prepared by simple electrophilic aromatic mercuration of the arene of interest (eq. 2.2). The yields of these reactions are generally high

$$ArH + HgX_2 \longrightarrow ArHgX + HX \qquad (2.2)$$

and a wide variety of functionality is tolerated in these reactions. Isomers formed in these reactions can be easily separated by recrystallization.

Vinylmercurials can be prepared from the corresponding organomagnesium, -lithium or -boron reagents. The preparation

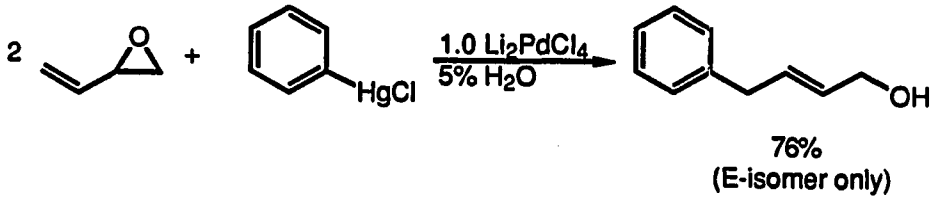
of vinylmercurials via the first two routes severely restricts the type of functionality that can be present in the molecule. Thus, only the boron reagents are of real synthetic utility. Vinylmercurials can be prepared in high yields using a hydroboration-mercuration procedure (eq. 2.3).[94-96]



(2.3)

Alkylmercurials can also be readily prepared.[97] Only alkylmercurials containing no β-hydrogens can be utilized in reactions where transmetallation with palladium and further elaboration (addition to olefins, carbonylation, etc.) is a desired synthetic step.

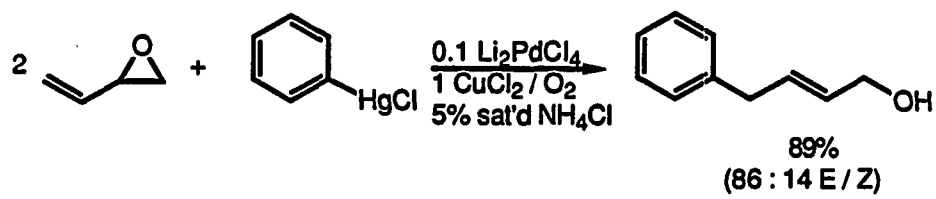
As mentioned in Chapter 1, Larock and Ilkka have reported that allylic alcohols can be prepared in high yields via aryl- and vinylpalladation of vinylic epoxides.[86,98] In the first reactions they studied, butadiene monoepoxide was treated with phenylmercuric chloride in the presence of a stoichiometric amount of dilithium tetrachloropalladate (eq. 2.4). They found that the desired allylic alcohol could be



(2.4)

prepared in high yield as only the E-isomer. When this reaction was studied over the course of time, Larock and Ilkka found that initially the allylic alcohol was produced as a mixture of stereoisomers. Under the reaction conditions, however, the Z-allylic alcohol was completely isomerized to the E-allylic alcohol.

Larock and Ilkka also found that the reaction illustrated in equation 2.4 could be run using a catalytic amount of dilithium tetrachloropalladate if cupric chloride was added to the reaction mixture and the reaction was run under an atmosphere of oxygen (eq. 2.5). Unfortunately, they were



(2.5)

unable to find conditions for the catalytic reaction, which would yield only the E-isomer of the allylic alcohol.

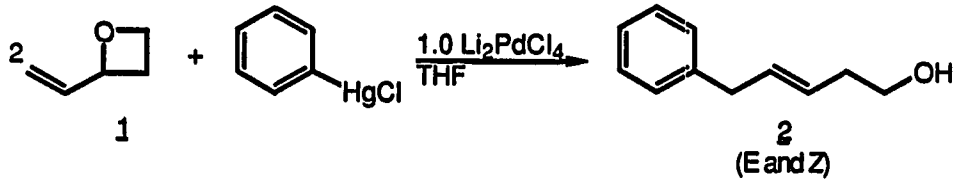
As a natural extension of this work, it was thought that the vinylic epoxide shown in equations 2.4 and 2.5 could be replaced with a vinylic oxetane. If this reaction was successful, it would be the first example of opening a vinylic oxetane with an organometallic reagent to form a homoallylic alcohol. In this chapter, a study of the reactions between vinylic oxetanes and organomercurials in the presence of palladium(II) salts 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 homoallylic alcohols in high yield with a high degree of stereoselectivity. It would also be 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 vinylic oxetanes that would undergo synthetically useful reactions. The first section of this chapter will cover the reactions between various organomercurials and 3,5-epoxy-1-pentene. Finally, the reactions between several other vinylic oxetanes and certain arylmercurials will be discussed.

Additions to 3,5-Epoxy-1-pentene

Compound 1, 3,5-epoxy-1-pentene, was prepared according to the procedure reported by Portnyagin and Pak.[99] In the first reactions studied, compound 1 was allowed to react with phenylmercuric chloride in the presence of a stoichiometric amount of dilithium tetrachloropalladate using several different reaction conditions. An examination of Table 2.1



1 2 (E and Z) (2.6)

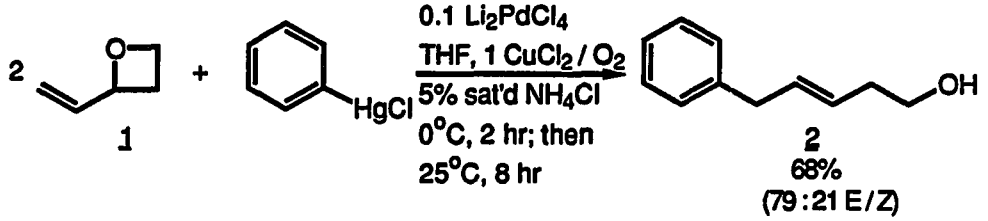
Table 2.1. Stoichiometric reactions between compound 1 and phenylmercuric chloride

Entry	Added reagent	% Yield 2	E/Z Ratio[a]	Reaction conditions
1	5% sat'd NH_4Cl	33	80:20	0°C, 12 hr
2	5% sat'd NH_4Cl	68	76:24	0°C, 2 hr; then 25°C, 8 hr
3	5% H_2O	47	75:25	0°C, 12 hr
4	5% H_2O	39	77:23	0°C, 18 hr; then 25°C, 3 hr

[a]The E- and Z-isomer ratio of homoallylic alcohols can generally be determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the aryl group.

shows that the highest yield of compound 2 was obtained when the stoichiometric reaction was run in the presence of 5% saturated ammonium chloride for two hours at 0°C and was then warmed to room temperature and stirred an additional eight hours. The stereochemical outcome of the reaction, however, did not seem to change when the reaction conditions were varied.

Compound 1 was also allowed to react with phenylmercuric chloride in the presence of a catalytic amount of dilithium tetrachloropalladate (eq. 2.7). Cupric chloride and oxygen

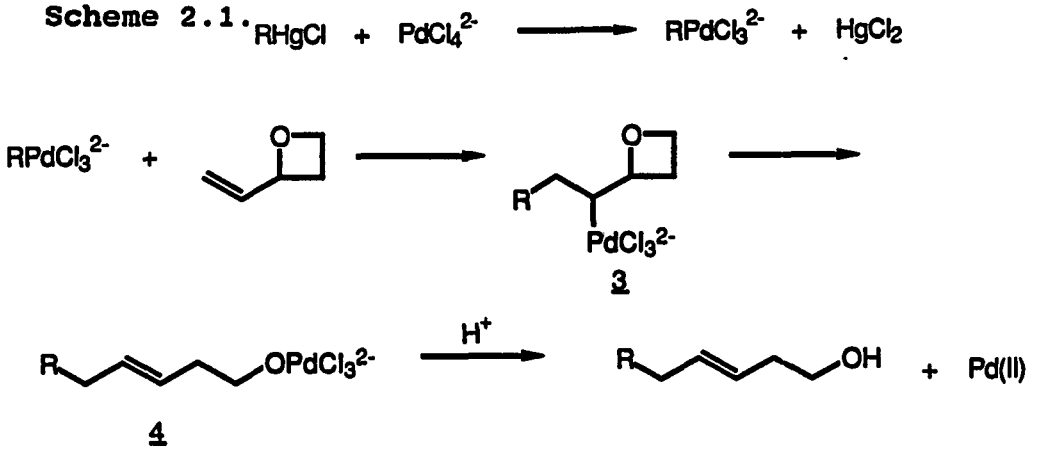


(2.7)

were added to the reaction in order to make it catalytic in palladium. By comparing the results shown in entry 2 of Table 2.1 and equation 2.7, one can see that the yield and stereochemistry of compound 2 did not seem to depend on whether a catalytic or stoichiometric amount of palladium was used in the reaction between compound 1 and phenylmercuric chloride.

A possible mechanism is shown which explains how the homoallylic alcohol is formed in these reactions (Scheme 2.1). While no experiments have been run to attempt to

Scheme 2.1.



support (or disprove) this mechanism, analogous mechanisms have been proposed to explain how vinylcyclopropanes and vinylic epoxides react with organomercurials in the presence of a palladium(II) salt.[98,100] The first step of the

mechanism involves transmetallation of the organomercurial with a palladium(II) salt. The organopalladium species then inserts into the double bond of the vinylic oxetane to form σ-palladium species 3. The organic ligand becomes attached to the least hindered end of the olefin. This σ-palladium species then undergoes palladium alkoxide elimination to form alkoxypalladium species 4. The water or ammonium chloride in the system then protonates the alkoxide to form the homoallylic alcohol and to regenerate palladium(II). No α,β-unsaturated aldehydes, formed by palladium hydride elimination from 4, were ever observed in this reaction.

The mechanism shown in Scheme 2.1 indicates that the reactions between vinylic oxetanes and organomercurials should be catalytic with respect to palladium(II). When Ilkka allowed butadiene monoepoxide to react with phenylmercuric chloride using a catalytic amount of palladium(II), however, he found that he obtained only a 1.8 catalytic turnover of palladium.[98] 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 palladium(II) from palladium(0) by using a copper(II) salt in a "Wacker-type" process (eq. 2.8).[101] In this process palladium(0) is oxidized to palladium(II), while copper(II) is

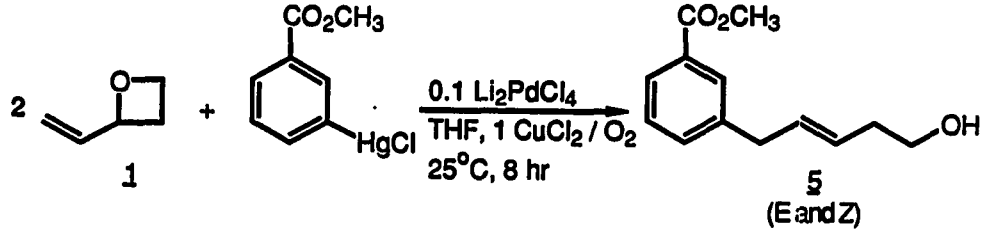
$$Pd(0) + 2Cu(II) \longrightarrow Pd(II) + 2Cu(I) \xrightarrow{O_2} 2Cu(II) \qquad (2.8)$$

reduced to copper(I). The copper(II) can then be regenerated, if the reaction is run under an atmosphere of oxygen. Thus, it is possible to obtain high yields of allylic or homoallylic alcohols from the reactions of the corresponding vinylic epoxides or oxetanes 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 homoallylic alcohols 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 mixtures of E- and Z-allylic alcohols, which were observed to isomerize to the pure E-alcohol under the reaction conditions.[86,98] 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-allyl)palladium species and reductive elimination. When catalytic amounts of dilithium tetrachloropalladate and cupric chloride were used in the reaction, vinylic epoxides afforded mixtures of E- and Z-allylic alcohols similar to those observed for the homoallylic alcohols. Since there is no longer an allylic carbon-oxygen bond in the oxetane products, it is not

surprising that the stoichiometric and catalytic reactions produce homoallylic alcohols with roughly the same yield and stereoselectivity. Because there is no advantage in using a stoichiometric amount of palladium to prepare homoallylic alcohols, the catalytic reaction has been employed in virtually all of the remaining reactions.

It has also been found that compound 1 will react with arylmercurials containing electron-withdrawing groups. Compound 1 was allowed to react with m-methoxycarbonylphenylmercuric chloride and a catalytic amount of dilithium tetrachloropalladate. Cupric chloride and oxygen were used to reoxidize the palladium(0) formed during the reaction. The reactions were run using several different conditions. By examining the results shown in Table 2.2, one can see that



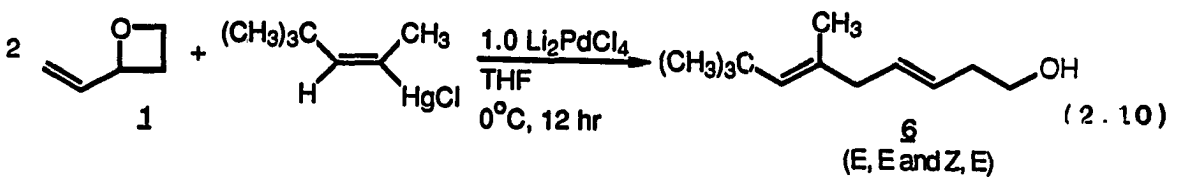
(2.9)

Table 2.2. Catalytic reactions between compound 1 and m-methoxycarbonylphenylmercuric chloride

Entry	Added reagent	% Yield 5	E/Z Ratio
1	none	78	80:20
2	5% H_2O	63	76:24
3	5% sat'd NH_4Cl	56	78:22

the best yield of compound 5 was obtained when the reaction was run in the absence of water and ammonium chloride. This observation is consistent with the results reported for the reactions of butadiene monoepoxide with arylmercurials containing electron-withdrawing groups in the presence of a catalytic amount of palladium(II).[86,98] Unfortunately, the stereochemistry of the double bond in compound 5 did not seem to depend upon the added reagent.

Vinylic oxetanes have also been observed to react with vinylmercurials in the presence of a stoichiometric amount of dilithium tetrachloropalladate. Compound 1 was allowed to react with E-2-chloromercurio-4,4-dimethyl-2-pentene and a stoichiometric amount of dilithium tetrachloropalladate using several different reaction conditions. An examination of



1

6
(E,E and Z,E)

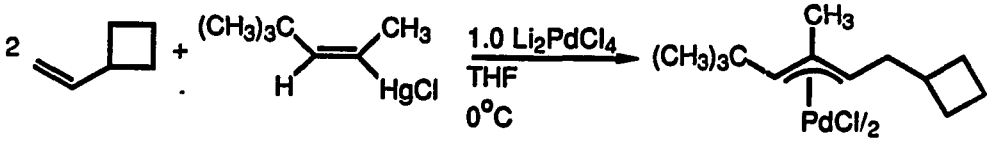
(2.10)

Table 2.3. Stoichiometric reactions between compound 1 and E-2-chloromercurio-4,4-dimethyl-2-pentene

Entry	Added reagent	% Yield 6	E,E/Z,E Ratio
1	none	23	88:12
2	5% H_2O	20	89:11
3	5% sat'd NH_4Cl	57	84:16

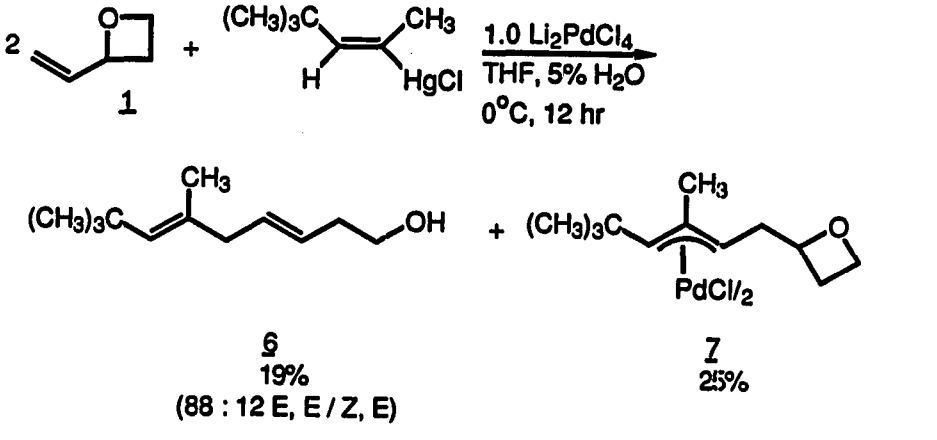
Table 2.3 shows that the highest yield of compound 6 was obtained when the stoichiometric reaction was run in the presence of 5% saturated ammonium chloride. The stereochemical outcome of the reaction did not seem to change significantly when the reaction conditions were varied.

Song has recently reported the following reaction (eq. 2.11).[102] It was thought that the reaction of compound 1



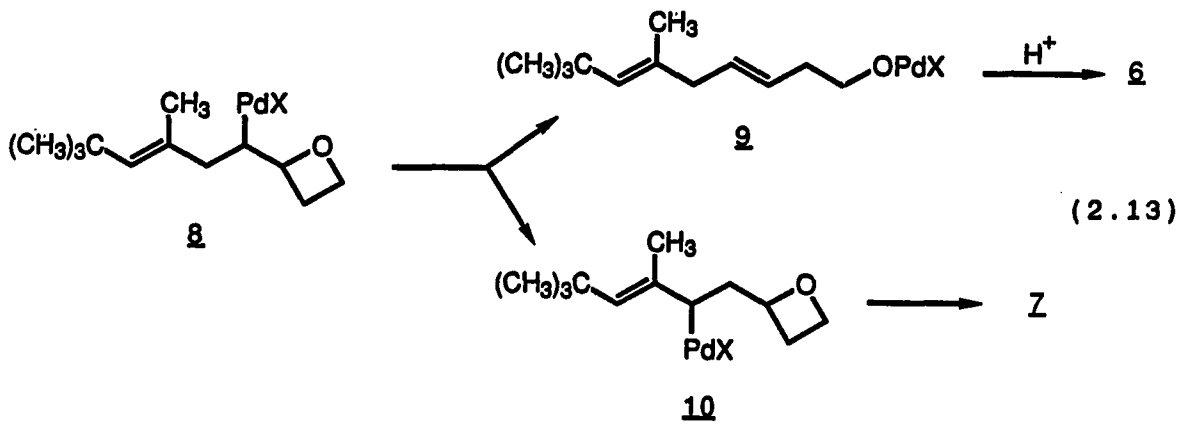
(2.11)

with E-2-chloromercurio-4,4-dimethyl-2-pentene in the presence of a stoichiometric amount of palladium(II) might also form a (π-allyl)palladium compound. The reaction reported in entry 2 of Table 2.3 was repeated; this time care was taken to isolate any (π-allyl)palladium compounds that might be formed (eq. 2.12).



(2.12)

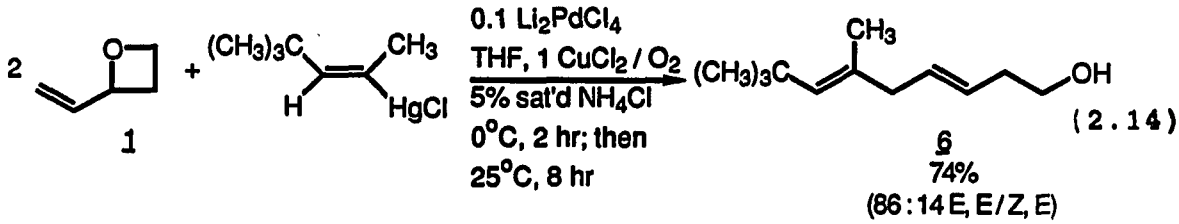
A mechanism is shown which explains how the homoallylic alcohol and the (π-allyl)palladium compound are formed in this reaction (eq. 2.13). The first step of the mechanism



involves transmetallation of the vinylmercurial with dilithium tetrachloropalladate to form a vinylpalladium species. This vinylpalladium species then adds across the double bond of the vinylic oxetane to form σ-palladium species 8. This σ-palladium species can then react in one of two ways. The first way it can react is that palladium alkoxide elimination can occur to yield alkoxypalladium species 9. This intermediate then yields the observed homoallylic alcohol. The second way it can react is that the σ-palladium species can undergo palladium hydride elimination, followed by readdition of palladium hydride to yield rearranged allylic palladium species 10.[103] This allylic palladium species then forms the observed (π-allyl)palladium compound.

Compound 1 was also allowed to react with

E-2-chloromercurio-4,4-dimethyl-2-pentene in the presence of a catalytic amount of dilithium tetrachloropalladate (eq 2.14).



(2.14)

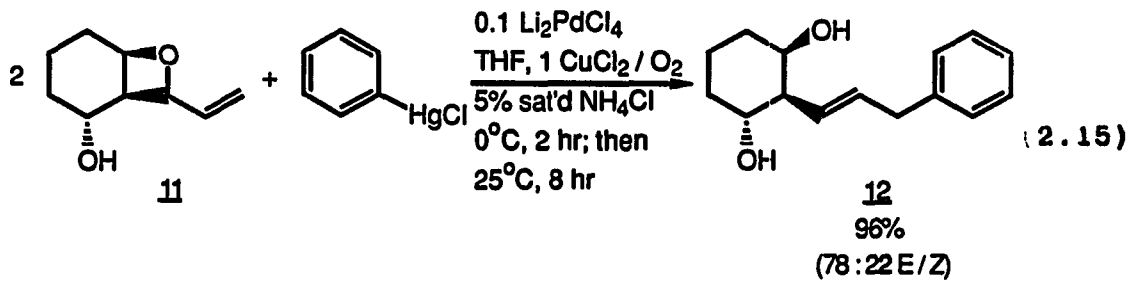
The yield of compound 6 is much higher in the catalytic than the corresponding stoichiometric reaction (compare the results in Table 2.3 to those shown in equation 2.14). The stereochemical outcome of the stoichiometric and catalytic reactions, however, is approximately the same.

When vinylmercurials were allowed to react with vinylic oxetanes, an additional complication was seen that was not observed when vinylic epoxides were studied.[86,98] When stoichiometric amounts of dilithium tetrachloropalladate were used in the reaction, epoxides afforded good yields of the expected dienol product. None of the corresponding (π-allyl)palladium compound was formed in these reactions. When a vinylic oxetane, compound 1, was allowed to react with E-2-chloromercurio-4,4-dimethyl-2-pentene and a stoichiometric amount of dilithium tetrachloropalladate, comparable amounts of the expected dienol product, compound 6, and a (π-allyl)palladium species, compound 7, were isolated (see equation 2.12). Evidently palladium hydride rearrangement to the (π-allyl)palladium compound is competitive with oxetane

ring-opening in this case. Oxetanes must not be ring-opened as readily as epoxides by palladium. High yields of the dienol product could be obtained, however, if the reaction of compound 1 with E-2-chloromercurio-4,4-dimethyl-2-pentene was run using a catalytic amount of dilithium tetrachloropalladate, cupric chloride, 5% saturated ammonium chloride and oxygen. When these conditions were used, ammonium chloride or cupric chloride coordination to the oxetane oxygen may be favoring the ring-opening process. This observation is also consistent with the fact that the highest yield of the dienol product was obtained from the stoichiometric reaction when ammonium chloride was added to the reaction mixture (see Table 2.3).

Additions to Substituted Vinylic Oxetanes

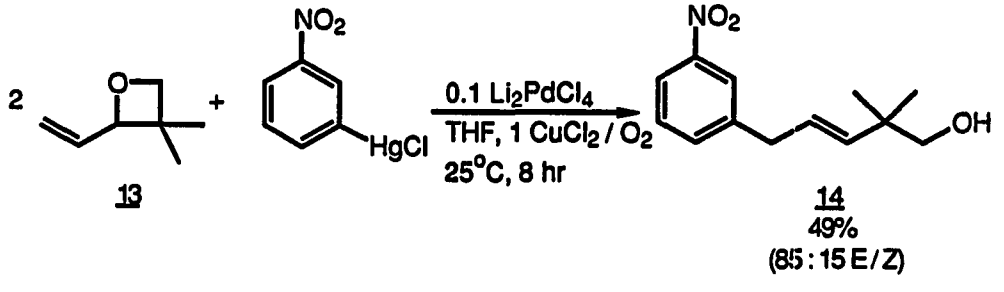
The reactions of substituted vinylic oxetanes with various arylmercurials have also been studied. Compound 11, 8-ethenyl-7-oxabicyclo[4.2.0]octan-2-ol, was prepared using the method reported by Still.[104] Compound 11 was allowed to react with phenylmercuric chloride in the presence of a catalytic amount of dilithium tetrachloropalladate (eq. 2.15).



(2.15)

In order to make this reaction catalytic in palladium(II), cupric chloride was added to the reaction mixture and the reaction was run under one atmosphere of oxygen. The reaction conditions were the same as those used for the catalytic reaction of compound 1 with phenylmercuric chloride (see eq. 2.7). The results shown in equation 2.15 demonstrate that homoallylic alcohols can be prepared in high yields as mixtures of stereoisomers from the reactions of substituted vinylic oxetanes with phenylmercuric chloride in the presence of a catalytic amount of dilithium tetrachloropalladate. This reaction will also tolerate functionality on the vinylic oxetane.

Compound 13, 4,4-dimethyl-3,5-epoxy-1-pentene, was prepared according to the procedure reported by Lucas and co-workers.[105] The reaction of compound 13 with m-nitrophenylmercuric chloride and a catalytic amount of dilithium tetrachloropalladate was investigated (eq. 2.16). Cupric chloride and oxygen were used to reoxidize the



13

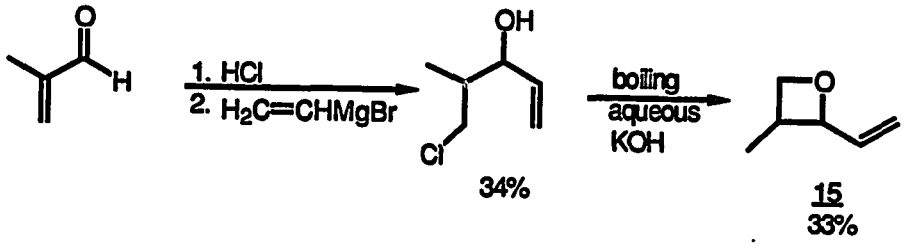
14
49%
(85:15 E/Z)

(2.16)

palladium(0) formed during the reaction. The reaction was run using the best conditions found for the reaction of compound 1

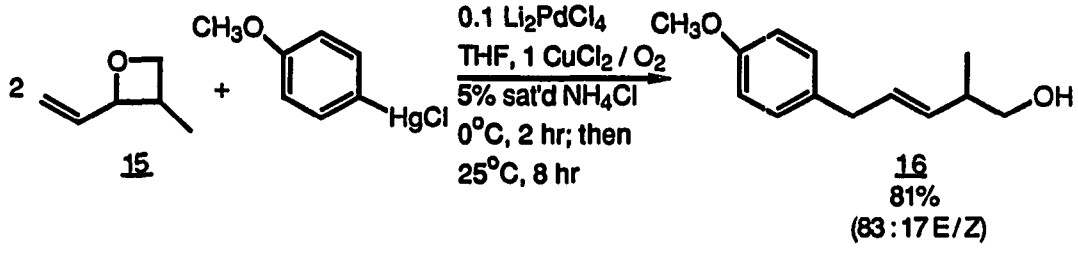
with m-methoxycarbonylphenylmercuric chloride and a catalytic amount of dilithium tetrachloropalladate (see Table 2.2). The reaction shown in equation 2.16 demonstrates that homoallylic alcohols can be formed as mixtures of stereoisomers from the reactions of substituted vinylic oxetanes with arylmercurials containing electron-withdrawing groups in the presence of a catalytic amount of palladium(II).

Compound 15, 4-methyl-3,5-epoxy-1-pentene, was synthesized by a procedure similar to the one reported by Portnyagin and Pak for the preparation of compound 1 (eq. 2.17).[99] The reaction of compound 15 with



(2.17)

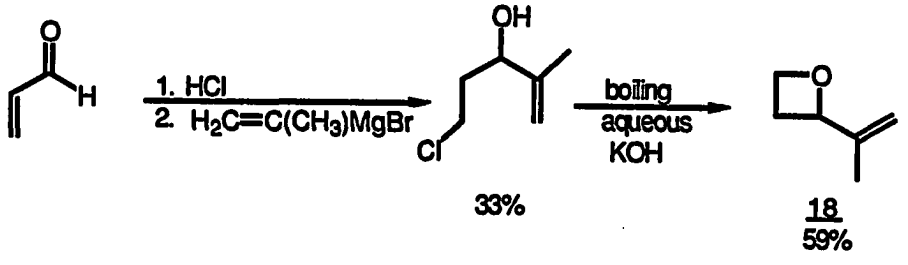
p-methoxyphenylmercuric chloride and a catalytic amount of dilithium tetrachloropalladate was studied (eq. 2.18). Cupric chloride and oxygen were used as a reoxidant. The reaction was run under the same conditions reported by Larock and



(2.18)

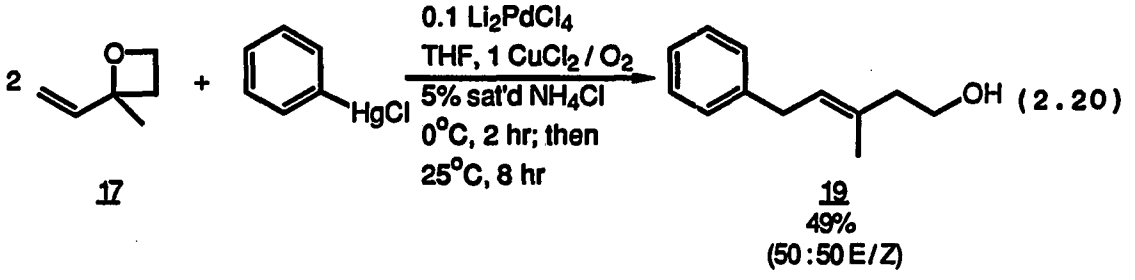
Ilkka for the reaction of butadiene monoepoxide with p-methoxyphenylmercuric chloride using a catalytic amount of palladium(II).[86,98] As one can see from the results shown in equation 2.18, arylmercurials containing electron-donating groups will react with vinylic oxetanes in the presence of dilithium tetrachloropalladate to produce homoallylic alcohols in high yields as mixtures of stereoisomers.

The reactions of 3-methyl-3,5-epoxy-1-pentene, compound 17, and 2-methyl-3,5-epoxy-1-pentene, compound 18, with phenylmercuric chloride and a catalytic amount of dilithium tetrachloropalladate were also investigated. These reactions produced trisubstituted homoallylic alcohols. Compound 17 was prepared by the method reported by Portnyagin and Pak.[99] A procedure similar to the one reported for the preparation of compound 1 was used to synthesize compound 18 (eq. 2.19).[99]

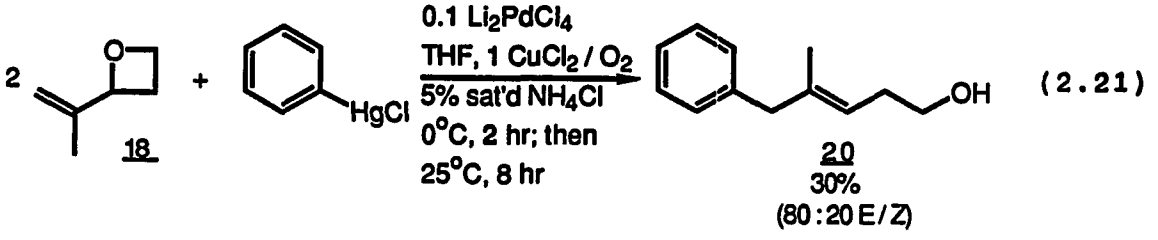


(2.19)

Both compounds 17 and 18 were allowed to react with phenylmercuric chloride using a catalytic amount of dilithium tetrachloropalladate (eqs. 2.20 and 2.21). The reactions



(2.20)



(2.21)

were run under the same conditions used for the catalytic reaction of compound 1 with phenylmercuric chloride (see eq. 2.7). Not surprisingly, the reactions illustrated in equations 2.20 and 2.21 produced trisubstituted homoallylic alcohols as mixtures of stereoisomers. The stereoselectivity of these reactions was very similar to those observed with the analogous epoxides.[86,98]

Conclusion

It has been shown that homoallylic alcohols can be prepared in high yields by allowing vinylic oxetanes to react with functionally substituted aryl- and vinylmercurials in the presence of a catalytic amount of dilithium tetrachloropalladate, if cupric chloride and oxygen were added to the reaction. These reactions are the first observed examples of vinylic oxetanes reacting with organometallic reagents to produce homoallylic alcohols. Unlike the

reactions of the corresponding vinylic epoxides, these reactions exhibit only modest stereoselectivity.

Experimental

Spectral data and analysis

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer at 300 and 75.5 MHz respectively. All infrared spectra were recorded on a Beckmann 4250 spectrophotometer. Exact mass spectral data were recorded on a Kratos MS-50 spectrometer. Elemental analyses were performed by Galbraith Laboratories.

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.[97,106] The vinylmercurials used were also synthesized previously by other Larock group members, probably through a hydroboration-mercuration procedure.[94-96]

Oxetanes

Compounds 1 and 17 were prepared using the procedure reported by Portnyagin and Pak.[99] Compound 11 was synthesized using the method reported by Still.[104] The procedure reported by Lucas et al. was used to prepare compound 13.[105]

The preparation of compound 15 Freshly distilled methacrolein (190 mmol) was added to 10 ml of dry ether. The mixture was cooled to -42°C in a solid carbon dioxide/ acetonitrile bath and dry HCl gas was passed through the solution for 30 min. The reaction mixture was neutralized with anhydrous sodium carbonate and dried with powdered calcium chloride. The ethereal solution of 3-chloro-2-methylpropanal was kept at -42°C until required.

3-Chloro-2-methylpropanal (190 mmol), maintained at -42°C, was added over 2 hr to a solution of vinylmagnesium bromide (224 mmol), cooled to -10°C. The reaction mixture was allowed to stir overnight at room temperature. The solution was cooled to 0°C and 100 ml of saturated ammonium chloride was added slowly to the reaction mixture. The solution was filtered through Celite and the organic layer separated. The aqueous layer was extracted with ether (2 X 50 ml). The combined organic layers were then washed with saturated sodium bicarbonate (2 X 15 ml), water (2 X 15 ml) and dried over anhydrous magnesium sulfate. After removal of solvents, 5-chloro-4-methyl-1-penten-3-ol was purified by distillation: 8.57 g, 34% yield; bp 52°C/2 mm Hg.

5-Chloro-4-methyl-1-penten-3-ol (64 mmol) was added rapidly to a boiling solution of potassium hydroxide (13.3 g) in 13 ml of water. As the product distilled off through a fractionating column, water was added to the flask, so that

the volume of the reaction mixture remained constant. The distillate was saturated with sodium chloride. The organic layer was separated and dried over anhydrous sodium sulfate. After filtering, 4-methyl-3,5-epoxy-1-pentene was purified by distillation: 2.21 g, 35% yield; bp 112-115°C/760 mm Hg.

Compound 15 was isolated as a 64:36 mixture of diastereomers. Major diastereomer: ^{1}H NMR ($CDCl_3$) δ1.22 (d, 3 H, J = 6.9 Hz, CH_3), 2.80 (m, 1 H, $CH_3C\underline{H}$), 4.24 (dd, 1 H, J = 6.3 Hz, J = 6.0 Hz, O-CH_2), 4.57 (dd, 1 H, J = 8.1 Hz, J = 6.0 Hz, O-CH_2), 4.74 (m, 1 H, O-CH), 5.15 (d, 1 H, J = 10.8 Hz, =OH_2 cis), 5.27 (d, 1 H, J = 17.4 Hz, =CH_2 trans), 6.04 (m, 1 H, =CH-); ^{13}C NMR ($CDCl_3$) δ17.3, 36.9, 74.9, 89.6, 115.5, 138.8. Minor diastereomer: ^{1}H NMR ($CDCl_3$) same as the major diastereomer except δ1.09 (d, 3 H, J = 7.2 Hz, CH_3), 3.12 (m, 1 H, $CH_3C\underline{H}$), 4.11 (dd, 1 H, J = 6.0 Hz, J = 5.7 Hz, O-CH_2); ^{13}C NMR ($CDCl_3$) δ14.4, 33.2, 75.8, 84.9, 116.8, 135.8.

The following spectral data were taken from a mixture of the diastereomers: IR (neat) 3120, 3050 (vinyl C-H), 2990, 2970, 2900 (aliphatic C-H), 1655 (C=C), 1465, 1440, 1415, 1390, 1120, 965, 920, 880, 845, 755 cm^{-1}; mass spectrum m/e 98.07339 (calculated for $C_6H_{10}O$ = 98.07317).

The preparation of compound 18 A solution of 2-bromopropene (0.40 mol) in 120 ml of dry THF was added slowly to a mixture of magnesium turnings (0.40 mol) in 120 ml

of dry THF. After addition, the reaction mixture was stirred for 30 min at room temperature and was then heated to 70°C for an additional 30 min. After cooling to room temperature, 60 ml of dry ether was added to the reaction mixture.

3-Chloropropanal was prepared according to the procedure reported by MacLeod and Rossiter.[107] 3-Chloropropanal (0.210 mol), cooled to -42°C, was added over 2 hr to the solution of 2-propenylmagnesium bromide (0.40 mol), maintained at -10°C. The reaction mixture was allowed to stir overnight at room temperature. The solution was cooled to 0°C and 100 ml of saturated ammonium chloride was added slowly to the reaction mixture. The solution was filtered through Celite and the organic layer was separated. The aqueous layer was extracted with ether (2 X 50 ml). The combined organic layers were then washed with saturated sodium bicarbonate (2 X 15 ml), water (2 X 15 ml) and dried over anhydrous magnesium sulfate. After removal of solvents, 5-chloro-2-methyl-1-penten-3-ol was purified by distillation: 9.37 g, 33% yield; bp 60°C/2.0 mm Hg.

5-Chloro-2-methyl-1-penten-3-ol (70 mmol) was added rapidly to a boiling solution of potassium hydroxide (29.74 g) in 13 ml of water. As the product distilled off through a fractionating column, water was added to the flask, so that the volume of the reaction mixture remained constant. The distillate was saturated with sodium chloride. The organic

layer was separated and dried over anhydrous sodium sulfate. After filtering, 2-methyl-3,5-epoxy-1-pentene was purified by distillation: 4.05 g, 59% yield; bp 62°C/85 mm Hg; ^{1}H NMR ($CDCl_3$) δ1.75 (s, 3 H, CH_3), 2.46 (m, 1 H, O-$CH_2C\underline{H}_2$), 2.76 (m, 1 H, O-$CH_2C\underline{H}_2$), 4.48 (m, 1 H, O-CH_2), 4.67 (m, 1 H, O-CH_2), 4.88 (s, 1 H, =CH_2), 5.05 (s, 1 H, =CH_2), 5.13 (t, 1 H, J = 7.5 Hz, O-CH); ^{13}C NMR ($CDCl_3$) δ16.5, 27.3, 67.9, 84.1, 109.9, 145.9; IR (neat) 3090 (vinyl C-H), 2985, 2950, 2895 (aliphatic C-H), 1660 (C=C), 1455, 1375, 1230, 1055, 1015, 980, 900 cm^{-1}; mass spectrum m/e 98.07305 (calculated for $C_6H_{10}O$ = 98.07317)

General stoichiometric procedure for the addition of organopalladium species to vinylic oxetanes

The dilithium tetrachloropalladate was prepared by adding 44 mg of palladium chloride (0.25 mmol) and 21 mg of anhydrous lithium chloride (0.50 mmol) to 6 ml of dry THF. The solution was allowed to stir under nitrogen for 4 to 6 hr. The formed dilithium tetrachloropalladate was cooled to 0°C. To this solution was added sequentially 0.3 ml of water, 2 equivalents (0.50 mmol) of the vinylic oxetane to be studied and 1 equivalent (0.25 mmol) of the organomercurial. The reaction mixture was allowed to stir at 0°C for 12 hr under nitrogen. Ether was added to the reaction mixture. The solution was washed with saturated ammonium chloride and dried over anhydrous magnesium sulfate. After removal of the solvents,

the residue was purified by flash column chromatography on silica gel.

General catalytic procedure for the addition of organopalladium species to vinylic oxetanes

The dilithium tetrachloropalladate was prepared by adding 4.4 mg of palladium chloride (0.025 mmol), 2.1 mg of anhydrous lithium chloride (0.050 mmol) and 33.5 mg of anhydrous cupric chloride (0.25 mmol) to 6 ml of dry THF. The solution was allowed to stir under nitrogen for 2 to 4 hr. The formed dilithium tetrachloropalladate was cooled to 0°C. To this solution was added sequentially 0.3 ml of saturated ammonium chloride, 2 equivalents (0.50 mmol) of the vinylic oxetane to be studied and 1 equivalent (0.25 mmol) of the organomercurial. The reaction flask was flushed with oxygen. The solution was allowed to stir at 0°C for 2 hr. The solution was then warmed to room temperature and stirred an additional 8 hr. Ether was added to the reaction mixture. The solution was washed with saturated ammonium chloride and dried over anhydrous magnesium sulfate. After removal of the solvents, the residue was purified by flash column chromatography on silica gel.

Spectral data for homoallylic alcohols prepared by either the general stoichiometric or catalytic procedure for the addition of organopalladium species to vinylic oxetanes

E- and Z-5-Phenyl-3-penten-1-ol (2) Compound 2 was prepared in 68% yield (79:21 E/Z) when compound 1 was allowed to react with phenylmercuric chloride using the general catalytic procedure.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the aryl group. E-isomer: ^{1}H NMR ($CDCl_3$) δ 1.39 (br s, 1 H, OH), 2.30 (dt, 2 H, J = 6.3 Hz, J = 6.6 Hz, $HOCH_2C\underline{H}_2$), 3.36 (d, 2 H, J = 6.6 Hz, $PhCH_2$), 3.65 (t, 2 H, J = 6.6 Hz, $HOC\underline{H}_2$), 5.49 (dt, 1 H, J = 15.0 Hz, J = 6.3 Hz, $HOCH_2CH_2C\underline{H}$=), 5.72 (dt, 1 H, J = 15.0 Hz, J = 6.6 Hz, $PhCH_2C\underline{H}$=), 7.12-7.32 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ35.9, 39.1, 62.1, 126.0, 127.6, 128.3, 128.4, 132.1, 140.6. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ2.45 (dt, 2 H, J = 6.3 Hz, J = 6.6 Hz, $HOCH_2C\underline{H}_2$), 3.42 (d, 2 H, J = 7.5 Hz, $PhCH_2$), 3.67 (t, 2 H, J = 6.6 Hz, $HOC\underline{H}_2$), cis vinyl protons buried under trans protons; ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ31.0, 33.6, 62.6, 126.3, 128.2, 128.3, 131.1, 140.8.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3500 (OH), 3030 (vinyl, aryl C-H), 2890-2940 (aliphatic C-H), 1605, 1500, 1455, 1050,

970, 910, 735, 700 cm^{-1}; mass spectrum m/e 162.1047 (calculated for $C_{11}H_{14}O$ = 162.1045).

E- and Z-5-(3-Methoxycarbonyl)-phenyl-3-penten-1-ol (5)

Compound 5 was prepared in 78% yield (80:20 E/Z), when compound 1 was allowed to react with m-methoxycarbonyl-phenylmercuric chloride using the general catalytic procedure. No saturated ammonium chloride was added to the reaction. The reaction was run at 25°C for 8 hr.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the aryl group. E-isomer: ^1H NMR ($CDCl_3$) δ1.80 (br s, 1 H, OH), 2.31 (dt, 2 H, J = 7.2 Hz, J = 6.0 Hz, $HOCH_2C\underline{H}_2$), 3.40 (d, 2 H, J = 6.3 Hz, $ArCH_2$), 3.65 (t, 2 H, J = 6.0 Hz, $HOC\underline{H}_2$), 3.90 (s, 3 H, $O-CH_3$), 5.15 (dt, 1 H, J = 15.0 Hz, J = 6.3 Hz, $ArCH_2C\underline{H}=$), 5.71 (dt, 1 H, J = 15.0 Hz, J = 7.2 Hz, $HOCH_2CH_2C\underline{H}=$), 7.37 (m, 2 H, Ar), 7.85 (m, 2 H, Ar); ^{13}C NMR ($CDCl_3$) δ35.8, 38.7, 51.6, 62.0, 127.2, 128.3, 128.4, 129.5, 130.1, 131.2, 133.0, 140.9, 167.1. Z-isomer: ^1H NMR ($CDCl_3$) same as the E-isomer except δ2.45 (dt, 2 H, J = 7.2 Hz, J = 6.0 Hz, $HOCH_2C\underline{H}_2$), 3.48 (d, 2 H, J = 6.3 Hz, $ArCH_2$), 3.91 (s, 3 H, $O-CH_3$), cis vinyl protons buried under trans protons; ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ30.8, 33.3, 44.9, 61.5, 127.0, 129.3, 132.8, 141.1.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3050 (vinyl,

aryl C-H), 2980 (aliphatic C-H), 1725 (C=O), 1620, 1600, 1455, 1440, 1290, 1220, 1205, 1110, 1045, 970, 750, 660 cm^{-1}; mass spectrum m/e 220.11007 (calculated for $C_{13}H_{16}O$ = 220.10995).

E,E- and Z,E-6,8,8-Trimethyl-3,6-nonadien-1-ol (6)

Compound 6 was prepared in 74% yield (86:14 E,E/Z,E), when compound 1 was allowed to react with E-2-chloromercurio-4,4-dimethyl-2-pentene using the general catalytic procedure.

The E,E- and Z,E-isomer ratio was determined by intergration of the 300 MHz NMR spectral peaks corresponding to the doubly allylic hydrogens. E,E-isomer: ^1H NMR ($CDCl_3$) δ1.05 (s, 9 H, $C(CH_3)_3$), 1.44 (br s, 1 H, OH), 1.64 (d, 3 H, J = 1.2 Hz, CCH_3), 2.25 (dt, 2 H, J = 6.3 Hz, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 2.58 (d, 2 H, J = 6.3 Hz, $=CC\underline{H}_2CH=$), 3.60 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 5.14 (d, 1 H, J = 1.2 Hz, C=CH), 5.35 (dt, 1 H, J = 15.3 Hz, J = 6.3 Hz, $HOCH_2CH_2C\underline{H}=$), 5.47 (dt, 1 H, J = 15.3 Hz, J = 6.3 Hz, $=CCH_2C\underline{H}=$); ^{13}C NMR ($CDCl_3$) δ17.1, 18.1, 31.2, 36.0, 45.1, 62.1, 127.0, 132.6, 132.7, 136.1.

Z,E-isomer: ^1H NMR ($CDCl_3$) same as the E,E-isomer except δ1.67 (d, 3 H, J = 1.2 Hz, CCH_3), 2.31 (dt, 2 H, J = 6.6 Hz, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 2.64 (d, 2 H, J = 7.5 Hz, $=CC\underline{H}_2CH=$), 3.61 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), cis vinyl protons buried under trans protons; ^{13}C NMR ($CDCl_3$) same as the E,E-isomer or not seen except δ17.4, 30.9, 32.2, 39.4, 62.4, 126.2, 131.6, 132.4, 135.7.

The following spectral data were taken from a mixture of

the E,E- and Z,E-isomers: IR (neat) 3200-3600 (OH), 3060 (vinyl C-H), 2860-2980 (aliphatic C-H), 1460, 1425, 1385, 1365, 1040, 970 cm^{-1}; mass spectrum m/e 182.16692 (calculated for $C_{12}H_{22}O$ = 182.16707).

Bis(μ-chloro) bis[(3,5-η)-2,2,4-trimethyl-7,9-epoxynonenyl] dipalladium(II) (7) Compound 7 was prepared in 25% yield when compound 1 was allowed to react with E-2-chloromercurio-4,4-dimethyl-2-pentene using the general stoichiometric procedure. Compound 7 was purified by recrystallization from a mixture of hexanes and methylene chloride: ^1H NMR ($CDCl_3$) δ1.24 (s, 9 H, $C(CH_3)_3$), 1.75-1.97 (m, 2 H, $CHC\underline{H}_2CH$), 2.19 (s, 3 H, CCH_3), 2.33-2.45 (m, 1 H, $O-CH_2C\underline{H}_2$), 2.67-2.80 (m, 1 H, $O-CH_2C\underline{H}_2$), 3.27 (t, 1 H, J = 6.6 Hz, $CH_2C\underline{H}-CCH_3$), 3.30 (s, 1 H, $C-C\underline{H}C(CH_3)_3$), 4.48-4.56 (m, 1 H, $O-CH_2$), 4.60-4.70 (m, 1 H, $O-CH_2$), 4.96-5.10 (m, 1 H, O-CH). Anal calcd for $C_{12}H_{21}OPdCl$: C, 44.56; H, 6.50. Found: C, 44.72; H, 6.64.

E- and Z-2-(3-Phenyl-1-propenyl)-trans-1,3-cyclohexanediol (12) Compound 12 was prepared in 96% yield (78:22 E/Z), when compound 11 was allowed to react with phenylmercuric chloride using the general catalytic procedure.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the aryl group. E-isomer: ^1H NMR ($CDCl_3$) δ1.41-2.12 (m, 7 H, 3 CH_2 and =CHC$\underline{H}$ cyclohexane ring), 3.42

(d, 2 H, J = 6.6 Hz, $PhCH_2$), 3.79 (m, 1 H, HOCH), 4.00 (m, 1 H, HOCH), 5.67 (dd, 1 H, J = 15.3 Hz, J = 8.4 Hz, HOCHCH=CH), 5.84 (dt, 1 H, J = 15.3 Hz, J = 6.6 Hz, $PhCH_2CH$=), 7.16-7.31 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 18.8, 32.4, 33.4, 39.3, 53.6, 68.4, 70.6, 126.2, 128.4, 128.5, 129.9, 133.8, 140.3. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ 3.46 (d, 2 H, J = 7.8 Hz, $PhCH_2$), cis vinyl protons buried under trans protons; ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ 32.5, 33.2, 34.2, 48.4, 69.5, 70.9, 128.3, 128.9, 129.8, 133.1, 140.4.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3105, 3060, 3045 (vinyl, aryl C-H), 2970, 2905 (aliphatic C-H), 1620, 1510, 1465, 1390, 1265, 1230, 1170, 1050, 985, 880, 760, 700 cm^{-1}; mass spectrum m/e 232.14642 (calculated for $C_{15}H_{20}O_2$ = 232.14633).

E- and Z-2,2-Dimethyl-5-(3-nitro)-phenyl-3-penten-1-ol (14) Compound 14 was prepared in 49% yield (85:15 E/Z), when compound 13 was allowed to react with m-nitrophenylmercuric chloride using the general catalytic procedure. No saturated ammonium chloride was added to the reaction. The reaction was run at 25°C for 8 h.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the aryl group. E-isomer: ^{1}H NMR ($CDCl_3$)

δ1.03 (s, 6 H, 2 CH_3's), 1.59 (br s, 1 H, OH), 3.34 (s, 2 H, $HOC\underline{H}_2$), 3.46 (d, 2 H, J = 5.4 Hz, $ArCH_2$), 5.53 (d, 1 H, J = 15.6 Hz, $(CH_3)_2CC\underline{H}$=), 5.60 (dt, 1 H, J = 15.6 Hz, J = 5.4 Hz, $ArCH_2C\underline{H}$=), 7.47 (m, 2 H, Ar), 8.04 (m, 2 H, Ar); ^{13}C NMR ($CDCl_3$) δ24.0, 38.5, 38.8, 71.7, 121.3, 123.3, 126.1, 129.3, 134.7, 140.1, 142.8, 148.5. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ3.13 (d, 2 H, J = 15.0 Hz, $ArCH_2$), cis vinyl protons buried under trans protons; ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ24.2, 39.1, 40.3, 72.0, 123.8, 126.2, 126.7, 135.4.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3071, 3028 (vinyl, aryl C-H), 2963, 2932, 2870 (aliphatic C-H), 1529 (NO_2), 1474, 1352, 1097, 1082, 1043, 976, 804, 735, 689 cm^{-1}; mass spectrum m/e 217.10990 (M - H_2O) (calculated for $C_{13}H_{15}NO_2$ = 217.11028).

E- and Z-2-Methyl-5-(4-methoxy)-phenyl-3-penten-1-ol (16)

Compound 16 was prepared in 81% yield (83:17 E/Z), when compound 15 was allowed to react with p-methoxyphenylmercuric chloride using the general catalytic procedure.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the vinylic hydrogen nearer the alcohol group. E-isomer: ^{1}H NMR ($CDCl_3$) δ0.99 (d, 3 H, J = 6.9 Hz, $CHC\underline{H}_3$), 1.40 (br s, 1 H, OH), 2.35 (m, 1 H, $CH_3C\underline{H}$), 3.30 (d, 2 H, J = 6.6 Hz, $ArCH_2$), 3.47 (m, 2

H, HOC<u>H</u>$_2$), 3.78 (s, 3 H, O-CH$_3$), 5.35 (dd, 1 H, J = 15.3 Hz, J = 7.8 Hz, CH$_3$CHC<u>H</u>=), 5.67 (dt, 1 H, J = 15.3 Hz, J = 6.6 Hz, ArCH$_2$C<u>H</u>=), 6.83 (d, 2 H, J = 8.7 Hz, Ar), 7.08 (d, 2 H, J = 8.7 Hz, Ar); ^{13}C NMR ($CDCl_3$) δ16.6, 38.2, 39.6, 55.3, 67.5, 114.0, 129,3, 131.0, 132.8, 133.6, 158.1. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ0.98 (d, 3 H, J = 6.6 Hz, CHC<u>H</u>$_3$), 3.78 (s, 3 H, O-CH$_3$), 5.25 (dd, 1 H, J = 10.8 Hz, J = 9.9 Hz, CH$_3$CHC<u>H</u>=); ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ17.1, 33.0, 34.9, 67.8, 129.2, 130.6, 132.7, 132.9.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3060, 3020 (vinyl, aryl C-H), 2980, 2930, 2890, 2860 (aliphatic C-H), 1615, 1590, 1515, 1465, 1445, 1300, 1240, 1175, 1030, 965, 815, 750 cm^{-1}; mass spectrum m/e 206.13094 (calculated for $C_{13}H_{18}O_2$ = 206.13068).

<u>E- and Z-3-Methyl-5-phenyl-3-penten-1-ol (19)</u>

Compound <u>19</u> was prepared in 49% yield (50:50 E/Z), when compound <u>17</u> was allowed to react with phenylmercuric chloride using the general catalytic procedure.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the alcohol group. E-isomer: ^{1}H NMR ($CDCl_3$) δ1.68 (s, 3 H, CH$_3$), 2.23 (t, 2 H, J = 6.3 Hz, =CCH$_2$), 3.32 (d, 2 H, J = 7.2 Hz, PhCH$_2$), 3.63 (t, 2 H, J = 6.3 Hz, HOC<u>H</u>$_2$),

5.39 (t, 1 H, J = 7.2 Hz, =CH), 6.98-7.30 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ15.9, 34.1, 42.6, 60.4, 126.0, 126.4, 128.2, 128.3, 132.5, 141.2. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ1.71 (s, 3 H, CH_3), 2.37 (t, 2 H, J = 6.3 Hz, $=CCH_2$), 5.46 (t, 1 H, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ23.4, 34.3, 35.1, 60.6, 125.8, 126.5, 132.3, 141.3.

The following spectral data were taken from a mixture of E- and Z-isomers: IR (neat) 3200-3600 (OH), 3070, 3040 (vinyl, aryl C-H), 2980, 2930, 2890 (aliphatic C-H), 1605, 1495, 1455, 1380, 1050, 735, 700 cm^{-1}; mass spectrum m/e 158.1087 (M - H_2O) (calculated for $C_{12}H_{14}$ = 158.1096).

E- and Z-4-Methyl-5-phenyl-3-penten-1-ol (20)

Compound 20 was prepared in 30% yield (80:20 E/Z), when compound 18 was allowed to react with phenylmercuric chloride using the general catalytic procedure.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the aryl group. E-isomer: ^{1}H NMR ($CDCl_3$) δ1.41 (br s, 1 H, OH), 1.65 (s, 3 H, CH_3), 2.39 (dt, 2 H, J = 7.2 Hz, J = 6.3 Hz, $=CHC\underline{H}_2$), 3.38 (s, 2 H, $PhCH_2$), 3.72 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 5.32 (t, 1 H, J = 7.2 Hz, =CH), 7.20-7.37 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ16.0, 31.6, 46.3, 62.3, 121.9, 125.9, 128.2, 128.8, 137.6, 140.0. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ1.72 (s, 3 H, CH_3),

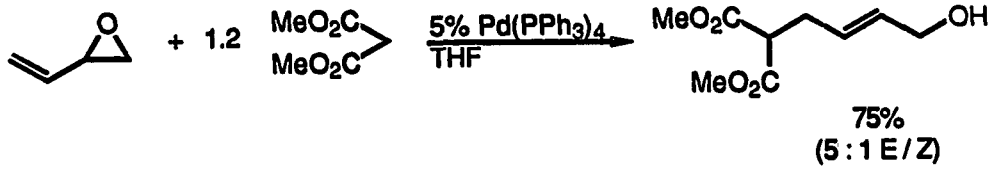
2.51 (dt, 2 H, J = 7.5 Hz, J = 6.6 Hz, =CHC$\underline{H}_2$), 3.47 (s, 2 H, $PhCH_2$), 5.38 (t, 1 H, J = 7.5 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 23.5, 31.7, 37.9, 62.5, 122.2, 125.9, 128.3, 128.4, 136.9, 139.8.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3103, 3084, 3062, 3026 (vinyl, aryl C-H), 2914 (aliphatic C-H), 1602, 1495, 1452, 1383, 1336, 1092, 1047, 910, 874, 733, 700 cm^{-1}; mass spectrum m/e 176.12040 (calculated for $C_{12}H_{16}O$ = 176.12012).

CHAPTER III. PALLADIUM(0)-CATALYZED NUCLEOPHILIC RING-OPENING OF VINYLIC OXETANES TO FORM DISUBSTITUTED HOMOALLYLIC ALCOHOLS

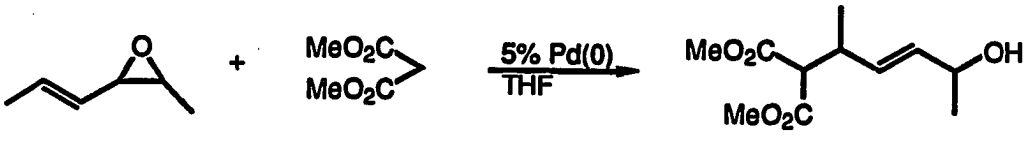
Introduction

It is well known that allylic compounds can react with various nucleophiles, via (π-allyl)palladium complexes, in the presence of a catalytic amount of palladium.[89] As discussed in Chapter I, Trost and Molander[56] and Tsuji et al.[57] have independently reported that diene monoepoxides can be attacked regioselectively by nucleophiles in the presence of a catalytic amount of a palladium(0) complex. Trost and Molander found that the treatment of butadiene monoepoxide with a catalytic amount of tetrakis(triphenylphosphine)-palladium(0) in the presence of 1.2 equivalents of malonic ester led to a single alkylation product, which was a mixture of stereoisomers (eq. 3.1). Trost and Molander[56] and Tsuji



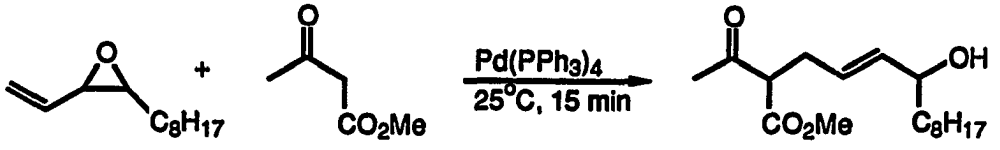
(3.1)

et al.[57] have found that they were able to form allylic alcohols stereoselectively, however, if a more highly substituted vinylic epoxide was used in the reaction (eqs. 3.2 and 3.3).



(3.2)

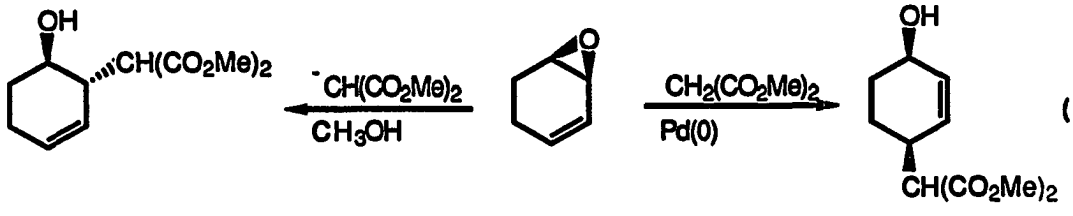
76%
(E-isomer only)



(3.3)

67%
(E-isomer only)

Trost and Molander have reported that cyclic vinylic epoxides will also participate in the the palladium(0)-catalyzed nucleophilic ring-opening of vinylic epoxides.[56] They found that the reaction proceeds with clean alkylation from the same face as the oxygen of the epoxide. Thus, this reaction compliments normal reactivity patterns (eq. 3.4).



(3.4)

For example, cyclohexadiene monoepoxide will react with dimethyl malonate in the presence of palladium(0) to produce solely the cis-1,4-addition product. On the other hand, when cyclohexadiene monoepoxide is allowed to react with the sodium salt of dimethyl malonate, the trans-1,2-addition product is formed exclusively.

It has been reported in the literature that vinylic epoxides will react with a wide variety of nucleophiles in the

presence of a catalytic amount of palladium(0) to form allylic alcohols. The reactions have been run using carbon,[56-70] oxygen,[75,76] nitrogen[57,72-74] and sulfur[78] nucleophiles. The reactions of carbon nucleophiles have recently found considerable synthetic utility in the synthesis of steroids,[58] vitamin D_3,[59] prostaglandins,[60] digitoxigenin,[61] punctaporonin B[62] and macrocycles.[63]

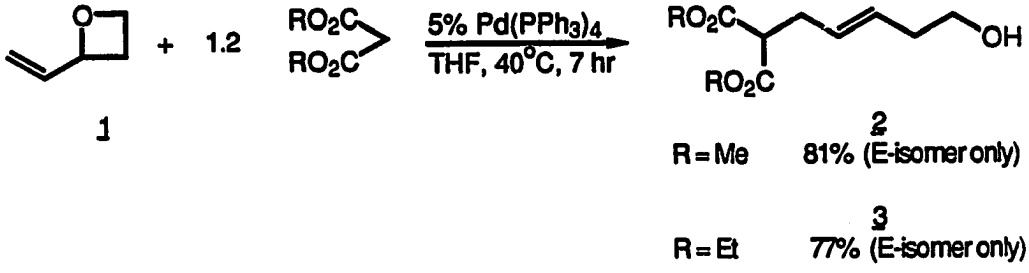
Since it has been demonstrated that vinylic oxetanes can be ring-opened to form homoallylic alcohols using organomercurials and palladium(II) salts,[108] it was thought that it might be possible to replace the vinylic epoxides shown in equations 3.1-3.4 with vinylic oxetanes. No such reactions of vinylic oxetanes have been reported previously. It was hoped that the palladium(0)-catalyzed nucleophilic ring-opening of vinylic oxetanes would produce homoallylic alcohols 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 carbon and heteroatom nucleophiles could be used in the reaction, that the reaction would tolerate a wide variety of functional groups, and that variously substituted vinylic oxetanes could be utilized in the reaction.

In this chapter, the reactions between vinylic oxetanes and various nucleophiles in the presence of a palladium(0)

catalyst will be discussed. The first section of this chapter covers the palladium(0)-catalyzed reactions of 3,5-epoxy-1-pentene with a variety of carbon nucleophiles. Next, the reactions of variously substituted vinylic oxetanes with carbon nucleophiles in the presence of a catalytic amount of palladium(0) will be discussed. Finally, the palladium(0)-catalyzed reactions of 3,5-epoxy-1-pentene with a variety of heteroatom nucleophiles will be presented.

Additions of Carbon Nucleophiles to 3,5-Epoxy-1-pentene

Compound 1, 3,5-epoxy-1-pentene, was prepared according to the procedure reported by Portnyagin and Pak.[99] Compound 1 was allowed to react with 1.2 equivalents of dimethyl or diethyl malonate in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (eq. 3.5). It was



1

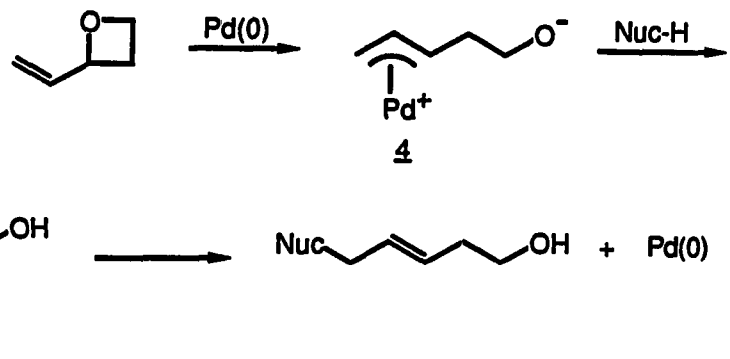
2
R = Me 81% (E-isomer only) (3.5)

3
R = Et 77% (E-isomer only)

found that the expected homoallylic alcohols could be isolated in high yield as only the E-isomer. This result was somewhat unexpected because Trost and Molander had reported that the palladium(0)-catalyzed reaction of butadiene monoepoxide with dimethyl malonate led to the formation of the corresponding allylic alcohol as a mixture of stereoisomers.[56]

A mechanism is shown which explains how the homoallylic alcohol is formed in the reactions illustrated in equation 3.5 (Scheme 3.1). While no experiments have been run to attempt

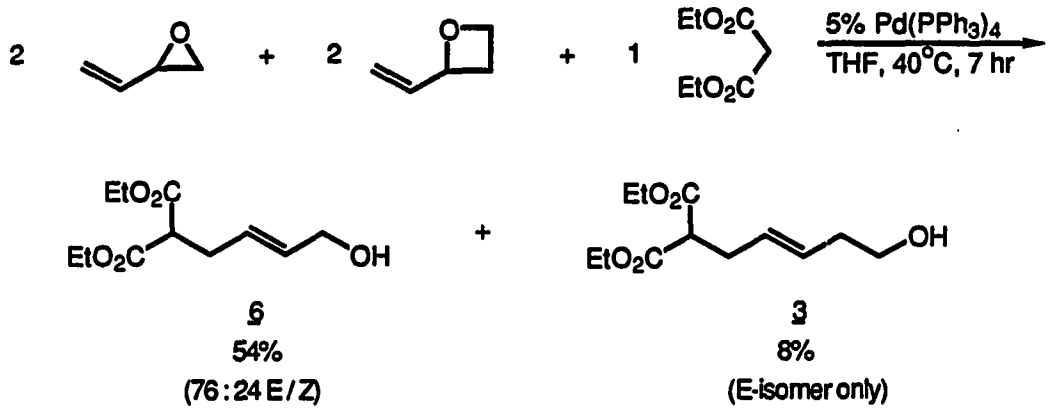
Scheme 3.1.



to support (or disprove) this mechanism, similar mechanisms have been proposed to explain the palladium(0)-catalyzed nucleophilic ring-opening of vinylic epoxides.[56,57] In the first step of the mechanism, palladium(0) oxidatively adds to the vinylic oxetane to generate (π-allyl)palladium species 4. The alkoxide ion formed then acts as a base to remove a proton from the nucleophile. The anion of the nucleophile attacks the least hindered end of (π-allyl)palladium species 5 to form the homoallylic alcohol and to regenerate palladium(0). Only the E-isomer of the homoallylic alcohol is formed in this reaction, because the most stable form of (π-allyl)palladium species 5 is the syn form. The syn form leads to formation of the E-isomer of the homoallylic alcohol.

Since it has been shown that both vinylic epoxides and oxetanes will react with nucleophiles in the presence of a catalytic amount of palladium(0), the following competition

reaction was run in order to determine which allylic ether will react faster. Two equivalents of butadiene monoepoxide and compound 1 were allowed to react with one equivalent of diethyl malonate in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (eq. 3.6). The



(3.6)

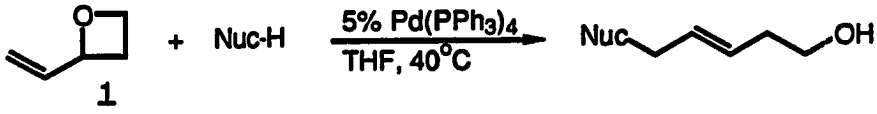
yields of compounds 3 and 6 were determined by gas chromatographic analysis of the crude reaction mixture using biphenyl as the internal standard. Based on the information reported in equation 3.6, it appears that butadiene monoepoxide reacts much faster than compound 1 in the palladium(0)-catalyzed reaction. Since the slow step of this reaction probably involves formation of the initial (π-allyl)palladium species, it appears that vinylic epoxides ring-open much more readily in the presence of palladium(0) than do the corresponding vinylic oxetanes.

In order to demonstrate the synthetic utility of the palladium(0)-catalyzed nucleophilic ring-opening of vinylic oxetanes, compound 1 was allowed to react with a wide variety

of carbon nucleophiles in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0). The results shown in Table 3.1 indicate that a wide variety of carbon nucleophiles will react with compound 1 in the presence of palladium(0) to give high yields of the corresponding homoallylic alcohols. These reactions were run under the same conditions used when compound 1 was treated with dimethyl or diethyl malonate and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (eq. 3.5). Higher yields of compounds 11-14 could be obtained, however, if 2.4 equivalents of the appropriate nucleophile were used in the reaction and the reaction was run for 3.5 hr at 40°C.

All of the reactions presented in Table 3.1 produced the corresponding homoallylic alcohols as exclusively the E-isomer, except when diethyl methylmalonate was used as the nucleophile (see entries 1 and 2 in Table 3.1). The low yield and stereoselectivity of this reaction could be due to the fact that diethyl methylmalonate may not be acidic enough to participate effectively in this reaction. When the same reaction was run using diethyl phenylmalonate, a similarly substituted but more acidic nucleophile, the homoallylic alcohol was formed in high yield as only the E-isomer (see entry 3 in Table 3.1).

When the palladium(0)-catalyzed ring-opening of compound 1 was run using 4-carbethoxy-3-methyl-2-cyclohexen-1-one,



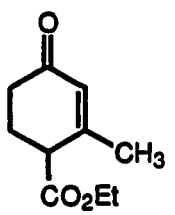
(3.7)

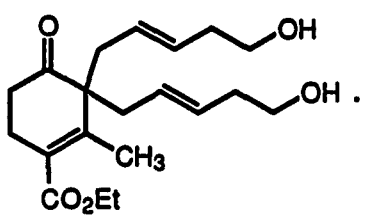
Table 3.1. Palladium(0)-catalyzed additions of carbon nucleophiles to compound 1

Entry	Nuc-H (equivalents)	Reaction time (hr)	% Yield	E/Z Ratio[a]	Compound
1	$(EtO_2C)_2CHCH_3$ (1.2)	7.0	36	61:39	7
2	$(EtO_2C)_2CHCH_3$ (1.2)	14.0	17	77:23	7
3	$(EtO_2C)_2CHPh$ (1.2)	7.0	83	100:0	8
4	$EtO_2CCH_2\overset{\overset{O}{\|}}{C}CH_3$ (1.2)	7.0	86	100:0	9
5	$EtO_2CCH(CH_3)\overset{\overset{O}{\|}}{C}CH_2CH_3$ (1.2)	7.0	83	100:0	10
6	$CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}CH_3$ (1.2)	7.0	61	100:0	11
7	$CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}CH_3$ (1.2)	3.5	68	100:0	11
8	$CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}CH_3$ (2.4)	3.5	86	100:0	11
9	EtO_2CCH_2CN (1.2)	7.0	58	100:0	12
10	EtO_2CCH_2CN (2.4)	3.5	74	100:0	12

[a]The E- and Z-isomer ratio of homoallylic alcohols can generally be determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the alcohol group.

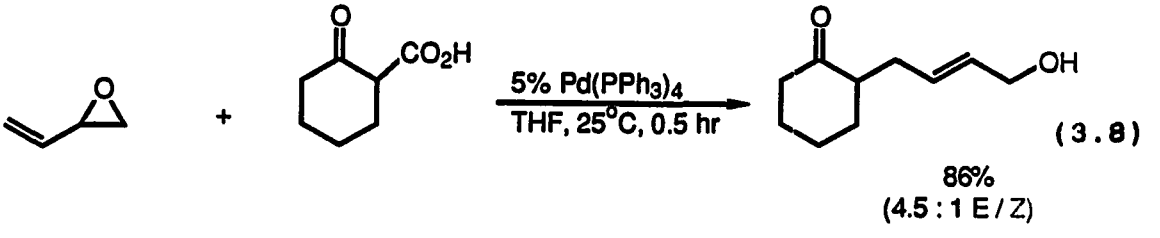
Table 3.1. Continued

Entry	Nuc-H (equivalents)	Reaction time (hr)	% Yield	E/Z Ratio[a]	Compound
11	$(EtO)_2P(=O)CH_2CO_2Et$ (1.2)	7.0	62	100:0	13
12	$(EtO)_2P(=O)CH_2CO_2Et$ (2.4)	3.5	75	100:0	13
13	$PhSCH_2CO_2Me$ (1.2)	7.0	38	100:0	14
14	$PhSCH_2CO_2Me$ (2.4)	3.5	46	100:0	14
15	$PhSO_2CH_2CO_2Me$ (1.2)	7.0	82	100:0	15
16	$PhSO_2CH_2CO_2Me$ (2.4)	3.5	79	100:0	15
17	 (1.2)	7.0	70	100:0	16[b]

[b]Compound 16 =  .

Hagemann's ester, as the nucleophile, the dialkylated homoallylic alcohol was isolated (see entry 17 in Table 3.1). This compound was dialkylated exclusively at the carbon α to the ketone. This result differs slightly from what is reported in the literature. While it is generally accepted that Hagemann's ester will be monoalkylated exclusively at the position α to the carbonyl, Nesipuri and co-workers have reported that when ethyl β-chloropropionate was used as the alkylating agent, they obtained two products.[109] One of the products was alkylated at the position α to the ketone, while the other α to the ester group. Although compound 16 is alkylated at the position α to the ketone as expected, it is not clear why only the dialkylated product was obtained in the palladium(0)-catalyzed nucleophilic ring-opening of compound 1.

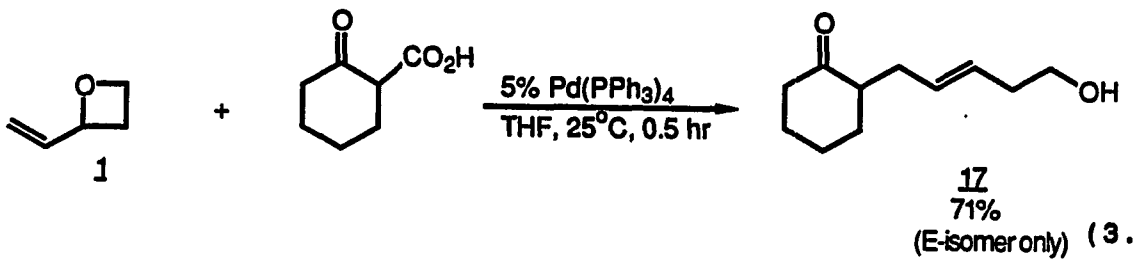
Recently, Tsuda and co-workers have reported the following reaction (eq. 3.8).[66] Cyclohexanone-2-carboxylic



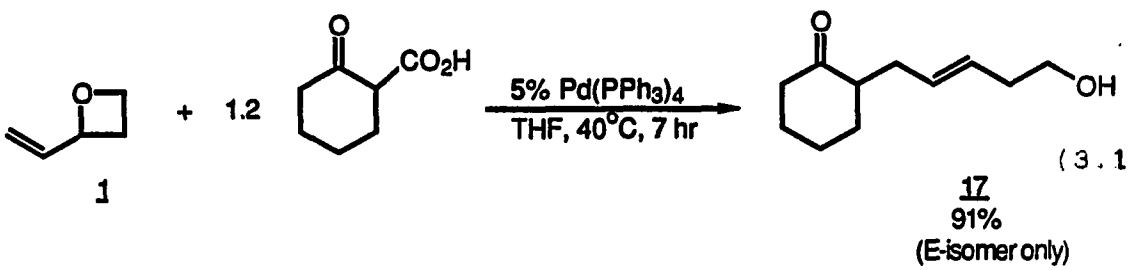
(3.8)

acid can be easily prepared by the method reported by Haruki et al.[110] In order to determine whether vinylic oxetanes would react with β-keto acids in the presence of

palladium(0), the following reactions were run (eqs. 3.9 and 3.10). The best yield of compound 17 was obtained when



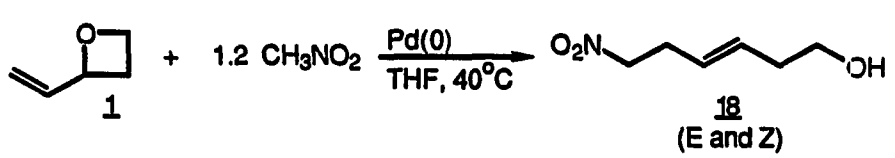
1 + → 17, 71% (E-isomer only) (3.9)



1 + 1.2 → 17, 91% (E-isomer only) (3.10)

compound 1 was treated with cyclohexanone-2-carboxylic acid under the same conditions used for the reaction of compound 1 with dimethyl malonate (eq 3.5). Compound 17 was formed stereoselectively in these reactions.

It has also been found that compound 1 will react with nitromethane in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0). By comparing the results shown in Table 3.2, one can see that the highest yield



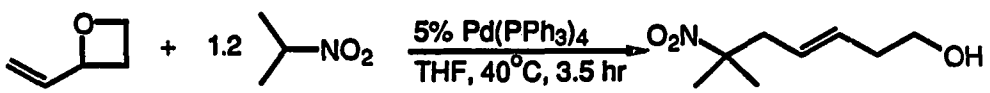
1 + 1.2 CH_3NO_2 → 18 (E and Z) (3.11)

Table 3.2. Palladium(0)-catalyzed additions of nitromethane to compound 1

Entry	Catalyst	Reaction time (hr)	% Yield 18	E/Z Ratio	Comments
1	5% $Pd(PPh_3)_4$	3.5	56	97:3	none
2	5% $Pd(PPh_3)_4$	7.0	44	96:4	none
3	5% $Pd(PPh_3)_4$	3.5	49	97:3	2.5 equiv. of CH_3NO_2
4	5% $Pd(PPh_3)_4$, 5% dppe	3.5	19	100:0	none
5	9% $Pd(PPh_3)_4$, 9% dppe	3.5	26	100:0	none
6	9% $Pd(PPh_3)_4$, 9% dppe	3.5	19	100:0	1.2 equiv. of triethyl-amine added

of compound 18 was obtained when the reaction shown in equation 3.11 was run in the presence of 1.2 equivalents of nitromethane for 3.5 hr at 40°C using tetrakis(triphenyl-phosphine)palladium(0) as the catalyst (see entry 1 in Table 3.2). When these reaction conditions were used however, compound 18 was isolated as a mixture of stereoisomers. On the other hand, compound 18 was formed stereoselectively as only the E-isomer if tetrakis(triphenylphosphine)palladium(0) and 1,2-bis(diphenylphosphino)ethane were used as the catalyst for the reaction (see entries 4-6 in Table 3.2). Unfortunately, when this catalyst system was used, the yield of compound 18 dropped significantly.

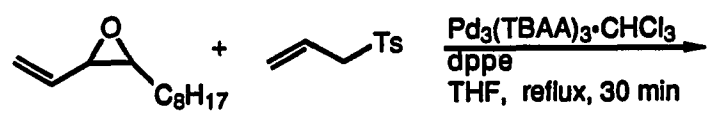
The reactions of compound 1 with 2-nitropropane and a catalytic amount of palladium(0) were also attempted (eq. 3.12). None of the expected product, compound 19, was



1 — 19, 0% (3.12)

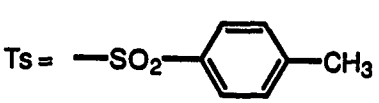
isolated from this reaction. There were at least five major compounds formed in this reaction, none of which were characterized.

Recently, Tsuji and co-workers have reported the following reaction (eq. 3.13).[57] Allylic sulfones can be



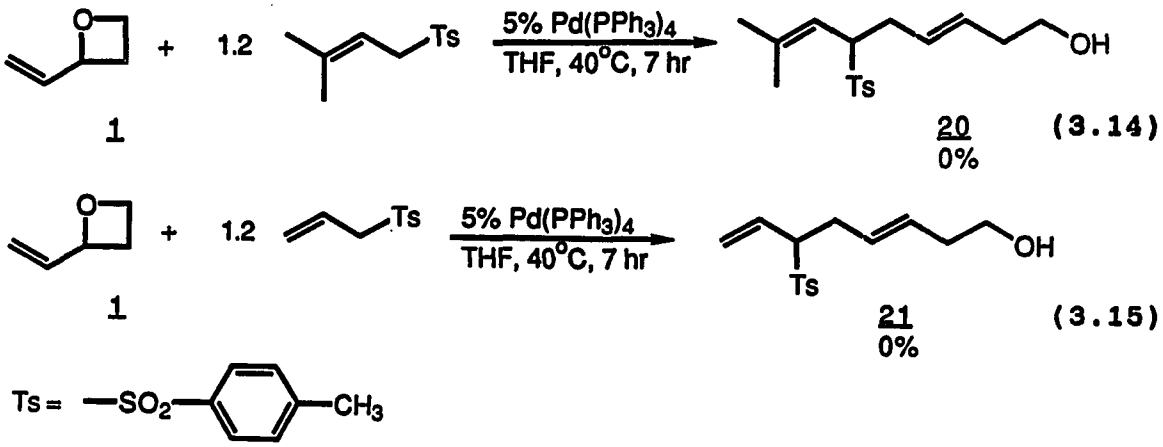
1 : 1 (3.13)

64%



readily synthesized according to the procedure reported by Terao et al.[111] In order to determine whether allylic sulfones could be used as nucleophiles in the palladium(0)-catalyzed ring-opening of vinylic oxetanes, similar reactions were run using compound 1 and

3-methyl-1-(p-tolylsulfonyl)but-2-ene and 1-(p-tolylsulfonyl)-prop-2-ene (eqs. 3.14 and 3.15). The reactions were run under

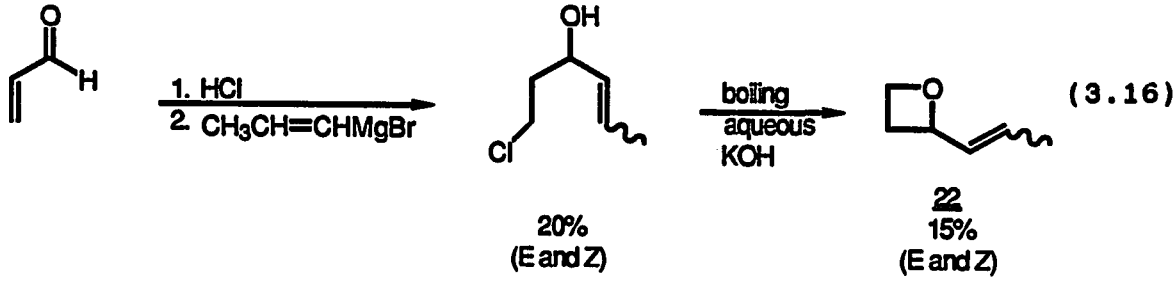


the same conditions used when compound 1 was treated with dimethyl malonate in the presence of a catalytic amount of palladium(0) (see eq. 3.5). Neither of the expected products was isolated from the reactions shown in equations 3.14 and 3.15. Instead, the unreacted allylic sulfone was isolated at the end of these reactions in quantitative yield.

The results presented in this section show that homoallylic alcohols can be formed in high yields from the reactions of compound 1 with various carbon nucleophiles in the presence of a palladium(0) catalyst. These reactions are regio- and stereoselective. Only the E-homoallylic alcohol is isolated, except when diethyl methylmalonate or nitromethane is used in the reaction. The palladium(0)-catalyzed ring-opening of compound 1 fails, however, if 2-nitropropane or an allylic sulfone is used as the nucleophile.

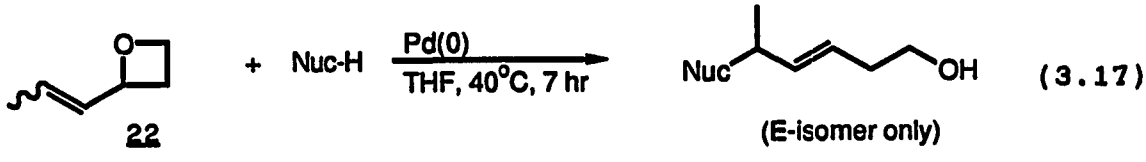
Additions of Carbon Nucleophiles to Substituted Vinylic Oxetanes

In order to determine the synthetic utility of the palladium(0)-catalyzed ring-opening of vinylic oxetanes, a variety of carbon nucleophiles were allowed to react with variously substituted vinylic oxetanes in the presence of a catalytic amount of palladium(0). Compound 22, E- and Z-4,6-epoxy-1-hexene was synthesized using a procedure similar to the one used by Portnyagin and Pak to prepare compound 1 (eq. 3.16).[99] Compound 22 was treated with either dimethyl



(3.16)

malonate or 2,4-pentanedione in the presence of a palladium(0) catalyst. From the results shown in Table 3.3, it is easy to



(3.17)

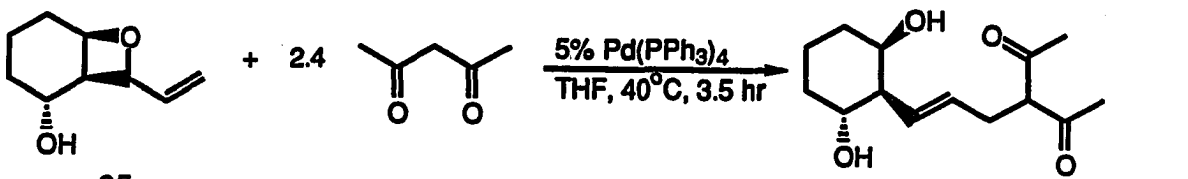
Table 3.3. Palladium(0)-catalyzed additions of carbon nucleophiles to compound 22

Entry	Nuc-H (equivalents)	Catalyst	Added reagent	% Yield	Compound
1	$(MeO_2C)_2CH_2$ (1.2)	5% $Pd(PPh_3)_4$	none	72	23
2	$(MeO_2C)_2CH_2$ (1.2)	9% $Pd(PPh_3)_4$, 9% dppe	1.2 Et_3N	75	23
3	$CH_3CCH_2CCH_3$ (2.4) (O O)	5% $Pd(PPh_3)_4$	none	54	24
4	$CH_3CCH_2CCH_3$ (2.4) (O O)	9% $Pd(PPh_3)_4$, 9% dppe	1.2 Et_3N	80	24

see that the highest yields of compounds 23 and 24 were obtained, when compound 22 was allowed to react with a nucleophile in the presence of 9% tetrakis(triphenylphosphine)palladium(0), 9% 1,2-bis(diphenylphosphino)ethane and 1.2 equivalents of triethylamine. Trost and Molander found, when they studied the palladium(0)-catalyzed nucleophilic ring-opening of vinylic epoxides, that bis[1,2-bis(diphenylphosphino)ethane]palladium(0) proved to be a superior catalyst with more sterically hindered substrates.[56] This is in agreement with the results summarized in Table 3.3. Triethylamine was added to the reaction in order to promote formation of the anion of the nucleophile.

Compound 25, 8-ethenyl-7-oxabicyclo[4.2.0]octan-2-ol, was prepared using the method reported by Still.[104] Compound 25

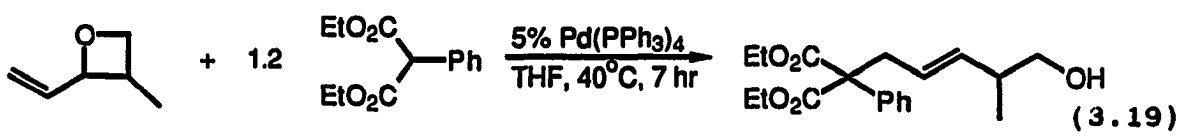
was allowed to react with 2,4-pentanedione in the presence of a catalytic amount of tetrakis(triphenylphosphine)-palladium(0). The conditions used in equation 3.18 were the



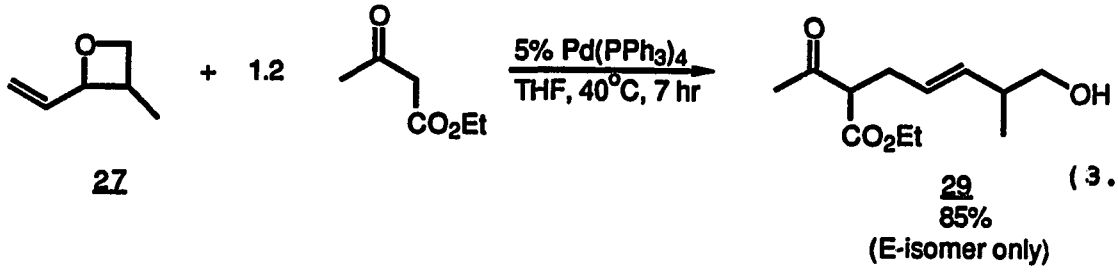
25 → 26, 82% (E-isomer only) (3.18)

best observed for the reaction of compound 1 with 2,4-pentanedione in the presence of a palladium(0) catalyst (see Table 3.1, entries 6-8).

Compound 27, 4-methyl-3,5-epoxy-1-pentene, was prepared by a procedure similar to one Portnyagin and Pak used for the synthesis of compound 1.[99] The preparation of compound 27 was discussed in Chapter II (see eq. 2.17). The reactions of compound 27 with ethyl acetoacetate and diethyl phenylmalonate were studied. The results presented in equations 3.19 and 3.20 indicate that a higher yield of the corresponding



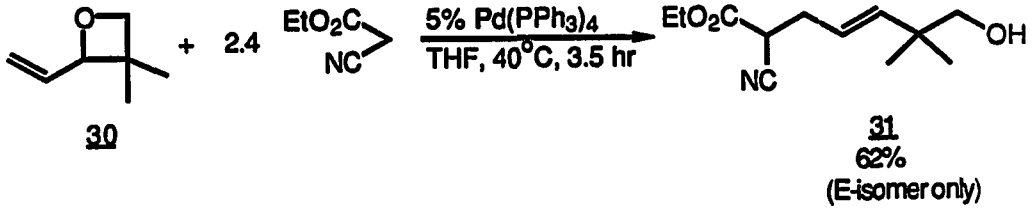
27 → 28, 42% (E-isomer only) (3.19)



27 29 85% (E-isomer only) (3.20)

homoallylic alcohol was obtained when ethyl acetoacetate was used as the nucleophile rather than diethyl phenylmalonate. This could be due to a difference in the steric bulk of the two nucleophiles or a difference in their acidities.

Lucas and co-workers have reported the synthesis of 4,4-dimethyl-3,5-epoxy-1-pentene, compound 30.[105] The reaction of compound 30 with ethyl cyanoacetate in the presence of a catalytic amount of tetrakis(triphenyl-phosphine)palladium(0) was explored. The conditions reported in equation 3.21 were the best observed for the reaction of



30 31 62% (E-isomer only) (3.21)

compound 1 with ethyl cyanoacetate using a catalytic amount of palladium(0) (see Table 3.1, entries 9 and 10).

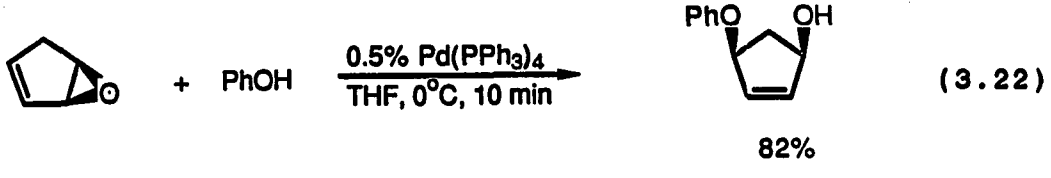
The reactions shown in equations 3.17-3.21 indicate that variously substituted vinylic oxetanes will react with a variety of carbon nucleophiles in the presence of palladium(0) to form the corresponding homoallylic alcohols in high yields.

These reactions are regio- and stereoselective; only the E-isomer of the homoallylic alcohol is formed.

Additions of Heteroatom Nucleophiles to 3,5-Epoxy-1-pentene

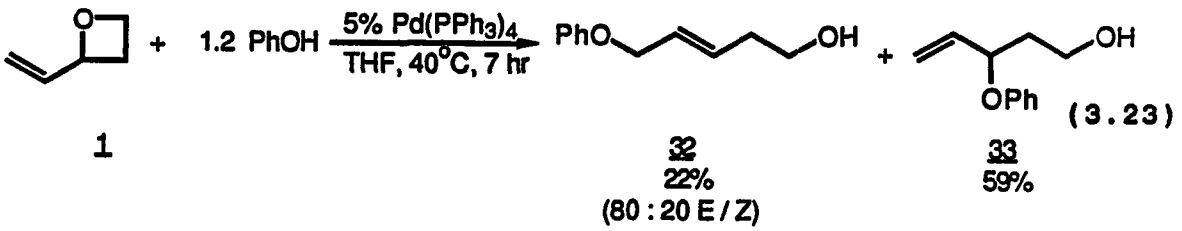
Additions of phenol

Since the reactions of vinylic oxetanes with carbon nucleophiles in the presence of a palladium(0) catalyst produced homoallylic alcohols in good yields with a high degree of regio- and stereoselectivity, the reactions of compound 1 with various heteroatom nucleophiles were also investigated. The reactions of oxygen,[75,76] nitrogen[57,72-74] and sulfur[78] nucleophiles with vinylic epoxides in the presence of palladium(0) catalysts have been studied previously. Deardorff and co-workers have recently reported that the treatment of cyclopentadiene monoepoxide with phenol and a catalytic amount of tetrakis(triphenylphosphine)-palladium(0) cleanly afforded the cis-1,4-addition product (eq. 3.22).[75]



(3.22)

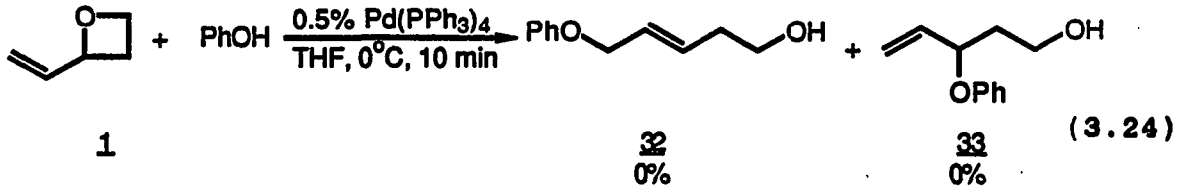
A similar reaction was run using compound 1. Compound 1 was allowed to react with phenol in the presence of a catalytic amount of palladium(0) (eq. 3.23). The reaction



1 32 22% (80 : 20 E / Z) 33 59% (3.23)

was run under the same conditions used when compound 1 was treated with dimethyl malonate (see eq. 3.5). As one can see from the results shown in equation 3.23, the ring-opened product was formed as a mixture of regio- and stereoisomers. The two regioisomers, compounds 32 and 33, could be separated by gas or flash column chromatography. Unfortunately, the two stereoisomers of compound 32 could not be separated, although the isomer ratio could be determined by integration of the 300 MHz nuclear magnetic resonance spectral peaks corresponding to the allylic hydrogens next to the phenoxy group. Even though a mixture of regio- and stereoisomers was formed from the reaction shown in equation 3.23, the overall yield was high.

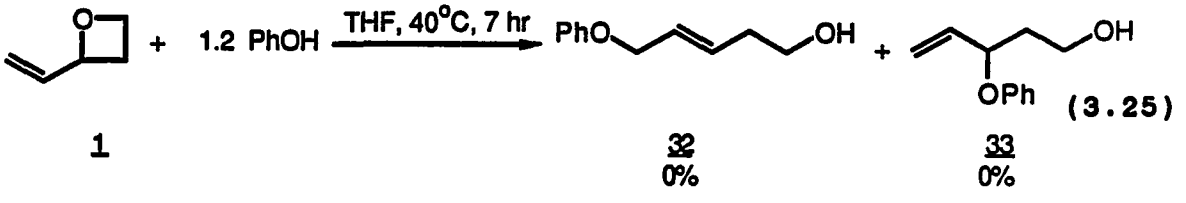
It was thought that the poor regio- and stereoselectivity observed in the reaction of compound 1 with phenol might be due to the fact that the conditions used to run the reaction were too harsh. Therefore, the reaction shown in equation 3.23 was repeated using exactly the conditions reported by Deardorff and co-workers for the reaction of cyclopentadiene monoepoxide with phenol (3.24).[75] Unfortunately, neither



1 32 0% 33 0% (3.24)

compound 32 nor 33 could be detected by gas chromatography when the reaction was run using these conditions.

In order to determine whether phenol was acidic enough to promote the opening of the oxetane ring in the absence of palladium(0), the following reaction was run (eq. 3.25). When

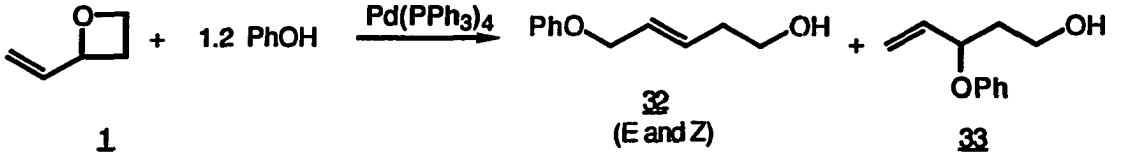


1 32 0% 33 0% (3.25)

compound 1 was allowed to react with phenol in the absence of a palladium(0) catalyst, neither compound 32 nor 33 was formed. The only compound isolated from this reaction was unreacted phenol. Therefore, it appears that palladium(0) is necessary for the formation of compounds 32 and 33.

In order to optimize the yields of compounds 32 and 33, a gas chromatographic study was done on the reaction illustrated in equation 3.23. It was hoped that the yields of the two regioisomers would change when the reaction conditions were varied (Table 3.4).

The data presented in Table 3.4 show that the highest yield of compound 32 was obtained when the reaction shown in equation 3.26 was run in the presence of 9% tetrakis-



1 32 (E and Z) 33 (3.26)

Table 3.4. Palladium(0)-catalyzed additions of phenol to compound 1

Entry	Reaction time (hr)	Reaction temp. (°C)	% $Pd(PPh_3)_4$	Solvent, mls	% Yield 32	% Yield 33	Comments
1	0.5	40	5	THF, 3	21	80	none
	1.5				20	79	
	2.5				25	70	
	3.5				27	66	
	5.5				23	61	
	7.5				20	60	
	9.5				25	57	
	11.5				25	60	
2	0.5	40	9	THF, 3	16	63	none
	1.5				21	57	
	2.5				34	52	
	3.5				44	41	
	5.5				49	32	
	7.5				50	23	
	9.5				44	22	
	11.5				46	20	
3	0.5	67	9	THF, 3	35	42	none
	1.5				47	27	
	2.5				50	24	
	3.5				52	22	
	5.5				52	21	
	7.5				47	19	
	9.5				38	18	

Table 3.4. Continued

Entry	Reaction time (hr)	Reaction temp. (°C)	% $Pd(PPh_3)_4$	Solvent, mls	% Yield 32	% Yield 33	Comments
4	0.5	40	9	THF, 1.5	29	62	none
	1.5				45	51	
	2.5				55	31	
	3.5				57	25	
	5.5				53	16	
	7.5				48	15	
	9.5				48	15	
	11.5				49	15	
5	0.5	40	9	THF, 3	31	45	2.4 equiv.
	1.5				45	29	of PhOH
	2.5				56	25	
	3.5				58	23	
	5.5				54	21	
	7.5				40	15	
	9.5				43	14	
	11.5				42	17	
6	0.5	40	2	THF, 3	12	65	none
	1.5				15	75	
	2.5				17	79	
	3.5				16	79	
	5.5				14	75	
	7.5				15	77	
	9.5				16	82	
	11.5				18	79	

Table 3.4. Continued

Entry	Reaction time (hr)	Reaction temp. (°C)	% $Pd(PPh_3)_4$	Solvent, mls	% Yield 32	% Yield 33	Comments
7	0.5	25	2	THF, 3	14	76	none
	1.5				13	82	
	2.5				16	84	
	3.5				16	78	
	5.5				14	83	
	7.5				14	81	
	9.5				16	81	
8	0.5	0	2	THF, 3	2	24	none
	1.5				8	65	
	2.5				11	73	
	3.5				11	76	
	5.5				13	78	
	7.5				9	76	
	9.5				9	75	
	11.5				12	79	
9	0.5	-20	2	THF, 3	1	12	none
	1.5				9	39	
	2.5				11	41	
	3.5				8	40	
	5.5				8	48	
	7.5				8	47	
	9.5				9	50	

Table 3.4. Continued

Entry	Reaction time (hr)	Reaction temp. (^{o}C)	% $Pd(PPh_3)_4$	Solvent, mls	% Yield 32	% Yield 33	Comments
10	0.5	40	2	THF, 6	10	76	none
	1.5				10	75	
	2.5				17	82	
	3.5				12	73	
	5.5				15	77	
	7.5				17	79	
	9.5				15	77	
	11.5				11	78	
11	0.5	25	2	THF, 3	11	73	1 equiv. of
	1.5				13	77	$NaNO_2$ added
	2.5				13	76	
	3.5				11	69	
	5.5				14	70	
	7.5				14	67	
	9.5				13	66	
12	0.5	25	2	DMF, 3	0	0	none
	1.5				0	10	
	2.5				1	27	
	3.5				2	39	
	5.5				6	61	
	7.5				3	61	
	9.5				7	69	
	24.0				7	65	

Table 3.4. Continued

Entry	Reaction time (hr)	Reaction temp. (°C)	% $Pd(PPh_3)_4$	Solvent, mls	% Yield 32	% Yield 33	Comments
13	0.5	25	2	DMF, 3	0	0	1 equiv. of $NaNO_2$ added
	1.5				0	0	
	2.5				0	0	
	3.5				0	0	
	5.5				0	0	
	7.5				0	2	
	9.5				0	17	
	24.0				0	22	
14	0.5	25	2	3:1 THF/H_2O, 3	25	58	none
	1.5				18	55	
	2.5				21	55	
	3.5				18	53	
	5.5				16	55	
	7.5				20	46	
	9.5				25	52	
15	0.5	25	2	3:1 THF/H_2O, 3	15	22	1 equiv. of $NaNO_2$ added
	1.5				12	15	
	2.5				10	10	
	3.5				10	9	
	5.5				13	8	
	7.5				14	8	
	9.5				12	9	

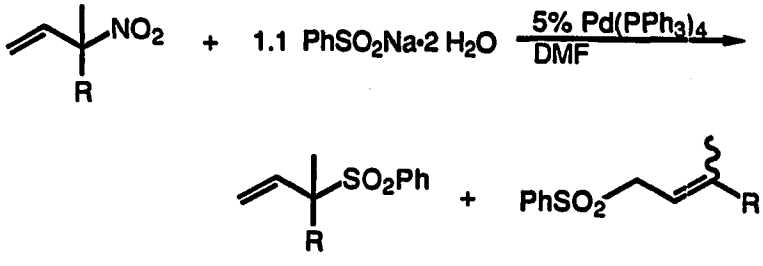
(triphenylphosphine)palladium(0) (compare entries 1, 2 and 6 in Table 3.4). The yield of compound 32 did not seem to depend on the reaction temperature, the concentration of reactants or on the amount of phenol used in the reaction (compare entries 2-5 in Table 3.4). Compound 32 was formed in higher yields at shorter reaction times, however, when the reaction was run at 67°C, in the presence of 2.4 equivalents of phenol or at twice the concentration. The highest yield of compound 32 was obtained when compound 1 was allowed to react with 2.4 equivalents of phenol in the presence of 9% tetrakis-(triphenylphosphine)palladium(0) for 3.5 hr at 40°C (see entry 5 in Table 3.4). When this reaction was repeated and run for 3.5 hr at 40°C, compound 32 was isolated by flash column chromatography in 57% yield (87:13 E/Z), and compound 33 was isolated in 25% yield.

On the other hand, the highest yield of compound 33 was obtained when the reaction shown in equation 3.26 was run using 2% tetrakis(triphenylphosphine)palladium(0) as the catalyst (compare entries 1, 2 and 6 in Table 3.4). A higher yield of compound 33 was formed early in the reaction, however, when 5% tetrakis(triphenylphosphine)palladium(0) was used in the reaction. The concentration of the reactants seemed to have little effect on the yield of compound 33 (compare entries 6 and 10 in Table 3.4). The ratio of compound 33 to 32 did depend, however, upon the temperature

used to run the reaction (compare entries 6-9 in Table 3.4). The highest ratio of compound 33 to 32 was obtained when the reaction was run at 0°C. The yield of compound 33 dropped when dimethylformamide or a 3:1 mixture of tetrahydrofuran and water was used as the solvent (compare entries 7, 12 and 14 in Table 3.4). The highest yield of compound 33 was obtained when compound 1 was treated with 1.2 equivalents of phenol in the presence of 2% tetrakis(triphenylphosphine)palladium(0) for 2.5 hr at 25°C (see entry 7 in Table 3.4).

The results shown in Table 3.4 suggest that compound 33 is the kinetic product of the palladium(0)-catalyzed reaction of compound 1 with phenol. Compound 33 is then slowly isomerized to compound 32, the thermodynamic product, in the presence of palladium(0).

Tamura and co-workers have recently reported the following reaction (eq. 3.27).[112] Tamura et al. found that the palladium(0)-catalyzed isomerization of compound 34, the



(3.27)

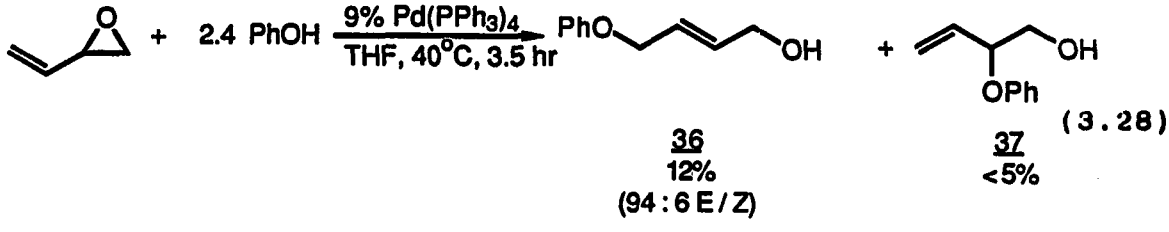
	34	35
no $NaNO_2$	77%	23%
1 equivalent $NaNO_2$	100%	0%

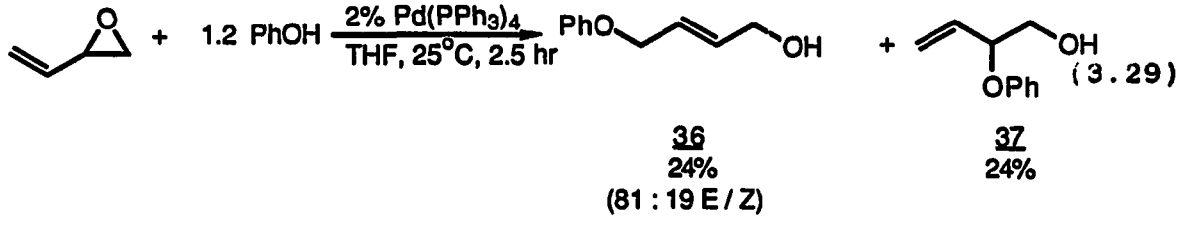
kinetic product, to compound 35, the thermodynamic product, was completely suppressed by the addition of sodium nitrite. They suggested that the results shown in equation 3.27 indicated that tetrakis(triphenylphosphine)palladium(0) was deactivated by sodium nitrite. This newly generated palladium species will oxidatively add to an allylic nitro compound but is inert to an allylic sulfone.

In an attempt to obtain compound 33 as the sole product, the reaction shown in equation 3.26 was run in the presence of one equivalent of sodium nitrate using several different solvents (see entries 11, 13 and 15 in Table 3.4). When the reaction was run using dimethylformamide as the solvent in the presence of one equivalent of sodium nitrite, the isomerization of compound 33 to 32 was completely suppressed (see entry 13 in Table 3.4). The yield of the reaction, however, was poor. When one equivalent of sodium nitrite was added to the reaction and tetrahydrofuran was used as the solvent, the isomerization was not stopped (see entry 11 in Table 3.4). This may be due to the fact that sodium nitrite was not completely soluble in tetrahydrofuran. The isomerization of compound 33 to 32 was also not suppressed when the palladium(0)-catalyzed reaction of compound 1 with phenol was run using a 3:1 mixture of tetrahydrofuran and water as the solvent in the presence of sodium nitrite (see entry 15 in Table 3.4). In this reaction, the water was not

miscible in the tetrahydrofuran, which may account for the poor results.

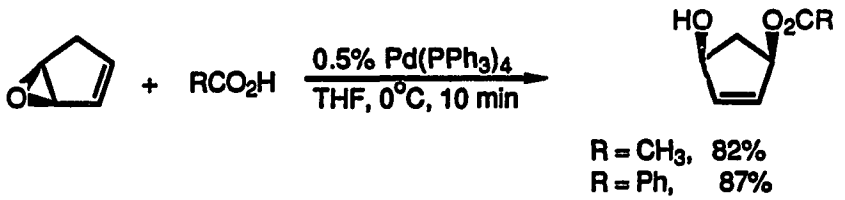
Once the best conditions for the formation of compounds 32 and 33 were found (see entries 5 and 7 in Table 3.4), these reactions were repeated using butadiene monoepoxide, to see if a mixture of regio- and stereoisomers would also be obtained. As predicted from the results given in Table 3.4, the reactions illustrated in equations 3.28 and 3.29 produced the ring-opened product as a mixture of regio- and stereoisomers.





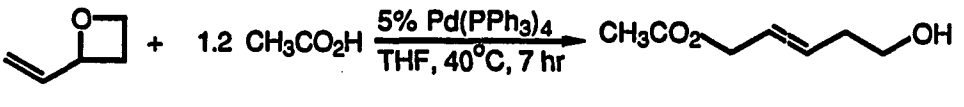
Additions of benzoic acid

Deardorff and co-workers have found that cyclopentadiene monoepoxide will react with benzoic or acetic acid in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) to produce only the cis-1,4-addition product (eq. 3.30).[75] In order to determine whether



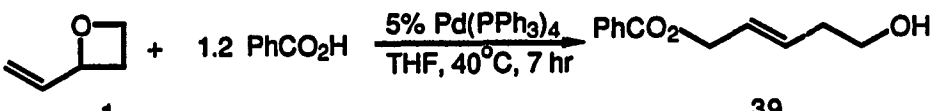
(3.30)

cyclopentadiene monoepoxide could be replaced with a vinylic oxetane, similar reactions were attempted using compound 1. Compound 1 was allowed to react with acetic or benzoic acid in the presence of a catalytic amount of palladium(0) (eqs. 3.31 and 3.32). These reactions were run under the same



1 — 38, 0%

(3.31)



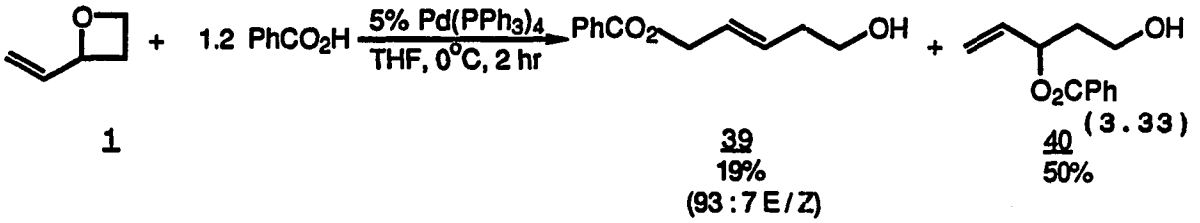
1 — 39, 0%

(3.32)

conditions used for the reaction of compound 1 with dimethyl malonate (see eq. 3.5). In both of the reactions shown in equations 3.31 and 3.32, neither of the expected products was isolated. Only a trace amount of an unidentified product could be isolated from these reactions. The starting materials or the reaction products may not be stable under the conditions of the reaction.

Since Deardorff et al. obtained high yields of the desired allylic alcohol when cyclopentadiene monoepoxide was treated with a catalytic amount of palladium(0) and benzoic

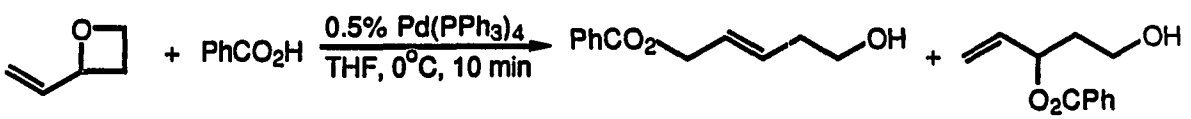
acid at 0°C, the reaction illustrated in equation 3.32 was repeated at this temperature (eq. 3.33). The reaction was



1 — 39, 19% (93:7 E/Z) — 40, 50% (3.33)

monitored by thin layer chromatography. The reaction was stopped as soon as it appeared that all of the benzoic acid had been consumed. The two regioisomers obtained from the reaction, compounds 39 and 40, could be separated by gas or flash column chromatography. The two stereoisomers of compound 39 could not be separated; however, the isomer ratio could be determined by integration of the nuclear magnetic resonance spectral peaks corresponding to the allylic hydrogens next to the benzoate group. The combined yield of compounds 39 and 40 was high.

The palladium(0)-catalyzed reaction of compound 1 with benzoic acid was also run using the exact conditions reported by Deardorff et al. for the reaction of cyclopentadiene monoepoxide with benzoic acid (eq. 3.34).[75] The expected



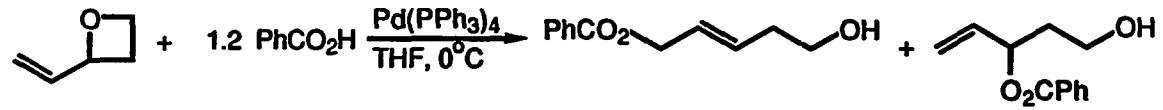
1 — 39, 0% — 40, 0% (3.34)

products could not be detected by gas chromatography.

A gas chromatographic study was done on the reaction shown in equation 3.33 to determine whether the yields of compounds 39 and 40 would change when the reaction conditions were varied (Table 3.5).

The data presented in Table 3.5 show that the best yields of compound 39 were obtained when the reaction of compound 1 with benzoic acid was run in the presence of 5% tetrakis-(triphenylphosphine)palladium(0) (compare entries 1, 2 and 5 in Table 3.5). The yield of compound 39 also depended on the amount of benzoic acid used in the reaction and the method of its addition (compare entries 2-4 in Table 3.5). The best yield of compound 39 was obtained when compound 1 was allowed to react with 2.4 equivalents of benzoic acid in the presence of 5% tetrakis(triphenylphosphine)palladium(0) for 2.5 hr at $0^{\circ}C$ (see entry 3 in Table 3.5). When this reaction was repeated and run for 2.5 hr at $0^{\circ}C$, compound 39 was isolated in 47% yield (88:12 E/Z) by flash chromatography, and compound 40 was isolated in 24% yield.

On the other hand, the best yields of compound 40 were obtained when compound 1 was treated with benzoic acid using 2% tetrakis(triphenylphosphine)palladium(0) (compare entries 1, 2 and 5 in Table 3.5). Higher yields of compound 40 were also isolated when the benzoic acid was added slowly to the solution containing compound 1 and the palladium(0) catalyst



1 39 (E and Z) 40 (3.35)

Table 3.5. Palladium(0)-catalyzed additions of benzoic acid to compound 1

Entry	Reaction time (hr)	% $Pd(PPh_3)_4$	% Yield 39	% Yield 40	Comments
1	0.5	9	22	11	none
	1.5		14	8	
	2.5		14	5	
	3.5		25	11	
	5.5		32	13	
	7.5		27	9	
	10.5		24	9	
2	0.5	5	21	32	none
	1.5		24	16	
	2.5		36	15	
	3.5		32	12	
	5.5		31	12	
	7.5		25	11	
	10.5		23	11	
3	0.5	5	28	55	2.4 equiv. of benzoic acid
	1.5		43	29	
	2.5		50	27	
	3.5		40	19	
	5.5		42	19	
	7.5		42	19	
	10.5		41	21	

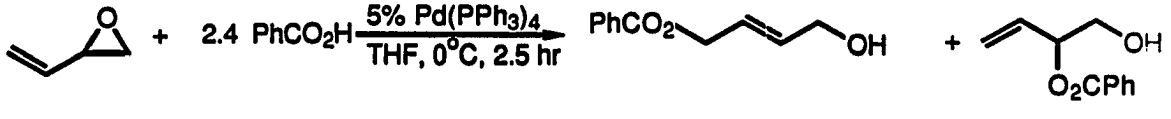
Table 3.5. Continued

Entry	Reaction time (hr)	% $Pd(PPh_3)_4$	% Yield 39	% Yield 40	Comments
4	0.5	5	6	28	Benzoic acid
	1.5		6	59	added over 30 min.
	2.5		6	52	
	3.5		12	45	
	5.5		9	43	
	7.5		11	50	
	10.5		10	44	
5	0.5	2	11	42	none
	1.5		25	70	
	3.5		31	72	
	5.5		30	64	
	7.5		35	61	
	10.5		30	60	
6	0.5	2	4	59	Benzoic acid
	1.5		16	84	added over 30 min.
	2.5		20	76	
	3.5		18	77	
	5.5		19	76	
	7.5		18	76	
	10.5		18	80	

(compare entries 5 and 6 in Table 3.5). The data presented in Table 3.5 show that compound 40 was formed in the highest yield, when compound 1 was treated with 2% tetrakis(triphenylphosphine)palladium(0) and 1.2 equivalents of benzoic acid, which had been added slowly to the reaction mixture, for 1.5 hr at 0°C (see entry 6 in Table 3.5).

The experimental data summarized in Table 3.5 suggest that compound 40 is the kinetic product of the palladium(0)-catalyzed reaction of compound 1 with benzoic acid. Compound 40 is then isomerized to compound 39, the thermodynamic product, in the presence of palladium(0). These results are similar to those obtained when compound 1 was treated with phenol and tetrakis(triphenylphosphine)palladium(0) (see Table 3.4).

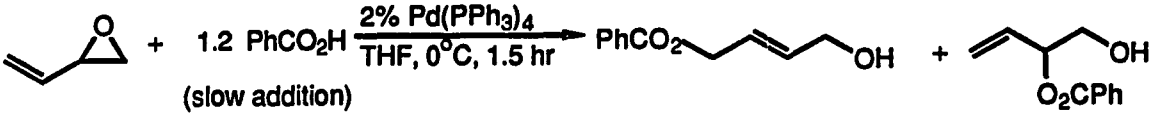
The best reaction conditions observed for the formation of compounds 39 and 40 were used for the reaction of butadiene monoepoxide with benzoic acid. These reactions were run to see if a mixture of regio- and stereoisomers would also be obtained (eqs. 3.36 and 3.37). As predicted by the results



41
22%
(90 : 10 E/Z)

42
77%

(3.36)



41
3%
(41 : 59 E / Z)

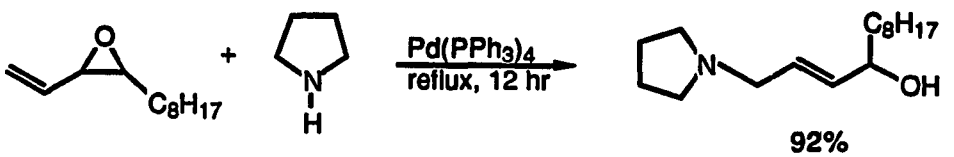
42
27%

(3.37)

reported in Table 3.5, a mixture of regio- and stereoisomers was formed when butadiene monoepoxide was allowed to react with benzoic acid in the presence of palladium(0).

Additions of diethylamine

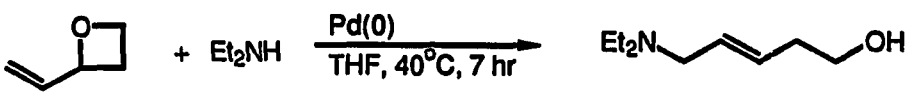
Tsuji and co-workers have recently reported the following reaction (eq. 3.38).[57] In order to determine if amines would



92%

(3.38)

react with vinylic oxetanes in the presence of palladium(0) to produce the corresponding homoallylic alcohols, the reactions of compound 1 with diethylamine were studied. The reactions were run using several different conditions (Table 3.6).



1

43
(E and Z)

(3.39)

Table 3.6. Palladium(0)-catalyzed additions of diethylamine to compound 1

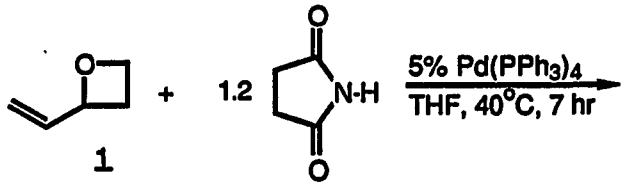
Entry	Catalyst	Equivalents diethylamine	% Yield 43	E/Z Ratio
1	5% $Pd(PPh_3)_4$	1.2	60	93:7
2	5% $Pd(PPh_3)_4$	2.4	98	79:21
3	5% $Pd(PPh_3)_4$, 5% dppe	2.4	80	82:18

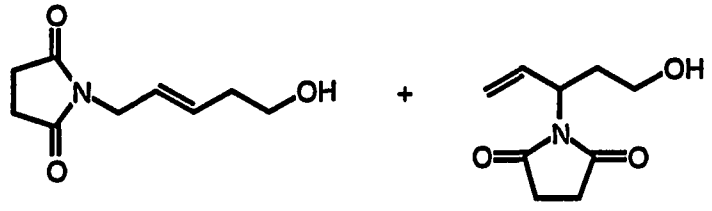
As one can see from the results shown in Table 3.6, the highest yield of compound 43 was obtained when compound 1 was treated with 2.4 equivalents of diethylamine using 5% tetrakis(triphenylphosphine)palladium(0) as the catalyst. The reason compound 43 was found in a higher yield in the presence of a large excess of diethylamine may be due to the fact that diethylamine boils at 55°C and thus might evaporate before it has a chance to react with compound 1. The stereochemical outcome of the reaction shown in equation 3.39 did not seem to depend upon the catalyst, although the product was formed with a higher degree of stereoselectivity when 1.2 equivalents of diethylamine were used in the reaction.

Additions of other heteroatom nucleophiles

The palladium(0)-catalyzed reactions of compound 1 with other heteronucleophiles were also investigated. Compound 1 was allowed to react with succinimide in the presence of a

catalytic amount of tetrakis(triphenylphosphine)palladium(0) (eq. 3.40). The conditions used for this reaction were the



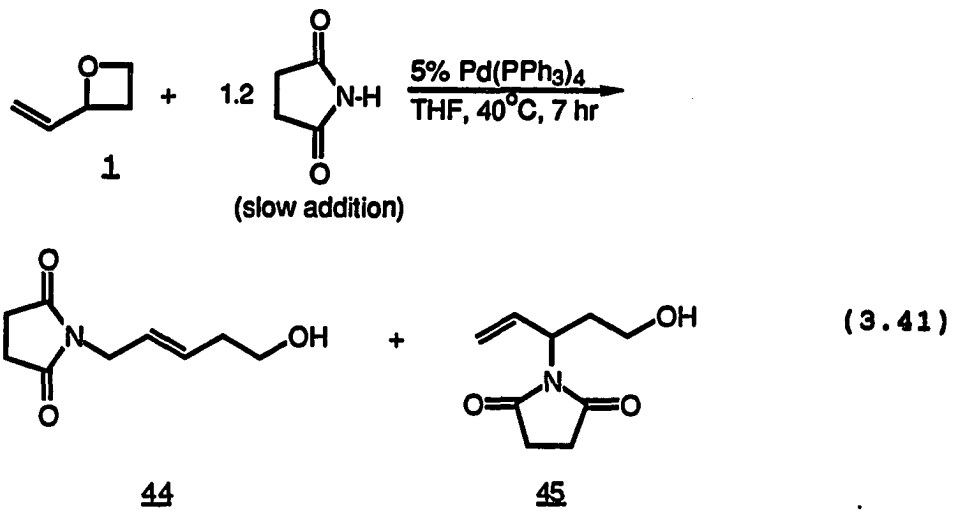


(3.40)

44 45

less than 5%

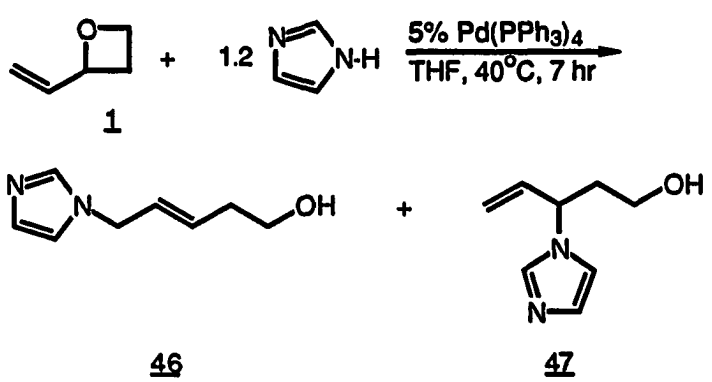
same as those reported for the reaction of compound 1 with dimethyl malonate (see eq. 3.5). Only a trace amount of the ring-opened product was obtained from the reaction illustrated in equation 3.40. The product isolated from this reaction was a mixture of the two possible regioisomers. No other products were formed in this reaction. As soon as the succinimide was added to the mixture of compound 1 and the palladium(0) catalyst, the color of the solution changed from yellow to colorless. Since it appeared that the succinimide had reacted with the palladium catalyst, the reaction shown in equation 3.40 was repeated. This time the succinimide was added to the reaction mixture over three hours (eq. 3.41). Even though the



(3.41)

color of the reaction mixture remained yellow throughout the course of the reaction, only a trace amount of the ring-opened products could be isolated. No other products were isolated from this reaction.

The reaction of compound 1 with imidazole in the presence of a catalytic amount of palladium(0) was also explored. When compound 1 was treated with imidazole using the conditions shown in equation 3.42, the conditions used for the reaction

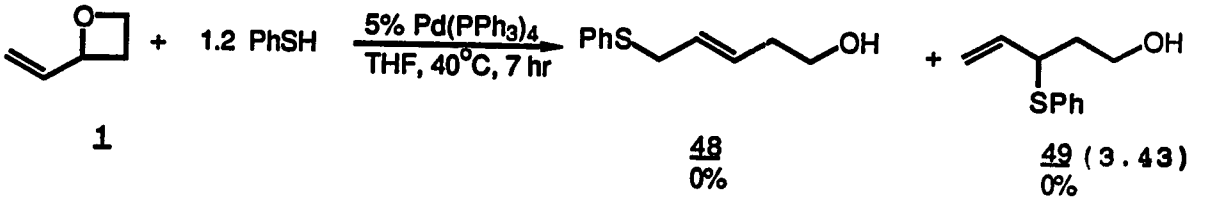


(3.42)

of compound 1 with dimethyl malonate, only a trace amount of the ring-opened product could be isolated as a mixture of regioisomers. No other products were formed in this reaction. Once again, the solution of tetrakis(triphenylphosphine)-palladium(0) and compound 1 turned colorless as soon as the imidazole was added.

There could be several explanations for the poor yields reported in equations 3.40-3.42. Since the color of the reaction mixture changed when either succinimide or imidazole was added, it appears that they may have reacted with the palladium(0) catalyst, rendering it inactive. Secondly, the anions of succinimide and imidazole could be very weak nucleophiles, unable to react effectively with the proposed (π-allyl)palladium intermediate. Finally, compounds 44-47 may be unstable under the reaction conditions.

It has previously been determined that compound 1 will react with phenol in the presence of a catalytic amount of palladium(0) to produce the ring-opened product as a mixture of regioisomers (see eq. 3.23). The reaction of compound 1 with thiophenol and a palladium(0) catalyst was explored, to see if a mixture of regioisomers would also be formed. Compound 1 was treated with thiophenol in the presence of a catalytic amount of palladium(0) (eq. 3.43). The conditions



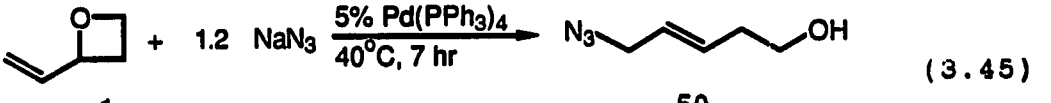
1 48 0% 49 0% (3.43)

used to run the reaction were the same as those employed for the reaction of compound 1 with dimethyl malonate (see eq. 3.5). Neither of the expected products was isolated from the reaction shown in equation 3.43. The only compound isolated from this reaction was unreacted thiophenol. Thiophenol, therefore, does not appear to react with compound 1 using the reaction conditions shown in equation 3.43.

Murahashi and co-workers have recently reported that allyl acetates will react with sodium azide in the presence of a catalytic amount of palladium(0), to yield the corresponding allylic azides (eq. 3.44).[113] Similar reactions were

(3.44)

attempted using compound 1. Compound 1 was allowed to react with sodium azide in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) using several different solvent systems (Table 3.7).



1 50 (3.45)

Table 3.7. Palladium(0)-catalyzed additions of sodium azide to compound 1

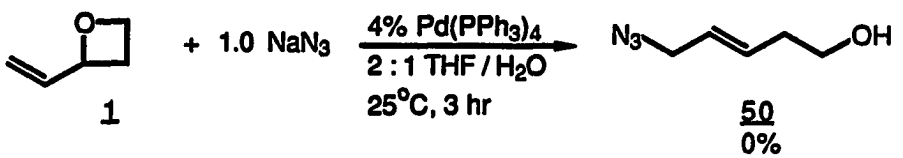
Entry	Solvent	Added reagent	% Yield 50
1	THF	none	0
2	THF	1 n-Bu_4NCl	0
3	2:1 THF/H_2O	none	0
4	4:1 THF/H_2O	none	0
5	DMF	none	0
6	DMF	1 n-Bu_4NCl	0
7	2:1 DMF/H_2O	none	0

As one can see from the results given in Table 3.7, none of the expected product, compound 50, was ever isolated from the palladium(0)-catalyzed reactions of compound 1 with sodium azide. When the reactions were run in the absence of water (see entries 1 and 5 in Table 3.7), the sodium azide was not soluble in the solvent used. The only product isolated was a polymeric material. Since the insolubility of the sodium azide may have accounted for its poor reactivity, tetra-n-butylammonium chloride was added as a phase transfer reagent when tetrahydrofuran or dimethylformamide was used as the solvent (see entries 2 and 6 in Table 3.7). When these reactions were run, once again the only product isolated was a polymeric material. The phase transfer reagent did not seem

to promote the formation of compound 50.

On the other hand, when the reactions of compound 1 with sodium azide were run in the presence of water (see entries 2, 4 and 7 in Table 3.7), the sodium azide was soluble in the reaction medium. However, there were at least nine different products formed in these reactions. None of the products was isolated or characterized.

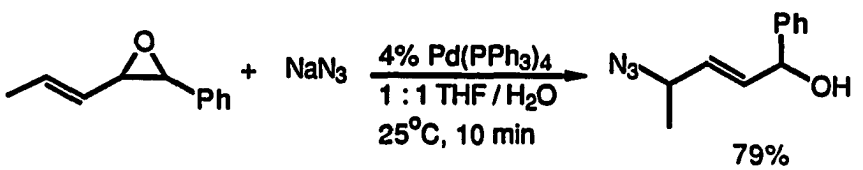
Since it was thought that the reaction conditions used in Table 3.7 may have been too harsh, the reaction of compound 1 with sodium azide was repeated using the exact conditions reported by Murahashi et al. (eq. 3.46).[113] None of the



1 — 50, 0% (3.46)

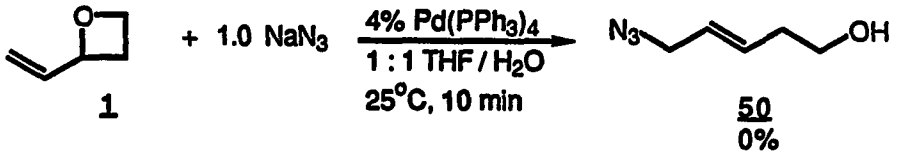
expected product, compound 50, was isolated from this reaction. Once again there were at least nine compounds formed in the reaction, none of which were characterized.

Tenaglia and Waegell have recently studied the palladium-catalyzed reactions of vinylic epoxides with sodium azide (eq. 3.47).[79] The reactions of compound 1 with sodium

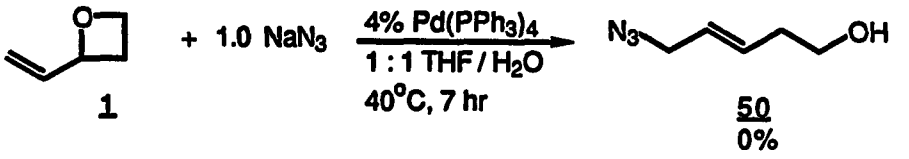


79% (3.47)

azide and a catalytic amount of palladium were run under similar conditions (eqs 3.48 and 3.49). Two different



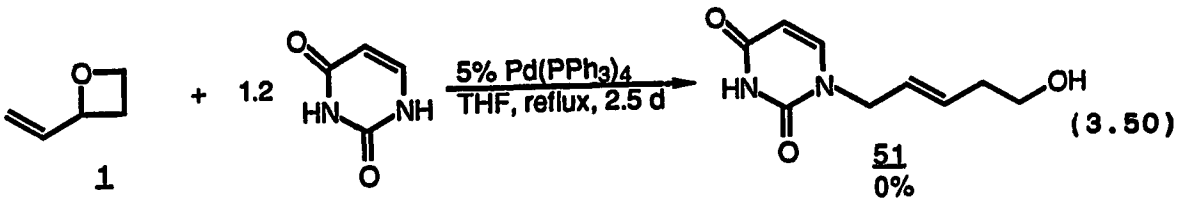
1 — 50, 0% (3.48)



1 — 50, 0% (3.49)

reaction times were employed. The expected homoallylic alcohol, compound 50, was not isolated from either of the reactions studied. Like the previously discussed reactions of compound 1 with sodium azide which used a mixture of tetrahydrofuran and water as the solvent (see entries 3, 4 and 7 in Table 3.7 and eq. 3.46), the reactions illustrated in equations 3.48 and 3.49 yielded a number of products. None of these products was isolated or characterized. Based on the results presented in Table 3.7 and equations 3.46, 3.48 and 3.49, it does not appear that sodium azide can be used as a nucleophile in the palladium(0)-catalyzed ring-opening of vinylic oxetanes.

Compound 1 was also allowed to react with uracil in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0). None of the expected product, compound 51, was isolated from the reaction shown in equation 3.50. There were at least seven compounds formed in this



reaction, none of which were characterized. The uracil was not very soluble in refluxing tetrahydrofuran, which may account for its poor reactivity.

Conclusion

The results presented in this chapter are the first observed examples of the palladium(0)-catalyzed nucleophilic ring-opening of vinylic oxetanes. The reactions of acidic hydrocarbons, β-keto acids, phenols, benzoic acid and diethylamine with vinylic oxetanes in the presence of a catalytic amount of palladium(0) produce the corresponding homoallylic alcohols in good yields. The carbon-carbon bond forming reactions are highly regio- and stereoselective. The amine system is regio-, but not stereoselective, while the oxygen substrates afford regio- and stereoisomeric mixtures. These reactions provide a convenient new synthetic route to homoallylic alcohols.

Experimental

Spectral data and analysis

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolot NT-300 spectrometer at 300 and 75.5

MHz respectively. All infrared spectra were recorded on a Beckmann 4250 spectrophotometer. Exact mass spectral analyses were recorded on a Kratos MS-50 spectrometer. Elemental analyses were performed by Galbraith Laboratories. Gas chromatographic analyses were performed on a Varian 3700 gas chromatograph using a six foot by one-eighth inch stainless steel column (3% OV-101 on chromosorb W). Biphenyl, naphthalene or tetradecane was used as the internal standard in all gas chromatographic analyses.

Reagents

All nucleophiles were distilled or recrystallized prior to use. Cyclohexanone-2-carboxylic acid was synthesized according to the procedure reported by Haruki and co-workers.[110] 3-Methyl-1-(p-tolylsulfonyl)but-2-ene and 1-(p-tolylsulfonyl)prop-2-ene were prepared by the method reported by Terao et al.[111]

The procedure reported by Coulson was used to prepare tetrakis(triphenylphosphine)palladium(0).[114]

Oxetanes and Epoxides

Compound 1 was prepared using the procedure reported by Portnyagin and Pak.[99] The procedure reported by Still was used to prepare compound 25.[104] Compound 27 was synthesized by a procedure similar to the one Portnyagin and Pak used for the preparation of compound 1.[99] The synthesis of compound 27

was discussed in Chapter II. Compound 30 was synthesized using the method reported by Lucas and co-workers.[105] Butadiene monoepoxide was purchased from Aldrich and used without further purification.

The preparation of compound 22 A solution of E- and Z-1-bromopropene (0.40 mol), purchased from Aldrich and used without further purification, in 120 ml of dry THF was added slowly to a mixture of magnesium turnings (0.40 mol) in 120 ml of dry THF. After complete addition, the reaction mixture was stirred for 30 min at room temperature and was then heated to 70°C for an additional 30 min. After cooling to room temperature, 60 ml of dry ether was added to the reaction mixture.

3-Chloropropanal was prepared according to the procedure reported by MacLeod and Rossiter.[107] 3-Chloropropanal (0.20 mol), cooled to -42°C, was added over 2 hr to the solution of E- and Z-1-propenylmagnesium bromide (0.40 mol), maintained at -10°C. The reaction mixture was allowed to stir overnight at room temperature. The solution was cooled to 0°C and 100 ml of saturated ammonium chloride was added slowly to the reaction mixture. The solution was filtered through Celite and the organic layer was separated. The aqueous layer was extracted with ether (2 X 50 ml). The combined organic layers were then washed with saturated sodium bicarbonate (2 X 15 ml), water (2 X 15 ml) and dried over anhydrous magnesium

sulfate. After removal of the solvents, E- and Z-6-chloro-2-hexen-4-ol was purified by distillation: 5.50 g, 20% yield; bp 67°C/1.7 mm Hg.

E- and Z-6-Chloro-2-hexen-4-ol (41 mmol) was added rapidly to a refluxing solution of potassium hydroxide (8.56 g) in 8 ml of water. As the product distilled off through a fractionating column, water was added to the flask, so that the volume of the reaction mixture remained constant. The distillate was saturated with sodium chloride. The organic layer was separated and dried over anhydrous sodium sulfate. After filtering, E- and Z-4,6-epoxy-2-hexene, was purified by distillation: 0.62 g, 15% yield; bp 35°C/20 mm Hg. The following spectral data were taken from a mixture of the E- and Z-isomers: ^{1}H NMR ($CDCl_3$) δ1.60 (d, 3 H, J = 6.9 Hz, CH_3), 1.68 (d, 3 H, J = 6.0 Hz, CH_3), 2.46 (m, 1 H, O-$CH_2C\underline{H}_2$), 2.74 (m, 1 H, O-$CH_2C\underline{H}_2$), 4.46 (m, 1 H, O-CH_2), 4.60 (m, 1 H, O-CH_2), 5.12 (m, 1 H, O-CH), 5.49-5.81 (m, 2 H, $CH_3C\underline{H}$= and O-CHC$\underline{H}$=); ^{13}C NMR ($CDCl_3$) δ13.2, 17.5, 28.9, 29.3, 65.8, 67.6, 77.2, 82.4, 127.0, 128.3, 132.8, 133.1; IR (neat) 3040, 3020 (vinyl C-H), 2980, 2950, 2900 (aliphatic C-H), 1670 (C=C), 1455, 1380, 1320, 1230, 980, 955, 910, 755 cm^{-1}; mass spectrum m/e 98.07292 (calculated for $C_6H_{10}O$ = 98.07317).

General procedure for the alkylation of vinylic epoxides and oxetanes using a palladium(0) catalyst

To a 25 ml round bottom flask was added 22.7 mg of tetrakis(triphenylphosphine)palladium(0) (0.020 mmol), 1.0 equivalent (0.40 mmol) of the olefin to be studied, 1.2 equivalents (0.48 mmol) of the appropriate nucleophile and 2.5 ml of dry THF. The solution was stirred at 40°C for 7 hr under nitrogen. Ether was then added to the reaction mixture. The solution was washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. After removal of the solvents, the residue was purified by flash column chromatography on silica gel.

Spectral data for allylic and homoallylic alcohols prepared by the general procedure for the alkylation of vinylic epoxides and oxetanes using a palladium(0) catalyst

Methyl E-7-hydroxy-2-methoxycarbonyl-4-heptenoate (2)

Compound 2 was prepared in 81% yield (E-isomer only), when compound 1 was allowed to react with dimethyl malonate using the general alkylation procedure: ^{1}H NMR ($CDCl_3$) δ 1.65 (br s, 1 H, OH), 2.24 (dt, 2 H, J = 4.2 Hz, J = 5.0 Hz, $HOCH_2C\underline{H}_2$), 2.62 (dd, 2 H, J = 6.0 Hz, J = 4.2 Hz, $O{=}CCHC\underline{H}_2$), 3.44 (t, 1 H, J = 6.0 Hz, O=CCH), 3.61 (t, 2 H, J = 5.0 Hz, $HOC\underline{H}_2$), 3.74 (s, 6 H, $O-CH_3$), 5.51 (t, 2 H, J = 4.2 Hz, $HOCH_2CH_2C\underline{H}=$ and $O{=}CCHCH_2C\underline{H}=$); ^{13}C NMR ($CDCl_3$) δ31.9, 35.8, 51.8, 52.3, 61.8, 128.4, 129.9, 169.3; IR (neat) 3280-3580 (OH), 3000 (vinyl

C-H), 2950 (aliphatic C-H), 1725 (C=O), 1430, 1335, 1225, 1150, 1030, 965, 905, 720 cm^{-1}; mass spectrum m/e 186.0893 (M - CH_2O) (calculated for $C_9H_{14}O_4$ = 186.0892). Anal. calcd for $C_{10}H_{16}O_5$: C, 55.56; H, 6.50. Found: C, 55.14; H, 6.64.

Ethyl E-2-ethoxycarbonyl-7-hydroxy-4-heptenoate (3)

Compound 3 was prepared in 77% yield (E-isomer only), when compound 1 was allowed to react with diethyl malonate using the general alkylation procedure: ^1H NMR ($CDCl_3$) δ1.26 (t, 6 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.69 (br s, 1 H, OH), 2.25 (dt, 2 H, J = 5.4 Hz, J = 6.0 Hz, $HOCH_2C\underline{H}_2$), 2.61 (dd, 2 H, J = 7.2 Hz, J = 6.3 Hz, $O{=}CCHC\underline{H}_2$), 3.40 (t, 1 H, J = 7.2 Hz, O=CCH), 3.61 (m, 2 H, $HOC\underline{H}_2$), 4.19 (q, 4 H, J = 7.2 Hz, $O-C\underline{H}_2CH_3$), 5.52 (m, 2 H, $HOCH_2CH_2C\underline{H}{=}$ and $O{=}CCHCH_2C\underline{H}{=}$); ^{13}C NMR ($CDCl_3$) δ13.9, 31.7, 35.7, 51.9, 61.2, 61.9, 128.4, 129.7, 168.8; IR (neat) 3200-3600 (OH), 3000 (vinyl C-H), 2980, 2880 (aliphatic C-H), 1735 (C=O), 1440, 1370, 1235, 1150, 1095, 1040, 970, 935 cm^{-1}; mass spectrum m/e 226.1198 (M - H_2O) (calculated for $C_{12}H_{18}O_4$ = 226.1205). Anal. calcd for $C_{12}H_{20}O_5$: C, 59.02; H, 8.20. Found: C, 58.71; H, 8.23.

Ethyl E- and Z-2-ethoxycarbonyl-6-hydroxy-4-hexenoate (6)

The synthesis of compound 6 has been previously described by Trost and Molander.[56]

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the alcohol group. E-isomer: ^1H NMR

($CDCl_3$) δ1.21 (t, 6 H, J = 6.9 Hz, $CH_2C\underline{H}_3$), 1.67 (br s, 1 H, OH), 2.65 (dd, 2 H, J = 7.2 Hz, J = 7.2 Hz, O=CCHC$\underline{H}_2$), 3.45 (t, 1 H, J = 7.2 Hz, O=CCH), 3.49 (d, 2 H, J = 6.9 Hz, HOC$\underline{H}_2$), 4.20 (q, 4 H, J = 6.9 Hz, O-C$\underline{H}_2CH_3$), 5.70 (m, 2 H, $HOCH_2C\underline{H}$= and O=CCHC$H_2C\underline{H}$=). Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ2.70 (dd, 2 H, J = 7.5 Hz, J = 7.5 Hz, O=CCHC$\underline{H}_2$), 3.40 (t, 1 H, J = 7.5 Hz, O=CCH), 3.41 (d, 2 H, J = 7.5 Hz, HOC$\underline{H}_2$), 5.48 (m, 2 H, $HOCH_2C\underline{H}$= and O=CCHC$H_2C\underline{H}$=).

Ethyl E- and Z-2-ethoxycarbonyl-7-hydroxy-2-methyl-4-heptenoate (7) Compound 7 was prepared in 36% yield (61:39 E/Z), when compound 1 was allowed to react with diethyl methylmalonate using the general alkylation procedure.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the alcohol group. E-isomer: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 6 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.39 (s, 3 H, CH_3), 2.26 (dt, 2 H, J = 5.7 Hz, J = 5.7 Hz, $HOCH_2C\underline{H}_2$), 2.57 (d, 2 H, J = 5.1 Hz, O=CCCH_2), 3.60 (t, 2 H, J = 5.7 Hz, HOC$\underline{H}_2$), 4.18 (q, 4 H, J = 7.2 Hz, O-C$\underline{H}_2CH_3$), 5.42-5.54 (m, 2 H, $HOCH_2CH_2C\underline{H}$= and O=CC$CH_2C\underline{H}$=); ^{13}C NMR ($CDCl_3$) δ14.1, 19.9, 33.4, 39.0, 53.9, 61.2, 61.8, 127.6, 131.0, 172.0. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ1.41 (s, 3 H, CH_3), 2.36 (dt, 2 H, J = 6.6 Hz, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 2.66 (d, 2 H, J = 6.9 Hz, O=CCCH_2), 3.67 (t, 2 H, J = 6.3 Hz, HOC$\underline{H}_2$), cis vinyl protons buried under trans protons; ^{13}C NMR ($CDCl_3$) same as

($CDCl_3$) same as the E-isomer or not seen except δ31.0, 36.0, 61.3, 62.1, 126.3, 129.3.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3500 (OH), 3060 (vinyl C-H), 2980, 2935 (aliphatic C-H), 1725 (C=O), 1455, 1375, 1245, 1100, 1015, 965, 855 cm^{-1}; mass spectrum m/e 258.1462 (calculated for $C_{13}H_{22}O_5$ = 258.1468).

Ethyl E-2-ethoxycarbonyl-7-hydroxy-2-phenyl-4-heptenoate (8) Compound 8 was prepared in 83% yield (E-isomer only), when compound 1 was treated with diethyl phenylmalonate using the general alkylation procedure: ^1H NMR ($CDCl_3$) δ1.24 (t, 6 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.50 (br s, 1 H, OH), 2.17 (dt, 2 H, J = 6.3 Hz, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 3.03 (d, 2 H, J = 6.9 Hz, $PhCCH_2$), 3.49 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 4.22 (m, 4 H, $O-C\underline{H}_2CH_3$), 5.38 (dt, 1 H, J = 15.6 Hz, J = 6.3 Hz, $HOCH_2CH_2C\underline{H}=$), 5.50 (dt, 1 H, J = 15.6 Hz, J = 6.9 Hz, $PhCCH_2C\underline{H}=$), 7.24-7.42 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ13.8, 35.8, 39.4, 61.4, 61.5, 63.1, 127.4, 128.0, 130.8, 136.8, 170.3, 2 carbons the same or not seen; IR (neat) 3200-3600 (OH), 3000 (vinyl, aryl C-H), 2920, 2880 (aliphatic C-H), 1740 (C=O), 1490, 1440, 1360, 1290, 1225, 1175, 1090, 1035, 965, 850, 790 cm^{-1}; mass spectrum m/e 320.16290 (calculated for $C_{18}H_{24}O_5$ = 320.16238). Anal. calcd for $C_{18}H_{24}O_5$: C, 67.50; H, 7.50. Found: C, 67.28; H, 7.64.

Ethyl E-2-acetyl-7-hydroxy-4-heptenoate (9) Compound 9 was synthesized in 86% yield (E-isomer only), when compound 1 was allowed to react with ethyl acetoacetate using the general alkylation procedure: ^{1}H NMR ($CDCl_3$) δ1.26 (t, 3 H, J = 6.9 Hz, $CH_2C\underline{H}_3$), 1.75 (br s, 1 H, OH), 2.12 (s, 3 H, $O{=}CCH_3$), 2.24 (m, 2 H, $HOCH_2C\underline{H}_2$), 2.49 (dd, 2 H, J = 7.2 Hz, J = 5.1 Hz, $O{=}CHC\underline{H}_2$), 3.47 (t, 1 H, J = 7.2 Hz, O=CCH), 3.60 (t, 2 H, J = 6.0 Hz, $HOC\underline{H}_2$), 4.18 (q, 2 H, J = 6.9 Hz, $O{-}C\underline{H}_2CH_3$), 5.47 (t, 1 H, J = 3.0 Hz, $HOCH_2CH_2C\underline{H}{=}$), 5.47 (t, 1 H, J = 5.1 Hz, $O{=}CCHCH_2C\underline{H}{=}$); ^{13}C NMR ($CDCl_3$) δ13.9, 28.9, 31.0, 35.7, 59.6, 61.2, 61.6, 128.4, 129.5, 169.2, 202.5; IR (neat) 3200-3600 (OH), 3020 (vinyl C-H), 2990, 2940 (aliphatic C-H), 1735, 1715 (C=O), 1375, 1360, 1220, 1155, 1050, 975, 755, 655 cm^{-1}; mass spectrum m/e 214.1204 (calculated for $C_{11}H_{18}O_4$ = 214.12051). Anal. calcd for $C_{11}H_{18}O_4$: C, 61.68; H, 8.41. Found: C, 61.48; H, 8.48.

Ethyl E-7-hydroxy-2-methyl-2-(1-oxopropyl)-4-heptenoate (10) Compound 10 was prepared in 83% yield (E-isomer only), when compound 1 was allowed to react with 2-carbethoxypentan-3-one using the general alkylation procedure: ^{1}H NMR ($CDCl_3$) δ1.05 (t, 3 H, J = 7.2 Hz, $O{=}CCH_2C\underline{H}_3$), 1.26 (t, 3 H, J = 6.9 Hz, $O{-}CH_2C\underline{H}_3$), 1.32 (s, 3 H, CH_3), 2.13 (br s, 1 H, OH), 2.24 (dt, 2 H, J = 6.6 Hz, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 2.41-2.63 (m, 4 H, $O{=}CCCH_2$ and $O{=}CCH_2$), 3.60 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 4.18 (q, 2 H, J = 6.9 Hz,

O-C<u>H</u>$_2$CH$_3$), 5.39 (dt, 1 H, J = 21.0 Hz, J = 6.6 Hz, HOCH$_2$CH$_2$C<u>H</u>=), 5.57 (dt, 1 H, J = 21.0 Hz, J = 6.3 Hz, O=CCCH$_2$C<u>H</u>=); ^{13}C NMR ($CDCl_3$) δ8.0, 13.9, 19.0, 31.7, 35.8, 38.2, 59.4, 61.1, 61.7, 127.2, 130.8, 172.7, 207.9; IR (neat) 3200-3600 (OH), 3000 (vinyl C-H), 2950, 2895 (aliphatic C-H), 1750, 1720 (C=O), 1460, 1385, 1230, 1135, 1100, 1050, 980, 860 cm^{-1}; mass spectrum m/e 224.14100 (M - H_2O) (calculated for $C_{13}H_{20}O_3$ = 224.14125). Anal. calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 63.96; H, 9.11.

<u>E-6-Acetyl-1-hydroxy-3-octen-7-one (11)</u> Compound <u>11</u> was synthesized in 86% yield (E-isomer only), when compound <u>1</u> was allowed to react with 2.4 equivalents of 2,4-pentanedione for 3.5 hr at 40°C using the general alkylation procedure. Both keto and enol forms of compound <u>11</u> were seen in the NMR and IR spectra: ^{1}H NMR ($CDCl_3$) δ1.65 (br s, 1 H, OH), 2.11 (s, 6 H, O=CCH$_3$ enol form), 2.18 (s, 6 H, O=CCH$_3$ keto form), 2.25 (m, 2 H, HOCH$_2$C<u>H</u>$_2$), 2.56 (dd, 2 H, J = 7.2 Hz, J = 6.0 Hz, O=CCHC<u>H</u>$_2$ keto form), 2.95 (d, 2 H, J = 5.1 Hz, HOC=CC<u>H</u>$_2$ enol form), 3.61 (t, 2 H, J = 6.0 Hz, HOC<u>H</u>$_2$), 3.69 (t, 1 H, J = 7.2 Hz, O=CCH keto form), 5.46 (m, 2 H, HOCH$_2$CH$_2$C<u>H</u>= and O=CCHCH$_2$C<u>H</u>=); ^{13}C NMR ($CDCl_3$) δ22.9, 29.3, 30.2, 31.2, 35.8, 35.9, 61.8, 62.1, 68.3, 107.9, 126.9, 128.4, 129.7, 130.3, 191.2, 203.8; IR (neat) 3200-3600 (OH), 2995 (vinyl C-H), 2930 (aliphatic C-H), 1722, 1699 (C=O), 1599, 1421, 1360, 1153,

1047, 972, 914, 733 cm^{-1}; mass spectrum m/e 184.1100 (calculated for $C_{10}H_{18}O_3$ = 184.10995).

Ethyl E-2-cyano-7-hydroxy-4-heptenoate (12) Compound 12 was prepared in 74% yield (E-isomer only), when compound 1 was treated with 2.4 equivalents of ethyl cyanoacetate for 3.5 hr at 40°C using the general alkylation procedure: ^1H NMR ($CDCl_3$) δ1.31 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.54 (br s, 1 H, OH), 2.31 (dt, 2 H, J = 6.3 Hz, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 2.65 (dd, 2 H, J = 6.6 Hz, J = 6.6 Hz, $NCCHC\underline{H}_2$), 3.54 (t, 1 H, J = 6.6 Hz, NCCH), 3.66 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 4.26 (q, 2 H, J = 7.2 Hz, $O-C\underline{H}_2CH_3$), 5.55 (dt, 1 H, J = 15.3 Hz, J = 6.6 Hz, $NCCHCH_2C\underline{H}=$), 5.67 (dt, 1 H, J = 15.3 Hz, J = 6.3 Hz, $HOCH_2CH_2C\underline{H}=$); ^{13}C NMR ($CDCl_3$) δ13.7, 32.7, 35.5, 37.8, 61.3, 62.6, 116.1, 125.4, 132.3, 165.4; IR (neat) 3200-3600 (OH), 3000 (vinyl C-H), 2950, 2890 (aliphatic C-H), 2260 (CN), 1745 (C=O), 1450, 1375, 1265, 1215, 1100, 1040, 980, 865, 760 cm^{-1}; mass spectrum m/e 198.11269 (M + H) (calculated for $C_{10}H_{16}NO_3$ = 198.11303). Anal. calcd for $C_{10}H_{15}NO_3$: C, 60.91; H, 7.61. Found: C, 60.84; H, 7.98.

Diethyl E-1-ethoxycarbonyl-6-hydroxy-3-hexenyl phosphonate (13) Compound 13 was prepared in 75% yield (E-isomer only), when compound 1 was allowed to react with 2.4 equivalents of triethyl phosphonoacetate for 3.5 hr at 40°C using the general alkylation procedure: ^1H NMR ($CDCl_3$) δ1.25 (t, 3 H, J = 7.2 Hz, $O=COCH_2C\underline{H}_3$), 1.31 (t, 6 H, J = 7.5 Hz,

P-$OCH_2C\underline{H}_3$), 2.21 (dt, 2 H, J = 5.4 Hz, J = 6.0 Hz, $HOCH_2C\underline{H}_2$), 2.59 (m, 2 H, P-$CHC\underline{H}_2$), 2.97 (ddd, 1 H, J = 22.2 Hz, J = 15.0 Hz, J = 7.5 Hz, P-CH), 3.57 (t, 2 H, J = 6.0 Hz, $HOC\underline{H}_2$), 4.13 (q, 4 H, J = 7.5 Hz, P-OCH_2), 4.18 (q, 2 H, J = 7.2 Hz, O=$COC\underline{H}_2CH_3$), 5.49 (t, 1 H, J = 3.0 Hz, P-$CHCH_2C\underline{H}$=), 5.49 (t, 1 H, J = 5.4 Hz, $HOCH_2CH_2C\underline{H}$=); ^{13}C NMR ($CDCl_3$) δ13.9, 16.1, 30.0 (d, J = 3.2 Hz), 35.7, 44.7, 46.5, 61.3 (d, J = 20.4 Hz), 62.5 (d, J = 4.9 Hz), 128.4, 129.6, 168 (d, J = 3.3 Hz); IR (neat) 3200-3600 (OH), 2980, 2930, 2860 (aliphatic C-H), 1720 (C=O), 1440, 1390, 1365, 1325, 1240, 1150, 1095, 1030, 965, 750 cm^{-1}; mass spectrum m/e 308.13875 (calculated for $C_{13}H_{25}O_6P$ = 308.13888). Anal. calcd for $C_{13}H_{25}O_6P$: C, 50.56; H, 8.12. Found: C, 50.48; H, 8.01.

Methyl E-7-hydroxy-2-thiophenoxy-4-heptenoate (14)

Compound 14 was synthesized in 46% yield (E-isomer only), when compound 1 was allowed to react with 2.4 equivalents of methyl thiophenoxyacetate for 3.5 hr at 40°C using the general alkylation procedure: ^1H NMR ($CDCl_3$) δ1.60 (br s, 1 H, OH), 2.26 (dt, 2 H, J = 5.7 Hz, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 2.55 (m, 2 H, S-$CHC\underline{H}_2$), 3.64 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 3.66 (s, 3 H, O-CH_3), 3.71 (dd, 1 H, J = 8.4 Hz, J = 6.6 Hz, S-CH), 5.50 (dt, 1 H, J = 13.5 Hz, J = 6.0 Hz, S-$CHCH_2C\underline{H}$=), 5.55 (dt, 1 H, J = 13.5 Hz, J = 5.7 Hz, $HOCH_2CH_2C\underline{H}$=), 7.27-7.47 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ34.9, 35.9, 50.8, 52.1, 61.7, 127.3, 127.9, 128.4, 128.9, 130.3, 132.9, 172.2; IR (neat) 3200-3600 (OH),

3020 (vinyl, aryl C-H), 2970, 2900 (aliphatic C-H), 1735 (C=O), 1588, 1485, 1440, 1340, 1265, 1230, 1190, 1155, 1040, 1025, 970, 750 cm^{-1}; mass spectrum m/e 266.09765 (calculated for $C_{14}H_{18}O_3S$ = 266.09767). Anal. calcd for $C_{14}H_{18}O_3S$: C, 63.16; H, 6.77. Found: C, 63.08; H, 6.73.

Phenyl E-6-hydroxy-1-methoxycarbonyl-3-hexenyl sulfone (15) Compound 15 was synthesized in 82% yield (E-isomer only), when compound 1 was allowed to react with methyl phenylsulfonylacetate using the general alkylation procedure: ^1H NMR ($CDCl_3$) δ2.21 (dt, 2 H, J = 6.3 Hz, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 2.70 (m, 2 H, S-$CHC\underline{H}_2$), 3.58 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 3.63 (s, 3 H, O-CH_3), 3.98 (dd, 1 H, J = 10.5 Hz, J = 4.5 Hz, S-CH), 5.38 (dt, 1 H, J = 15.3 Hz, J = 6.3 Hz, $HOCH_2CH_2C\underline{H}$=), 5.53 (dt, 1 H, J = 15.3 Hz, J = 7.2 Hz, S-$CHCH_2C\underline{H}$=), 7.50-7.90 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ29.9, 35.6, 52.6, 61.4, 70.3, 125.6, 128.9, 129.0, 131.5, 134.2, 137.1, 165.1; IR (neat) 3200-3600 (OH), 3060 (vinyl, aryl C-H), 3000, 2950, 2880 (aliphatic C-H), 1735 (C=O), 1590, 1440, 1375, 1320, 1235, 1200, 1190, 1080, 1040, 970, 910, 850, 720, 685 cm^{-1}; mass spectrum m/e 268.07683 (M - CH_2O) (calculated for $C_{13}H_{16}O_4S$ = 268.07693). Anal. calcd for $C_{14}H_{18}O_5S$: C, 56.38; H, 6.04. Found: C, 55.92; H, 6.18.

E-4-Ethoxycarbonyl-2,2-di(5-hydroxy-2-pentenyl)-3-methyl-3-cyclohexen-1-one (16) Compound 16 was prepared in 70% yield (E-isomer only), when compound 1 was allowed to react with 4-carbethoxy-3-methyl-2-cyclohexen-1-one using the general alkylation procedure: ^{1}H NMR ($CDCl_3$) δ1.31 (t, 3 H, J = 7.2 Hz, $CH_2O\underline{H}_3$), 1.73 (br s, 2 H, OH), 1.95 (s, 3 H, $=CCH_3$), 2.17 (dt, 4 H, J = 6.3 Hz, J = 6.0 Hz, $HOCH_2C\underline{H}_2$), 2.24 (t, 2 H, J = 6.9 Hz, $O=CCH_2C\underline{H}_2C=$), 2.37 (t, 2 H, J = 6.9 Hz, $O=CC\underline{H}_2CH_2C=$), 2.54 (m, 4 H, $O=CCCH_2$), 3.55 (t, 4 H, J = 6.0 Hz, $HOC\underline{H}_2$), 4.22 (q, 2 H, J = 7.2 Hz, $O-C\underline{H}_2CH_3$), 5.21 (dt, 2 H, J = 15.3 Hz, J = 7.2 Hz, $O=CCCH_2C\underline{H}=$), 5.36 (dt, 2 H, J = 15.3 Hz, J = 6.3 Hz, $HOCH_2CH_2C\underline{H}=$); ^{13}C NMR ($CDCl_3$) δ14.3, 15.7, 24.8, 36.0, 38.9, 40.2, 58.1, 60.7, 61.9, 127.7, 128.8, 130.4, 144.2, 168.8, 212.5; IR (neat) 3200-3600 (OH), 2934 (aliphatic C-H), 1710 (C=O), 1630 (C=C), 1551, 1447, 1371, 1306, 1254, 1200, 1088, 1047, 972, 918, 864, 845, 775, 731 cm^{-1}; mass spectrum m/e 350.20875 (calculated for $C_{20}H_{30}O_5$ = 350.20933).

E-2-(5-Hydroxy-2-pentenyl)cylcohexanone (17) Compound 17 was prepared in 91% yield (E-isomer only), when compound 1 was allowed to react with 1.2 equivalents of cyclohexanone-2-carboxylic acid using the general alkylation procedure: ^{1}H NMR ($CDCl_3$) δ1.26-2.51 (m, 14 H, 4 CH_2's cyclohexane ring, O=CCH, $O=CCHC\underline{H}_2$, $HOCH_2C\underline{H}_2$ and OH), 3.59 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 5.38 (dt, 1 H, J = 15.6 Hz, J = 6.6 Hz, $O=CCHCH_2C\underline{H}=$),

5.49 (dt, 1 H, J = 15.6 Hz, J = 6.6 Hz, $HOCH_2CH_2C\underline{H}$=); ^{13}C NMR ($CDCl_3$) δ 24.8, 27.8, 32.7, 33.4, 35.9, 41.9, 50.5, 61.9, 128.0, 130.9, 212.6; IR (neat) 3200-3600 (OH), 2935, 2862 (aliphatic C-H), 1709 (C=O), 1448, 1429, 1373, 1313, 1242, 1130, 1047, 972, 732 cm^{-1}; mass spectrum m/e 182.13061 (calculated for $O_{11}H_{18}O_2$ = 182.13068).

E- and Z-6-Nitro-3-hexen-1-ol (18) Compound 18 was synthesized in 56% yield (97:3 E/Z), when compound 1 was treated with nitromethane for 3.5 hr at 40°C using the general alkylation procedure.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the alcohol group. E-isomer: ^1H NMR ($CDCl_3$) δ 1.96 (br s, 1 H, OH), 2.21 (dt, 2 H, J = 6.3 Hz, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 2.63 (dt, 2 H, J = 6.3 Hz, J = 6.9 Hz, $O_2NCH_2C\underline{H}_2$), 3.55 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 4.35 (t, 2 H, J = 6.9 Hz, O_2NCH_2), 5.44 (dt, 1 H, J = 16.5 Hz, J = 6.3 Hz, $HOCH_2CH_2C\underline{H}$=), 5.50 (dt, 1 H, J = 16.5 Hz, J = 6.3 Hz, $O_2NCH_2CH_2C\underline{H}$=); ^{13}C NMR ($CDCl_3$) δ30.5, 35.8, 61.7, 75.3, 126.2, 131.2. Z-isomer: ^1H NMR ($CDCl_3$) same as the E-isomer except δ2.26 (dt, 2 H, J = 6.6 Hz, J = 5.4 Hz, $HOCH_2C\underline{H}_2$), 2.71 (dt, 2 H, J = 7.2 Hz, J = 7.2 Hz, $O_2NCH_2C\underline{H}_2$), 3.60 (t, 2 H, J = 5.4 Hz, $HOC\underline{H}_2$), cis vinyl protons buried under trans protons; ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ30.8, 74.9, 125.2, 130.5.

The following spectral data were taken from a mixture of

the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3000 (vinyl C-H), 2840-2980 (aliphatic C-H), 1550 (NO_2), 1430, 1380, 1040, 970, 905, 725 cm^{-1}; mass spectrum m/e 115.0632 (M - CH_2O) (calculated for $C_5H_9NO_2$ = 115.0633). Anal. calcd for $C_6H_{11}NO_3$: C, 49.64; H, 7.63. Found: C, 49.63; H, 7.76.

Methyl E-7-hydroxy-2-methoxycarbonyl-3-methyl-4-heptenoate (23) Compound 23 was prepared in 75% yield (E-isomer only), when compound 22 was allowed to react with dimethyl malonate in the presence of 1.2 equivalents of triethylamine, 9% tetrakis(triphenylphosphine)palladium(0) and 9% 1,2-bis(diphenylphosphino)ethane using the general alkylation procedure. The solution of tetrakis(triphenylphosphine)palladium(0) and 1,2-bis(diphenylphosphino)ethane in THF was allowed to reflux for 1 hr before the addition of the other reagents: ^1H NMR ($CDCl_3$) δ1.08 (d, 3 H, J = 6.6 Hz, $CHC\underline{H}_3$), 1.65 (br s, 1 H, OH), 2.23 (dt, 2 H, J = 6.0 Hz, J = 6.0 Hz, $HOCH_2C\underline{H}_2$), 2.93 (m, 1 H, $CH_3C\underline{H}$), 3.30 (d, 1 H, J = 8.7 Hz, O=CCH), 3.59 (m, 2 H, $HOC\underline{H}_2$), 3.69 (s, 3 H, O-CH_3), 3.73 (s, 3 H, O-CH_3), 5.47 (m, 2 H, $HOCH_2CH_2C\underline{H}$= and $CH_3CHC\underline{H}$=); ^{13}C NMR ($CDCl_3$) δ18.4, 35.8, 37.4, 52.3, 57.8, 61.7, 127.6, 134.6, 168.8; IR (neat) 3200-3600 (OH), 3050, 3030 (vinyl C-H), 2980, 2900 (aliphatic C-H), 1750 (C=O), 1440, 1340, 1250, 1200, 1155, 1045, 1020, 970, 750, 660 cm^{-1}; mass spectrum m/e 200.10504 (M - CH_2O) (calculated for $C_{10}H_{16}O_4$ =

200.10486). Anal. calcd for $C_{11}H_{18}O_5$: C, 57.39; H, 7.83. Found: C, 56.90; H, 7.99.

E-6-Acetyl-1-hydroxy-5-methyl-3-octen-7-one (24)

Compound 24 was prepared in 80% yield (E-isomer only), when compound 22 was allowed to react with 2.4 equivalents of 2,4-pentanedione in the presence of 1.2 equivalents of triethylamine, 9% tetrakis(triphenylphosphine)palladium(0) and 9% 1,2-bis(diphenylphosphino)ethane using the general alkylation procedure. The solution of tetrakis(triphenylphosphine)palladium(0) and 1,2-bis(diphenylphosphino)ethane in THF was allowed to reflux for 1 hr before the addition of the other reagents: ^{1}H NMR ($CDCl_3$) δ0.97 (d, 3 H, J = 6.6 Hz, $CHC\underline{H}_3$), 2.10 (s, 3 H, $O{=}CCH_3$), 2.12 (s, 3 H, $O{=}CCH_3$), 2.21 (dt, 2 H, J = 6.6 Hz, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 3.00 (m, 1 H, $CH_3C\underline{H}$), 3.55 (d, 1 H, J = 9.0 Hz, O=CCH), 3.59 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 5.32 (dd, 1 H, J = 15.6 Hz, J = 8.1 Hz, $CH_3CHC\underline{H}{=}$), 5.46 (dt, 1 H, J = 15.6 Hz, J = 6.6 Hz, $HOCH_2CH_2C\underline{H}{=}$); ^{13}C NMR ($CDCl_3$) δ18.8, 29.9, 30.1, 35.8, 37.7, 61.8, 75.5, 127.8, 134.3, 203.6, 203.9; IR (neat) 3200-3600 (OH), 2940, 2910, 2860 (aliphatic C-H), 1680 (C=O), 1410, 1345, 1185, 1140, 1035, 960, 900, 715 cm^{-1}; mass spectrum m/e 198.12540 (calculated for $C_{11}H_{18}O_3$ = 198.12560).

E-2-(4-Acetyl-5-oxo-1-hexenyl)-trans-1,3-cyclohexanediol (26) Compound 26 was synthesized in 82% yield (E-isomer only), when compound 25 was allowed to react with 2.4 equivalents of 2,4-pentanedione for 3.5 hr at 40°C using the general alkylation procedure. Both keto and enol forms of compound 26 were seen in the NMR and IR spectra: ^{1}H NMR ($CDCl_3$) δ1.36-2.04 (m, 9 H, 3 CH_2's cyclohexane ring, HOCHCH, and 2 OH's), 2.15 (s, 6 H, O=CCH_3 keto form), 2.16 (s, 6 H, O=CCH_3 enol form), 2.58 (dd, 2 H, J = 6.9 Hz, J = 6.9 Hz, O=CCHCH_2 keto form), 2.90 (d, 2 H, J = 3.6 Hz, HOC=CCH_2 enol form), 3.69 (t, 1 H, J = 6.9 Hz, O=CCH keto form), 3.73 (m, 1 H, HOCH), 3.92-3.97 (m, 1 H, HOCH), 5.50 (dt, 1 H, J = 15.6 Hz, J = 6.9 Hz, O=CCHCH_2CH=), 5.63 (dd, 1 H, J = 15.6 Hz, J = 7.8 Hz, HOCHCHCH=); ^{13}C NMR ($CDCl_3$) δ18.7, 22.9, 29.3, 29.4, 30.5, 31.3, 32.2, 32.3, 33.9, 53.2, 53.4, 67.8, 68.3, 68.5, 70.3, 70.5, 107.9, 129.0, 129.8, 131.0, 132.8, 191.2, 204.0, 1 carbon the same or not seen; IR (neat) 3200-3600 (OH), 3040 (vinyl C-H), 2960, 2890 (aliphatic C-H), 1730, 1700 (C=O), 1440, 1360, 1215, 1155, 1120, 1045, 975, 740, 715, 690, 655 cm^{-1}; mass spectrum m/e 254.15125 (calculated for $C_{14}H_{22}O_4$ = 254.15181).

Ethyl E-2-ethoxycarbonyl-7-hydroxy-6-methyl-2-phenyl-4-heptenoate (28) Compound 28 was prepared in 42% yield (E-isomer only), when compound 27 was allowed to react with diethyl phenylmalonate using the general alkylation procedure:

^{1}H NMR ($CDCl_3$) δ0.89 (d, 3 H, J = 6.9 Hz, $CHC\underline{H}_3$), 1.23 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.24 (t, 3 H, J = 6.9 Hz, $CH_2C\underline{H}_3$), 1.49 (br s, 1 H, OH), 2.22 (m, 1 H, $CH_3C\underline{H}$), 3.01 (m, 2 H, $PhCCH_2$), 3.19 (m, 1 H, $HOC\underline{H}_2$), 3.37 (m, 1 H, $HOC\underline{H}_2$), 4.21 (q, 4 H, J = 7.2 Hz, $O\text{-}C\underline{H}_2CH_3$), 5.20 (dd, 1 H, J = 15.6 Hz, J = 7.8 Hz, $CH_3CHC\underline{H}$=), 5.45 (dt, 1 H, J = 15.6 Hz, J = 7.2 Hz, $PhCCH_2C\underline{H}$=), 7.27-7.39 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ14.0, 16.2, 39.6, 61.6, 63.2, 67.0, 126.2, 127.5, 128.0, 136.8, 137.2, 170.3, 2 carbons the same or not seen; IR (neat) 3200-3600 (OH), 3160, 3120 (vinyl, aryl C-H), 2985, 2910 (aliphatic C-H), 1740 (C=O), 1515, 1460, 1405, 1380, 1305, 1210, 1190, 1105, 1035, 980, 865, 755, 700, 665 cm^{-1}; mass spectrum m/e 334.17741 (calculated for $C_{19}H_{26}O_5$ = 334.17803). Anal. calcd for $C_{19}H_{26}O_5$: C, 68.26; H, 7.78. Found: C, 68.38; H, 7.93.

Ethyl E-2-acetyl-7-hydroxy-6-methyl-4-heptenoate (29)

Compound 29 was prepared in 85% yield (E-isomer only), when compound 27 was allowed to react with ethyl acetoacetate using the general alkylation procedure: ^{1}H NMR ($CDCl_3$) δ0.94 (d, 3 H, J = 6.9 Hz, $CHC\underline{H}_3$), 1.26 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.60 (br s, 1 H, OH), 2.21 (s, 3 H, $O{=}CCH_3$), 2.28 (m, 1 H, $CH_3C\underline{H}$), 2.54 (dd, 2 H, J = 7.8 Hz, J = 6.6 Hz, $O{=}CCHC\underline{H}_2$), 3.32 (t, 1 H, J = 7.8 Hz, O=CCH), 3.67 (dd, 2 H, J = 7.2 Hz, J = 3.0 Hz, $HOC\underline{H}_2$), 4.18 (q, 2 H, J = 7.2 Hz, $O\text{-}C\underline{H}_2CH_3$), 5.33 (dd, 1 H, J = 15.9 Hz, J = 7.5 Hz, $CH_3CHC\underline{H}$=), 5.45 (dt, 1 H, J = 15.9 Hz,

J = 6.6 Hz, O=CCHCH$_2$C<u>H</u>=); ^{13}C NMR ($CDCl_3$) δ14.0, 16.3, 28.9, 31.2, 39.5, 59.6, 61.3, 67.1, 126.7, 135.9, 169.3, 202.5; IR (neat) 3200-3600 (OH), 3000 (vinyl C-H), 2960, 2900 (aliphatic C-H), 1745, 1720 (C=O), 1450, 1365, 1335, 1300, 1215, 1180, 1150, 1095, 1030, 970, 855, 750, 660 cm^{-1}; mass spectrum m/e 228.13641 (calculated for $C_{12}H_{20}O_4$ = 228.13616). Anal. calcd for $C_{12}H_{20}O_4$: C, 63.16; H, 8.77. Found: C, 62.39; H, 8.90.

<u>Ethyl E-2-cyano-7-hydroxy-6,6-dimethyl-4-heptenoate (31)</u>

Compound <u>31</u> was synthesized in 62% yield (E-isomer only), when compound <u>30</u> was treated with 2.4 equivalents of ethyl cyanoacetate for 3.5 hr at 40°C using the general alkylation procedure: ^{1}H NMR ($CDCl_3$) δ1.01 (s, 6 H, 2 CH_3's), 1.32 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.58 (br s, 1 H, OH), 2.66 (dd, 2 H, J = 6.9 Hz, J = 6.9 Hz, NCCHC<u>H</u>$_2$), 3.31 (s, 1 H, HOC<u>H</u>$_2$), 3.33 (s, 1 H, HOC<u>H</u>$_2$), 3.54 (t, 1 H, J = 6.9 Hz, NCCH), 4.26 (q, 2 H, J = 7.2 Hz, O-C<u>H</u>$_2$CH$_3$), 5.43 (dt, 1 H, J = 15.6 Hz, J = 6.9 Hz, NCCHCH$_2$C<u>H</u>=), 5.63 (d, 1 H, J = 15.6 Hz, $(CH_3)_2$CC<u>H</u>=); ^{13}C NMR ($CDCl_3$) δ14.1, 23.7, 33.3, 38.3, 38.7, 62.9, 71.5, 116.3, 121.8, 143.3, 165.6; IR (neat) 3200-3600 (OH), 2964, 2934 (aliphatic C-H), 2253 (CN), 1744 (C=O), 1626, 1472, 1445, 1371, 1298, 1259, 1205, 1096, 1043, 976, 901, 860 cm^{-1}; mass spectrum m/e 195.12642 (M - CH_2O) (calculated for $C_{11}H_{17}NO_2$ = 195.1260). Anal. calcd for $C_{12}H_{19}NO_3$: C, 64.00; H, 8.44. Found: C, 62.87; H, 8.49.

E- and Z-5-Phenoxy-3-penten-1-ol (32) Compound 32 was prepared in 58% yield (87:13 E/Z), when compound 1 was allowed to react with 2.4 equivalents of phenol in the presence of 9% tetrakis(triphenylphosphine)palladium(0) for 3.5 hr at 40°C using the general alkylation procedure. The yield of compound 32 was determined by gas chromatographic analysis of the crude reaction mixture using biphenyl as the internal standard.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the phenoxy group. E-isomer: ^{1}H NMR ($CDCl_3$) δ 1.45 (br s, 1 H, OH), 2.37 (dt, 2 H, J = 5.4 Hz, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 3.70 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 4.49 (d, 2 H, J = 3.3 Hz, $PhOCH_2$), 5.39 (m, 2 H, $HOCH_2CH_2C\underline{H}=$ and $PhOCH_2C\underline{H}=$), 6.74-7.38 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ35.8, 61.8, 68.4, 114.8, 120.9, 128.0, 129.4, 130.9, 158.6. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ2.44 (dt, 2 H, J = 6.3 Hz, J = 7.2 Hz, $HOCH_2C\underline{H}_2$), 4.57 (d, 2 H, J = 6.0 Hz, $PhOCH_2$), cis vinyl protons buried under trans protons; ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ31.4, 63.8, 121.0, 127.7, 130.3.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3063, 3028 (vinyl, aryl C-H), 2932, 2878 (aliphatic C-H), 1599, 1587, 1497, 1302, 1242, 1173, 1045, 1030, 972, 754, 692 cm^{-1}; mass spectrum m/e 178.0993 (calculated for $C_{11}H_{14}O_2$ = 178.09938).

Anal. calcd for $C_{11}H_{14}O_2$: C, 74.16; H, 7.86. Found: C, 74.37; H, 8.03.

3-Phenoxy-4-penten-1-ol (33) Compound 33 was prepared in 84% yield, when compound 1 was treated with phenol in the presence of 2% tetrakis(triphenylphosphine)palladium(0) for 2.5 hr at 25°C using the general alkylation procedure. The yield of compound 33 was determined by gas chromatographic analysis of the crude reaction mixture using biphenyl as the internal standard: ^{1}H NMR ($CDCl_3$) δ1.88 (br s, 1 H, OH), 1.92-2.01 (m, 2 H, $HOCH_2C\underline{H}_2$), 3.76-3.92 (m, 2 H, $HOC\underline{H}_2$), 4.87 (dt, 1 H, J = 6.0 Hz, J = 6.6 Hz, PhOCH), 5.22 (dd, 1 H, J = 10.8 Hz, J = 1.2 Hz, $=CH_2$ cis), 5.29 (dd, 1 H, J = 17.7 Hz, J = 1.2 Hz, $=CH_2$ trans), 5.88 (ddd, J = 17.7 Hz, J = 10.8 Hz, J = 6.0 Hz, =CH-), 6.89-7.31 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 36.3, 59.5, 77.1, 116.2, 116.6, 121.2, 129.4, 137.7, 158.1; IR (neat) 3200-3600 (OH), 3065, 3039, 3012 (vinyl, aryl C-H), 2951, 2885 (aliphatic C-H), 1599, 1587, 1495, 1290, 1240, 1173, 1053, 999, 988, 930, 754, 692 cm^{-1}; mass spectrum m/e 178.0992 (calculated for $C_{11}H_{14}O_2$ = 178.09938). Anal. calcd for $C_{11}H_{14}O_2$: C, 74.16; H, 7.86. Found: C, 73.77; H, 8.09.

E- and Z-4-Phenoxy-2-buten-1-ol (36) Compound 36 was prepared in 24% yield (81:19 E/Z), when butadiene monoepoxide was allowed to react with phenol in the presence of 2% tetrakis(triphenylphosphine)palladium(0) for 2.5 hr at 25°C using the general alkylation procedure.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the phenoxy group. E-isomer: ^{1}H NMR ($CDCl_3$) δ1.65 (br s, 1 H, OH), 4.20 (d, 2 H, J = 3.9 Hz, $HOC\underline{H}_2$), 4.54 (d, 2 H, J = 4.5 Hz, $PhOCH_2$), 5.95 (dt, 1 H, J = 15.9 Hz, J = 3.9 Hz, $HOCH_2C\underline{H}$=), 6.03 (dt, 1 H, J = 15.9 Hz, J = 4.5 Hz, $PhOCH_2C\underline{H}$=), 6.90-7.15 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ62.9, 67.8, 114.8, 120.9, 126.3, 129.5, 132.8, 158.6. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ4.28 (d, 2 H, J = 4.8 Hz, $HOC\underline{H}_2$), 4.61 (d, 2 H, J = 4.8 Hz, $PhOCH_2$), cis vinyl protons buried under trans protons; ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ58.9, 64.0, 121.1, 127.3, 132.4.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3103, 3065 (vinyl, aryl C-H), 2922, 2866 (aliphatic C-H), 1599, 1587, 1497, 1458, 1383, 1302, 1242, 1175, 1090, 1030, 1009, 754, 692 cm^{-1}; mass spectrum m/e 164.0835 (calculated for $C_{10}H_{12}O_2$ = 164.0837).

2-Phenoxy-3-buten-1-ol (37) Compound 37 was synthesized in 24% yield, when butadiene monoepoxide was treated with phenol in the presence of 2% tetrakis(triphenylphosphine)palladium(0) for 2.5 hr at 25°C using the general alkylation procedure: ^{1}H NMR ($CDCl_3$) δ2.25 (br s, 1 H, OH), 3.77 (m, 2 H, $HOC\underline{H}_2$), 4.76 (dt, 1 H, J = 6.0 Hz, J = 5.1 Hz,

PhOCH), 5.31 (dd, 1 H, J = 10.5 Hz, J = 1.2 Hz, $=CH_2$ cis), 5.38 (dd, 1 H, J = 17.7 Hz, J = 1.2 Hz, $=CH_2$ trans), 5.82 (ddd, 1 H, J = 17.7 Hz, J = 10.5 Hz, J = 6.0 Hz, =CH-), 6.92-7.29 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ65.4, 79.9, 116.2, 118.8, 121.4, 129.5, 134.3, 157.5; IR (neat) 3200-3600 (OH), 3098, 3018 (vinyl, aryl C-H), 2920, 2870 (aliphatic C-H), 1599, 1495, 1238, 1217, 1080, 1043, 752, 692, 667 cm^{-1}; mass spectrum m/e 164.08378 (calculated for $O_{10}H_{12}O_2$ = 164.08373).

E- and Z-5-Hydroxy-2-pentenyl benzoate (39) Compound 39 was prepared in 50% yield (88:12 E/Z), when compound 1 was allowed to react with 2.4 equivalents of benzoic acid for 2.5 hr at 0°C using the general alkylation procedure. The yield of compound 39 was determined by gas chromatographic analysis of the crude reaction mixture using naphthalene as the internal standard.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the benzoate group. E-isomer: ^1H NMR ($CDCl_3$) δ1.67 (br s, 1 H, OH), 2.37 (dt, 2 H, J = 5.7 Hz, J = 6.0 Hz, $HOCH_2C\underline{H}_2$), 3.71 (t, 2 H, J = 6.0 Hz, $HOC\underline{H}_2$), 4.79 (d, 2 H, J = 5.1 Hz, $O{=}COCH_2$), 5.81 (dt, 1 H, J = 17.1 Hz, J = 5.1 Hz, $O{=}COCH_2C\underline{H}{=}$), 5.85 (dt, 1 H, J = 17.1 Hz, J = 5.7 Hz, $HOCH_2CH_2C\underline{H}{=}$), 7.39-7.62 (m, 3 H, Ph), 8.00-8.12 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ35.7, 61.8, 65.3, 127.0, 128.4, 129.6, 130.4, 131.9, 132.9, 166.4. Z-isomer: ^1H NMR ($CDCl_3$) same as

the E-isomer except δ2.48 (dt, 2 H, J = 6.3 Hz, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 4.90 (d, 2 H, J = 6.0 Hz, $O{=}COCH_2$), cis vinyl protons buried under trans protons; ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ31.2, 60.9, 61.9, 126.4, 131.4.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3070, 3030 (vinyl, aryl C-H), 2940, 2880 (aliphatic C-H), 1720 (C=O), 1605, 1587, 1453, 1380, 1315, 1270, 1180, 1110, 1070, 1045, 1030, 970, 710 cm^{-1}; mass spectrum m/e 176.0838 (M - CH_2O) (calculated for $C_{11}H_{12}O_2$ = 176.0837). Anal. calcd for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 69.26; H, 6.98.

3-Benzoyloxy-4-penten-1-ol (40) Compound 40 was prepared in 84% yield, when benzoic acid dissolved in 1 ml of THF was added over 30 min to a solution of compound 1 and 2% tetrakis(triphenylphosphine)palladium(0) in 1.5 ml of THF, cooled to 0°C. The reaction mixture was then allowed to stir under nitrogen at 0°C for an additional hour. The yield of compound 40 was determined by gas chromatographic analysis of the crude reaction mixture using naphthalene as the internal standard: ^1H NMR ($CDCl_3$) δ1.91-2.10 (m, 2 H, $HOCH_2C\underline{H}_2$), 2.23 (br s, 1 H, OH), 3.64-3.78 (m, 2 H, $HOC\underline{H}_2$), 5.24 (dd, 1 H, J = 10.2 Hz, J = 1.2 Hz, $=CH_2$ cis), 5.39 (dd, 1 H, J = 17.1 Hz, J = 1.2 Hz, $=CH_2$ trans), 5.66-5.78 (m, 1 H, O=COCH), 5.97 (ddd, 1 H, J = 17.1 Hz, J = 10.2 Hz, J = 6.0 Hz, =CH-), 7.39-7.63

(m, 3 H, Ph), 8.01-8.13 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ37.6, 58.6, 72.5, 116.7, 128.4, 129.7, 130.2, 133.1, 136.3, 166.3; IR (neat) 3200-3600 (OH), 3190, 3170 (vinyl, aryl C-H), 2980, 2880 (aliphatic C-H), 1715 (C=O), 1640 (C=C), 1600, 1586, 1450, 1310, 1265, 1175, 1110, 1065, 1020, 930, 710 cm^{-1}; mass spectrum m/e 176.0836 (M - CH_2O) (calculated for $C_{11}H_{12}O_2$ = 176.0837). Anal. calcd for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 69.25; H, 6.89.

E- and Z-4-Hydroxy-2-butenyl benzoate (41) Compound 41 was prepared in 22% yield (90:10 E/Z), when butadiene monoepoxide was allowed to react with 2.4 equivalents of benzoic acid for 2.5 hr at 0°C using the general alkylation procedure.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the alcohol group. E-isomer: ^{1}H NMR ($CDCl_3$) δ3.30 (br s, 1 H, OH), 4.21 (d, 2 H, J = 4.5 Hz, $HOC\underline{H}_2$), 4.83 (d, 2 H, J = 5.1 Hz, $O{=}COC\underline{H}_2$), 5.94 (dt, 1 H, J = 15.6 Hz, J = 5.1 Hz, $O{=}COCH_2C\underline{H}{=}$), 6.03 (dt, 1 H, J = 15.6 Hz, J = 4.5 Hz, $HOCH_2C\underline{H}{=}$), 7.42-8.15 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ62.5, 64.7, 125.0, 128.3, 129.6, 130.1, 133.0, 133.6, 166.3. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ4.34 (d, 2 H, J = 6.6 Hz, $HOC\underline{H}_2$), 4.93 (d, 2 H, J = 6.9 Hz, $O{=}COC\underline{H}_2$), cis vinyl protons buried under trans protons; ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ58.5,

60.7, 125.5, 130.0, 133.1.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3063, 3034 (vinyl, aryl C-H), 2941, 2874 (aliphatic C-H), 1718 (C=O), 1601, 1585, 1493, 1452, 1381, 1315, 1273, 1177, 1113, 1070, 1025, 968, 712 cm^{-1}; mass spectrum m/e 192.0779 (calculated for $C_{11}H_{12}O_3$ = 192.07865).

2-Benzoyloxy-3-buten-1-ol (42) Compound 42 was prepared in 77% yield, when butadiene monoepoxide was treated with 2.4 equivalents of benzoic acid for 2.5 hr at 0°C using the general alkylation procedure: ^1H NMR ($CDCl_3$) δ 3.86 (m, 2 H, $HOCH_2$), 5.33 (dd, 1 H, J = 10.8 Hz, J = 1.2 Hz, $=CH_2$ cis), 5.46 (dd, 1 H, J = 17.1 Hz, J = 1.2 Hz, $=CH_2$ trans), 5.61 (dt, 1 H, J = 6.0 Hz, J = 4.5 Hz, O=COCH), 5.93 (ddd, J = 17.1 Hz, J = 10.8 Hz, J = 6.0 Hz, =CH-), 7.42-8.15 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ64.2, 75.9, 118.1, 128.2, 129.5, 129.9, 132.8, 132.9, 165.9; IR (neat) 3200-3600 (OH), 3072, 3036 (vinyl, aryl C-H), 2937, 2876 (aliphatic C-H), 1720 (C=O), 1647 (C=C), 1603, 1585, 1493, 1452, 1339, 1315, 1273, 1119, 1070, 1026, 935, 733, 712 cm^{-1}; mass spectrum m/e 192.0795 (calculated for $C_{11}H_{12}O_3$ = 192.07865).

E- and Z-5-Diethylamino-3-penten-1-ol (43) Compound 43 was synthesized in 98% yield (79:21 E/Z), when compound 1 was allowed to react with 2.4 equivalents of diethylamine using the general alkylation procedure. The yield of compound

43 was determined by gas chromatographic analysis of the crude reaction mixture using tetradecane as the internal standard.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the amino group. E-isomer: ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 6 H, J = 7.2 Hz, $NCH_2C\underline{H}_3$), 2.29 (dt, 2 H, J = 5.7 Hz, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 2.50 (q, 4 H, J = 7.2 Hz, $NC\underline{H}_2CH_3$), 3.04 (d, 2 H, J = 5.4 Hz, $NC\underline{H}_2CH=$), 3.62 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 5.55 (dt, 1 H, J = 14.7 Hz, J = 5.7 Hz, $HOCH_2CH_2C\underline{H}=$), 5.61 (dt, 1 H, J = 14.7 Hz, J = 5.4 Hz, $NCH_2C\underline{H}=$); ^{13}C NMR ($CDCl_3$) δ11.1, 35.8, 46.2, 54.8, 61.4, 128.7, 130.1. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ1.02 (t, 6 H, J = 7.2 Hz, $NCH_2C\underline{H}_3$), 2.35 (dt, 2 H, J = 6.9 Hz, J = 6.9 Hz, $HOCH_2C\underline{H}_2$), 2.95 (d, 2 H, J = 6.3 Hz, $NC\underline{H}_2CH=$), cis vinyl protons buried under trans protons; ^{13}C NMR ($CDCl_3$) δ10.8, 30.9, 45.8, 48.5, 60.7, 128.7, 130.7.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3100-3600 (OH), 3020 (vinyl C-H), 2970, 2920, 2880 (aliphatic C-H), 1460, 1375, 1290, 1195, 1165, 1050, 970 cm^{-1}; mass spectrum m/e 157.14636 (calculated for $C_9H_{19}NO$ = 157.14667).

CHAPTER IV. PALLADIUM(0)-CATALYZED NUCLEOPHILIC RING-OPENING OF VINYLIC OXETANES TO FORM TRISUBSTITUTED HOMOALLYLIC ALCOHOLS

Introduction

Since it has been demonstrated in Chapter III that disubstituted homoallylic alcohols can be formed in excellent yields with a high degree of regio- and stereoselectivity via palladium(0)-catalyzed nucleophilic ring-opening of vinylic oxetanes, it was thought that it might be possible to form trisubstituted homoallylic alcohols stereoselectively using this methodology. Thus, the reactions of substituted vinylic oxetanes with nucleophiles in the presence of a palladium(0) catalyst were explored.

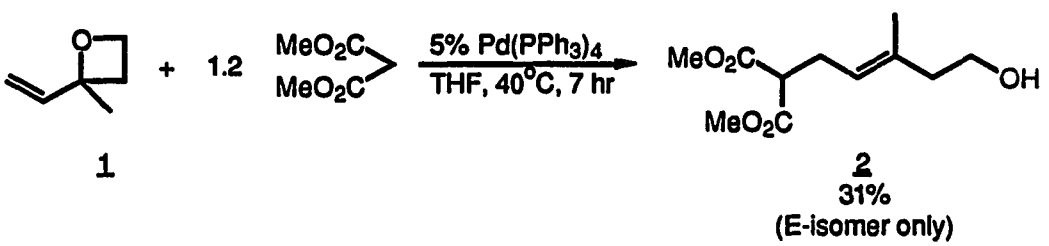
Several objectives and goals were set forth before and during the course of this project. First, it was hoped that the palladium(0)-catalyzed reactions of substituted vinylic oxetanes with nucleophiles would produce trisubstituted homoallylic alcohols in good yields with a high degree of regio- and stereoselectivity. These reactions should also have a high catalytic turnover of palladium. It would also be desirable if a number of different carbon and heteroatom nucleophiles could be used in the reactions, if the reaction would tolerate a wide variety of functional groups, and if variously substituted vinylic oxetanes could be utilized in the reaction.

In this chapter, the palladium(0)-catalyzed reactions of variously substituted vinylic oxetanes with carbon and heteroatom nucleophiles will be discussed. These reactions form trisubstituted homoallylic alcohols. The first section of this chapter covers the palladium(0)-catalyzed reactions of 3-methyl-3,5-epoxy-1-pentene with a variety of carbon and heteroatom nucleophiles. Finally, the reactions of other substituted vinylic oxetanes with carbon nucleophiles in the presence of a palladium(0) catalyst will be presented.

Additions of Nucleophiles to 3-Methyl-3,5-epoxy-1-pentene

Carbon nucleophiles

Compound 1, 3-methyl-3,5-epoxy-1-pentene, was prepared according to the procedure reported by Portnyagin and Pak.[99] Compound 1 was allowed to react with 1.2 equivalents of dimethyl malonate in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (eq. 4.1). It was



1

2
31%
(E-isomer only)

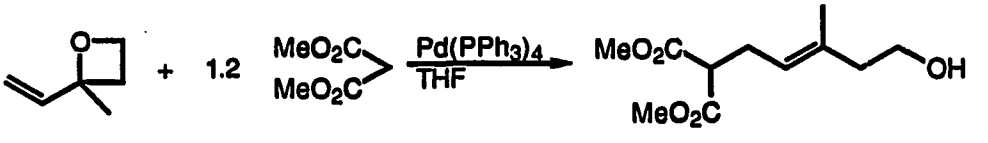
(4.1)

found that the corresponding trisubstituted homoallylic alcohol, compound 2, could be isolated as the pure E-isomer.

Compound 2 was determined to be the E-isomer on the basis of its carbon nuclear magnetic resonance spectrum. Allylic

methyl carbons present in the E-conformation in trisubstituted olefins typically have chemical shifts between 15 and 16 ppm, while those present in the Z-conformation have chemical shifts between 22 and 23 ppm.[115,116] In the carbon nuclear magnetic resonance spectrum of compound 2, the allylic methyl carbon had a chemical shift of 15.9 ppm. This indicated that compound 2 was the E-isomer.

In order to determine if the yield of compound 2 could be increased when the reaction conditions were varied, a gas chromatographic analysis was done on the reaction illustrated in equation 4.1. The data presented in Table 4.1 show that the highest yield of compound 2 was obtained when compound 1 was allowed to react with 1.2 equivalents of dimethyl malonate in the presence of 9% tetrakis(triphenylphosphine)palladium(0) at 40°C (see entry 5 in Table 4.1). When the reaction was run under these conditions, the highest yield of compound 2 occurred after six hours. The yield of compound 2 did not seem to depend on the reaction temperature, so long as the reaction was run above room temperature (compare entries 1-3 in Table 4.1).



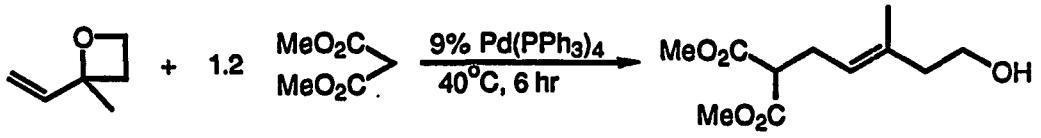
1 2 (4.2)

Table 4.1. Palladium(0)-catalyzed additions of dimethyl malonate to compound 1

Entry	Reaction time (hr)	Reaction temp. (°C)	% $Pd(PPh_3)_4$	% Yield 2[a]	Comments
1	3	25	5	8	none
	6			14	
	9			9	
	12			14	
	22			13	
2	3	40	5	28	none
	6			31	
	9			29	
	12			31	
	22			33	
3	3	67	5	28	none
	6			31	
	9			28	
	12			29	
	22			16	
4	3	40	2	7	none
	6			7	
	9			7	
	12			12	
	22			9	
5	3	40	9	41	none
	6			43	
	9			37	
	12			34	
	22			38	
6	3	40	9	21	2.4 equiv. $(MeO_2C)_2CH_2$ used
	6			25	
	9			31	
	12			27	
	22			24	

[a]Yield determined by gas chromatographic analysis of the crude reaction mixture using tridecane as the internal standard.

Compound 1 was treated with dimethyl malonate in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) using a variety of solvents, to determine what effect different solvents would have on the yield of compound 2. The results presented in Table 4.2 show



(4.3)

1

2
(E and Z)

Table 4.2. Palladium(0)-catalyzed additions of dimethyl malonate to compound 1 using various solvents

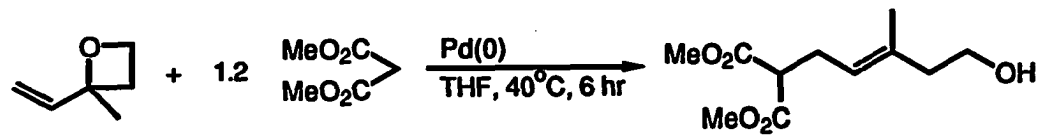
Entry	Solvent	% Yield 2[a]	E/Z Ratio[b]	Comments
1	1,4-dioxane	0	-	none
2	$(CH_3CH_2)_2O$	20	95:5	34°C reaction temperature
3	THF	29	100:0	none
4	CH_3CH_2CN	31	98:2	none
5	CH_3CN	48	90:10	3 hr reaction time
6	PhCN	51	83:17	none
7	DMSO	40	86:14	9 hr reaction time

[a]Yield of isolated, purified product.

[b]The E- and Z-isomer ratio of trisubstituted homoallylic alcohols can generally be determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the alcohol group.

that the highest yields of compound 2 were obtained when the reaction illustrated in equation 4.3 was run in solvents more polar than tetrahydrofuran. Unfortunately, compound 2 was isolated as a mixture of stereoisomers when these more polar solvents were used. When tetrahydrofuran was used as the solvent, the trisubstituted homoallylic alcohol was obtained in a lower yield, but as a single stereoisomer (see entry 3 in Table 4.2). Based on the results reported in Table 4.2, it appears that tetrahydrofuran is the best solvent to use for the palladium(0)-catalyzed reaction of compound 1 with dimethyl malonate.

Compound 1 was also allowed to react with dimethyl malonate using a variety of palladium(0) catalysts. The data presented in Table 4.3 show that the highest yield of compound 2 was obtained when the reaction illustrated in equation 4.4 was run in the presence of 9% tetrakis(triphenylphosphine)-palladium(0), 9% 1,2-bis(diphenylphosphino)ethane and 1.2 equivalents of triethylamine (see entry 12 in Table 4.3). When the reaction was run using $Pd_2(dba)_3 \cdot CHCl_3$, with one exception, only trace amounts of compound 2 could be isolated (see entries 2-6 in Table 4.3). When tetrakis(triphenyl-phosphine)palladium(0) was used as the catalyst, the yield of compound 2 improved when 9% 1,2-bis(diphenylphosphino)ethane was added to the reaction mixture (compare entries 7 and 9 in Table 4.3). When 18% 1,2-bis(diphenylphosphino)ethane was



1 2 (E and Z) (4.4)

Table 4.3. Palladium(0)-catalyzed additions of dimethyl malonate to compound 1 using various catalysts

Entry	Catalyst	Added reagent	% Yield 2[a]	E/Z Ratio	Comments
1	9% $Pd(OAc)_2$, 18% n-BuLi, 54% $(n\text{-BuO})_3P$	none	3	-	none
2	4.5% $Pd_2(dba)_3 \cdot CHCl_3$	none	0	-	none
3	4.5% $Pd_2(dba)_3 \cdot CHCl_3$, 54% PPh_3	none	< 2	-	none
4	4.5% $Pd_2(dba)_3 \cdot CHCl_3$, 54% $(n\text{-BuO})_3P$	none	0	-	none
5	4.5% $Pd_2(dba)_3 \cdot CHCl_3$, 54% $(n\text{-BuO})_3P$	none	31	90:10	none
6	4.5% $Pd_2(dba)_3 \cdot CHCl_3$, 27% dppe	none	0	-	none
7	9% $Pd(PPh_3)_4$	none	29	100:0	none
8	9% $Pd(PPh_3)_4$	1.2 Et_3N	37	95:5	none
9	9% $Pd(PPh_3)_4$, 9% dppe	none	59	100:0	none

[a]Yield of isolated, purified product.

Table 4.3. Continued

Entry	Catalyst	Added reagent	% Yield 2[a]	E/Z Ratio	Comments
10	9% $Pd(PPh_3)_4$, 9% dppe	none	63	92:8	CH_3CN solvent
11	9% $Pd(PPh_3)_4$, 18% dppe	none	20	100:0	none
12	9% $Pd(PPh_3)_4$, 9% dppe	1.2 Et_3N	82	100:0	none
13	9% $Pd(PPh_3)_4$, 9% dppe	2.4 Et_3N	55	90:10	none
14	9% $Pd(PPh_3)_4$, 9% dppe	0.12 $NaCH(CO_2Me)_2$	69	83:17	none
15	9% $Pd(dppe)_2$	none	55	100:0	none

used, however, the yield of compound 2 decreased (compare entries 7, 9 and 11 in Table 4.3). Finally, if 9% bis[1,2-bis(diphenylphosphino)ethane]palladium(0) was used as the catalyst, the yield of the reaction was slightly lower than when 9% tetrakis(triphenylphosphine)palladium(0) and 9% 1,2-bis(diphenylphosphino)ethane were employed (compare entries 9 and 15 in Table 4.3).

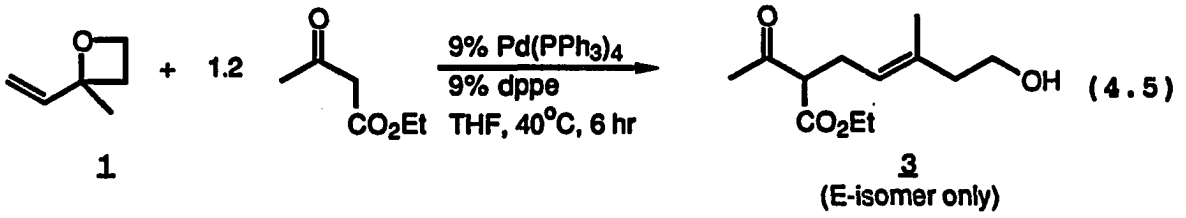
Trost and Molander found when they studied the palladium(0)-catalyzed nucleophilic ring-opening of vinylic epoxides, that bis[1,2-bis(diphenylphosphino)ethane]-palladium(0) proved to be a superior catalyst with more sterically hindered substrates.[56] This is in agreement with the results observed in Table 4.3. The highest yields of compound 2 were obtained when either bis[1,2-bis(diphenyl-phosphino)ethane]palladium(0) or tetrakis(triphenyl-phosphine)palladium(0) and 1,2-bis(diphenylphosphino)ethane were used as the catalyst.

When 9% tetrakis(triphenylphosphine)palladium(0) and 9% 1,2-bis(diphenylphosphino)ethane were employed as the catalyst using tetrahydrofuran as the solvent, compound 2 was isolated as a single stereoisomer (see entry 10 in Table 4.3). When acetonitrile was used as the solvent, the yield of compound 2 increased, but the product was formed as a mixture of stereoisomers (see entry 10 in Table 4.3). When compound 1 was allowed to react with dimethyl malonate in the presence of

9% tetrakis(triphenylphosphine)palladium(0) and 9% 1,2-bis(diphenylphosphino)ethane using tetrahydrofuran as the solvent, the yield of compound 2 increased when 1.2 equivalents of triethylamine were added to the reaction (compare entries 9 and 12 in Table 4.3). Triethylamine was added to the reaction in order to promote formation of the anion of the nucleophile. If 2.4 equivalents of triethylamine were used, however, the yield of the reaction decreased, and compound 2 was isolated as a mixture of stereoisomers (compare entries 12 and 13 in Table 4.3). Similar results were obtained when 0.12 equivalents of the sodium salt of dimethyl malonate were added to the reaction (compare entries 12 and 14 in Table 4.3).

The results summarized in Tables 4.1-4.3 indicate that compound 2 can be prepared stereoselectively in the highest yield when compound 1 is allowed to react for six hours at 40°C with 1.2 equivalents of dimethyl malonate in the presence of 9% tetrakis(triphenylphosphine)palladium(0), 9% 1,2-bis(diphenylphosphino)ethane and 1.2 equivalents of triethylamine using tetrahydrofuran as the solvent.

Once the best conditions had been found for the palladium(0)-catalyzed reaction of compound 1 with dimethyl malonate, the reactions of compound 1 with ethyl acetoacetate were studied. The reactions were run using several different conditions. The results illustrated in Table 4.4 show that



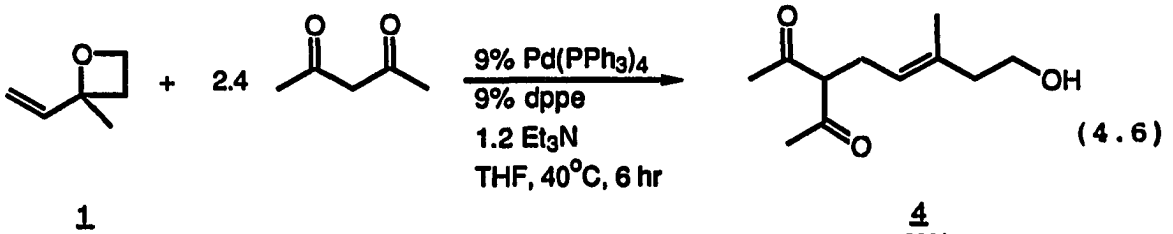
1 3 (E-isomer only)

Table 4.4. Palladium(0)-catalyzed additions of ethyl acetoacetate to compound 1

Entry	Added reagent	% Yield 3
1	none	63
2	1.2 Et_3N	64
3	0.12 $[EtO_2CCHCOCH_3]^-Na^+$	67

the yield of compound 3 was almost identical whether one ran the reaction without any additional reagents or added 1.2 equivalents of triethylamine or 0.12 equivalents of the sodium salt of dimethyl malonate. In all cases studied, compound 3 was isolated as the pure E-isomer.

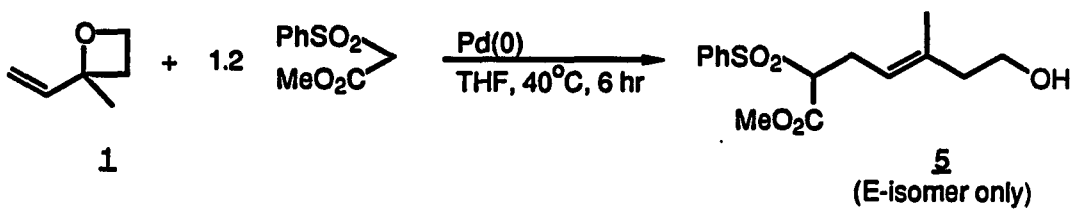
Compound 1 was also treated with 2,4-pentanedione using 9% tetrakis(triphenylphosphine)palladium(0) and 9% 1,2-bis(diphenylphosphino)ethane as the catalyst. The reaction illustrated in equation 4.6 was run using 2.4



1 4 69% (E-isomer only)

equivalents of 2,4-pentanedione because a higher yield of the corresponding homoallylic alcohol was obtained when 3,5-epoxy-1-pentene was treated with 2.4 equivalents of 2,4-pentanedione rather than 1.2 equivalents (see entries 6-8 in Table 3.1). Once again the desired trisubstituted homallylic alcohol, compound 4, was produced regio- and stereoselectively.

Compound 1 was also allowed to react with methyl phenylsulfonylacetate in the presence of a catalytic amount of palladium(0) using several different reaction conditions.



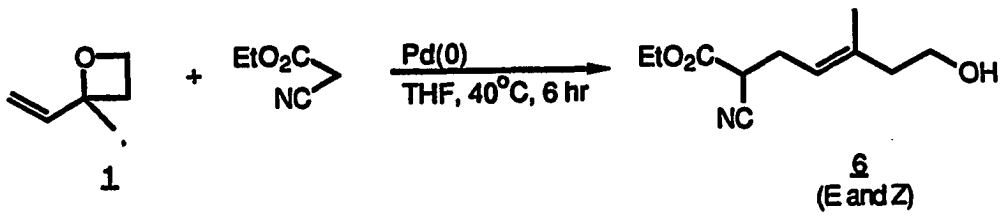
1 5 (E-isomer only) (4.7)

Table 4.5. Palladium(0)-catalyzed additions of methyl phenylsulfonylacetate to compound 1

Entry	Catalyst	Added reagent(s)	% Yield 5
1	9% $Pd(PPh_3)_4$, 9% dppe	none	36
2	9% $Pd(PPh_3)_4$, 9% dppe	1.2 Et_3N	46
3	9% $Pd(PPh_3)_4$, 9% dppe	0.12 $[PhSO_2CHCO_2Me]^-Na^+$	54
4	9% $Pd(PPh_3)_4$, 9% dppe	1.2 $[PhSO_2CHCO_2Me]^-Na^+$	0
5	9% $Pd(PPh_3)_4$, 9% dppe	0.12 $[PhSO_2CHCO_2Me]^-Na^+$ and 1.2 Et_3N	49
6	9% $Pd(dba)_2$, 9% dppe	none	10
7	9% $Pd(dba)_2$, 9% dppe	1.2 Et_3N	22

By examining the results shown in Table 4.5, one can see that higher yields of compound 5 were obtained when tetrakis-(triphenylphosphine)palladium(0) and 1,2-bis(diphenyl-phosphino)ethane were used as the catalyst. Compound 5 was produced in the highest yield when 0.12 equivalents of methyl sodiophenylsulfonylacetate were also added to the reaction (compare entries 1-5 in Table 4.5). Compound 5 was formed exclusively as the E-isomer in all of the reactions studied.

The palladium(0)-catalyzed reactions of compound 2 with ethyl cyanoacetate were also explored. The reactions were run under several different conditions (Table 4.6). The highest yields of compound 6 were obtained when compound 1 was treated with 2.4 equivalents of ethyl cyanoacetate in the presence of triethylamine (1.2 or 2.4 equivalents), 9% tetrakis(triphenyl-phosphine)palladium(0), and 9% 1,2-bis(diphenylphosphino)-ethane or 1,3-bis(diphenylphosphino)propane (see entries 2, 3 and 5 in Table 4.6). The stereoselectivity was the greatest, however, when the reaction was run in the presence of 1.2 equivalents of triethylamine, 9% tetrakis(triphenyl-phosphine)palladium(0) and 9% 1,2-bis(diphenylphosphino)ethane (see entry 2 in Table 4.6). Unfortunately, the pure E-homoallylic alcohol was never obtained from ethyl cyanoacetate under any reaction conditions examined.

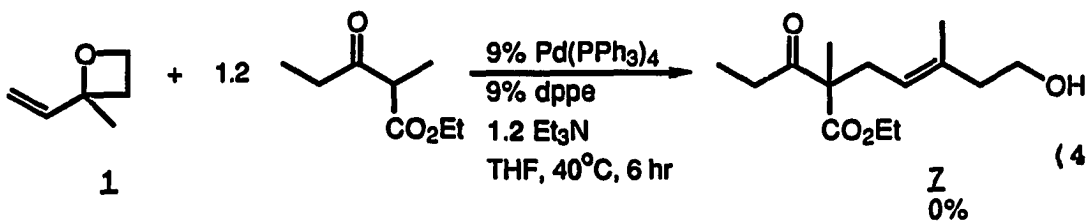


1 6 (E and Z) (4.8)

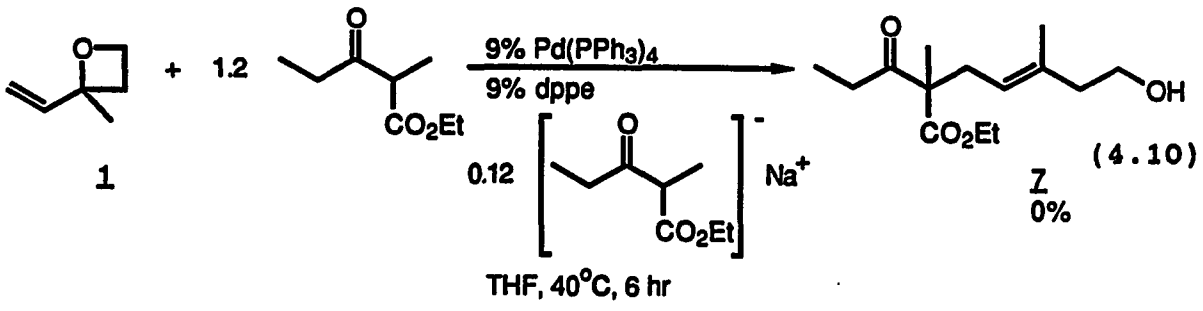
Table 4.6. Palladium(0)-catalyzed additions of ethyl cyanoacetate to compound 1

Entry	Catalyst	Added reagent	Equiv. ethyl cyanoacetate	% Yield 6	E/Z Ratio
1	9% $Pd(PPh_3)_4$, 9% dppe	1.2 Et_3N	1.2	42	87:13
2	9% $Pd(PPh_3)_4$, 9% dppe	1.2 Et_3N	2.4	66	89:11
3	9% $Pd(PPh_3)_4$, 9% dppe	2.4 Et_3N	2.4	71	83:17
4	9% $Pd(PPh_3)_4$, 9% dppe	0.24 $[EtO_2CCHCN]^-Na^+$	2.4	49	75:25
5	9% $Pd(PPh_3)_4$, 9% dppp	1.2 Et_3N	2.4	70	84:16
6	9% $Pd(PPh_3)_4$, 18% dppp	1.2 Et_3N	2.4	61	80:20

Compound 1 was also allowed to react with 2-carbethoxypentan-3-one in the presence of a catalytic amount of palladium(0). When the reactions were run using the conditions shown in equations 4.9 and 4.10, the only



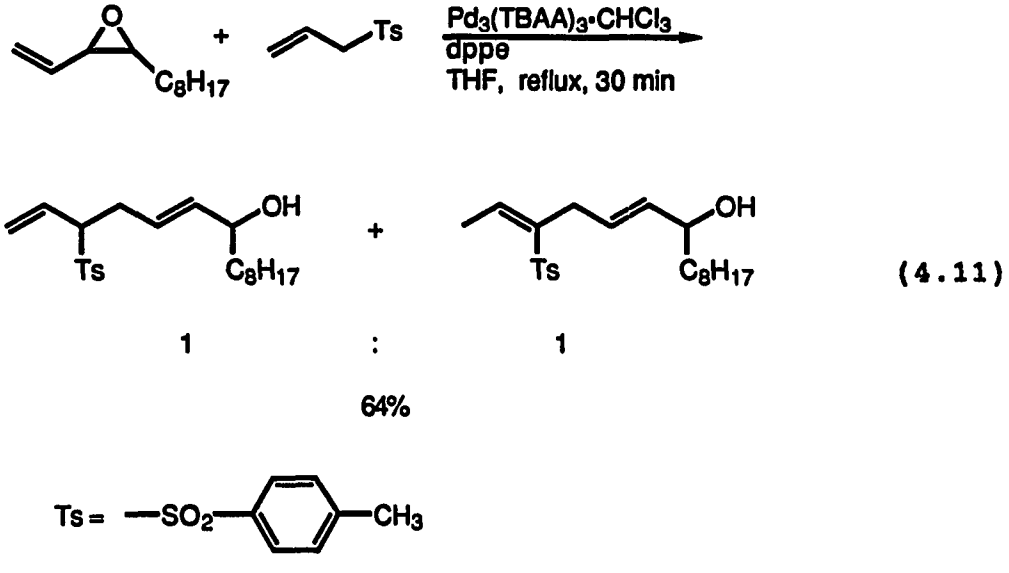
1 7 0% (4.9)



1 Z 0% (4.10)

compounds isolated at the end of the reaction were a trace amount of an unidentified product and unreacted 2-carbethoxypentan-3-one. Since the palladium(0)-catalyzed reaction of compound 1 with ethyl acetoacetate produced the corresponding trisubstituted homoallylic alcohol in good yield (see Table 4.4), it appears that compound 1 reacts poorly with sterically hindered nucleophiles.

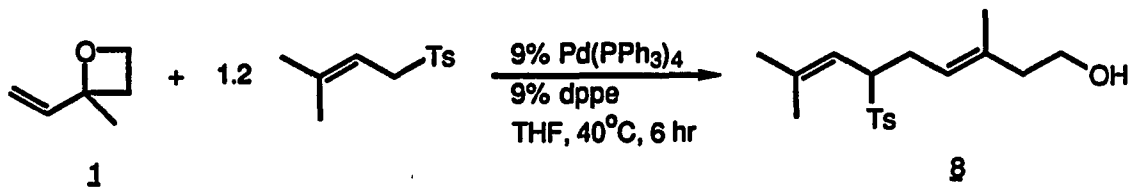
Recently, Tsuji and co-workers have reported the following reaction (eq. 4.11).[57] Allylic sulfones can be



(4.11)

readily synthesized using the procedure reported by Terao et al.[111] In order to determine whether allylic sulfones could

be used as nucleophiles in the palladium(0)-catalyzed ring-opening of substituted vinylic oxetanes, similar reactions were run using compound 1 and 3-methyl-1-(p-tolylsulfonyl)but-2-ene (Table 4.7). It was hoped that the



1 8

(4.12)

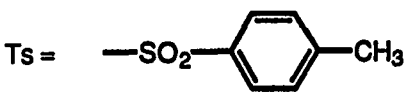


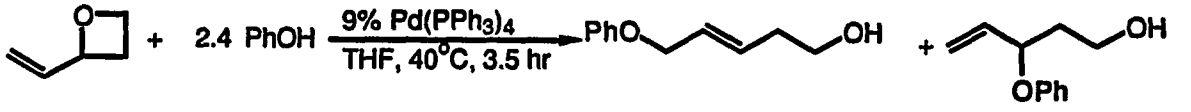
Table 4.7. Palladium(0)-catalyzed additions of 3-methyl-1-(p-tolylsulfonyl)but-2-ene to compound 1

Entry	Added reagent	% Yield 8	Comments
1	none	0	none
2	none	0	2.4 equiv. of allylic sulfone
3	1.2 Et_3N	0	none
4	2.4 Et_3N	0	none
5	0.12 $[(CH_3)_2C{=}CHCHTs]^-Na^+$	0	none

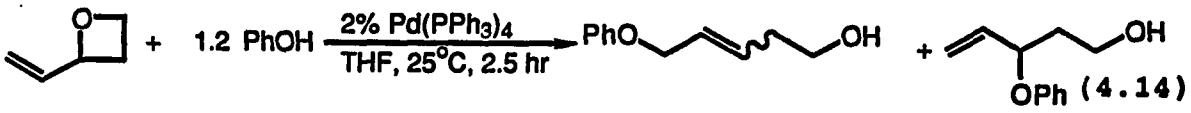
expected product, compound 8, could be used in the synthesis of naturally occurring terpenes. Unfortunately, none of the expected product was ever isolated from the reactions shown in Table 4.7. Instead, the unreacted allylic sulfone was isolated at the end of these reactions in quantitative yield. Similar results were obtained when 3,5-epoxy-1-pentene was allowed to react with allylic sulfones in the presence of a palladium(0) catalyst (see eqs. 3.14 and 3.15).

Heteroatom nucleophiles

In Chapter III, the palladium(0)-catalyzed reactions of 3,5-epoxy-1-pentene with phenol were discussed. The reaction conditions shown in equations 4.13 and 4.14 were the best

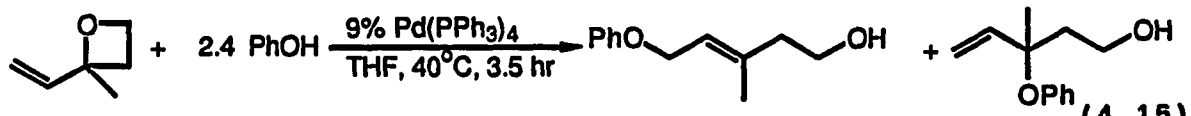


58% (88 : 12 E / Z) 23% (4.13)

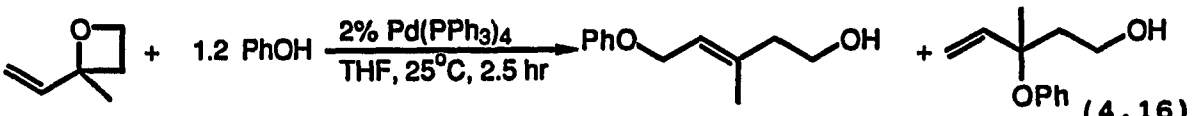


16% (E and Z) 84% (4.14)

observed for the formation of the homoallylic and bishomoallylic alcohols, respectively. In order to determine whether trisubstituted homoallylic alcohols would also be formed as a mixture of regio- and stereoisomers, the reactions of compound 1 with phenol and a catalytic amount of palladium(0) were studied (eqs. 4.15 and 4.16). The reactions



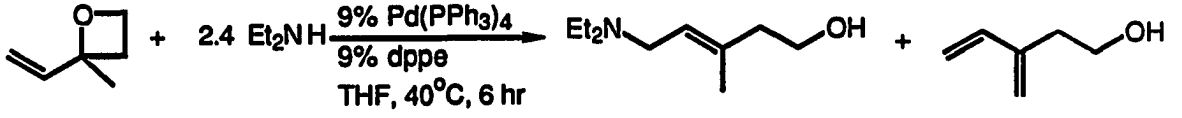
1 — 9 9% (41 : 59 E / Z) — 10 trace (4.15)



1 — 9 5% (31 : 69 E / Z) — 10 38% (4.16)

were run using the conditions reported in equations 4.13 and 4.14. As expected, the reactions illustrated in equations 4.15 and 4.16 produced the ring-opened product as a mixture of regio- and stereoisomers. Unfortunately, the overall yield and stereoselectivity of these reactions were poor. Unlike the reactions of 3,5-epoxy-1-pentene with phenol, the two regioisomers, compounds 9 and 10, could not be separated by flash column chromatography. The ratio of regioisomers was therefore determined by integration of the 300 MHz nuclear magnetic resonance spectral peaks corresponding to the vinylic hydrogens.

Compound 1 was also allowed to react with diethylamine in the presence of 9% tetrakis(triphenylphosphine)palladium(0) and 9% 1,2-bis(diphenylphosphino)ethane (eq. 4.17). The



1 11 (E and Z) 12 (4.17)

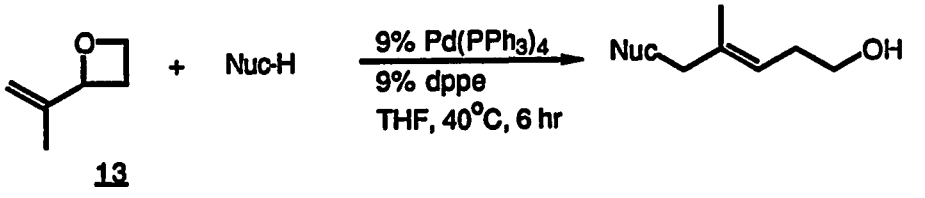
+ other products

reaction was run under conditions similar to those used when 3,5-epoxy-1-pentene was treated with diethylamine (see Table 3.6). When the reaction of compound 1 with diethylamine was run using the conditions shown in equation 4.17, the isolated product was an inseparable mixture of four compounds. Products like compound 12 have previously been synthesized via

palladium(0)-catalyzed ring-opening of vinylic epoxides. Suzuki and co-workers have found that β,γ-unsaturated ketones could be prepared in good yields when cyclic vinylic epoxides were allowed to react with a palladium(0) catalyst in the absense of a nucleophile.[117] Since the mixture of products isolated from the reaction shown in equation 4.17 contained a significant amount of compound 12, it appeared that diethylamine was unable to react effectively with the proposed (π-allyl)palladium intermediate.

Additions of Carbon Nucleophiles to Other Substituted Vinylic Oxetanes

In order to determine whether the formation of trisubstituted homoallylic alcohols via palladium(0)-catalyzed nucleophilic ring-opening of vinylic oxetanes is a useful, general synthetic method, the reactions of variously substituted vinylic oxetanes with carbon nucleophiles and a palladium(0) catalyst were studied. Compound 13, 2-methyl-3,5-epoxy-1- pentene, was synthesized using a procedure similar to the one Portnyagin and Pak used to prepare 3,5-epoxy-1-pentene.[99] The preparation of compound 13 was discussed in Chapter II (see eq. 2.19). Compound 13 was allowed to react with a variety of carbon nucleophiles in the presence of a catalytic amount of tetrakis(triphenyl-phosphine)palladium(0) and 1,2-bis(diphenylphosphino)ethane (Table 4.8). The reactions were run under the best conditions



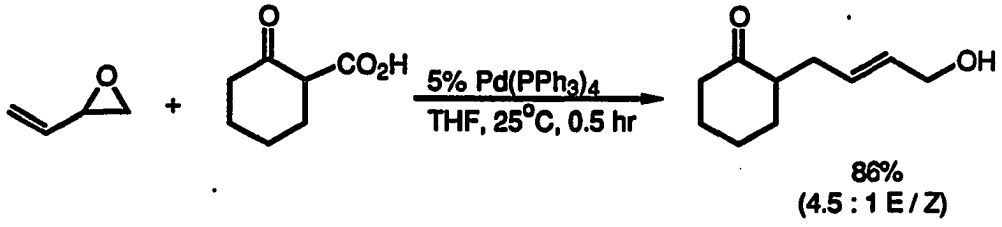
13 (4.18)

Table 4.8. Palladium(0)-catalyzed additions of carbon nucleophiles to compound 13

Entry	Nuc-H (equivalents)	Added reagent	% Yield	E/Z Ratio	Compound
1	(1.2)	1.2 Et_3N	89	100:0	14
2	(1.2)	0.12 $[EtO_2CCHCOCH_3]^-Na^+$	69	100:0	15
3	(2.4)	1.2 Et_3N	95	100:0	16
4	(2.4)	1.2 Et_3N	76	90:10	17

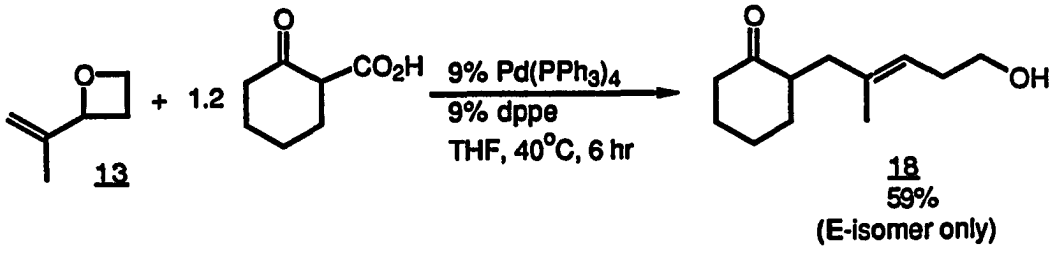
observed for the palladium(0)-catalyzed additions of these nucleophiles to compound 1 (see eq. 4.6 and Tables 4.3, 4.4 and 4.6). As one can see from the results reported in Table 4.8, the reactions of compound 13 with carbon nucleophiles in the presence of a catalytic amount of palladium(0) produced the expected trisubstituted homoallylic alcohols regioselectively in good yield. The reactions were also stereoselective, except when ethyl cyanoacetate was used as the nucleophile. The results shown in Table 4.8 are similar to those observed when compound 1 was allowed to react with these nucleophiles.

Recently, Tsuda and co-workers have reported the following reaction (eq. 4.19).[66] Cyclohexanone-2-carboxylic

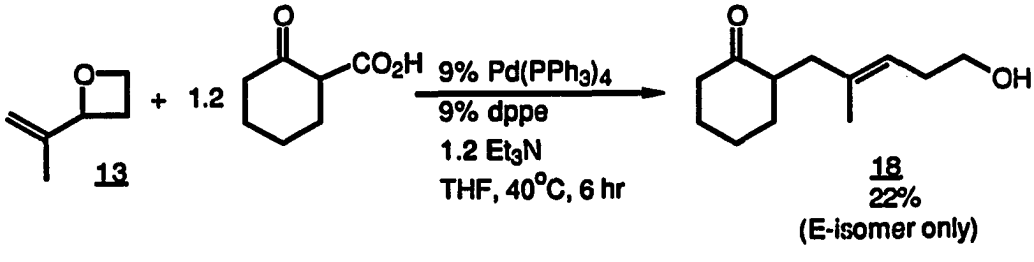


(4.19)

acid can be easily prepared by the procedure reported by Haruki et al.[110] In order to determine whether substituted vinylic oxetanes would react with β-keto acids in the presence of a palladium(0) catalyst, the following reactions were run (eqs. 4.20 and 4.21). The highest yield of compound 18 was obtained when compound 13 was allowed to react with



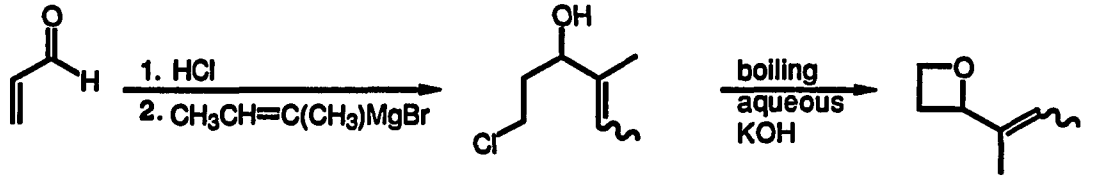
(4.20)



(4.21)

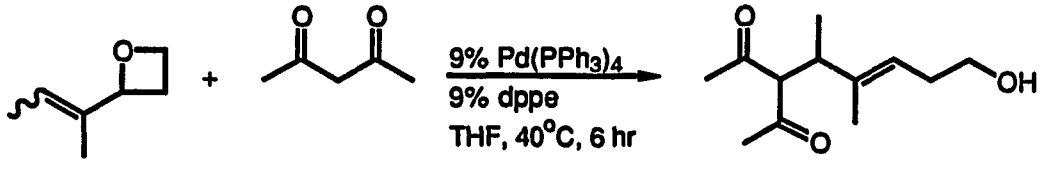
cyclohexanone-2-carboxylic acid and a catalytic amount of palladium(0) in the absence of triethylamine. Compound 18 was formed regio- and stereoselectively in both of the reactions studied.

Compound 19, E- and Z-3-methyl-4,6-epoxy-2-hexene, was prepared by a procedure similar to the one used by Portnyagin and Pak for the preparation of 3,5-epoxy-1-pentene (eq. 4.22).[99] Compound 19 was allowed to react with



19 (4.22)
38%
(E and Z)
34%
(E and Z)

2,4-pentanedione in the presence of a catalytic amount of palladium(0) using several different reaction conditions. As one can see from the results summarized in Table 4.9, the



19

20
(E-isomer only)

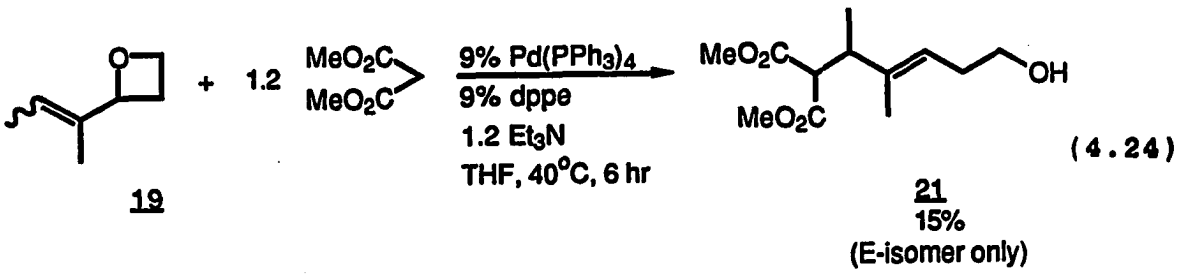
(4.23)

Table 4.9. Palladium(0)-catalyzed additions of 2,4-pentanedione to compound 19

Entry	Equivalents 2,4-pentanedione	Added reagent	% Yield 20	Comments
1	1.2	none	35	none
2	2.4	none	41	none
3	2.4	1.2 Et_3N	67	none
4	2.4	2.4 Et_3N	17	none
5	2.4	0.12 $[CH_3COCHCOCH_3]^-Na^+$	10	none
6	2.4	0.24 $[CH_3COCHCOCH_3]^-Na^+$	< 5	none
7	2.4	1.2 Et_3N	53	14 hr reaction time

highest yield of compound 20 was obtained when compound 19 was treated with 2.4 equivalents of 2,4-pentanedione in the presence of 9% tetrakis(triphenylphosphine)palladium(0), 9% 1,2-bis(diphenylphosphino)ethane and 1.2 equivalents of triethylamine (see entry 3 in Table 4.9). Compound 20 was produced as only the E-isomer in all of the reactions studied.

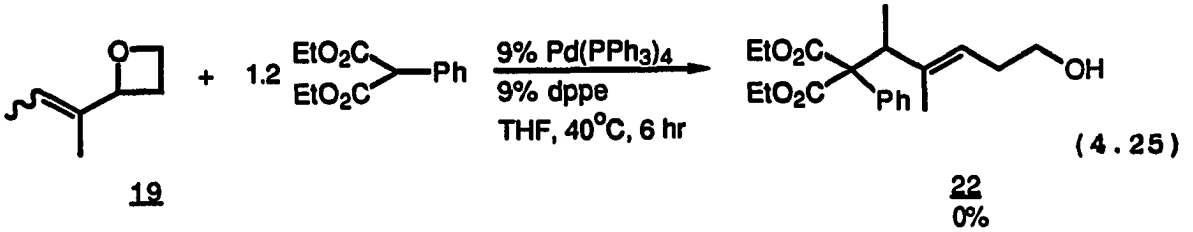
Compound 19 was also allowed to react with dimethyl malonate using tetrakis(triphenylphosphine)palladium(0) and 1,2-bis(diphenylphosphino)ethane as the catalyst (eq. 4.24).



19 21 15% (E-isomer only) (4.24)

The reaction was run using the best conditions observed for the reaction of compound 1 with dimethyl malonate (see Table 4.3). When dimethyl malonate was allowed to react with compound 19 in the presence of a catalytic amount of palladium(0), the expected trisubstituted homoallylic alcohol was formed stereoselectively, but in a much lower yield than when 2,4-pentanedione was used as the nucleophile (see Table 4.9).

Compound 19 was also treated with diethyl phenylmalonate in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and 1,2-bis(diphenylphosphino)ethane. When the reaction was run using the conditions shown in equation 4.25, the only compound isolated was unreacted

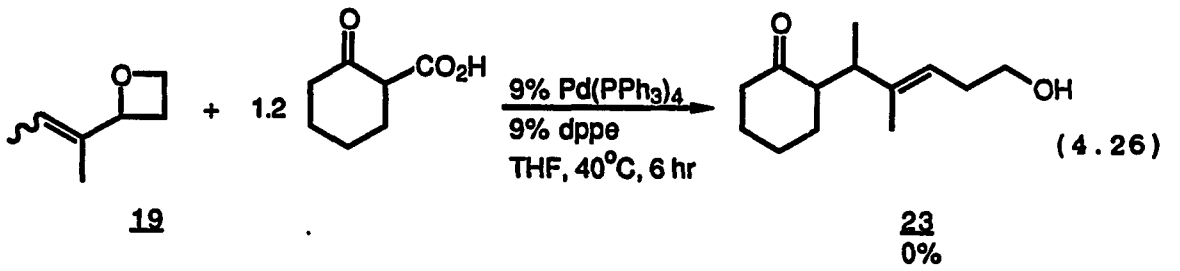


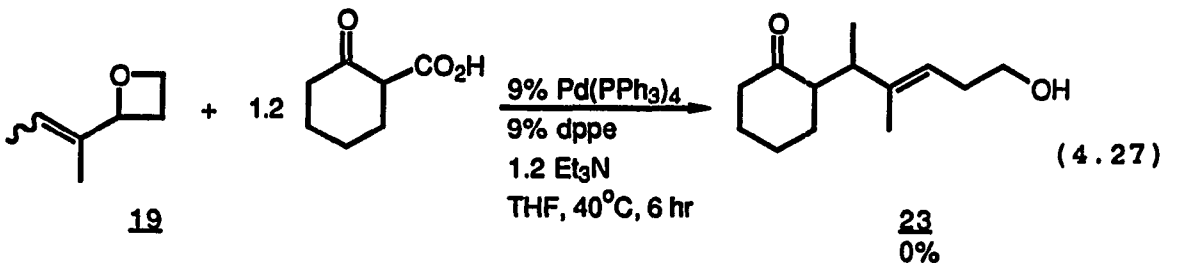
19 22 0% (4.25)

diethyl phenylmalonate. Since the palladium(0)-catalyzed nucleophilic ring-opening of compound 19 with dimethyl malonate produced the corresponding homoallylic alcohol, at

least in low yield, and the reaction where diethyl phenylmalonate was used yielded none of the expected product (compare eqs. 4.24 and 4.25), it appears that compound 19 does not react effectively with sterically hindered nucleophiles.

Compound 19 was allowed to react with cyclohexanone-2-carboxylic acid in the presence of a catalytic amount of palladium(0) using two different reaction conditions (eqs. 4.26 and 4.27). When these reactions were run, the only



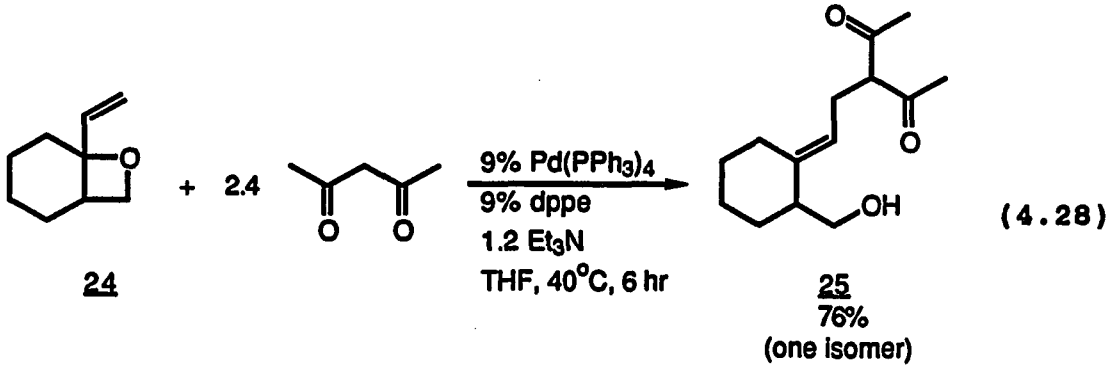


compounds isolated were a trace amount of an unidentified product and cyclohexanone.

The palladium(0)-catalyzed nucleophilic ring-opening of compound 19 produced homoallylic alcohols regio- and stereoselectively, although the yield of the reaction depended upon the nucleophile used. When bulky nucleophiles, such as diethyl phenylmalonate or cyclohexanone-2-carboxylic acid, were used in the reaction, the expected homoallyic alcohol was

not formed.

Compound 24, 1-ethenyl-8-oxabicyclo[4.2.0]octane, was prepared using the method reported by Portnyagin and Pak.[99] The reaction of compound 24 with 2,4-pentanedione in the presence of a palladium(0) catalyst was studied (eq. 4.28).

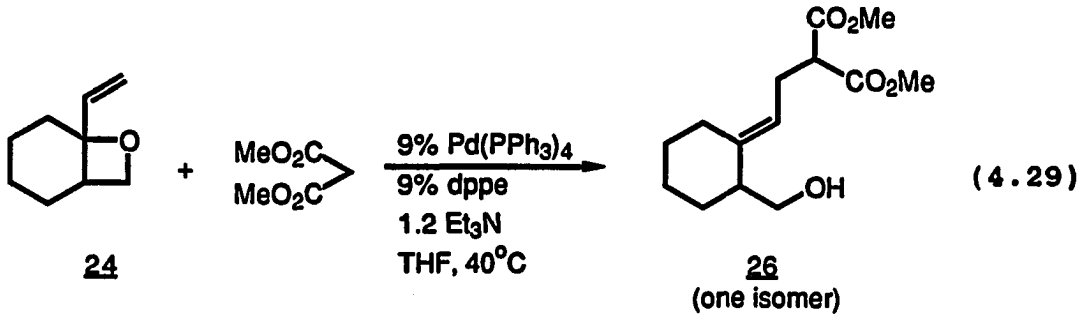


24 25 76% (one isomer) (4.28)

The reaction was run under the best conditions observed when compound 19 was treated with 2,4-pentanedione and a catalytic amount of palladium(0) (see Table 4.9). When compound 24 was allowed to react with 2,4-pentanedione using the conditions shown in equation 4.28, the desired trisubstituted homoallylic alcohol was formed regio- and stereoselectively in a high yield. The stereochemistry of compound 25 was not determined. The mechanism proposed for the palladium(0)-catalyzed nucleophilic ring-opening of vinylic oxetanes predicts, however, that compound 25 is the E-isomer (see Scheme 3.1).

Compound 24 was also treated with dimethyl malonate in the presence of 1.2 equivalents of triethylamine, 9% tetrakis(triphenylphosphine)palladium(0) and 9%

1,2-bis(diphenylphosphino)ethane. The reactions were run using several different conditions. As one can see from the data summarized in Table 4.10, the highest yields of compound



24 26 (one isomer) (4.29)

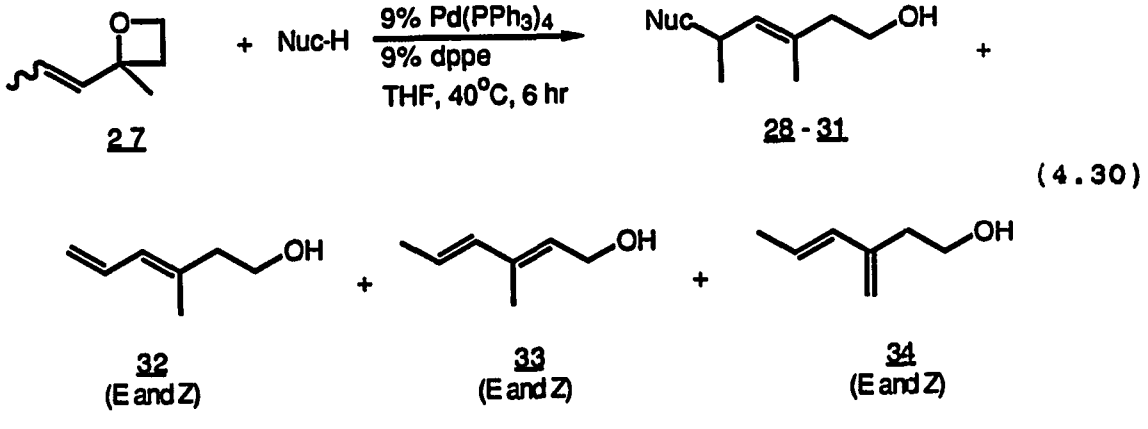
Table 4.10. Palladium(0)-catalyzed additions of dimethyl malonate to compound 24

Entry	Equivalents dimethyl malonate	Reaction time (hr)	% Yield 26
1	1.2	6	29
2	2.4	6	14
3	1.2	16	28

26 were obtained when compound 24 was allowed to react with 1.2 equivalents of dimethyl malonate in the presence of a palladium(0) catalyst. The yield of compound 26, however, did not seem to depend upon the reaction time. Like the corresponding reactions of compound 19 (see Table 4.9 and eq. 4.24), the trisubstituted homoallylic alcohol was formed in a higher yield if compound 24 was allowed to react with 2,4-pentanedione rather than dimethyl malonate (see Table 4.10 and eq. 4.28). In all of the reactions presented in Table

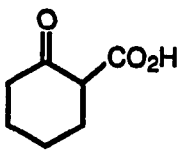
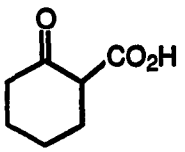
4.10, compound 26 was formed stereoselectively. The stereochemistry of compound 26 was not established, however the proposed mechanism for this reaction predicts that homoallylic alcohols are produced as the E-isomer (see Scheme 3.1).

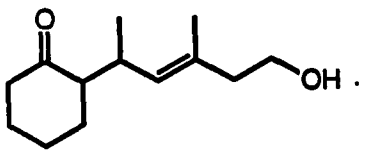
Compound 27, 3-methyl-1,3-epoxy-4-hexene, was prepared by the procedure reported by Portnyagin and Pak.[99] Compound 27 was treated with several different carbon nucleophiles in the presence of a catalytic amount of palladium(0) using a variety of reaction conditions. The nucleophiles studied included: 2,4-pentanedione, dimethyl malonate, triethyl phosphonoacetate and cyclohexanone-2-carboxylic acid. In the reactions shown in Table 4.11, none of the expected products were isolated. The only compounds isolated at the end of these reactions were the unreacted nucleophile plus a small amount of a mixture of diene products. The exact composition of this mixture was not determined; however, it may have included compounds 32, 33 and/or 34. In all cases, the diene products were isolated in



(4.30)

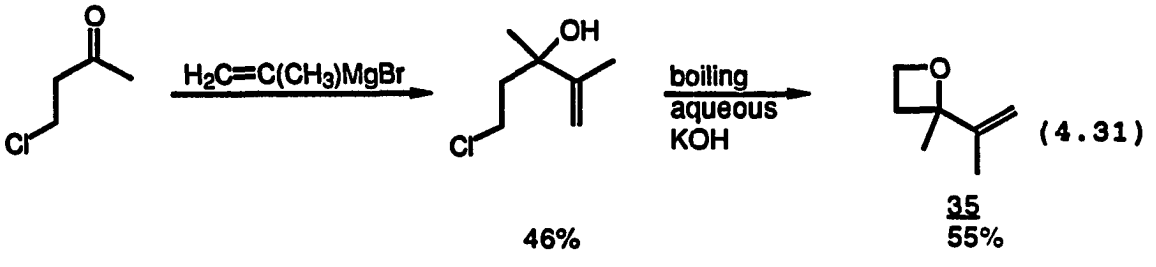
Table 4.11. Palladium(0)-catalyzed additions of carbon nucleophiles to compound 27

Entry	Nuc-H (equivalents)	Added reagent	% Yield	Compound	Comments
1	$CH_3C(=O)CH_2C(=O)CH_3$ (2.4)	1.2 Et_3N	0	28	none
2	$CH_3C(=O)CH_2C(=O)CH_3$ (2.4)	none	0	28	5% $Pd(PPh_3)_4$ catalyst; 3.5 hr reaction time
3	$(MeO_2C)_2CH_2$ (1.2)	1.2 Et_3N	0	29	none
4	$(EtO)_2P(=O)CH_2CO_2Et$ (1.2)	none	0	30	none
5	$(EtO)_2P(=O)CH_2CO_2Et$ (2.4)	none	0	30	none
6	 (1.2)	none	0	31[a]	none
7	 (1.2)	1.2 Et_3N	0	31[a]	none

[a]Compound 31 =  .

less than twenty percent yield. Similar products were formed when compound 1 was allowed to react with diethylamine and a catalytic amount of palladium(0) (see eq. 4.17). Suzuki and co-workers have also reported that β,γ-unsaturated ketones could be prepared in good yields when cyclic vinylic epoxides were allowed to react with a palladium(0) catalyst in the absence of a nucleophile.[117] Based on the results reported in Table 4.11, it appears that compound 27 will not react effectively with carbon nucleophiles in the presence of a catalytic amount of palladium(0).

Compound 35, 2,3-dimethyl-3,5-epoxy-1-pentene, was prepared by a method similar to the one Portnyagin and Pak used to synthesize 3,5-epoxy-1-pentene (eq. 4.31).[99] Since it



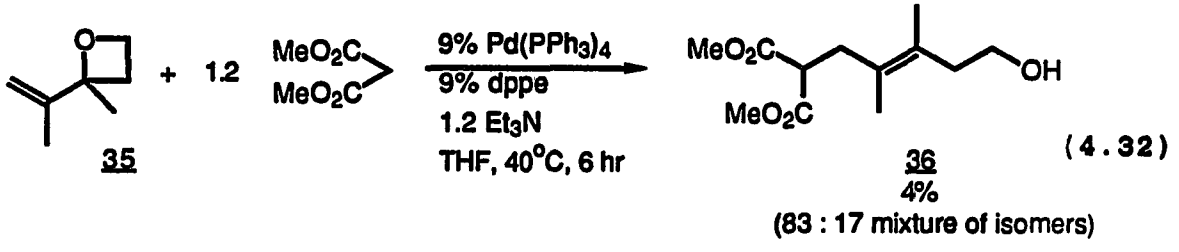
46%

35
55%

(4.31)

has been demonstrated that certain trisubstituted homoallylic alcohols can be prepared in good yield with a high degree of regio- and stereoselectivity, the reactions of compound 35 with carbon nucleophiles in the presence of a palladium(0) catalyst were explored to see if tetrasubstituted olefins could be prepared with the same high regio- and stereoselectivity. Thus, compound 35 was treated with

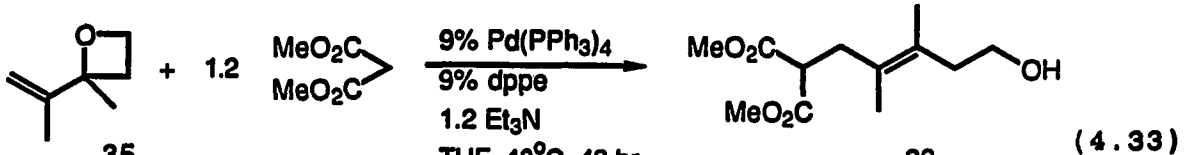
dimethyl malonate in the presence of a catalytic amount of palladium(0) (eqs. 4.32 and 4.33). The reactions were run



35 36 (4.32)

4%

(83 : 17 mixture of isomers)



35 36 (4.33)

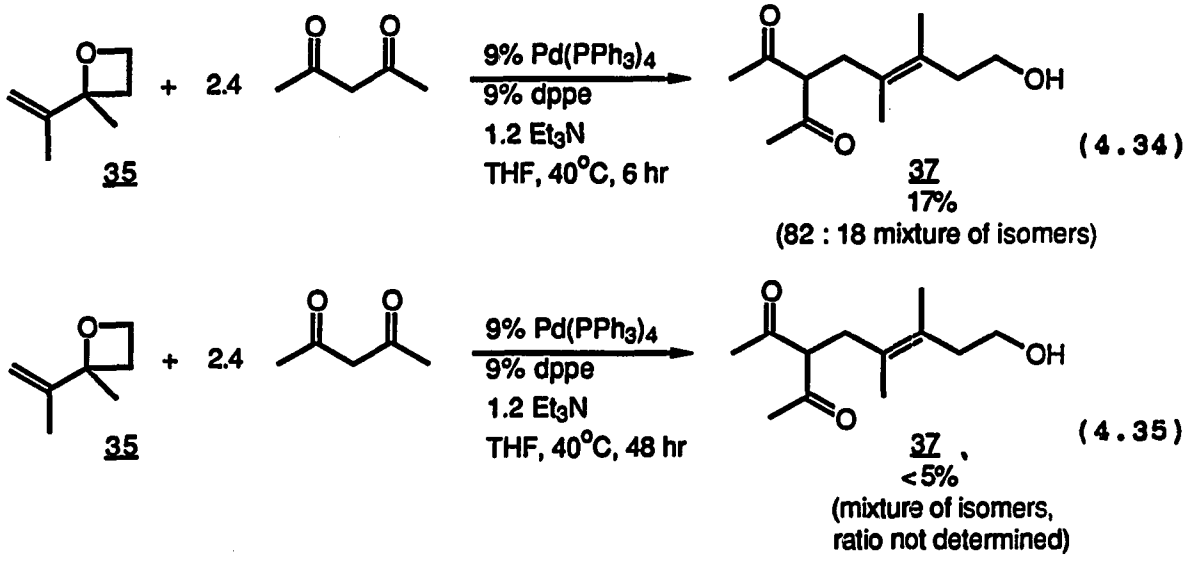
16%

(76 : 24 mixture of isomers)

using the best conditions observed for the reaction of compound 1 with dimethyl malonate (see Table 4.3). Two different reaction times were employed.

As one can see from the results shown in equations 4.32 and 4.33, the highest yield of compound 36 was obtained when compound 35 was allowed to react with dimethyl malonate in the presence of 9% tetrakis(triphenylphosphine)palladium(0), 9% 1,2-bis(diphenylphosphino)ethane and 1.2 equivalents of triethylamine for 48 hours at 40°C. In both reactions, compound 36 was obtained as a mixture of stereoisomers, although one isomer seemed to predominate. Since the yield of compound 36 was so low, the stereochemistry of the major isomer was not assigned.

Compound 35 was also treated with 2,4-pentanedione in the presence of a palladium(0) catalyst (eqs. 4.34 and 4.35). The



reactions were run under the best conditions observed when compound 19 was treated with 2,4-pentanedione (see Table 4.9). Two different reaction times were employed.

The results reported in equations 4.34 and 4.35 show that compound 37 was obtained in the highest yield when compound 35 was allowed to react with 2,4-pentanedione in the presence of 9% tetrakis(triphenylphosphine)palladium(0), 9% 1,2-bis(diphenylphosphino)ethane and 1.2 equivalents of triethylamine for six hours at 40°C. When these reaction conditions were used, compound 37 was obtained as a mixture of stereoisomers, although one isomer seemed to predominate. Because compound 37 was prepared in such a low yield and was relatively unstable, the stereochemistry of the major isomer was not determined.

Conclusion

The results presented in this chapter show that trisubstituted homoallylic alcohols can be prepared regioselectively in good yields when substituted vinylic oxetanes are allowed to react with carbon nucleophiles in the presence of a palladium(0) catalyst. Only the E-isomer of the corresponding homoallylic alcohol is formed, except when ethyl cyanoacetate is used as the nucleophile. Higher yields of trisubstituted homoallylic alcohols can sometimes be obtained if 2,4-pentanedione is used as the nucleophile rather than dimethyl malonate. Unfortunately, tetrasubstituted homoallylic alcohols are produced in low yields as mixtures of stereoisomers when this methodology is employed.

Experimental

Spectral data and analysis

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer at 300 and 75.5 MHz respectively. All infrared spectra were recorded on a Beckmann 4250 spectrophotometer. Exact mass spectral analyses were recorded on a Kratos MS-50 spectrometer. Elemental analyses were performed by Galbraith Laboratories. Gas chromatographic analyses were performed on a Varian 3700 gas chromatograph using a six foot by one-eighth inch stainless

steel column (3% OV-101 on chromosorb W). Tridecane was used as the internal standard in all gas chromatographic analyses.

Reagents

All nucleophiles were distilled or recrystallized prior to use. 3-Methyl-1-(p-tolylsulfonyl)but-2-ene was prepared by the method reported by Terao et al.[111] The procedure reported by Haruki and co-workers was used to synthesize cyclohexanone-2-carboxylic acid.[110]

Tetrakis(triphenylphosphine)palladium(0) and bis[1,2-bis(diphenylphosphino)ethane]palladium(0) were prepared by the procedure reported by Coulson.[114] The method reported by Ukai and co-workers was used to synthesize $Pd_2(dba)_3 \cdot CHCl_3$.[118] Bis(dibenzylideneacetone)palladium(0) was prepared according to the method reported by Takahashi et al.[119]

Oxetanes

Compounds 1, 24, and 27 were prepared according to the method reported by Portnyagin and Pak.[99] Compound 13 was synthesized by a procedure similar to the one Portnyagin and Pak used for the preparation of 3,5-epoxy-1-pentene.[99] The synthesis of compound 13 was discussed in Chapter II.

The preparation of compound 19 A solution of E- and Z-2-bromo-2-butene (0.45 mol), purchased from Aldrich and used without further purification, in 40 ml of dry THF was added

slowly to a mixture of magnesium turnings (0.40 mol) in 120 ml of dry THF. After complete addition, the reaction mixture was stirred for 30 min at room temperature and was then heated to 70°C for an additional 30 min. After cooling to room temperature, 60 ml of dry ether was added to the reaction mixture.

3-Chloropropanal was prepared according to the procedure reported by MacLeod and Rossiter.[107] 3-Chloropropanal (0.21 mol), cooled to -42°C, was added over 2 hr to the solution of E- and Z-2-butenylmagnesium bromide (0.40 mol), maintained at -10°C. The reaction mixture was allowed to stir overnight at room temperature. The solution was cooled to 0°C and 100 ml of saturated ammonium chloride was added slowly to the reaction mixture. The solution was filtered through Celite and the organic layer was separated. The aqueous layer was extracted with ether (2 X 50 ml). The combined organic layers were then washed with saturated sodium bicarbonate (2 X 15 ml), water (2 X 15 ml) and dried over anhydrous magnesium sulfate. After removal of the solvents, E- and Z-6-chloro-3-methyl-2-hexen-4-ol was purified by distillation: 11.82 g, 38% yield; bp 74°C/0.6 mm Hg.

E- and Z-6-Chloro-3-methyl-2-hexen-4-ol (80 mmol) was added rapidly to a boiling solution of potassium hydroxide (33.88 g) in 15 ml of water. As the product distilled off through a fractionating column, water was added to the flask,

so that the volume of the reaction mixture remained constant. The distillate was saturated with sodium chloride. The organic layer was separated and dried over anhydrous sodium sulfate. After filtering, E- and Z-3-methyl-4,6-epoxy-2-hexene was purified by distillation: 3.00 g, 34% yield; bp 86°C/75 mm Hg. The following spectral data were taken from a mixture of the E- and Z-isomers: ^{1}H NMR ($CDCl_3$) δ1.56 (d, 3 H, J = 6.9 Hz, =CHC<u>H</u>$_3$), 1.62 (d, 3 H, J = 6.9 Hz, =CHC<u>H</u>$_3$), 1.70 (s, 3 H, =CC<u>H</u>$_3$), 1.90 (s, 3 H, =CC<u>H</u>$_3$), 2.50-2.80 (m, 2 H, O-CH$_2$C<u>H</u>$_2$), 4.49 (m, 1 H, O-C<u>H</u>$_2$), 4.65 (m, 1 H, O-C<u>H</u>$_2$), 5.11 (t, 1 H, J = 7.5 Hz, O-CH), 5.32 (q, 1 H, J = 6.9 Hz, =CH), 5.54 (q, 1 H, J = 6.9 Hz, =CH), 5.75 (t, 1 H, J = 7.5 Hz, O-CH); ^{13}C NMR ($CDCl_3$) δ12.9, 13.0, 17.6, 26.9, 27.0, 67.8, 68.2, 79.6, 86.2, 120.6, 122.0, 136.5, 136.6, 1 carbon the same or not seen; IR (neat) 3000 (vinyl C-H), 2970, 2920, 2880 (aliphatic C-H), 1685 (C=C), 1450, 1375, 1225, 1010, 970, 920, 815 cm^{-1}; mass spectrum m/e 112.08877 (calculated for $C_7H_{12}O$ = 112.08882).

<u>The preparation of compound 35</u> A solution of 2-bromopropene (170 mmol) in 15 ml of dry THF was added slowly to a mixture of magnesium turnings (160 mmol) in 50 ml of dry THF. After complete addition, the reaction mixture was stirred for 30 min at room temperature and was then heated to 70°C for an additional 30 min. After cooling to room temperature, 25 ml of dry ether was added to the reaction

mixture.

4-Chloro-2-butanone was prepared using the procedure reported by Sondheimer and Woodward.[120] 4-Chloro-2-butanone (81 mmol) was added over 2 hr to the solution of 2-propenylmagnesium bromide (160 mmol), maintained at -10°C. The reaction mixture was allowed to stir overnight at room temperature. The solution was cooled to 0°C and 100 ml of saturated ammonium chloride was added slowly to the reaction mixture. The solution was filtered through Celite and the organic layer was separated. The aqueous layer was extracted with ether (2 X 50 ml). The combined organic layers were then washed with saturated sodium bicarbonate (2 X 15 ml), water (2 X 15 ml) and dried over anhydrous magnesium sulfate. After removal of the solvents, 5-chloro-2,3-dimethyl-1-penten-3-ol was purified by distillation: 5.46 g, 46% yield; bp 65°C/2.3 mm Hg.

5-Chloro-2,3-dimethyl-1-penten-3-ol (37 mmol) was added rapidly to a boiling solution of potassium hydroxide (15.55 g) in 7 ml of water. As the product distilled off through a fractionating column, water was added to the flask, so that the volume of the reaction mixture remained constant. The distillate was saturated with sodium chloride. The organic layer was separated and dried over anhydrous sodium sulfate. After filtering, 2,3-dimethyl-3,5-epoxy-1-pentene was purified by distillation: 2.27 g, 55% yield; bp 67°C/93 mm Hg; ^{1}H NMR

($CDCl_3$) δ1.49 (s, 3 H, O-CCH_3), 1.71 (s, 3 H, =CCH_3), 2.40-2.58 (m, 2 H, O-CH_2CH_2), 4.34-4.51 (m, 2 H, O-CH_2), 4.82 (s, 1 H, =CH_2), 5.05 (s, 1 H, =CH_2); ^{13}C NMR ($CDCl_3$) δ17.3, 27.3, 33.1, 64.0, 87.5, 108.4, 149.3; IR (neat) 3100 (vinyl C-H), 2980, 2940, 2890 (aliphatic C-H), 1660 (C=C), 1450, 1375, 1235, 1180, 1145, 1110, 1000, 970, 905, 875 cm^{-1}; mass spectrum m/e 112.08863 (calculated for $C_7H_{12}O$ = 112.08882).

General procedure for the alkylation of substituted vinylic oxetanes using a palladium(0) catalyst

To a 25 ml round bottom flask was added 51.9 mg of tetrakis(triphenylphosphine)palladium(0) (0.045 mmol), 17.9 mg of 1,2-bis(diphenylphosphino)ethane (0.045mmol) and 2.5 ml of dry THF. The solution was refluxed for 1 hr under nitrogen. To the resulting solution was added 1.2 equivalents (0.60 mmol) of triethylamine, 1.0 equivalent (0.50 mmol) of the vinylic oxetane to be studied and 1.2 equivalents (0.60 mmol) of the appropriate nucleophile. The solution was stirred at 40°C for 6 hr under nitrogen. Ether was then added to the reaction mixture. The solution was washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. After removal of the solvents, the residue was purified by flash column chromatography on silica gel.

Spectral data for tri- and tetrasubstituted homoallylic alcohols prepared by the general procedure for the alkylation of substituted vinylic oxetanes using a palladium(0) catalyst

Methyl E- and Z-7-hydroxy-2-methoxycarbonyl-5-methyl-4-heptenoate (2) Compound 2 was prepared in 82% yield (E-isomer only), when compound 1 was allowed to react with dimethyl malonate using the general alkylation procedure.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the alcohol group. E-isomer: ^{1}H NMR ($CDCl_3$) δ1.64 (s, 3 H, $=CCH_3$), 2.21 (t, 2 H, J = 6.0 Hz, $=CCH_2$), 2.63 (dd, 2 H, J = 7.5 Hz, J = 7.2 Hz, $=CHCH_2$), 3.40 (t, 1 H, J = 7.5 Hz, O=CCH), 3.62 (t, 2 H, J = 6.0 Hz, $HOCH_2$), 3.71 (s, 6 H, $O-CH_3$), 5.18 (t, 1 H, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ15.9, 27.7, 42.8, 51.7, 52.5, 60.0, 122.7, 135.2, 169.5; IR (neat) 3200-3600 (OH), 3020 (vinyl C-H), 2980, 2940, 2860 (aliphatic C-H), 1720 (C=O), 1430, 1385, 1330, 1265, 1230, 1190, 1140, 1030, 900, 720 cm^{-1}; mass spectrum m/e 200.10464 (M - CH_2O) (calculated for $C_{10}H_{16}O_4$ = 200.10486). Anal. calcd for $C_{11}H_{18}O_5$: C, 57.39; H, 7.83. Found: C, 57.10; H, 7.78.

Z-isomer (in mixture with the E-isomer): ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ1.71 (s, 3 H, $=CCH_3$), 2.34 (t, 2 H, J = 6.0 Hz, $=CCH_2$), 3.68 (s, 6 H, $O-CH_3$), cis vinyl proton buried under trans proton; ^{13}C NMR ($CDCl_3$) same as the

E-isomer or not seen except δ23.2, 27.1, 34.8, 51.6, 60.1, 122.2, 136.5, 169.3.

Ethyl E-2-acetyl-7-hydroxy-5-methyl-4-heptenoate (3)

Compound 3 was synthesized in 67% yield (E-isomer only), when compound 1 was allowed to react with ethyl acetoacetate using the general alkylation procedure. Ethyl sodioacetoacetate, 0.12 equivalents (0.06 mmol), was added to the reaction in place of triethylamine. The ethyl sodioacetoacetate was prepared by adding sodium hydride (0.06 mmol) and ethyl acetoacetate (0.60 mmol) to 0.5 ml of dry THF. The resulting solution was then transferred by cannula to the reaction mixture, which contained tetrakis(triphenylphosphine)-palladium(0), 1,2-bis(diphenylphosphino)ethane and compound 1 in THF: ^{1}H NMR ($CDCl_3$) δ1.26 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.47 (br s, 1 H, OH), 1.65 (s, 3 H, $=CCH_3$), 2.22 (s, 3 H, $O=CCH_3$), 2.24 (m, 2 H, $=CCH_2$), 2.57 (m, 2 H, $=CHC\underline{H}_2$), 3.43 (t, 1 H, J = 7.5 Hz, O=CCH), 3.63 (t, 2 H, J = 6.0 Hz, $HOC\underline{H}_2$), 4.18 (q, 2 H, J = 7.2 Hz, $O-C\underline{H}_2CH_3$), 5.14 (t, 1 H, J = 7.5 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ14.1, 15.9, 26.8, 28.9, 42.7, 59.6, 60.1, 61.4, 122.7, 134.8, 169.5, 202.6; IR (neat) 3200-3600 (OH), 2984, 2939 (aliphatic C-H), 1736, 1713 (C=O), 1447, 1369, 1331, 1300, 1265, 1236, 1207, 1151, 1097, 1047, 858 cm^{-1}. Anal. calcd for $C_{12}H_{20}O_4$: C, 63.16; H, 8.77. Found: C, 62.54; H, 8.88.

E-6-Acetyl-1-hydroxy-3-methyl-3-octen-7-one (4)

Compound 4 was synthesized in 69% yield (E-isomer only), when compound 1 was allowed to react with 2.4 equivalents of 2,4-pentanedione using the general alkylation procedure. Both keto and enol forms of compound 4 were seen in the NMR and IR spectra: ^{1}H NMR ($CDCl_3$) δ1.65 (s, 3 H, =CCH_3 keto form), 1.72 (s, 3 H, =CCH_3 enol form), 2.10 (s, 6 H, O=CCH_3 enol form), 2.16 (s, 6 H, O=CCH_3 keto form), 2.21 (t, 2 H, J = 6.0 Hz, =CCH_2), 2.56 (dd, 2 H, J = 7.2 Hz, J = 6.6 Hz, =CHC$\underline{H}_2$ keto form), 2.94 (d, 2 H, J = 5.7 Hz, =CHC$\underline{H}_2$ enol form), 3.63 (t, 2 H, J = 6.0 Hz, HOC$\underline{H}_2$), 3.68 (t, 1 H, J = 6.6 Hz, O=CCH keto form), 5.07 (t, 1 H, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ14.1, 16.0, 23.1, 26.3, 27.0, 29.3, 42.7, 60.3, 60.4, 60.5, 68.2, 107.6, 122.5, 125.7, 132.3, 135.0, 190.9, 204.0; IR (neat) 3200-3600 (OH), 2920, 2880 (aliphatic C-H), 1690 (C=O), 1600, 1420, 1355, 1250, 1150, 1040, 905, 725 cm^{-1}; mass spectrum m/e 180.11533 (M - H_2O) (calculated for $C_{11}H_{16}O_2$ = 180.11503).

Phenyl E-6-hydroxy-1-methoxycarbonyl-4-methyl-3-hexenyl sulfone (5) Compound 5 was prepared in 54% yield (E-isomer only), when compound 1 was allowed to react with methyl phenylsulfonylacetate using the general alkylation procedure. Methyl sodiophenylsulfonylacetate, 0.12 equivalents (0.06 mmol), was added to the reaction in place of triethylamine. The methyl sodiophenylsulfonylacetate was prepared by adding sodium hydride (0.06 mmol) and methyl phenylsulfonylacetate

(0.60 mmol) to 0.5 ml of dry THF. The resulting solution was then transferred by cannula to the reaction mixture, which contained tetrakis(triphenylphosphine)palladium(0), 1,2-bis(diphenylphosphino)ethane and compound 1 in THF: ^{1}H NMR ($CDCl_3$) δ1.57 (br s, 1 H, OH), 1.63 (s, 3 H, $=CCH_3$), 2.21 (t, 2 H, J = 6.0 Hz, $=CCH_2$), 2.76 (m, 2 H, $=CHC\underline{H}_2$), 3.62 (m, 5 H, $HOC\underline{H}_2$ and $O-CH_3$), 3.95 (dd, 1 H, J = 9.3 Hz, J = 5.7 Hz, S-CH), 5.10 (t, 1 H, J = 6.9 Hz, =CH), 7.52-7.92 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ15.9, 25.7, 42.5, 52.8, 60.0, 70.2, 119.8, 129.0, 134.2, 137.0, 137.2, 166.0, 1 carbon the same or not seen; IR (neat) 3200-3600 (OH), 3063 (vinyl, aryl C-H), 2955 (aliphatic C-H), 1742 (C=O), 1585, 1479, 1448, 1437, 1327, 1310, 1269, 1246, 1202, 1148, 1084, 1045, 760, 737, 702, 689 cm^{-1}. Anal. calcd for $C_{15}H_{20}O_5S$: C, 57.69; H, 6.41. Found: C, 56.81; H, 6.40.

Ethyl E- and Z-2-cyano-7-hydroxy-5-methyl-4-heptenoate (6) Compound 6 was synthesized in 66% yield (89:11 E/Z), when compound 1 was treated with 2.4 equivalents of ethyl cyanoacetate using the general alkylation procedure.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic methyl hydrogens. E-isomer: ^{1}H NMR ($CDCl_3$) δ1.27 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.66 (s, 3 H, $=CCH_3$), 1.92 (br s, 1 H, OH), 2.24 (t, 2 H, J = 6.3 Hz, $=CCH_2$), 2.65 (dd, 2 H, J = 7.2 Hz, J = 6.9 Hz, $=CHC\underline{H}_2$), 3.50 (t, 1 H, J = 6.9 Hz, NCCH), 3.64 (t, 2

H, J = 6.3 Hz, $HOC\underline{H}_2$), 4.21 (q, 2 H, J = 7.2 Hz, $O\text{-}C\underline{H}_2CH_3$), 5.22 (t, 1 H, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ14.0, 16.2, 28.7, 37.8, 42.7, 60.2, 62.9, 116.5, 120.0, 137.9, 165.8. Z-isomer: ^1H NMR ($CDCl_3$) same as the E-isomer except δ1.73 (s, 3 H, $=CCH_3$), 2.31 (t, 2 H, J = 6.0 Hz, $=CCH_2$), 5.28 (t, 1 H, J = 6.3 Hz, =CH); ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ14.2, 23.5, 28.3, 35.2, 40.7, 62.6, 119.6, 120.5, 137.7, 165.9.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 2986, 2943 (aliphatic C-H), 2225 (CN), 1744 (O=O), 1466, 1447, 1371, 1302, 1263, 1205, 1032, 908, 733, 650 cm^{-1}. Anal. calcd for $C_{11}H_{17}NO_3$: C, 62.56; H, 8.06. Found: C, 62.66; H, 7.91.

E- and Z-3-Methyl-5-phenoxy-3-penten-1-ol (9)

Compound 9 was prepared in 9% yield (41:59 E/Z), when compound 1 was allowed to react with 2.4 equivalents of phenol using 9% tetrakis(triphenylphosphine)palladium(0) as the catalyst for 3.5 hr at 40°C.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the alcohol group. E-isomer: ^1H NMR ($CDCl_3$) δ1.57 (br s, 1 H, OH), 1.70 (s, 3 H, CH_3), 2.27 (t, 2 H, J = 6.3 Hz, $=CCH_2$), 3.66 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 4.48 (d, 2 H, J = 6.6 Hz, $PhOCH_2$), 5.52 (t, 1 H, J = 6.6 Hz, =CH), 6.75-6.93 (m, 3 H, Ph), 7.10-7.35 (m, 2 H, Ph). Z-isomer: ^1H

NMR ($CDCl_3$) same as the E-isomer except δ1.77 (s, 3 H, CH_3), 2.35 (t, 2 H, J = 6.3 Hz, $=CCH_2$), 4.44 (d, 2 H, J = 6.9 Hz, $PhOCH_2$), 5.87 (t, 1 H, J = 6.9 Hz, =CH). Insufficient material was obtained for a complete analysis.

3-Methyl-3-phenoxy-4-penten-1-ol (10) Compound 10 was synthesized in 38% yield, when compound 1 was allowed to react with 1.2 equivalents of phenol using 2% tetrakis(triphenylphosphine)palladium(0) as the catalyst for 2.5 hr at 25°C: ^1H NMR ($CDCl_3$) δ1.41 (s, 3 H, CH_3), 2.00 (t, 2 H, J = 6.0 Hz, $HOCH_2C\underline{H}_2$), 3.89 (t, 2 H, J = 6.0 Hz, $HOC\underline{H}_2$), 5.17 (dd, 1 H, J = 17.4 Hz, J = 2.1 Hz, $=CH_2$ trans), 5.19 (dd, 1 H, J = 10.8 Hz, J = 2.1 Hz, $=CH_2$ cis), 6.12 (dd, 1 H, J = 17.4 Hz, J = 10.8 Hz, =CH-). Insufficient material was obtained for a complete analysis.

Methyl E-7-hydroxy-2-methoxycarbonyl-4-methyl-4-heptenoate (14) Compound 14 was prepared in 89% yield (E-isomer only), when compound 13 was treated with dimethyl malonate using the general alkylation procedure: ^1H NMR ($CDCl_3$) δ1.59 (br s, 1 H, OH), 1.65 (s, 3 H, $=CCH_3$), 2.24 (dt, 2 H, J = 7.5 Hz, J = 6.6 Hz, $=CHC\underline{H}_2$), 2.60 (d, 2 H, J = 8.1 Hz, $=CCH_2$), 3.57 (m, 3 H, O=CCH and $HOC\underline{H}_2$), 3.71 (s, 6 H, $O-CH_3$), 5.19 (t, 1 H, J = 7.5 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ15.8, 31.5, 38.7, 50.5, 52.3, 62.0, 123.6, 133.9, 169.4; IR (neat) 3200-3600 (OH), 3000 (vinyl C-H), 2960, 2920, 2880 (aliphatic C-H), 1740 (C=O), 1435, 1385, 1340, 1285, 1240,

1200, 1155, 1105, 1045, 1015, 915, 885, 730 cm^{-1}. Anal. calcd for $C_{11}H_{18}O_5$: C, 57.39; H, 7.83. Found: C, 56.85; H, 7.88.

Ethyl E-2-acetyl-7-hydroxy-4-methyl-4-heptenoate (15)

Compound 15 was synthesized in 69% yield (E-isomer only), when compound 13 was treated with ethyl acetoacetate using the general alkylation procedure. Ethyl sodioacetoacetate, 0.12 equivalents (0.06 mmol), was added to the reaction in place of triethylamine. The ethyl sodioacetoacetate was prepared by adding sodium hydride (0.06 mmol) and ethyl acetoacetate (0.60 mmol) to 0.5 ml of dry THF. The resulting solution was then transferred by cannula to the reaction mixture, which contained tetrakis(triphenylphosphine)palladium(0), 1,2-bis(diphenylphosphino)ethane and compound 13 in THF: ^1H NMR ($CDCl_3$) δ1.25 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.53 (br s, 1 H, OH), 1.64 (s, 3 H, $=CCH_3$), 2.03 (s, 3 H, $O=CCH_3$), 2.24 (dt, 2 H, J = 7.2 Hz, J = 6.3 Hz, $=CHC\underline{H}_2$), 2.55 (d, 2 H, J = 7.8 Hz, $=CCH_2$), 3.57 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 3.60 (t, 1 H, J = 7.8 Hz, O=CCH), 4.16 (q, 2 H, J = 7.2 Hz, $O-C\underline{H}_2CH_3$), 5.17 (t, 1 H, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ14.0, 16.0, 28.7, 31.5, 38.0, 59.4, 61.3, 62.0, 123.3, 134.1, 169.5, 202.7; IR (neat) 3200-3600 (OH), 3000 (vinyl C-H), 2950, 2890 (aliphatic C-H), 1740, 1720 (C=O), 1450, 1375, 1345, 1305, 1280, 1250, 1225, 1185, 1160, 1105, 1055, 1030 cm^{-1}. Anal. calcd for $C_{12}H_{20}O_4$: C, 63.16; H, 8.77. Found: C, 63.15; H, 8.96.

E-6-Acetyl-1-hydroxy-4-methyl-3-octen-7-one (16)

Compound 16 was prepared in 95% yield (E-isomer only), when compound 13 was treated with 2.4 equivalents of 2,4-pentanedione using the general alkylation procedure. Both keto and enol forms of compound 16 were seen in the NMR and IR spectra: ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 3 H, $=CCH_3$ keto form), 1.68 (s, 3 H, $=CCH_3$ enol form), 2.05 (s, 6 H, $O=CCH_3$ enol form), 2.16 (s, 6 H, $O=CCH_3$ keto form), 2.24 (dt, 2 H, J = 6.6 Hz, J = 6.6 Hz, $=CHC\underline{H}_2$ enol form), 2.30 (dt, 2 H, J = 6.9 Hz, J = 6.6 Hz, $=CHC\underline{H}_2$ keto form), 2.54 (d, 2 H, J = 7.5 Hz, $=CCH_2$ keto form), 2.90 (s, 2 H, $=CCH_2$ enol form), 3.59 (t, 2 H, J = 6.6 Hz, $HOC\underline{H}_2$), 3.83 (t, 1 H, J = 7.5 Hz, O=CCH keto form), 5.05 (t, 1 H, J = 6.6 Hz, =CH enol form), 5.16 (t, 1 H, J = 6.9 Hz, =CH keto form); ^{13}C NMR ($CDCl_3$) δ 16.1, 16.9, 22.9, 29.1, 31.5, 36.5, 38.0, 62.1, 62.3, 66.9, 107.3, 120.1, 123.4, 133.9, 135.4, 191.8, 204.1, 1 carbon the same or not seen; IR (neat) 3200-3600 (OH), 2920, 2880 (aliphatic C-H), 1695 (C=O), 1600, 1420, 1355, 1280, 1215, 1150, 1100, 1045, 1015, 940, 730 cm^{-1}; mass spectrum m/e 198.12523 (calculated for $C_{11}H_{18}O_3$ = 198.12560).

Ethyl E- and Z-2-cyano-7-hydroxy-4-methyl-4-heptenoate (17) Compound 17 was prepared in 76% yield (90:10 E/Z), when compound 13 was allowed to react with 2.4 equivalents of ethyl cyanoacetate using the general alkylation procedure.

The E- and Z-isomer ratio was determined by integration

of the 300 MHz NMR spectral peaks corresponding to the allylic methyl hydrogens. E-isomer: ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.61 (br s, 1 H, OH), 1.70 (s, 3 H, $=CCH_3$), 2.31 (dt, 2 H, J = 6.3 Hz, J = 8.7 Hz, $=CHC\underline{H}_2$), 2.63 (m, 2 H, $=CCH_2$), 3.63 (m, 3 H, NCCH and $HOC\underline{H}_2$), 4.25 (q, 2 H, J = 7.2 Hz, $O-C\underline{H}_2CH_3$), 5.38 (t, 1 H, J = 6.3 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 13.9, 15.7, 31.6, 37.0, 39.9, 61.9, 62.8, 116.3, 126.3, 131.8, 165.4. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ 1.79 (s, 3 H, $=CCH_3$), cis vinyl proton buried under trans proton; ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ 13.6, 22.9, 32.1, 32.6, 36.2, 62.0, 129.0, 133.7.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 2980, 2930, 2870 (aliphatic C-H), 2240 (CN), 1740 (C=O), 1580, 1465, 1440, 1390, 1370, 1335, 1260, 1205, 1160, 1095, 1040, 905, 850, 730, 690, 640 cm^{-1}. Anal. calcd for $C_{11}H_{17}NO_3$: C, 62.56; H, 8.06. Found: C, 62.52; H, 7.98.

E-2-(5-Hydroxy-2-methyl-2-pentenyl)cyclohexanone (18)

Compound 18 was prepared in 59% yield (E-isomer only), when compound 13 was treated with cyclohexanone-2-carboxylic acid using the general alkylation procedure. No triethylamine was added to the reaction: ^{1}H NMR ($CDCl_3$) δ 1.56-2.63 (m, 17 H, 4 CH_2's cyclohexane ring, O=CCH, $=CCH_2$, $=CHC\underline{H}_2$, $=CCH_3$ and OH), 3.59 (t, 2 H, J = 6.0 Hz, $HOC\underline{H}_2$), 5.10 (t, 1 H, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 15.9, 24.4, 27.8, 31.5, 33.0, 39.4,

41.7, 48.2, 62.2, 122.1, 135.4, 213.1; IR (neat) 3200-3600 (OH), 3040 (vinyl C-H), 2940, 2860 (aliphatic C-H), 1710 (C=O), 1450, 1270, 1130, 1045, 735 cm^{-1}; mass spectrum m/e 178.13587 (M - H_2O) (calculated for $C_{12}H_{18}O$ = 178.13576).

E-6-Acetyl-1-hydroxy-4,5-dimethyl-3-octen-7-one (20)

Compound 20 was synthesized in 67% yield (E-isomer only), when compound 19 was treated with 2.4 equivalents of 2,4-pentanedione using the general alkylation procedure: ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, J = 6.6 Hz, $CHC\underline{H}_3$), 1.52 (br s, 1 H, OH), 1.57 (s, 3 H, $=CCH_3$), 2.05 (s, 3 H, $O=CCH_3$), 2.18 (s, 3 H, $O=CCH_3$), 2.21 (dt, 2 H, J = 6.9 Hz, J = 6.0 Hz, $=CHC\underline{H}_2$), 3.02 (dq, 1 H, J = 11.4 Hz, J = 6.6 Hz, $CH_3C\underline{H}$), 3.57 (t, 2 H, J = 6.0 Hz, $HOC\underline{H}_2$), 3.78 (d, 1 H, J = 11.4 Hz, O=CCH), 5.24 (t, 1 H, J = 6.9 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 12.9, 17.7, 28.3, 30.4, 31.1, 43.5, 61.9, 74.2, 122.9, 138.1, 202.6, 203.0; IR (neat) 3200-3600 (OH), 3040 (vinyl C-H), 2970, 2920, 2860 (aliphatic C-H), 1690 (C=O), 1415, 1350, 1260, 1190, 1150, 1035, 885, 720 cm^{-1}. Anal. calcd for $C_{12}H_{20}O_3$: C, 67.92; H, 9.43. Found: C, 67.77; H, 9.59.

Methyl E-7-hydroxy-2-methoxycarbonyl-3,4-dimethyl-4-heptenoate (21) Compound 21 was prepared in 15% yield (E-isomer only), when compound 19 was allowed to react with dimethyl malonate using the general alkylation procedure: ^1H NMR ($CDCl_3$) δ 1.07 (d, 3 H, J = 6.9 Hz, $CHC\underline{H}_3$), 1.62 (s, 3 H, $=CCH_3$), 2.24 (m, 2 H, $=CHC\underline{H}_2$), 2.94 (dq, 1 H, J = 10.8 Hz, J =

6.9 Hz, $CH_3C\underline{H}$), 3.44 (d, 1 H, J = 10.8 Hz, O=CCH), 3.57 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 3.65 (s, 3 H, $O-CH_3$), 3.72 (s, 3 H, $O-CH_3$), 5.25 (t, 1 H, J = 7.5 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ13.1, 17.5, 31.4, 43.4, 52.3, 52.4, 56.8, 62.2, 122.7, 139.1, 168.8, 169.0; IR (neat) 3200-3600 (OH), 3040 (vinyl C-H), 2960, 2870 (aliphatic C-H), 1730 (C=O), 1435, 1375, 1335, 1265, 1195, 1150, 1040, 1015, 730 cm^{-1}; mass spectrum m/e 244.13157 (calculated for $C_{12}H_{20}O_5$ = 244.13108). Insufficient material was isolated to obtain an elemental analysis.

1-(3,3-Diacetylpropylidene)-2-(hydroxymethyl)cyclohexane (25) Compound 25 was prepared in 76% yield (one isomer), when compound 24 was allowed to react with 2.4 equivalents of 2,4-pentanedione using the general alkylation procedure. Both keto and enol forms of compound 25 were seen in the NMR and IR spectra: ^{1}H NMR ($CDCl_3$) δ1.38-1.69 (m, 8 H, 4 CH_2's cyclohexane ring), 2.09 (s, 6 H, $O=CCH_3$ enol form), 2.14 (s, 3 H, $O=CCH_3$ keto form), 2.15 (s, 3 H, $O=CCH_3$ keto form), 2.20 (m, 1 H, =CCH), 2.55 (dd, 2 H, J = 7.5 Hz, J = 7.2 Hz, $=CHC\underline{H}_2$ keto form), 2.94 (m, 2 H, $=CHC\underline{H}_2$ enol form), 3.48 (dd, 1 H, J = 10.5 Hz, J = 6.0 Hz, $HOC\underline{H}_2$ keto form), 3.52 (dd, 1 H, J = 10.5 Hz, J = 6.3 Hz, $HOC\underline{H}_2$ enol form), 3.62 (t, 1 H, J = 7.5 Hz, O=CCH keto form), 3.67 (dd, 1 H, J = 10.5 Hz, J = 8.4 Hz, $HOC\underline{H}_2$ keto form), 3.72 (m, 1 H, $HOC\underline{H}_2$ enol form), 4.95 (t, 1 H, J = 7.2 Hz, =CH enol form), 4.99 (t, 1 H, J = 7.2 Hz, =CH

keto form); ^{13}C NMR ($CDCl_3$) δ 23.1, 23.2, 23.5, 25.5, 26.3, 26.5, 26.6, 27.7, 29.4, 29.5, 30.0, 46.9, 47.0, 63.6, 63.7, 68.6, 109.6, 118.3, 121.3, 139.5, 142.3, 191.0, 204.1, 1 carbon the same or not seen; IR (neat) 3200-3600 (OH), 2940, 2865 (aliphatic C-H), 1700 (C=O), 1600, 1452, 1428, 1362, 1255, 1205, 1160, 1040, 955, 735 cm^{-1}; mass spectrum m/e 238.15741 (calculated for $C_{14}H_{22}O_3$ = 238.15690). An elemental analysis was not obtained because compound 25 decomposed slowly upon standing at room temperature.

2-(Hydroxymethyl)-1-(3,3-dimethoxycarbonylpropylidene)-cyclohexane (26) Compound 26 was synthesized in 29% yield (one isomer), when compound 24 was treated with dimethyl malonate using the general alkylation procedure: ^1H NMR ($CDCl_3$) δ 1.46-1.66 (m, 6 H, 3 CH_2's cyclohexane ring), 1.95-2.07 (m, 1 H, =CCH), 2.16-2.28 (m, 2 H, $=CCH_2$), 2.60 (ddd, 1 H, J = 14.4 Hz, J = 7.5 Hz, J = 7.2 Hz, $=CHC\underline{H}_2$), 2.68 (ddd, 1 H, J = 14.4 Hz, J = 7.8 Hz, J = 7.5 Hz, $=CHC\underline{H}_2$), 3.36 (dd, 1 H, J = 7.8 Hz, J = 7.5 Hz, O=CCH), 3.49 (m, 2 H, $HOC\underline{H}_2$), 3.70 (s, 3 H, $O-CH_3$), 3.71 (s, 3 H, $O-CH_3$), 5.12 (dd, 1 H, J = 7.5 Hz, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 23.2, 26.0, 26.7, 27.5, 29.8, 46.9, 51.9, 52.4, 63.5, 118.4, 142.3, 169.3; IR (neat) 3200-3600 (OH), 3080 (vinyl C-H), 2970, 2950, 2875 (aliphatic C-H), 1740 (C=O), 1445, 1345, 1280, 1250, 1165, 1048, 790 cm^{-1}. Anal. calcd for $C_{14}H_{22}O_5$: C, 62.22; H, 8.14. Found: C, 61.64; H, 8.19.

Methyl E- and Z-7-hydroxy-2-methoxycarbonyl-4,5-dimethyl-4-heptenoate (36) Compound 36 was isolated in 16% yield (76:24 mixture of isomers), when compound 35 was treated with dimethyl malonate for 48 hr at 40°C using the general alkylation procedure.

The isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the alcohol group. The isomers were not assigned due to the low yield of compound 36. Major isomer: ^{1}H NMR ($CDCl_3$) δ1.24 (br s, 1 H, OH), 1.67 (s, 3 H, $=CCH_3$), 1.69 (s, 3 H, $=CCH_3$), 2.32 (t, 2 H, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 2.70 (d, 2 H, J = 8.1 Hz, $O=CCHC\underline{H}_2$), 3.53 (t, 1 H, J = 8.1 Hz, O=CCH), 3.64 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 3.71 (s, 6 H, $O-CH_3$); ^{13}C NMR ($CDCl_3$) δ18.0, 18.2, 34.0, 37.9, 50.3, 52.4, 60.6, 127.0, 128.5, 169.7. Minor isomer: ^{1}H NMR ($CDCl_3$) same as the major isomer except δ1.57 (s, 3 H, $=CCH_3$), 1.64 (s, 3 H, $=CCH_3$), 2.37 (t, 2 H, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 2.72 (d, 2 H, J = 6.9 Hz, $O=CCHC\underline{H}_2$); ^{13}C NMR ($CDCl_3$) same as the major isomer or not seen except δ18.4, 29.7, 33.2, 37.2, 50.6, 60.8, 126.5, 128.6, 169.8.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 2980, 2870 (aliphatic C-H), 1730 (C=O), 1435, 1375, 1340, 1265, 1195, 1150, 1105, 1035, 735 cm^{-1}; mass spectrum m/e 244.13170

(calculated for $C_{12}H_{20}O_5$ = 244.13108). Insufficient material was isolated to obtain an elemental analysis.

E- and Z-6-Acetyl-1-hydroxy-3,4-dimethyl-3-octen-7-one (37) Compound 37 was prepared in 17% yield (82:18 mixture of isomers), when compound 35 was allowed to react with 2.4 equivalents of 2,4-pentanedione using the general alkylation procedure.

The isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the acetyl group. The isomers were not assigned due to the low yield and instability of compound 37. Both keto and enol forms of compound 37 were seen in the NMR and IR spectra. Major isomer: ^{1}H NMR ($CDCl_3$) δ1.66 (s, 3 H, $=CCH_3$), 1.67 (s, 3 H, $=CCH_3$), 2.09 (s, 6 H, $O=CCH_3$ enol form), 2.17 (s, 6 H, $O=CCH_3$ keto form), 2.31 (t, 2 H, J = 6.6 Hz, $HOCH_2C\underline{H}_2$), 2.61 (d, 2 H, J = 7.5 Hz, $O=CHC\underline{H}_2$ keto form), 3.07 (s, 2 H, $HOC=CC\underline{H}_2$ enol form), 3.64 (t, 2 H, J = 6.6 Hz, $HOC\underline{H}_2$), 3.78 (t, 1 H, J = 7.5 Hz, O=CCH keto form). Minor isomer: ^{1}H NMR ($CDCl_3$) same as the major isomer except δ1.55 (s, 3 H, $=CCH_3$), 1.58 (s, 3 H, $=CCH_3$), 2.37 (t, 2 H, J = 7.2 Hz, $HOCH_2C\underline{H}_2$), 2.64 (d, 2 H, J = 7.2 Hz, $O=CCHC\underline{H}_2$ keto form), 3.11 (s, 2 H, $HOC=CC\underline{H}_2$ enol form), 3.87 (t, 1 H, J = 7.2 Hz, O=CCH keto form).

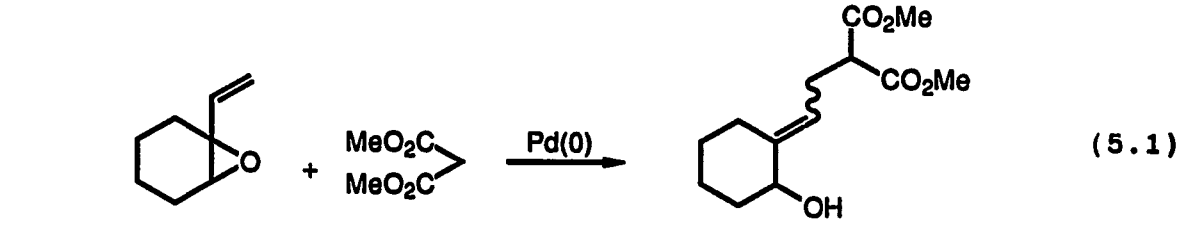
The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 2990, 2950,

2890 (aliphatic C-H), 1700 (C=O), 1560, 1520, 1445, 1380, 1325, 1120, 1090, 1045, 950, 840, 730 cm^{-1}. Compound 37 decomposed before a ^{13}C NMR spectrum or an elemental analysis could be obtained.

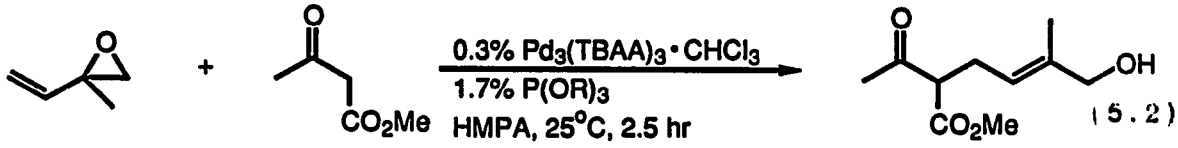
CHAPTER V. PALLADIUM(0)-CATALYZED NUCLEOPHILIC RING-OPENING OF VINYLIC EPOXIDES TO FORM TRISUBSTITUTED ALLYLIC ALCOHOLS

Introduction

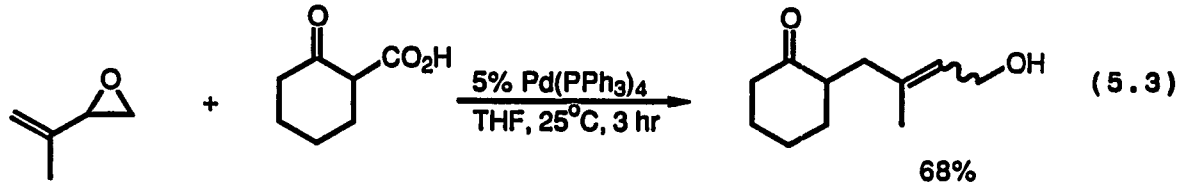
It is well known that vinylic epoxides can react with various nucleophiles, via (π-allyl)palladium complexes, in the presence of a catalytic amount of palladium to form the corresponding allylic alcohols. As discussed in Chapter I, there are many examples of these reactions which produce disubstituted allylic alcohols regio- and stereoselectively. There are only four reactions reported in the literature, however, where trisubstituted acyclic or exocyclic allylic alcohols are formed.[56,57,66,79] In each of the reactions



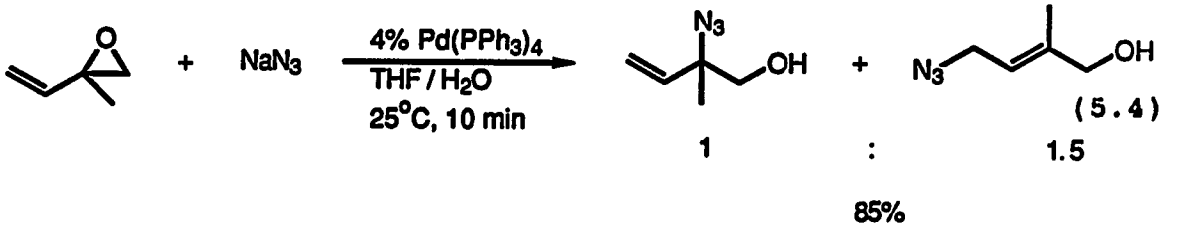
76% (5.1)



62% (5:2 E/Z) (5.2)



68% (5.3)



shown in equations 5.1-5.4, the trisubstituted allylic alcohol was formed as either a mixture of regio- or stereoisomers.

Since it has been demonstrated in Chapter IV that certain trisubstituted homoallylic alcohols can be produced regio- and stereoselectively via palladium(0)-catalyzed nucleophilic ring-opening of substituted vinylic oxetanes, it was thought that it might be possible to also form trisubstituted allylic alcohols with a high degree of regio- and stereoselectivity. Thus, the reactions of substituted vinylic epoxides with carbon nucleophiles in the presence of palladium(0) catalysts were studied.

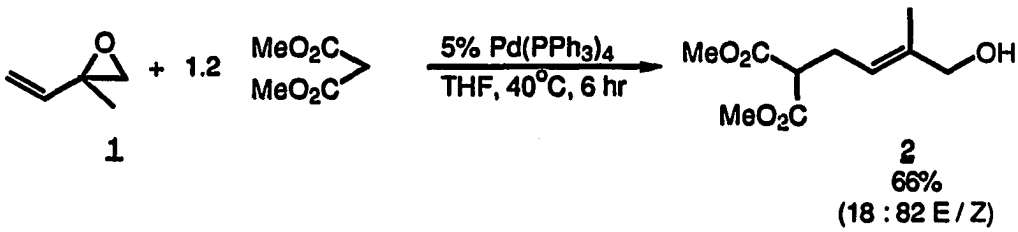
Several goals and objectives were set forth before and during the course of this project. First, these reactions should form trisubstituted allylic alcohols regio- and stereoselectively in high yields. If these reactions produced mixtures of stereoisomers, it was hoped that conditions could be found for the reactions which would yield either the E- or Z-allylic alcohols predominantly. Secondly, it would be desirable if these reactions had a high catalytic turnover of palladium. Finally, it was hoped that a number of different carbon nucleophiles could be used in the reaction, that the

reaction would tolerate a wide variety of functional groups, and that variously substituted vinylic epoxides could be utilized in the reaction.

In this chapter, the palladium(0)-catalyzed reactions of variously substituted vinylic epoxides with carbon nucleophiles will be presented. These reactions will form trisubstituted allylic alcohols. The first section of this chapter covers the reactions of 3-methyl-3,4-epoxy-1-butene with a variety of carbon nucleophiles in the presence of a catalytic amount of palladium(0). Finally, the palladium(0)-catalyzed reactions of other substituted vinylic epoxides with carbon nucleophiles will be discussed.

Additions of Carbon Nucleophiles to 3-Methyl-3,4-epoxy-1-butene

Compound 1, 3-methyl-3,4-epoxy-1-butene, was prepared using the method reported by Reist et al.[121] Compound 1 was allowed to react with dimethyl malonate in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (eq. 5.5). It was found that the corresponding trisubstituted



1 2 66% (18 : 82 E / Z) (5.5)

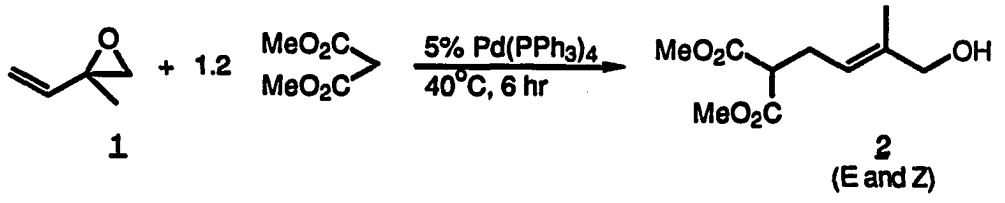
allylic alcohol could be isolated in good yield as a mixture of stereoisomers. Even though the product of the reation

shown in equation 5.5 was formed as a mixture of stereoisomers, the Z-isomer of compound 2 was separated from the E-isomer by flash column chromatography on silica gel using 1:1 hexanes/ethyl acetate as the eluent. In all subsequent reactions, however, compound 2 was isolated as a mixture of stereoisomers and the E- and Z-isomer ratio was determined by integration of the 300 MHz nuclear magnetic resonance spectral peaks corresponding to the allylic hydrogens next to the alcohol group.

Compound 2 was determined to be predominantly the Z-isomer on the basis of its carbon nuclear magnetic resonance spectrum. Allylic methyl carbons present in the E-conformation in trisubstituted olefins typically have chemical shifts between 15 and 16 ppm; while those present in the Z-conformation have chemical shifts between 22 and 23 ppm.[115,116] In the carbon nuclear magnetic resonance spectrum of compound 2, the allylic methyl carbon of the major isomer had a chemical shift of 21.5 ppm, while the same carbon of the minor isomer had a chemical shift of 13.6 ppm. This indicated that the major isomer of the product of the reaction shown in equation 5.5 was the Z-isomer.

In order to determine what effect various solvents would have on the yield and stereochemistry of compound 2, compound 1 was treated with dimethyl malonate in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0)

using a variety of different solvents. As one can see from the results shown in Table 5.1, the Z-isomer of compound 2 was



1 2 (E and Z) (5.6)

Table 5.1. Palladium(0)-catalyzed additions of dimethyl malonate to compound 1 using various solvents

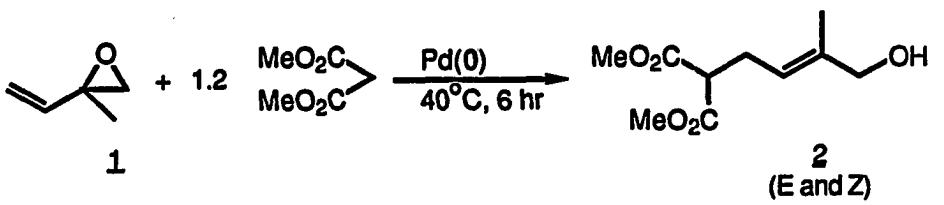
Entry	Solvent	% Yield 2	E/Z Ratio	Comments
1	$PhCH_3$	53	40:60	none
2	$(CH_3CH_2)_2O$	59	36:64	none
3	THF	66	18:82	none
4	THF	59	16:84	2.4 equiv. of $(MeO_2C)_2CH_2$
5	THF	51	21:79	reaction was run at twice the conc.
6	1,4-dioxane	56	26:74	none
7	CH_3CN	68	32:68	none
8	CH_3CH_2CN	35	38:62	none
9	PhCN	55	25:75	none
10	DMSO	65	20:80	none

most strongly favored when tetrahydrofuran, 1,4-dioxane, benzonitrile or dimethyl sulfoxide was used as the solvent for the palladium(0)-catalyzed reaction of compound 1 with dimethyl malonate (see entries 3-6, 9 and 10 in Table 5.1).

The ratio of the Z-isomer of compound 2 to the E-isomer was the highest when tetrahydrofuran was employed as the solvent. Therefore, tetrahydrofuran was the solvent used in all subsequent reactions where it was postulated the Z-isomer of compound 2 would predominate. When tetrahydrofuran was used as the solvent, using 2.4 equivalents of dimethyl malonate or running the reaction at twice the concentration seemed to have little effect on the stereochemical outcome of the reaction (compare entries 3-5 in Table 5.1).

Unfortunately, no solvent was found for the palladium(0)-catalyzed reaction of compound 1 with dimethyl malonate where the E-isomer of compound 2 was the major isomer formed. When toluene, diethyl ether, acetonitrile or propionitrile was used as the solvent, however, the E-isomer of compound 2 was more strongly favored than when tetrahydrofuran was used as the solvent (see entries 1, 2, 7 and 8 in Table 5.1). Since the yield of compound 2 was the highest when acetonitrile was used as the solvent, it was employed in all subsequent reactions where it was hoped the E-isomer of compound 2 would predominate.

Compound 1 was also allowed to react with dimethyl malonate using a variety of palladium(0) catalysts. The data presented in Table 5.2 show that the Z-isomer of compound 2 was strongly favored when tetrakis(triphenylphosphine)-palladium(0) was used as the catalyst for the reaction of



1 2 (E and Z) (5.7)

Table 5.2. Palladium(0)-catalyzed additions of dimethyl malonate to compound 1 using various catalysts

Entry	Catalyst	Added reagent
1	5% $Pd(OAc)_2$, 10% n-BuLi, 30% $(n\text{-}BuO)_3P$	none
2	5% $Pd(dba)_2$	none
3	5% $Pd(dba)_2$, 5% dppe	none
4	5% $Pd(dba)_2$, 5% dppe	none
5	5% $Pd(dba)_2$, 5% dppe	none
6	5% $Pd(dba)_2$, 5% dppe	1.2 Et_3N
7	5% $Pd(dba)_2$, 5% dppe	0.12 $NaCH(CO_2Me)_2$
8	5% $Pd(dba)_2$, 5% dppp	0.12 $NaCH(CO_2Me)_2$
9	5% $Pd(dba)_2$, 5% dppp	0.12 $NaCH(CO_2Me)_2$
10	5% $Pd(dba)_2$, 5% n-Bu_3P	0.12 $NaCH(CO_2Me)_2$
11	5% $Pd(dba)_2$, 10% n-Bu_3P	0.12 $NaCH(CO_2Me)_2$
12	5% $Pd(dba)_2$, 5% n-Bu_3P	0.24 $NaCH(CO_2Me)_2$
13	5% $Pd(dba)_2$, 5% n-Bu_3P	0.12 $NaCH(CO_2Me)_2$
14	5% $Pd(dba)_2$, 5% n-Bu_3P	0.12 $NaCH(CO_2Me)_2$
15	2.5% $Pd_2(dba)_3 \cdot CHCl_3$	none
16	2.5% $Pd_2(dba)_3 \cdot CHCl_3$, 30% PPh_3	none
17	2.5% $Pd_2(dba)_3 \cdot CHCl_3$, 30% $(o\text{-}MeC_6H_4)_3P$	none
18	2.5% $Pd_2(dba)_3 \cdot CHCl_3$, 30% $(p\text{-}FC_6H_4)_3P$	none

Solvent	% Yield 2	E/Z Ratio	Comments
THF	8	-	none
THF	0	-	none
THF	69	58:42	none
$PhCH_3$	55	56:44	none
CH_3CN	72	60:40	none
CH_3CN	72	57:43	none
CH_3CN	57	68:32	none
CH_3CN	< 5	-	none
CH_3CN	40	73:27	$0^{\circ}C$ reaction temp.
CH_3CN	50	72:28	none
CH_3CN	20	53:47	none
CH_3CN	18	61:39	none
CH_3CN	46	54:46	$25^{\circ}C$ for 3 hr
CH_3CN	38	67:33	$25^{\circ}C$ reaction temp.
THF	0	-	none
THF	64	16:84	none
THF	0	-	none
THF	63	24:76	none

Table 5.2. Continued

Entry	Catalyst	Added reagent
19	2.5% $Pd_2(dba)_3 \cdot CHCl_3$, 30% $(\underline{p}\text{-}MeOC_6H_4)_3P$	none
20	2.5% $Pd_2(dba)_3 \cdot CHCl_3$, 30% $(\underline{p}\text{-}Me_2NC_6H_4)_3P$	none
21	2.5% $Pd_2(dba)_3 \cdot CHCl_3$, 30% $(\underline{n}\text{-}BuO)_3P$	none
22	2.5% $Pd_2(dba)_3 \cdot CHCl_3$, 30% $\underline{n}\text{-}Bu_3P$	none
23	2.5% $Pd_2(dba)_3 \cdot CHCl_3$, 15% dppe	none
24	5% $Pd(PPh_3)_4$	none
25	5% $Pd(PPh_3)_4$	1.2 Et_3N
26	5% $Pd(PPh_3)_4$	1.2 Et_3N
27	5% $Pd(PPh_3)_4$	1.2 Et_3N
28	5% $Pd(PPh_3)_4$	1.2 Et_3N
29	5% $Pd(PPh_3)_4$	1.2 Et_3N
30	5% $Pd(PPh_3)_4$	1.2 Et_3N
31	10% $Pd(PPh_3)_4$	1.2 Et_3N
32	5% $Pd(PPh_3)_4$	3.0 Et_3N
33	5% $Pd(PPh_3)_4$	1.2 PPh_3
34	5% $Pd(PPh_3)_4$	0.12 $NaCH(CO_2Me)_2$
35	5% $Pd(PPh_3)_4$, 5% dppe	none
36	5% $Pd(PPh_3)_4$, 10% dppe	none
37	5% $Pd(dppe)_2$	none

Solvent	% Yield 2	E/Z Ratio	Comments
THF	53	32:68	none
THF	61	56:44	none
THF	0	-	none
THF	64	55:45	none
THF	72	35:65	none
THF	66	18:82	none
THF	60	26:74	25°C reaction temp.
THF	59	20:80	25°C for 24 hr
THF	64	15:85	none
THF	57	15:85	24 hr reaction time
THF	64	17:83	66°C reaction temp.
THF	52	16:84	66°C for 24 hr
THF	69	17:83	none
THF	50	14:86	none
THF	41	15:85	none
THF	68	31:69	none
THF	49	59:41	none
THF	50	54:46	none
THF	60	55:45	none

compound 1 with dimethyl malonate (see entries 24-34 in Table 5.2). When 5% tetrakis(triphenylphosphine)palladium(0) was used as the catalyst, the Z-isomer of compound 2 became more strongly favored if triethylamine or extra triphenylphosphine was added to the reaction (compare entries 24, 27, 32 and 33 in Table 5.2). However, when three equivalents of triethylamine or extra triphenylphosphine was added to the reaction, the yield of compound 2 dropped significantly. When 0.12 equivalents of dimethyl sodiomalonate was added to the reaction, the Z-isomer was less favored than when triethylamine or extra triphenylphosphine was added (compare entries 27 and 32-34 in Table 5.2). Using 10% tetrakis(triphenylphosphine)palladium(0) as the catalyst, instead of 5%, seemed to have little effect on the stereochemical outcome of the reaction, but the yield of compound 2 increased slightly (compare entries 27 and 31 in Table 5.2). When the reaction was run in the presence of 5% tetrakis(triphenylphosphine)palladium(0) and 1.2 equivalents of triethylamine, the E- and Z-isomer ratio of compound 2 depended upon the reaction temperature (compare entries 25-30 in Table 5.2). Reactions run at 40°C or in refluxing tetrahydrofuran seemed to more strongly favor the Z-isomer of compound 2. The yield of compound 2 dropped, however, if the reaction was run at 40°C or in refluxing tetrahydrofuran for twenty-four hours instead of six.

When the reaction of compound 1 with dimethyl malonate was run using $Pd_2(dba)_3 \cdot CHCl_3$ and triphenylphosphine or tris(p-fluorophenyl)phosphine as the catalyst, the Z-isomer of compound 2 was also strongly favored (see entries 16 and 18 in Table 5.2). When phosphine ligands with electron-donating groups on the aryl ring were employed, however, the Z-isomer of compound 2 became less strongly favored (compare entries 16 and 18-20 in Table 5.2). Finally, when $Pd_2(dba)_3 \cdot CHCl_3$ and either tris(o-methylphenyl)phosphine or tri-n-butyl phosphite were used in the reaction, none of the expected product was isolated (see entries 17 and 21 in Table 5.2).

On the other hand, the E-isomer of compound 2 was found to be favored when the reaction of compound 1 with dimethyl malonate was run in the presence of a palladium(0) catalyst and 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane or tri-n-butylphosphine (see entries 3-14, 22, 23, 35 and 36 in Table 5.2). The E-isomer of compound 2 also predominated when bis[1,2-bis(diphenylphosphino)ethane]-palladium(0) was used as the catalyst (see entry 37 in Table 5.2). When the reaction was run in the presence of 5% bis(dibenzylideneacetone)palladium(0) and 5% 1,2-bis(diphenylphosphino)ethane, the E-isomer of compound 2 was more highly favored if 0.12 equivalents of dimethyl sodiomalonate was added to the reaction (compare entries 5 and 7 in Table 5.2). However, when triethylamine was added, the E-isomer of

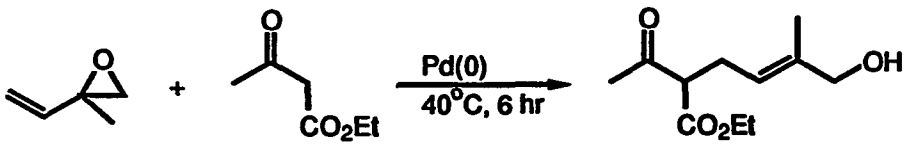
compound 2 predominated less strongly (compare entries 5-7 in Table 5.2). Also, when 5% bis(dibenzylideneacetone)-palladium(0) and 5% tri-n-butylphosphine were used as the catalyst, the yield of compound 2 dropped significantly if 0.24 equivalents of dimethyl sodiomalonate was added to the reaction instead of 0.12 equivalents (compare entries 10 and 12 in Table 5.2). Finally, when 5% bis(dibenzylideneacetone)-palladium(0) and 5% tri-n-butylphosphine were used as the catalytic system, the E-isomer of compound 2 became less highly favored when the reaction was run at room temperature rather than 40°C (compare entries 10, 13 and 14 in Table 5.2).

The data presented in Table 5.2 show that compound 2 was prepared in the highest yield with the highest selectivity for the Z-isomer when compound 1 was allowed to react with 1.2 equivalents of dimethyl malonate in the presence of 10% tetrakis(triphenylphosphine)palladium(0) and 1.2 equivalents of triethylamine using tetrahydrofuran as the solvent for six hours at 40°C (see entry 31 in Table 5.2). On the other hand, compound 2 could be prepared in the highest yield with the highest selectivity for the E-isomer when compound 1 was treated with 1.2 equivalents of dimethyl malonate and 0.12 equivalents of dimethyl sodiomalonate for six hours at 40°C using 5% bis(dibenzylideneacetone)palladium(0) and 5% 1,2-bis(diphenylphosphino)ethane as the catalyst with acetonitrile as the solvent (see entry 7 in Table 5.2).

Once the best conditions for forming either the E- or Z-isomer of compound 2 had been found (see entries 7 and 31 in Table 5.2, respectively), compound 1 was treated with ethyl acetoacetate using these reaction conditions. Even though compound 3 was isolated as a mixture of stereoisomers from the reactions shown in Table 5.3, the E- and Z-isomers could be separated from one another by thin layer chromatography.

As expected, the E-isomer of compound 3 predominated when the reaction of compound 1 with ethyl acetoacetate was run in the presence of 5% bis(dibenzylideneacetone)palladium(0), 5% 1,2-bis(diphenylphosphino)ethane and 0.12 equivalents of ethyl sodioacetoacetate using acetonitrile as the solvent (see entries 1 and 2 in Table 5.3). If these reaction conditions were employed, the highest yield of compound 3 was obtained when 2.4 equivalents of ethyl acetoacetate were used in the reaction. The isomer ratio of compound 3, however, did not depend greatly on the amount of ethyl acetoacetate added.

Unfortunately, the reaction of compound 1 with ethyl acetoacetate yielded nearly equal amounts of the E- and Z-isomers of compound 3 when the reaction was run under the same conditions that had given a predominance of the Z-isomer of compound 2 (see entries 3 and 4 in Table 5.3). The yield of compound 3 was greater and the Z-isomer was more strongly favored when compound 1 was allowed to react with 1.2 equivalents of ethyl acetoacetate rather than 2.4 equivalents.



1 3 (E and Z) (5.8)

Table 5.3. Palladium(0)-catalyzed additions of ethyl acetoacetate to compound 1

Entry	Catalyst	Added reagent	Solvent	Equiv. ethyl acetoacetate	% Yield 3	E/Z Ratio
1	5% $Pd(dba)_2$, 5% dppe	0.12 $[EtO_2CCHCOCH_3]^-Na^+$	CH_3CN	1.2	57	80:20
2	5% $Pd(dba)_2$, 5% dppe	0.12 $[EtO_2CCHCOCH_3]^-Na^+$	CH_3CN	2.4	76	77:23
3	10% $Pd(PPh_3)_4$	1.2 Et_3N	THF	1.2	43	51:49
4	10% $Pd(PPh_3)_4$	1.2 Et_3N	THF	2.4	35	58:42

The results presented in this section show that trisubstituted allylic alcohols can be isolated in good yields when substituted vinylic epoxides are allowed to react with either dimethyl malonate or ethyl acetoacetate in the presence of a palladium(0) catalyst. Conditions have been found for the reaction of compound 1 with dimethyl malonate where either the E- or the Z-isomer of the corresponding trisubstituted allylic alcohol can be produced preferentially. However, these reaction conditions seem to be somewhat dependent upon the nucleophile. In spite of the fact that mixtures of E- and Z-isomers are formed, these reactions are synthetically useful because the two stereoisomers can be separated by thin layer chromatography.

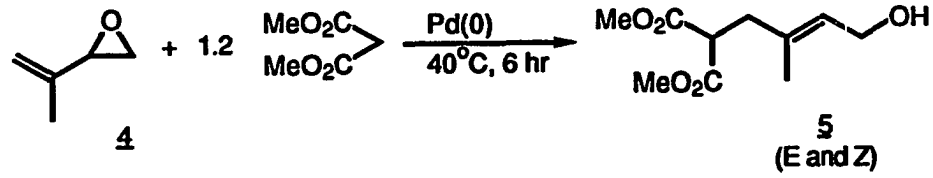
Additions of Carbon Nucleophiles to Other Substituted Vinylic Epoxides

In order to determine whether the formation of trisubstituted allylic alcohols via palladium(0)-catalyzed nucleophilic ring-opening of vinylic epoxides is a useful, general synthetic method, the reactions of variously substituted vinylic epoxides with carbon nucleophiles and a palladium(0) catalyst were investigated. Compound 4, 2-methyl-3,4-epoxy-1-butene, was prepared by the method reported by Savu and Katzenellenbogen.[37] Compound 4 was allowed to react with dimethyl malonate in the presence of a catalytic amount of palladium(0) using several different

reaction conditions. Compound 5 was isolated as a mixture of stereoisomers from all of the reactions reported in Table 5.4. However, the Z-isomer of compound 5 has been separated from the E-isomer by flash chromatography on silica gel using 1:2 hexanes/ethyl acetate as the eluent.

As predicted, reactions which used bis(dibenzylideneacetone)palladium(0) and 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane or tri-n-butylphosphine as the catalyst and acetonitrile as the solvent favored the E-isomer of compound 5 (see entries 1-4 in Table 5.4). Similar results were obtained when compound 1 was treated with dimethyl malonate in the presence of a palladium(0) catalyst (see Table 5.2). The E-isomer of compound 5 was more strongly favored when 0.12 equivalents of dimethyl sodiomalonate was added to the reaction. When the reaction was run in the presence of dimethyl sodiomalonate, the yield of compound 5 was the greatest if 5% bis(dibenzylideneacetone)palladium(0) and 5% 1,2-bis(diphenylphosphino)ethane were used as the catalyst. The stereochemical outcome of the reaction, however, did not seem to depend upon the phosphine ligand added to the reaction.

On the other hand, reactions that used tetrakis-(triphenylphosphine)palladium(0) as the catalyst and tetrahydrofuran as the solvent favored the Z-isomer of compound 5 (see entries 5-7 in Table 5.2). Similar results



4 5 (E and Z) (5.9)

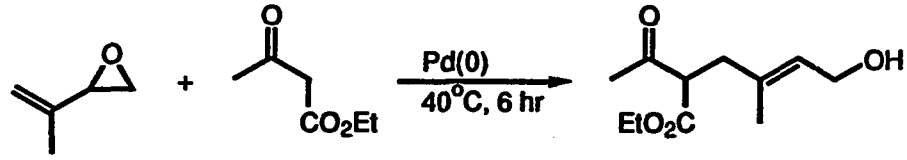
Table 5.4. Palladium(0)-catalyzed additions of dimethyl malonate to compound 4

Entry	Catalyst	Added reagent	Solvent	% Yield 5	E/Z Ratio	Comments
1	5% $Pd(dba)_2$, 5% dppe	none	CH_3CN	45	53:47	none
2	5% $Pd(dba)_2$, 5% dppe	0.12 $NaCH(CO_2Me)_2$	CH_3CN	53	75:25	none
3	5% $Pd(dba)_2$, 5% dppp	0.12 $NaCH(CO_2Me)_2$	CH_3CN	7	72:28	0°C reaction temp.
4	5% $Pd(dba)_2$, 5% n-Bu_3P	0.12 $NaCH(CO_2Me)_2$	CH_3CN	32	73:27	none
5	5% $Pd(PPh_3)_4$	none	THF	89	42:58	none
6	5% $Pd(PPh_3)_4$	1.2 Et_3N	THF	86	40:60	none
7	10% $Pd(PPh_3)_4$	1.2 Et_3N	THF	76	38:62	none

were found when compound 1 was allowed to react with dimethyl malonate and a palladium(0) catalyst (see Table 5.2). The isomer ratio of compound 5 did not depend on the amount of catalyst used in the reaction. Adding triethylamine also did not change the stereochemical outcome of the reaction. The yield of compound 5 dropped significantly if 10% tetrakis-(triphenylphosphine)palladium(0) was used rather than 5% of the catalyst.

The reactions of compound 4 with ethyl acetoacetate and a palladium(0) catalyst were also explored (Table 5.5). The reactions were run under conditions that had given a predominance of either the E- or Z-isomer of compound 5 when compound 4 was treated with dimethyl malonate (see entries 2 and 5-7 in Table 5.4). Even though compound 6 was isolated as a mixture of stereoisomers from the reactions shown in Table 5.5, the E- and Z-isomers could be separated from one another by thin layer chromatography.

As expected, the E-isomer of compound 6 was favored when compound 4 was allowed to react with ethyl acetoacetate in the presence of 5% bis(dibenzylideneacetone)palladium(0), 5% 1,2-bis(diphenylphosphino)ethane and 0.12 equivalents of ethyl sodioacetoacetate using acetonitrile as the solvent (see entries 1 and 2 in Table 5.5). The yield of compound 6 was the greatest when compound 4 was treated with 2.4 equivalents of ethyl acetoacetate. However, the E-isomer of compound 6



4 6 (E and Z) (5.10)

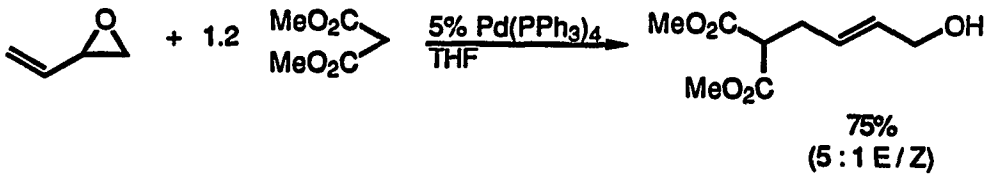
Table 5.5. Palladium(0)-catalyzed additions of ethyl acetoacetate to compound 4

Entry	Catalyst	Added reagent	Solvent	Equiv. ethyl acetoacetate	% Yield 6	E/Z Ratio
1	5% $Pd(dba)_2$, 5% dppe	0.12 $[EtO_2CCHCOCH_3]^-Na^+$	CH_3CN	1.2	60	70:30
2	5% $Pd(dba)_2$, 5% dppe	0.12 $[EtO_2CCHCOCH_3]^-Na^+$	CH_3CN	2.4	73	64:36
3	10% $Pd(PPh_3)_4$	1.2 Et_3N	THF	1.2	57	49:51
4	10% $Pd(PPh_3)_4$	1.2 Et_3N	THF	2.4	74	53:47
5	5% $Pd(PPh_3)_4$	1.2 Et_3N	THF	1.2	58	57:43
6	5% $Pd(PPh_3)_4$	none	THF	1.2	32	68:32

was more strongly favored when 1.2 equivalents of ethyl acetoacetate were used in the reaction.

When the reactions of compound 4 with ethyl acetoacetate were run using tetrakis(triphenylphosphine)palladium(0) as the catalyst and tetrahydrofuran as the solvent, equal amounts of the E- and Z-isomers of compound 6 were isolated (see entries 3 and 4 in Table 5.5), or the E-isomer of compound 6 was favored (see entries 5 and 6 in Table 5.5). Unfortunately, the results presented in Tables 5.2 and 5.4 predicted that compound 6 should have been produced as predominantly the Z-isomer under these reaction conditions. The highest yield of compound 6 was obtained when compound 4 was treated with 2.4 equivalents of ethyl acetoacetate, 1.2 equivalents of triethylamine and 10% tetrakis(triphenylphosphine)palladium(0) (see entry 4 in Table 5.5). However, the Z-isomer of compound 6 was most strongly favored when 1.2 equivalents of ethyl acetoacetate, 1.2 equivalents of triethylamine and 10% tetrakis(triphenylphosphine)palladium(0) were used in the reaction (see entry 3 in Table 5.5).

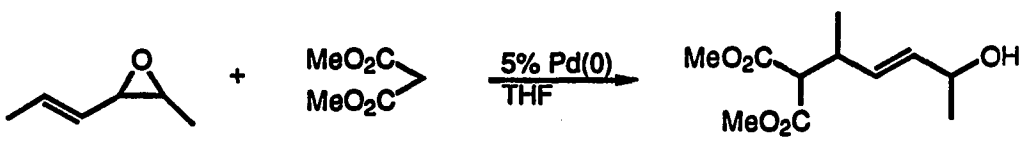
Trost and Molander have recently reported that the treatment of butadiene monoepoxide with a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and 1.2 equivalents of dimethyl malonate led to the formation of the corresponding allylic alcohol as a mixture of stereoisomers (eq. 5.11).[56]



75%
(5:1 E/Z)

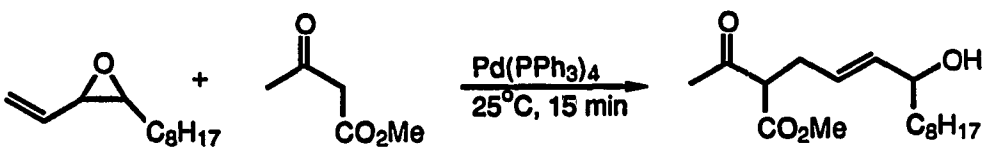
(5.11)

Both Trost and Molander[56] and Tsuji et al.[57] have found that they were able to form E-allylic alcohols stereoselectively, however, if a more highly substituted vinylic epoxide was used in the reaction (eqs. 5.12 and 5.13).



76%
(E-isomer only)

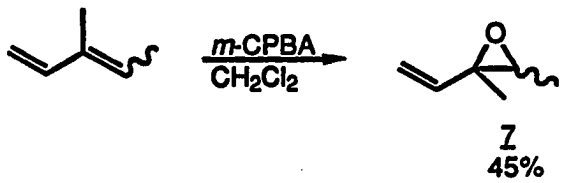
(5.12)



67%
(E-isomer only)

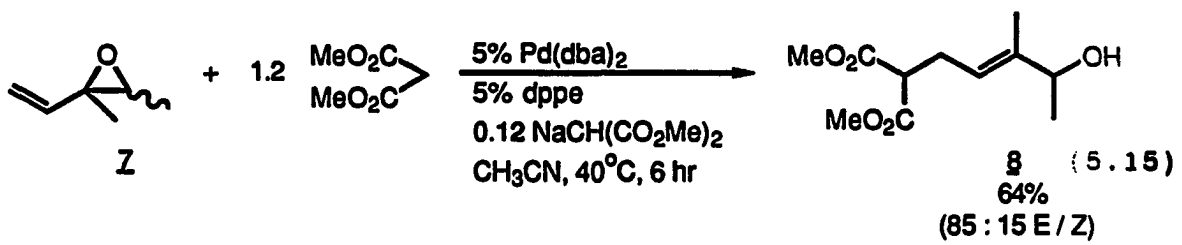
(5.13)

In order to determine what effect using a more highly substituted vinylic epoxide would have on the stereochemistry of trisubstituted allylic alcohols, the reactions of compound 7, cis- and trans-3-methyl-3,4-epoxy-1-pentene, with various carbon nucleophiles in the presence of a palladium(0) catalyst were studied. Compound 7 was prepared by treating a mixture of E- and Z-3-methyl-1,3-pentadiene with m-chloroperoxybenzoic acid (eq. 5.14). Coumpound 7 was isolated as a 63:37 mixture of diastereomers.

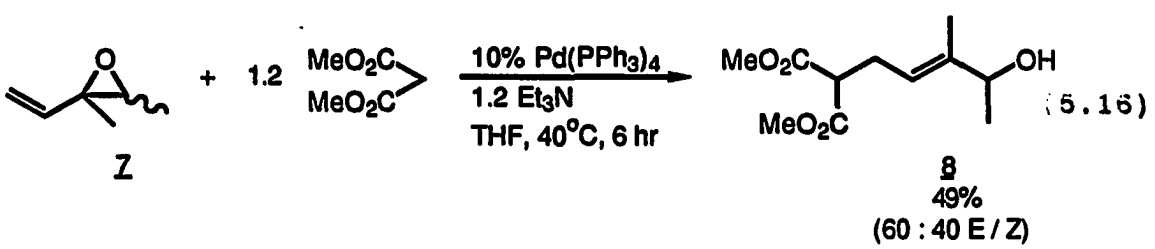


(5.14)

The palladium(0)-catalyzed reactions of compound 7 with dimethyl malonate were explored (eqs. 5.15 and 5.16). The reactions were run under the best conditions observed for



(5.15)



(5.16)

forming either the E- or Z-isomer of compound 2 (see entries 7 and 31 in Table 5.2, respectively). In both of the reactions studied, compound 8 was isolated as a mixture of E- and Z-isomers, however, the E- and Z-isomers could be separated by thin layer chromatography.

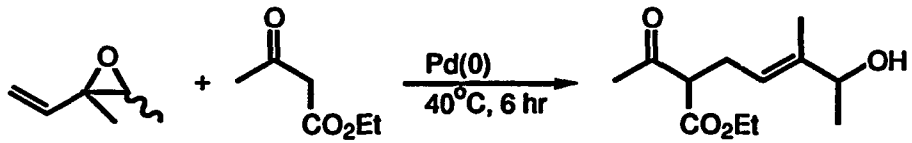
As predicted, the E-isomer of compound 8 was strongly favored when compound 7 was allowed to react with dimethyl malonate in the presence of 5% bis(dibenzylideneacetone)-palladium(0), 5% 1,2-bis(diphenylphosphino)ethane and 0.12

equivalents of dimethyl sodiomalonate using acetonitrile as the solvent. The E-isomer of compound 8 was also favored, however, when compound 7 was treated with dimethyl malonate using the reaction conditions shown in equation 5.16; these conditions had yielded a predominance of the Z-isomer of compound 2 when compound 1 was allowed to react with dimethyl malonate.

The palladium(0)-catalyzed reactions of compound 7 with ethyl acetoacetate were also studied (Table 5.6). The reactions were run using the best conditions observed for forming either the E- or Z-isomer of compound 2 (see entries 7 and 31 in Table 5.2, respectively). Even though compound 9 was isolated as mixture of stereoisomers from all of the reactions presented in Table 5.6, the E- and Z-isomers could be separated from one another by thin layer chromatography.

In all of the reactions shown in Table 5.6, the E-isomer of compound 9 was favored strongly, even when the reaction was run under conditions that had yielded predominantly the Z-isomer of compound 2 (see entries 3 and 4 in Table 5.6). The highest yields of compound 9 were obtained when the reaction was run in the presence of 2.4 equivalents of ethyl acetoacetate. The amount of ethyl acetoacetate used, however, seemed to have little effect on the stereochemical outcome of the reaction.

The results summarized in Table 5.6 and equations 5.15



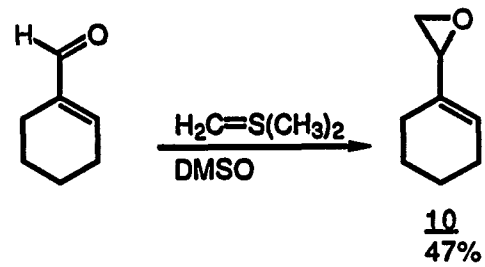
7 9 (E and Z) (5.17)

Table 5.6. Palladium(0)-catalyzed additions of ethyl acetoacetate to compound 7

Entry	Catalyst	Added reagent	Solvent	Equiv. ethyl acetoacetate	% Yield 9	E/Z Ratio
1	5% $Pd(dba)_2$, 5% dppe	0.12 $[EtO_2CCHCOCH_3]^-Na^+$	CH_3CN	1.2	49	83:17
2	5% $Pd(dba)_2$, 5% dppe	0.12 $[EtO_2CCHCOCH_3]^-Na^+$	CH_3CN	2.4	63	82:18
3	10% $Pd(PPh_3)_4$	1.2 Et_3N	THF	1.2	58	89:11
4	10% $Pd(PPh_3)_4$	1.2 Et_3N	THF	2.4	61	90:10

and 5.16 indicate that when highly substituted vinylic epoxides are allowed to react with carbon nucleophiles in the presence of a catalytic amount of palladium(0), the E-isomers of the corresponding trisubstituted allylic alcohols are strongly favored.

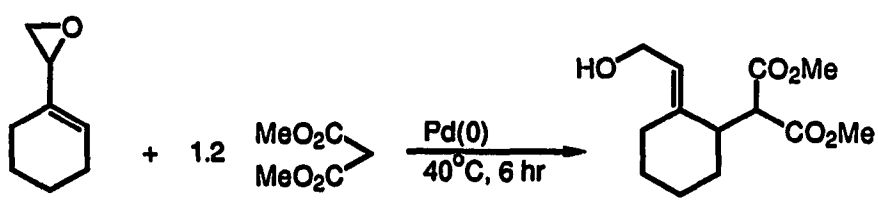
In an effort to determine whether the stereochemistry of exocyclic trisubstituted allylic alcohols could be controlled, the palladium(0)-catalyzed nucleophilic ring-opening of compound 10, (1-cyclohexenyl)epoxyethane, was studied. Compound 10 was synthesized by a method similar to the one Savu and Katzenellenbogen used to prepare compound 4 (eq. 5.18).[37]



10
47%

(5.18)

The reactions of compound 4 with dimethyl malonate in the presence of a catalytic amount of palladium(0) were explored. The reactions shown in Table 5.7 were run under the best



10

11
(E and Z)

(5.19)

Table 5.7. Palladium(0)-catalyzed additions of dimethyl malonate to compound 10

Entry	Catalyst	Added reagent	Solvent	% Yield 11	E/Z Ratio
1	5% $Pd(dba)_2$, 5% dppe	0.12 $NaCH(CO_2Me)_2$	CH_3CN	15	83:17
2	5% $Pd(PPh_3)_4$	1.2 Et_3N	THF	47	54:46
3	10% $Pd(PPh_3)_4$	1.2 Et_3N	THF	46	52:48

conditions observed for forming either the E- or Z-isomer of compound 2 (see entries 7, 27 and 31 in Table 5.2). Compound 11 was isolated as a mixture of stereoisomers from all of the reactions studied, however, the E- and Z-isomers could be separated from one another by thin layer chromatography.

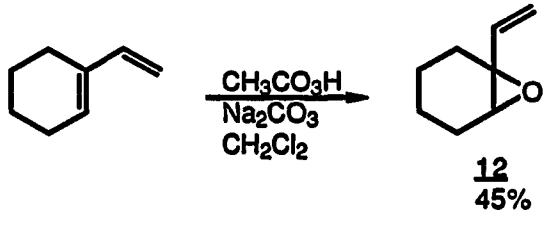
The results presented in Table 5.7 show that the E-isomer of compound 11 was strongly favored when compound 10 was treated with dimethyl malonate in the presence of 5% bis(dibenzylideneacetone)palladium(0), 5% 1,2-bis(diphenylphosphino)ethane and 0.12 equivalents of dimethyl sodiomalonate using acetonitrile as the solvent (see entry 1 in Table 5.7). This is consistent with the results summarized in Table 5.2.

On the other hand, when the reaction of compound 10 with dimethyl malonate was run under conditions that had led to a predominance of the Z-isomer of compound 2, nearly equal amounts of the E- and Z-isomers of compound 11 were isolated

(see entries 2 and 3 in Table 5.7). The amount of tetrakis-(triphenylphosphine)palladium(0) used in the reaction did not seem to have an effect on the yield or stereochemistry of compound 11.

The E- and Z-isomers of compound 11 were assigned by comparing its proton nuclear magnetic resonance spectrum to the spectrum of compound 5, a similarly substituted allylic alcohol. The vinyl hydrogen of the E-isomer of compound 5 had a chemical shift of 5.43 ppm, while the vinyl hydrogen of the Z-isomer had a chemical shift of 5.55 ppm. The mixture of isomers of compound 11 showed two vinyl hydrogen absorbances at 5.38 and 5.49 ppm. Thus, the peak at 5.38 ppm was assigned to the E-isomer of compound 11, and the peak at 5.49 ppm was assigned to the Z-isomer.

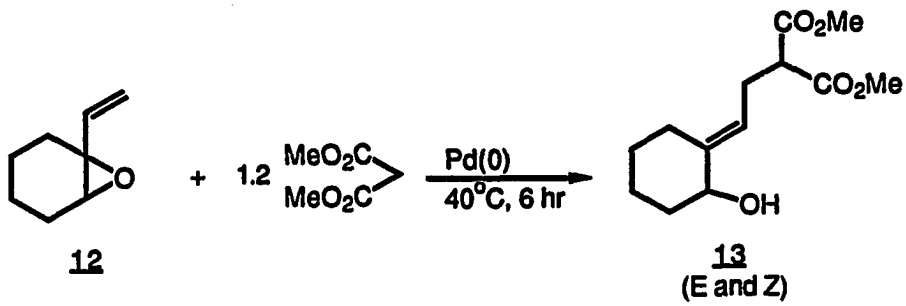
The palladium(0)-catalyzed nucleophilic ring-opening of compound 12, 1-ethenyl-7-oxabicyclo[4.1.0]heptane, was studied. These reactions also produce exocyclic trisubstituted allylic alcohols. Compound 12 was prepared by treating 1-ethenylcyclohexene with peroxyacetic acid (eq. 5.20).



12
45%

(5.20)

The reactions of compound 12 with dimethyl malonate and a catalytic amount of palladium(0) were explored. The reactions reported in Table 5.8 were run under the best conditions



12 13 (E and Z) (5.21)

Table 5.8. Palladium(0)-catalyzed additions of dimethyl malonate to compound 12

Entry	Catalyst	Added reagent	Solvent	% Yield 13	E/Z Ratio
1	5% $Pd(dba)_2$, 5% dppe	0.12 $NaCH(CO_2Me)_2$	CH_3CN	58	73:27
2	5% $Pd(PPh_3)_4$	1.2 Et_3N	THF	65	36:64
3	10% $Pd(PPh_3)_4$	1.2 Et_3N	THF	68	35:65

observed for forming either the E- or Z-isomer of compound 2 (see entries 7, 27 and 31 in Table 5.2). In all of the reactions studied, the homoallylic alcohol was isolated as a mixture of stereoisomers. The E- and Z-isomers of compound 13 can be separated, however, by thin layer chromatography.

As predicted from the results reported in Table 5.2, the E-isomer of compound 13 was favored when compound 12 was treated with dimethyl malonate in the presence of 5%

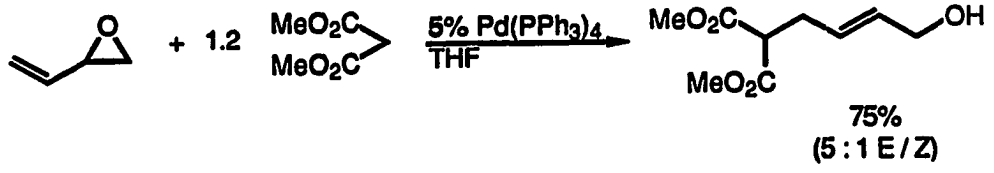
bis(dibenzylideneacetone)palladium(0), 5% 1,2-bis(diphenylphosphino)ethane and 0.12 equivalents of dimethyl sodiomalonate using acetonitrile as the solvent (see entry 1 in Table 5.8).

The Z-isomer of compound 13 was found to predominate, however, when compound 12 was allowed to react with dimethyl malonate and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) in tetrahydrofuran (see entries 2 and 3 in Table 5.8). These were the best conditions found for forming the Z-isomer of compound 2 preferentially. The yield and stereochemistry of compound 13 did not seem to depend upon the amount of tetrakis(triphenylphosphine)palladium(0) used in the reaction.

The E- and Z-isomers of compound 13 were assigned by comparing its proton nuclear magnetic resonance spectrum to the spectrum of compound 2, a similarly substituted allylic alcohol. The vinyl hydrogen of the E-isomer of compound 2 had a chemical shift of 5.35 ppm; the Z-isomer showed an absorbance at 5.17 ppm. The mixture of isomers of compound 13 showed two vinyl hydrogen absorbances at 5.30 and 5.06 ppm. Therefore, the absorbance at 5.30 ppm was assigned to the E-isomer of compound 13, and the peak at 5.06 ppm was attributed to the Z-isomer.

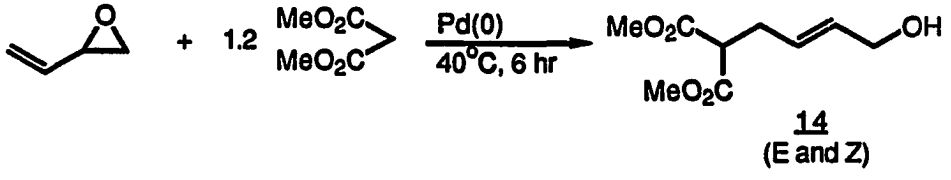
As discussed previously, when butadiene monoepoxide was treated with dimethyl malonate and a catalytic amount of

palladium(0), Trost and Molander obtained the corresponding allylic alcohol as a mixture of stereoisomers (eq. 5.22).[56]



(5.22)

In order to determine whether the stereoselectivity of this reaction could be controlled, butadiene monoepoxide was allowed to react with dimethyl malonate (Table 5.9), using the conditions that had led to a predominance of either the E- or Z-isomer of compound 2 (see entries 7, 27 and 31 in Table



(5.23)

Table 5.9. Palladium(0)-catalyzed additions of dimethyl malonate to butadiene monoepoxide

Entry	Catalyst	Added reagent	Solvent	% Yield 14	E/Z Ratio
1	5% $Pd(dba)_2$, 5% dppe	0.12 $NaCH(CO_2Me)_2$	CH_3CN	45	100:0
2	5% $Pd(PPh_3)_4$	1.2 Et_3N	THF	50	55:45
3	10% $Pd(PPh_3)_4$	1.2 Et_3N	THF	44	55:45

5.2). When the reaction was run under conditions that had favored the E-isomer of compound 2, compound 14 was formed exclusively as the E-isomer (see entry 1 in Table 5.9).

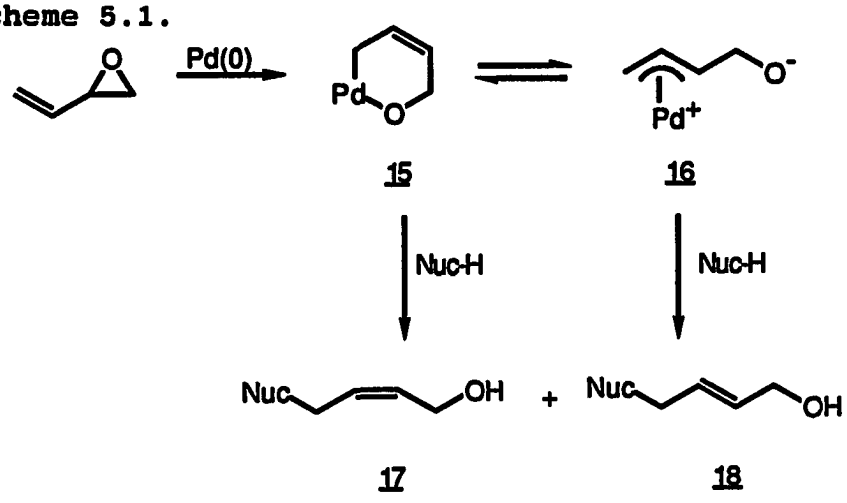
On the other hand, when the reaction of butadiene

monoepoxide with dimethyl malonate was run in the presence of tetrakis(triphenylphosphine)palladium(0) and 1.2 equivalents of triethylamine using tetrahydrofuran as the solvent, conditions that had led to the formation of a predominance of the Z-isomer of compound 2, the E-isomer of compound 14 was still slightly favored (see entries 2 and 3 in Table 5.9). However, the E-isomer of compound 14 was less strongly favored than in the reaction reported by Trost and Molander (see equation 5.22).[56] The yield of compound 14 was the highest when 5% tetrakis(triphenylphosphine)palladium(0) was used in the reaction, although the stereochemistry of the product did not depend on whether 5% or 10% of the catalyst was added. Even though compound 14 was isolated as a mixture of stereoisomers from the reactions shown in entries 2 and 3 of Table 5.9, the E- and Z-isomers could be separated by thin layer chromatography.

Mechanism

A possible mechanism is shown in Scheme 5.1 which explains why the palladium(0)-catalyzed additions of nucleophiles to vinylic epoxides form E-allylic alcohols preferentially under one set of reaction conditions and Z-allylic alcohols under another. While no experiments have been run to attempt to support (or disprove) this mechanism, it explains the observed experimental results. In the first step of the mechanism, palladium(0) oxidatively adds to the

Scheme 5.1.



reaction conditions for forming E-allylic alcohols preferentially: $Pd(dba)_2$
dppe
CH_3CN
$(MeO_2C)_2CH_2$

reaction conditions for forming Z-allylic alcohols preferentially: $Pd(PPh_3)_4$
THF
Et_3N

vinylic epoxide to generate oxygen-chelated allylic palladium species 15 which is in equilibrium with (π-allyl)palladium species 16. The alkoxide ion formed acts as a base to remove a proton from the nucleophile. If the anion of the nucleophile attacks oxygen-chelated allylic palladium species 15, the Z-isomer of the corresponding allylic alcohol is formed. If it attacks (π-allyl)palladium species 16, the E-allylic alcohol is produced.

The equilibrium between oxygen-chelated allylic palladium species 15 and (π-allyl)palladium species 16 may be affected by the ligands present in solution. If there are many

reagents present in solution to act as ligands for palladium, the equilibrium shown in Scheme 5.1 is forced toward (π-allyl)palladium species 16, and E-allylic alcohols are produced predominantly. On the other hand, if there are few ligands present, the equilibrium shifts toward oxygen-chelated allylic palladium species 15, and Z-allylic alcohols are formed preferentially. As one can see from the information shown in Scheme 5.1, when reaction conditions which produce E-allylic alcohols predominantly are used, there are many reagents present in solution to act as ligands for palladium. Dibenzylideneacetone, 1,2-bis(diphenylphosphino)ethane, acetonitrile and dimethyl sodiomalonate can all act as ligands for palladium. On the other hand, when reaction conditions which favor Z-allylic alcohols are utilized, only triphenylphosphine and triethylamine can become ligands for palladium.

The E-isomers of allylic alcohols are produced predominantly when 1,2-bis(diphenylphosphino)ethane is used in the reaction. This may be due to the fact that 1,2-bis(diphenylphosphino)ethane occupies two coordination sites on palladium, making oxygen-chelated allylic palladium species 15 less highly favored. This leads to the preferential formation of E-allylic alcohols. It, therefore, appears that the equilibrium between intermediates 15 and 16, and thus the stereochemistry of the allylic alcohol product,

may be affected by the ligands present solution.

The structure of the vinylic epoxide can also have an effect on the equilibrium shown in Scheme 5.1. When the reactions of compound 7 were studied, E-allylic alcohols were favored under all of the reaction conditions explored (see Table 5.6 and eqs. 5.15 and 5.16). This may be due to the fact that when there is a substituent present in the position α to the alcohol, the alkoxide ion becomes sterically hindered and can not act as effectively as a ligand for palladium. This forces the equilibrium shown in Scheme 5.1 toward (π-allyl)palladium species 16, and the E-isomer of the corresponding allylic alcohol is formed predominantly. Similar results were obtained by Trost and Molander[56] and Tsuji et al.[57] when they studied the palladium(0)-catalyzed nucleophilic ring-opening of vinylic epoxides (see eqs. 5.11-5.13).

The acidity of the nucleophile may also affect the stereochemistry of the product. When compound 1 was treated with dimethyl malonate, conditions were found for the reaction which led to a predominance of either the E- or the Z-isomer of compound 2 (see Table 5.2). When compound 1 or 4 was allowed to react with ethyl acetoacetate under reaction conditions that had favored the E-isomer of compound 2, the E-isomer of the corresponding allylic alcohol was produced predominantly (see Tables 5.3 and 5.5). However, if compound

1 or 4 was treated with ethyl acetoacetate using reaction conditions that had led to a predominance of the Z-isomer of compound 2, approximately equal amounts of the E- and Z-allylic alcohols were obtained. This may be due to the fact that dimethyl malonate is less acidic and therefore more reactive than ethyl acetoacetate in the palladium(0)-catalyzed nucleophilic ring-opening of vinylic epoxides. If allylic palladium species 15 is the first formed intermediate, dimethyl malonate may react with it before the equilibrium with (π-allyl)palladium species 16 can be established when the reaction is run under conditions which favored the Z-isomer of compound 2. On the other hand, when less reactive ethyl acetoacetate is allowed to react with compound 1 or 4 using conditions that favored the Z-isomer of compound 2, the equilibrium between intermediates 15 and 16 may occur before the nucleophile can attack. Thus, equal amounts of the corresponding E- and Z-allylic alcohols are obtained

The mechanism shown in Scheme 5.1 also explains why di- and trisubstituted homoallylic alcohols are formed stereoselectively (see Chapters III and IV), while trisubstituted allylic alcohols are produced as mixtures of stereoisomers. When vinylic epoxides are allowed to react with nucleophiles in the presence of a palladium(0) catalyst, six-membered ring oxygen-chelated allylic palladium species 15 may be formed as an intermediate. This intermediate leds to

the formation of Z-allylic alcohols. When vinylic oxetanes are used in these reactions, however, the oxygen-chelated allylic palladium species is a seven-membered ring, and thus is not likely to be formed. This is why di- and trisubstituted homoallylic alcohols can be prepared exclusively as the E-isomer.

Conclusion

The results discussed in this chapter show that trisubstituted allylic alcohols can be prepared regioselectively in good yields via palladium(0)-catalyzed nucleophilic ring-opening of substituted vinylic epoxides. Conditions have been found for the reaction of compound 1 with dimethyl malonate which led to a predominance of either the E- or Z-isomer of compound 2. When other substituted vinylic epoxides were allowed to react with dimethyl malonate or ethyl acetoacetate under reaction conditions that had favored the E-isomer of compound 2, generally the E-isomer of the corresponding allylic alcohol was formed preferentially. However, if other vinylic epoxides were treated with nucleophiles using reaction conditions that had led to a predominance of the Z-isomer of compound 2, approximately equal amounts of the corresponding E- and Z-allylic alcohols were produced. In spite of the fact that trisubstituted allylic alcohols are formed as mixtures of stereoisomers via palladium(0)-catalyzed nucleophilic ring-opening of vinylic

epoxides, these reactions are synthetically useful since the E- and Z-isomers can be readily separated from one another.

Experimental

Spectral data and analysis

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer at 300 and 75.5 MHz respectively. All infrared spectra were recorded on a Beckmann 4250 spectrophotometer. Exact mass spectral analyses were recorded on a Kratos MS-50 spectrometer. Elemental analyses were performed by Galbraith Laboratories.

Reagents

All nucleophiles were distilled or recrystallized prior to use. Tetrakis(triphenylphosphine)palladium(0) and bis[1,2-bis(diphenylphosphino)ethane]palladium(0) were prepared by the procedure reported by Coulson.[114] The method reported by Ukai and co-workers was used to synthesize $Pd_2(dba)_3 \cdot CHCl_3$.[118] Bis(dibenzylideneacetone)palladium(0) was prepared according to the procedure reported by Takahashi et al.[119]

Epoxides

Compound 1 was synthesized according to the procedure used by Reist et al.[121] The method reported by Savu and Katzenellenbogen was followed when preparing compound 4.[37]

Butadiene monoepoxide was purchased from Aldrich and used without further purification.

The preparation of compound 7 To an ice-cold solution of 5.0 g of E- and Z-3-methyl-1,3-pentadiene (61 mmol), purchased from Aldrich and used without further purification, in 60 ml of dry CH_2Cl_2 was added 13.00 g of 85% m-chloroperoxybenzoic acid (64.0 mmol) over 30 min. The solution was warmed to room temperature and stirred overnight under nitrogen. The reaction mixture was then tested with starch/iodide paper, to make certain all of the peroxide had been consumed. The solution was diluted with 50 ml of CH_2Cl_2, washed with saturated potassium bicarbonate (4 X 50 ml) and dried over anhydrous magnesium sulfate. After removal of the solvents, cis- and trans-3-methyl-3,4-epoxy-1-pentene was purified by distillation: 2.67 g, 45% yield; bp 40°C/78 mm Hg.

Compound 7 was isolated as a 63:37 mixture of isomers. Major isomer: ^{1}H NMR ($CDCl_3$) δ 1.31 (d, 3 H, J = 5.4 Hz, $CHC\underline{H}_3$), 1.36 (s, 3 H, CCH_3), 2.90 (q, 1 H, J = 5.4 Hz, $CH_3C\underline{H}$), 5.14 (dd, 1 H, J = 10.8 Hz, J = 0.9 Hz, $=CH_2$ cis), 5.29 (dd, 1 H, J = 17.7 Hz, J = 0.9 Hz, $=CH_2$ trans), 5.64 (dd, 1 H, J = 17.7 Hz, J = 10.8 Hz, =CH-); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.8, 59.4, 60.8, 115.6, 141.0. Minor isomer: ^{1}H NMR ($CDCl_3$) same as the major isomer except δ 1.22 (d, 3 H, J = 5.4 Hz, $CHC\underline{H}_3$), 1.40 (s, 3 H, CCH_3), 3.00 (q, 1 H, J = 5.4 Hz, $CH_3C\underline{H}$), 5.27

(d, 1 H, J = 10.8 Hz, $=CH_2$ cis), 5.77 (dd, 1 H, J = 17.7 Hz, J = 10.8 Hz, =CH-); ^{13}C NMR ($CDCl_3$) δ13.9, 21.4, 60.3, 61.4, 117.7, 136.1.

The following spectral data were taken from a mixture of the cis and trans isomers: IR (neat) 3094 (vinyl C-H), 2995, 2968 (aliphatic C-H), 1448, 1408, 1387, 1076, 1061, 991, 924, 860, 739, 665 cm^{-1}; mass spectrum m/e 98.07308 (calculated for $C_6H_{10}O$ = 98.07317).

The preparation of compound 10 A solution of 4.37 g of sodium hydride (181 mmol) in 100 ml of dry DMSO was heated to 80°C for 1 hr and was then cooled to room temperature. To this solution was added 100 ml of dry THF. The reaction mixture was cooled to -10°C and a solution of 35.86 g of trimethylsulfonium iodide (176 mmol) in 100 ml of dry DMSO was added. After the addition was complete, 16.07 g of 1-cyclohexenecarboxaldehyde (146 mmol), prepared previously by the procedure reported by Minami et al.,[122] was added slowly to the reaction mixture. Stirring was continued at -10°C for 15 min and then at room temperature for an additional 45 min. The solution was poured into 500 ml of ice water and extracted with ether (4 X 100 ml). The combined ether extracts were dried over anhydrous potassium carbonate. After removal of the solvents, (1-cyclohexenyl)epoxyethane was purified by distillation: 8.63 g, 47% yield; bp 73°C/16 mm Hg; ^1H NMR ($CDCl_3$) δ 1.46-2.14 (m, 8 H, 4 CH_2's cyclohexane ring), 2.77

(dd, 1 H, J = 5.1 Hz, J = 3.3 Hz, O-CH_2), 2.81 (dd, 1 H, J = 5.1 Hz, J = 4.2 Hz, O-CH_2), 3.30 (dd, 1 H, J = 4.2 Hz, J = 3.3 Hz, O-CH), 5.87 (m, 1 H, =CH); ^{13}C NMR ($CDCl_3$) δ22.2, 22.5, 25.2, 46.0, 55.1, 127.5, 133.7, 1 carbon the same or not seen; IR (neat) 3060, 3000 (vinyl C-H), 2940, 2870, 2850 (aliphatic C-H), 1455, 1440, 1395, 1310, 1255, 1142, 958, 925, 882, 840, 807, 780 cm^{-1}; mass spectrum m/e 124.08885 (calculated for $C_8H_{12}O$ = 124.08882).

The preparation of compound 12 To an ice-cold solution of 6.77 g of 1-ethenylcyclohexene (63 mmol), prepared previously by the procedure Thummel and Nutakul used to synthesize 1-ethenylcyclobutene,[123] and 25.87 g of sodium carbonate in 67 ml of dry CH_2Cl_2 was added 12.75 ml of a 32% solution of peroxyacetic acid (61 mmol) over 30 min. The solution was warmed to room temperature and stirred overnight under nitrogen. The reaction mixture was then tested with starch/iodide paper, to make certain all of the peroxide had been consumed. The reaction mixture was diluted with 100 ml of CH_2Cl_2, filtered through Celite and dried over anhydrous magnesium sulfate. After removal of the solvents, 1-ethenyl-7-oxabicyclo[4.1.0]heptane was purified by distillation: 3.50 g, 45% yield; bp 61°C/20 mm Hg; ^1H NMR ($CDCl_3$) δ1.14-1.56 (m, 4 H, 2 CH_2's cyclohexane ring), 1.83-1.97 (m, 4 H, 2 CH_2's cyclohexane ring), 2.99 (t, 1 H, J = 3.0 Hz, O-CH), 5.14 (dd, 1 H, J = 10.8 Hz, J = 1.2 Hz, =CH_2

cis), 5.29 (dd, 1 H, J = 17.4 Hz, J = 1.2 Hz, $=CH_2$ trans), 5.69 (dd, 1 H, J = 17.4 Hz, J = 10.8 Hz, =CH-); ^{13}C NMR ($CDCl_3$) δ 19.7, 19.8, 24.7, 26.2, 58.8, 60.8, 115.5, 140.3; IR (neat) 3090 (vinyl C-H), 2940, 2870 (aliphatic C-H), 1640 (C=C), 1450, 1435, 1400, 1185, 1175, 1015, 980, 915, 875, 865, 840, 820, 765, 660 cm^{-1}; mass spectrum m/e 124.08888 (calculated for $C_8H_{12}O$ = 124.08882).

General procedure for forming E-allylic alcohols preferentially via alkylation of vinylic epoxides using a palladium(0) catalyst

To a 25 ml round bottom flask was added 14.4 mg of bis(dibenzylideneacetone)palladium(0) (0.025 mmol), 10.0 mg of 1,2-bis(diphenylphosphino)ethane (0.025 mmol) and 2.5 ml of dry CH_3CN. The solution was allowed to stir under nitrogen for 15 min at 40°C. To the resulting solution was added 1.0 equivalent (0.50 mmol) of the vinylic epoxide to be studied and a 10% solution of the sodium salt of the appropriate nucleophile, prepared by adding 0.12 equivalents (0.06 mmol) of sodium hydride and 1.2 equivalents (0.60 mmol) of the nucleophile to 0.5 ml of dry CH_3CN. The solution was stirred at 40°C for 6 hr under nitrogen. Ether was then added to the reaction mixture. The solution was washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. After removal of the the solvents, the residue was purified by flash column chromatography on silica gel.

General procedure for forming Z-allylic alcohols preferentially via alkylation of vinylic epoxides using a palladium(0) catalyst

To a 25 ml round bottom flask was added 57.7 mg of tetrakis(triphenylphosphine)palladium(0) (0.050 mmol), 1.2 equivalents (0.60 mmol) of triethylamine, 1.0 equivalent (0.50 mmol) of the vinylic epoxide to be studied, 1.2 equivalents (0.60 mmol) of the appropriate nucleophile and 2.5 ml of dry THF. The solution was allowed to stir for 6 hr at 40°C under nitrogen. Ether was then added to the reaction mixture. The solution was washed with saturated sodium chloride and dried over anhydrous magnesium sulfate. After removal of the solvents, the residue was purified by flash column chromatography on silica gel.

Spectral data for allylic alcohols prepared by the general procedures for the alkylation of vinylic epoxides using a palladium(0) catalyst

Methyl E- and Z-6-hydroxy-2-methoxycarbonyl-5-methyl-4-hexenoate (2) Compound 2 was prepared in 57% yield (68:32 E/Z), when compound 1 was allowed to react with dimethyl malonate using the general procedure for forming E-allylic alcohols preferentially. Compound 2 was also synthesized in 69% yield (17:83 E/Z), when compound 1 was treated with dimethyl malonate using the general procedure for the preferential formation of Z-allylic alcohols. The Z-isomer of

compound 2 has been separated from the E-isomer by flash column chromatography on silica gel using 1:1 hexanes/ethyl acetate as the eluent (R_f Z-isomer = 0.27, R_f E-isomer = 0.34).

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the alcohol group. Z-isomer: ^{1}H NMR ($CDCl_3$) δ 1.63 (br s, 1 H, OH), 1.78 (s, 3 H, $=CCH_3$), 2.66 (dd, 2 H, J = 7.8 Hz, J = 7.5 Hz, $=CHC\underline{H}_2$), 3.42 (t, 1 H, J = 7.5 Hz, O=CCH), 3.72 (s, 6 H, $O-CH_3$), 4.09 (s, 2 H, $HOC\underline{H}_2$), 5.17 (t, 1 H, J = 7.8 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 21.5, 27.1, 51.7, 52.4, 61.2, 122.6, 138.5, 169.4. E-isomer: ^{1}H NMR ($CDCl_3$) same as the Z-isomer except δ 1.67 (s, 3 H, $=CCH_3$), 2.64 (dd, 2 H, J = 7.5 Hz, J = 7.2 Hz, $=CHC\underline{H}_2$), 3.40 (t, 1 H, J = 7.5 Hz, O=CCH), 3.97 (s, 2 H, $HOC\underline{H}_2$), 5.35 (t, 1 H, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) same as the Z-isomer or not seen except δ 13.6, 27.2, 51.6, 52.5, 68.3, 120.4, 138.3.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3120 (vinyl C-H), 2960 (aliphatic C-H), 1730 (C=O), 1440, 1345, 1270, 1250, 1215, 1150, 1000, 750 cm^{-1}; mass spectrum m/e 198.08931 (M - H_2O) (calculated for $C_{10}H_{14}O_4$ = 198.08921). Anal. calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.41. Found: C, 54.71; H, 7.35.

Ethyl E- and Z-2-acetyl-6-hydroxy-5-methyl-4-hexenoate (3) Compound 3 was prepared in 76% yield (77:23 E/Z), when compound 1 was allowed to react with 2.4 equivalents of ethyl acetoacetate using the general procedure for forming E-allylic alcohols preferentially. Compound 3 was also synthesized in 43% yield (51:49 E/Z), when compound 1 was treated with ethyl acetoacetate using the general procedure for the preferential formation of Z-allylic alcohols. The E- and Z-isomers of compound 3 can be separated by TLC on silica gel using 1:2 hexanes/ethyl acetate as the eluent (R_f = 0.42 and 0.48).

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the vinylic hydrogen. E-isomer: ^{1}H NMR ($CDCl_3$) δ1.26 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.67 (s, 3 H, $=CCH_3$), 2.22 (s, 3 H, $O=CCH_3$), 2.58 (dd, 2 H, J = 7.5 Hz, J = 7.2 Hz, $=CHC\underline{H}_2$), 3.45 (t, 1 H, J = 7.5 Hz, O=CCH), 3.97 (s, 2 H, $HOC\underline{H}_2$), 4.18 (q, 2 H, J = 7.2 Hz, $O-C\underline{H}_2CH_3$), 5.31 (t, 1 H, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ13.6, 14.0, 26.2, 28.9, 59.4, 61.3, 68.0, 120.5, 137.8, 168.3, 202.6. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ1.77 (s, 3 H, $=CCH_3$), 2.23 (s, 3 H, $O=CCH_3$), 3.49 (t, 1 H, J = 7.5 Hz, O=CCH), 4.08 (s, 2 H, $HOC\underline{H}_2$), 5.14 (t, 1 H, J = 7.5 Hz, =CH); ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ21.5, 29.8, 59.5, 61.1, 61.4, 77.3, 122.8, 137.9, 168.5, 202.7.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 2984, 2920 (aliphatic C-H), 1738, 1717 (C=O), 1447, 1360, 1331, 1242, 1151, 1096, 1069, 1016, 951, 858 cm^{-1}. Anal. calcd for $C_{11}H_{18}O_4$: C, 61.68; H, 8.41. Found: C, 61.46; H, 8.53.

Methyl E- and Z-6-hydroxy-2-methoxycarbonyl-4-methyl-4-hexenoate (5) Compound 5 was prepared in 53% yield (75:25 E/Z), when compound 4 was treated with dimethyl malonate using the general procedure for the preferential formation of E-allylic alcohols. Compound 5 was also synthesized in 86% yield (40:60 E/Z), when compound 4 was allowed to react with dimethyl malonate in the presence of 5% tetrakis-(triphenylphosphine)palladium(0) using the general procedure for forming Z-allylic alcohols preferentially. The Z-isomer of compound 2 has been separated from the E-isomer by flash column chromatography on silica gel using 1:2 hexanes/ethyl acetate as the eluent (R_f Z-isomer = 0.34, R_f E-isomer = 0.45).

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the ester group. Z-isomer: ^1H NMR ($CDCl_3$) δ1.50 (br s, 1 H, OH), 1.71 (s, 3 H, $=CCH_3$), 2.68 (d, 2 H, J = 7.8 Hz, $=CCH_2$), 3.61 (t, 1 H, J = 7.8 Hz, O=CCH), 3.72 (s, 6 H, $O-CH_3$), 4.08 (d, 2 H, J = 7.5 Hz, $HOC\underline{H}_2$), 5.55 (t, 1 H, J = 7.5 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 22.6, 31.0, 49.9, 52.6, 58.5,

128.0, 134.4, 169.5. E-isomer: ^{1}H NMR ($CDCl_3$) same as the Z-isomer except δ1.67 (s, 3 H, $=CCH_3$), 2.61 (d, 2 H, J = 7.8 Hz, $=CCH_2$), 3.58 (t, 1 H, J = 7.8 Hz, O=CCH), 4.11 (d, 2 H, J = 6.9 Hz, $HOC\underline{H}_2$), 5.43 (t, 1 H, J = 6.9 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ16.1, 38.3, 50.4, 52.5, 59.1, 126.5, 134.9, 169.3.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3000 (vinyl C-H), 2970, 2920, 2850 (aliphatic C-H), 1740 (C=O), 1435, 1385, 1340, 1250, 1200, 1150, 1090, 1045, 1010, 955, 750 cm^{-1}; mass spectrum m/e 198.08929 (M - H_2O) (calculated for $C_{10}H_{14}O_4$ = 198.08921). Anal. calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.41. Found: C, 55.29; H, 7.61.

Ethyl E- and Z-2-acetyl-6-hydroxy-4-methyl-4-hexenoate (6) Compound 6 was synthesized in 60% yield (70:30 E/Z), when compound 4 was treated with ethyl acetoacetate using the general procedure for the preferential formation of E-allylic alcohols. Compound 6 was also prepared in 57% yield (49:51 E/Z), when compound 4 was allowed to react with ethyl acetoacetate using the general procedure for forming Z-allylic alcohols preferentially. The E- and Z-isomers of compound 6 can be separated by TLC on silica gel using 1:2 hexanes/ethyl acetate as the eluent (R_f = 0.38 and 0.45).

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the vinylic hydrogen. E-isomer: ^{1}H NMR ($CDCl_3$) δ1.24 (t, 3 H, J = 7.2

Hz, $CH_2C\underline{H}_3$), 1.66 (s, 3 H, $=CCH_3$), 2.21 (s, 3 H, $O=CCH_3$), 2.55 (d, 2 H, J = 7.8 Hz, $=CCH_2$), 3.62 (t, 1 H, J = 7.8 Hz, O=CCH), 4.09 (d, 2 H, J = 6.6 Hz, $HOC\underline{H}_2$), 4.17 (q, 2 H, J = 7.2 Hz, $O-C\underline{H}_2CH_3$), 5.40 (t, 1 H, J = 6.6 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 13.9, 15.9, 28.6, 37.3, 58.0, 58.7, 61.2, 126.3, 134.4, 169.2, 202.3. Z-isomer: ^1H NMR ($CDCl_3$) same as the E-isomer except δ1.25 (t, 3 H, J = 6.9 Hz, $CH_2C\underline{H}_3$), 1.70 (s, 3 H, $=CCH_3$), 2.23 (s, 3 H, $O=CCH_3$), 2.68 (d, 2 H, J = 8.7 Hz, $=CCH_2$), 3.67 (t, 1 H, J = 8.7 Hz, O=CCH), 5.53 (t, 1 H, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ 22.6, 29.0, 30.0, 57.5, 58.3, 58.6, 61.4, 127.6, 134.5, 169.4.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 2982, 2935 (aliphatic C-H), 1738, 1715 (C=O), 1447, 1369, 1329, 1288, 1246, 1178, 1097, 1018 cm^{-1}. Anal. calcd for $C_{11}H_{18}O_4$: C, 61.68; H, 8.41. Found: C, 61.25; H, 8.53.

Methyl E- and Z-6-hydroxy-2-methoxycarbonyl-5-methyl-4-heptenoate (8) Compound 8 was synthesized in 64% yield (85:15 E/Z), when compound 7 was allowed to react with dimethyl malonate using the general procedure for the preferential formation of E-allylic alcohols. Compound 8 was also prepared in 49% yield (60:40 E/Z), when compound 7 was treated with dimethyl malonate using the general procedure for forming Z-allylic alcohols preferentially. The E- and Z-

isomers of compound 8 can be separated by TLC on silica gel using 1:1 hexanes/ethyl acetate as the eluent (R_f = 0.29 and 0.35).

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the vinylic hydrogen. E-isomer: ^{1}H NMR ($CDCl_3$) δ1.21 (d, 3 H, J = 6.0 Hz, $CHC\underline{H}_3$), 1.50 (br s, 1 H, OH), 1.63 (s, 3 H, $=CCH_3$), 2.62 (dd, 2 H, J = 7.2 Hz, J = 7.2 Hz, $=CHC\underline{H}_2$), 3.41 (t, 1 H, J = 7.2 Hz, O=CCH), 3.72 (s, 6 H, $O-CH_3$), 4.17 (q, 1 H, J = 6.0 Hz, HOC<u>H</u>), 5.34 (t, 1 H, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ12.0, 21.4, 26.8, 51.3, 52.2, 72.4, 119.0, 142.0, 169.3. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ1.69 (s, 3 H, $=CCH_3$), 2.77 (dd, 2 H, J = 8.4 Hz, J = 8.1 Hz, $=CHC\underline{H}_2$), 3.34 (t, 1 H, J = 8.4 Hz, O=CCH), 4.79 (q, 1 H, J = 6.6 Hz, HOC<u>H</u>), 5.09 (t, 1 H, J = 8.1 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ17.2, 20.6, 26.4, 50.3, 52.5, 64.8, 120.7, 141.5, 168.9.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 2970, 2950, 2920 (aliphatic C-H), 1730 (C=O), 1665 (C=C), 1435, 1345, 1280, 1240, 1155, 1080, 1030, 955, 890 cm^{-1}. Anal. calcd for $C_{11}H_{18}O_5$: C, 57.39; H, 7.83. Found: C, 57.68; H, 7.99.

<u>Ethyl E- and Z-2-acetyl-6-hydroxy-5-methyl-4-heptenoate (9)</u> Compound 9 was prepared in 63% yield (82:18 E/Z), when compound 7 was allowed to react with 2.4 equivalents of ethyl acetoacetate using the general procedure for the preferential

formation of E-allylic alcohols. Compound 9 was also synthesized in 61% yield (90:10 E/Z), when compound 7 was treated with 2.4 equivalents of ethyl acetoacetate using the general procedure for forming Z-allylic alcohols preferentially. The E- and Z-isomers of compound 9 can be separated by TLC on silica gel using 1:1 hexanes/ethyl acetate as the eluent (R_f = 0.29 and 0.34).

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic methyl hydrogens. E-isomer: ^{1}H NMR ($CDCl_3$) δ1.21 (d, 3 H, J = 6.3 Hz, $CHC\underline{H}_3$), 1.26 (t, 3 H, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.45 (br s, 1 H, OH), 1.64 (s, 3 H, $=CCH_3$), 2.22 (s, 3 H, $O=CCH_3$), 2.56 (dd, 2 H, J = 7.5 Hz, J = 7.2 Hz, $=CHC\underline{H}_2$), 3.44 (t, 1 H, J = 7.5 Hz, O=CCH), 4.17 (m, 3 H, HOC$\underline{H}$ and O-$C\underline{H}_2CH_3$), 5.30 (t, 1 H, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ11.3, 13.7, 21.3, 25.9, 28.7, 59.0, 61.0, 72.1, 119.1, 141.5, 169.1, 202.5. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ1.68 (s, 3 H, $=CCH_3$), cis vinyl proton buried under trans proton; ^{13}C NMR ($CDCl_3$) δ11.2, 17.0, 25.0, 25.5, 27.0, 57.9, 61.3, 64.6, 120.8, 138.1, 168.6, 201.4.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 2980, 2930, 2870 (aliphatic C-H), 1735, 1710 (C=O), 1665 (C=C), 1445, 1365, 1260, 1205, 1150, 1080, 1025, 955, 890, 855, 735 cm^{-1}.

Anal. calcd for $C_{12}H_{20}O_4$: C, 63.16; H, 8.77. Found: C, 62.73; H, 8.61.

E- and Z-1-(2-Hydroxyethylidene)-2-(dimethoxycarbonylmethyl)cyclohexane (11) Compound 11 was synthesized in 15% yield (83:17 E/Z), when compound 10 was allowed to react with dimethyl malonate using the general procedure for the preferential formation of E-allylic alcohols. Compound 11 was also prepared in 46% yield (52:48 E/Z), when compound 10 was treated with dimethyl malonate using the general procedure for forming Z-allylic alcohols preferentially. The E- and Z-isomers of compound 11 can be separated by TLC on silica gel using 1:1 hexanes/ethyl acetate as the eluent (R_f = 0.28 and 0.35).

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the vinylic hydrogen. E-isomer: ^{1}H NMR ($CDCl_3$) δ 1.52-1.72 (m, 6 H, 3 CH_2's cyclohexane ring), 2.11 (ddd, 1 H, J = 13.5 Hz, J = 10.2 Hz, J = 3.3 Hz, =CCH_2), 2.28 (ddd, 1 H, J = 13.5 Hz, J = 5.1 Hz, J = 4.2 Hz, =CCH_2), 2.96 (ddd, 1 H, J = 11.4 Hz, J = 8.4 Hz, J = 4.2 Hz, =CCH), 3.65 (s, 3 H, O-CH_3), 3.73 (s, 3 H, O-CH_3), 3.77 (d, 1 H, J = 8.4 Hz, O=CCH), 4.08 (m, 2 H, HO$C\underline{H}_2$), 5.38 (t, 1 H, J = 6.9 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 22.3, 25.9, 27.2, 30.3, 44.3, 52.2, 52.4, 53.3, 57.7, 123.0, 141.1, 168.3, 168.6. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ 3.63 (s, 3 H, O-CH_3), 3.75 (s, 3 H, O-CH_3),

3.91 (d, 1 H, J = 8.4 Hz, O=CCH), 3.97 (m, 1 H, HOC$\underline{H}_2$), 4.28 (m, 1 H, HOC$\underline{H}_2$), 5.49 (t, 1 H, J = 6.6 Hz, =CH); ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ20.7, 27.9, 29.4, 32.6, 36.2, 52.1, 52.3, 52.5, 57.6, 124.7, 140.4, 169.0.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 2950, 2930, 2855 (aliphatic C-H), 1730 (C=O), 1660 (C=C), 1450, 1430, 1320, 1275, 1240, 1190, 1150, 1040, 1015, 990, 915, 750 cm^{-1}. Anal. calcd for $C_{13}H_{20}O_5$: C, 60.94; H, 7.81. Found: C, 61.41; H, 8.07.

<u>E- and Z-2-Hydroxy-1-(3,3-dimethoxycarbonylpropylidene)-cyclohexane (13)</u> Compound <u>13</u> was prepared in 58% yield (73:27 E/Z), when compound <u>12</u> was allowed to react with dimethyl malonate using the general procedure for forming E-allylic alcohols preferentially. Compound <u>13</u> was also synthesized in 68% yield (35:65 E/Z), when compound <u>12</u> was treated with dimethyl malonate using the general procedure for the preferential formation of Z-allylic alcohols. The E- and Z-isomers of compound <u>13</u> can be separated by TLC on silica gel using 1:1 hexanes/ethyl acetate as the eluent (R_f = 0.35 and 0.42).

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the vinylic hydrogen. Z-isomer: ^{1}H NMR ($CDCl_3$) δ1.40-1.99 (m, 6 H, 3 CH_2's cyclohexane ring), 2.11 (m, 1 H, =CCH_2), 2.41 (m, 1 H,

=CC$\underline{H}_2$), 2.52 (ddd, 1 H, J = 14.1 Hz, J = 7.5 Hz, J = 6.3 Hz, =CHC$\underline{H}_2$), 2.83 (ddd, 1 H, J = 14.1 Hz, J = 9.0 Hz, J = 8.7 Hz, =CHC$\underline{H}_2$), 3.40 (dd, 1 H, J = 8.7 Hz, J = 6.3 Hz, O=CCH), 3.72 (s, 6 H, O-CH_3), 4.72 (m, 1 H, HOC$\underline{H}$), 5.06 (dd, 1 H, J = 9.0 Hz, J = 7.5 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 20.4, 26.2, 27.6, 32.2, 33.6, 51.8, 52.3, 64.9, 118.8, 144.5, 169.2. E-isomer: ^{1}H NMR ($CDCl_3$) same as the Z-isomer except δ 2.64 (dd, 2 H, J = 7.5 Hz, J = 7.5 Hz, =CHC$\underline{H}_2$), 3.38 (t, 1 H, J = 7.5 Hz, O=CCH), 4.03 (m, 1 H, HOC$\underline{H}$), 5.30 (t, 1 H, J = 7.5 Hz, =CH); ^{13}C NMR ($CDCl_3$) same as the Z-isomer or not seen except δ 22.8, 26.0, 27.1, 36.1, 51.6, 52.2, 72.9, 115.1, 143.7, 169.5.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 2940, 2870 (aliphatic C-H), 1740 (C=O), 1440, 1345, 1280, 1245, 1165, 1085, 1035, 990, 918, 735 cm^{-1}. Anal. calcd for $C_{13}H_{20}O_5$: C, 60.94; H, 7.81. Found: C, 61.12; H, 7.88.

Methyl E- and Z-6-hydroxy-2-methoxycarbonyl-4-hexenoate (14) Compound 14 was prepared in 45% yield (E-isomer only), when butadiene monoepoxide was allowed to react with dimethyl malonate using the general procedure for the preferential formation of E-allylic alcohols. Compound 14 was also synthesized in 50% yield (55:45 E/Z), when butadiene monoepoxide was treated with dimethyl malonate in the presence of 5% tetrakis(triphenylphosphine)palladium(0) using the

general procedure for forming Z-allylic alcohols preferentially. The E- and Z-isomers of compound 14 can be separated by TLC on silica gel using 1:2 hexanes/ethyl acetate as the eluent (R_f E-isomer = 0.31, R_f Z-isomer = 0.38).

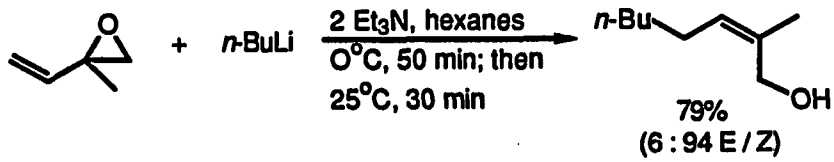
The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the alcohol group. E-isomer: ^{1}H NMR ($CDCl_3$) δ 2.64 (dd, 2 H, J = 7.5 Hz, J = 6.6 Hz, O=CCHC$\underline{H}_2$), 3.44 (t, 1 H, J = 7.5 Hz, O=CC$\underline{H}$), 3.72 (s, 6 H, O-CH_3), 4.07 (d, 2 H, J = 5.1 Hz, HOC$\underline{H}_2$), 5.63 (dt, 1 H, J = 15.3 Hz, J = 6.6 Hz, O=CCHCH$_2$C$\underline{H}$=), 5.74 (dt, 1 H, J = 15.3 Hz, J = 5.1 Hz, HOCH$_2$C$\underline{H}$=); ^{13}C NMR ($CDCl_3$) δ 31.1, 52.1, 52.2, 62.3, 128.4, 132.3, 169.0. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ 2.68 (dd, 2 H, J = 7.8 Hz, J = 7.5 Hz, O=CCHC$\underline{H}_2$), 3.45 (t, 1 H, J = 7.5 Hz, O=CC$\underline{H}$), 3.73 (s, 6 H, O-CH_3), 4.18 (d, 2 H, J = 5.1 Hz, HOC$\underline{H}_2$), 5.45 (dt, 1 H, J = 10.8 Hz, J = 7.8 Hz, O=CCHCH$_2$C$\underline{H}$=); ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ 26.5, 51.0, 51.2, 57.5, 131.8.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3020 (vinyl C-H), 2975, 2870 (aliphatic C-H), 1740 (C=O), 1442, 1350, 1280, 1245, 1210, 1165, 1105, 1030, 980 cm^{-1}. Anal. calcd for $C_9H_{14}O_5$: C, 53.47; H, 6.93. Found: C, 53.74; H, 7.03.

CHAPTER VI. ADDITIONS OF OTHER ORGANOMETALLIC REAGENTS TO VINYLIC OXETANES

Introduction

Over the past several decades, reactions involving nucleophilic and organometallic displacements of allylic compounds have been well studied and reviewed.[1] These reactions have become useful synthetic reactions when the regio- and stereochemistry of the product can be controlled. It has been shown that allylic alcohols can be prepared with a high degree of regio- and stereoselectivity when vinylic epoxides are allowed to react with organolithium,[26] -copper[14,32,50] and -boron[53] reagents (eqs. 6.1-6.5).



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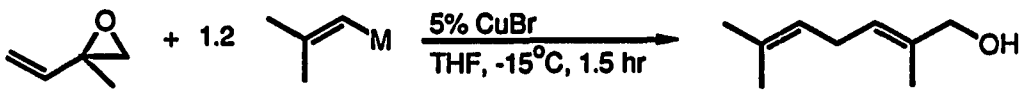

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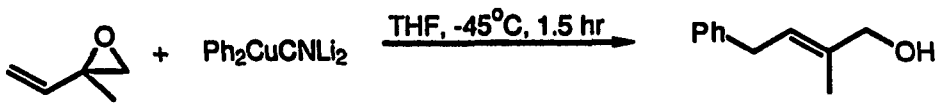
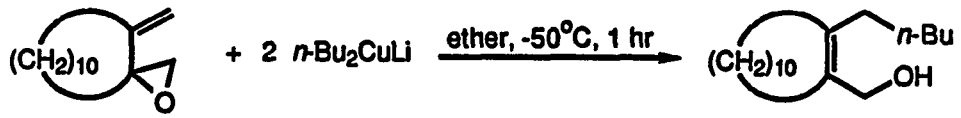
M = MgBr — 79% (96 : 4 E/Z)

M = Li — 86% (90 : 10 E/Z)



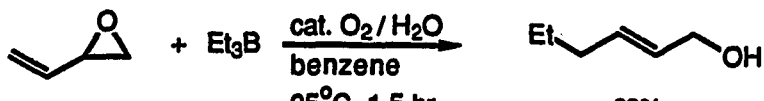
(6.3)

96%
(77 : 23 E / Z)



77%
(98 : 2 E / Z)

(6.4)



68%
(88 :12 E / Z)

(6.5)

Since it has been demonstrated that vinylic oxetanes can be ring-opened to form homoallylic alcohols using organomercurials and palladium(II) salts,[108] it was thought that it might be possible to replace the vinylic epoxides shown in equations 6.1-6.5 with vinylic oxetanes. No such reactions of vinylic oxetanes have been reported previously. It was hoped that the reactions of vinylic oxetanes with organolithium, -copper and -boron reagents would produce homoallylic alcohols in good yields with a high degree of regio- and stereoselectivity. It would also be desirable if a number of different organometallic reagents could be utilized and if variously substituted vinylic oxetanes would participate in the reaction.

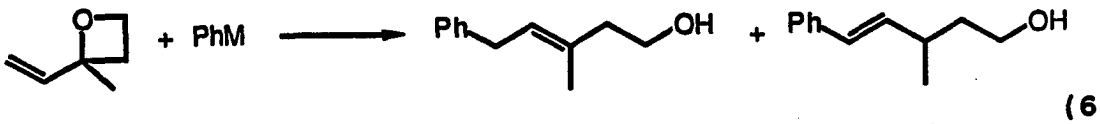
In this chapter, the reactions of vinylic oxetanes with various organometallic reagents will be presented. The first section of this chapter covers the reactions of vinylic oxetanes with organolithium and -copper reagents. Finally, additions of organoboron reagents to vinylic oxetanes will be discussed.

Additions of Organolithium and -Copper Reagents to Vinylic Oxetanes

Additions to 3-methyl-3,5-epoxy-1-pentene

Compound 1, 3-methyl-3,5-epoxy-1-pentene, was prepared using the procedure reported by Portnyagin and Pak.[99] Compound 3 was allowed to react with phenyllithium and various phenylcopper reagents (Table 6.1). The reactions were run using conditions similar to those illustrated in equations 6.1-6.4. By comparing the results shown in Table 6.1, one can see that the highest yield of compound 2 was obtained when compound 1 was treated with phenylmagnesium bromide in the presence of a catalytic amount of cuprous iodide (see entry 1 in Table 6.1). Except when phenyllithium and catalytic cuprous iodide were used as the organometallic reagent (see entry 2 in Table 6.1), all of the reactions studied yielded a single regioisomer. In this case, compounds 2 and 3 were isolated as an inseparable mixture in low yield.

The E-isomer of compound 2 was most strongly favored when the reaction was run in the presence of phenylmagnesium bromide and a catalytic amount of cuprous iodide. Unfortunately, compound 2 was isolated as predominantly the Z-isomer when the reactions were run using the conditions shown in entries 2, 5 and 6 in Table 6.1. The results reported in the literature for the reactions of these organometallic reagents with vinylic epoxides predicted that



(6.6)

1 2 (E and Z) 3

Table 6.1. Additions of phenyllithium and phenylcopper reagents to compound 1

Entry	Organometallic reagent	Conditions	% Yield 2 and 3	2/3 Ratio[a]	E/Z Ratio of 2[b]
1	5% CuI, 1.2 PhMgBr	THF, -15°C, 1.5 hr	79	100:0	66:34
2	5% CuI, 1.2 PhLi	THF, -15°C, 1.5 hr	34	81:19	29:71
3	1.0 PhLi	2 Et_3N, pentane, 0°C, 50 min; then 25°C, 30 min	71	100:0	17:83
4	1.5 PhLi	3 Et_3N, pentane, 0°C, 50 min; then 25°C, 30 min	72	100:0	17:83
5	2 Ph_2CuLi	ether, -50°C, 1 hr	72	100:0	43:57
6	1.1 $Ph_2CuCNLi_2$	THF, -45°C, 1.5 hr	49	100:0	43:57

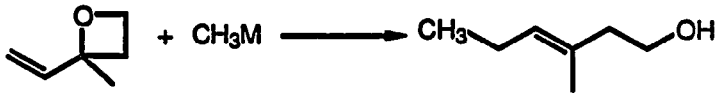
[a]The ratio of regioisomers can be determined by integration of the 300 MHz NMR spectral peaks corresponding to the vinylic hydrogens.

[b]The E- and Z-isomer ratio of homoallylic alcohols can generally be determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the alcohol group.

the E-isomer of compound 2 should be favored under these reaction conditions (see equations 6.2-6.4).[14,32,50] The Z-isomer of compound 2 most strongly predominated, however, when phenyllithium and triethylamine were allowed to react with compound 1 (see entries 3 and 4 in Table 6.1). This result was expected because the reactions of vinylic epoxides with organolithium reagents in the presence of a base produced Z-allylic alcohols preferentially (see eq. 6.1).[26]

The E- and Z-isomers of compound 2 were assigned on the basis of the carbon nuclear magnetic resonance spectrum of a mixture of the two isomers. Allylic methyl carbons present in the E-conformation in trisubstituted olefins typically have chemical shifts between 15 and 16 ppm, while those present in the Z-conformation have chemical shifts between 22 and 23 ppm.[115,116] The mixture of isomers of compound 2 showed two allylic methyl carbon absorbances at 15.9 and 23.4 ppm. Thus, the peak at 15.9 ppm was assigned to the E-isomer of compound 2, and the peak at 23.4 ppm was assigned to the Z-isomer.

Compound 1 was also allowed to react with methyllithium and various methylcopper reagents (Table 6.2). The reactions



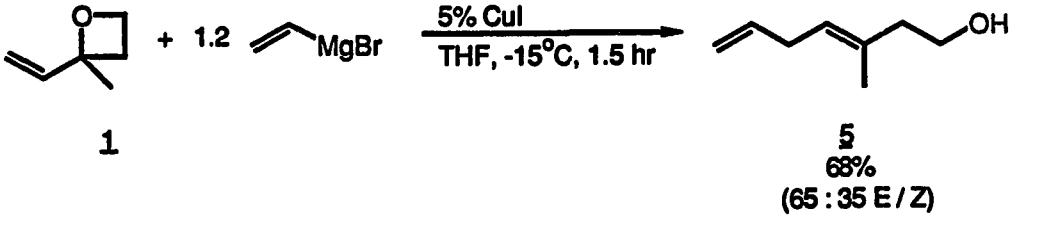
1 4 (E and Z) (6.7)

Table 6.2. Additions of methyllithium and methylcopper reagents to compound 1

Entry	Organometallic reagent	Conditions	% Yield 4	E/Z Ratio
1	5% CuI, 1.2 CH_3MgBr	THF, -15°C, 1.5 hr	83	56:44
2	1.0 CH_3Li	2 Et_3N, pentane, 0°C, 50 min; then 25°C, 30 min	28	44:56
3	1.5 CH_3Li	3 Et_3N, pentane, 0°C, 50 min; then 25°C, 30 min	8	35:65
4	2 $(CH_3)_2CuLi$	ether, -50°C, 1 hr	79	59:41

were run under conditions similar to those illustrated in equations 6.1, 6.2 and 6.4. Compound 4 was formed in high yield as predominantly the E-isomer when compound 1 was treated with methylmagnesium bromide and a catalytic amount of cuprous iodide or dimethylcopper lithium (see entries 1 and 4 in Table 6.2). The yield and stereochemical outcome of the reaction did not depend greatly upon which methylcopper reagent was utilized. On the other hand, the Z-isomer of compound 4 was favored when compound 1 was allowed to react with methyllithium in the presence of triethylamine, but the yields of these reactions were very low (see entries 2 and 3 in Table 6.2). All the reactions shown in Table 6.2 formed the homoallylic alcohol as the sole regioisomer.

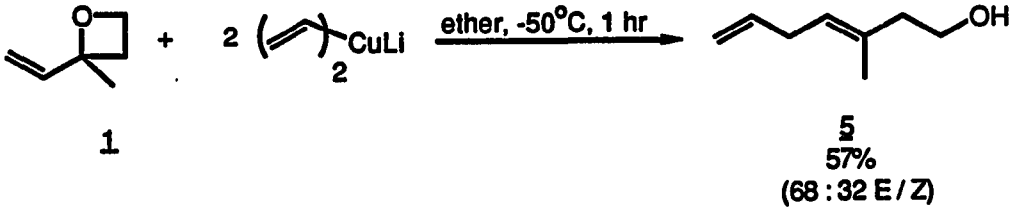
The reactions of compound 1 with vinylcopper reagents were also investigated (eqs. 6.8 and 6.9). Compound 5 was



1

5
68%
(65 : 35 E / Z)

(6.8)



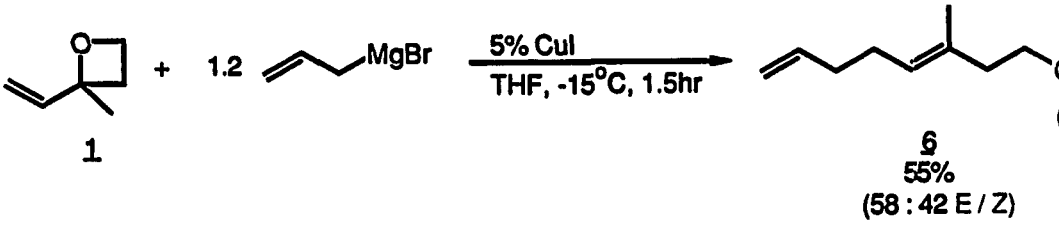
1

5
57%
(68 : 32 E / Z)

(6.9)

isolated in the highest yield when compound 1 was treated with vinylmagnesium bromide and catalytic cuprous iodide. In each of the examples studied, compound 5 was formed regioselectively as a mixture of stereoisomers. The E- and Z-isomer ratio did not seem to depend upon the organocopper reagent used in the reaction.

Compound 1 was also treated with allylmagnesium bromide and a catalytic amount of cuprous iodide (eq. 6.10). The



1

6
55%
(58 : 42 E / Z)

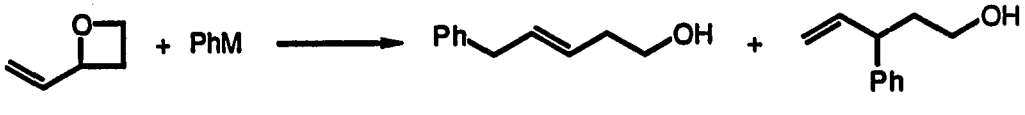
(6.10)

expected homoallylic alcohol was formed regioselectively, but as a mixture of E- and Z-isomers.

The reactions discussed in this section show that compound 1 will react with organocopper reagents to form the corresponding homoallylic alcohols in good yield as a single regioisomer. Unlike the reactions of vinylic epoxides with organocopper reagents, which form allylic alcohols with a high degree of stereoselectivity, the E- to Z-isomer ratios of homoallylic alcohols were generally less than 65:35. When compound 1 was treated with organolithium reagents in the presence of triethylamine, the desired homoallylic alcohols were formed predominantly as the Z-isomer, but the yields of these reactions were sometimes low.

Additions to 3,5-epoxy-1-pentene

The procedure reported by Portnyagin and Pak was used to synthesize compound 7, 3,5-epoxy-1-pentene.[99] The reactions of compound 7 with phenyllithium and various phenylcopper reagents were explored (Table 6.3). The reaction conditions



(6.11)

7

8 (E and Z)

9

Table 6.3. Additions of phenyllithium and phenylcopper reagents to compound 1

Entry	Organometallic reagent	Conditions	% Yield 8 and 9	8/9 Ratio	E/Z Ratio of 8
1	5% CuI, 1.2 PhMgBr	THF, -15°C, 1.5 hr	67	85:15	47:53
2	5% CuI, 1.2 PhLi	THF, -15°C, 1.5 hr	8	-[a]	-
3	1.0 PhLi	2 Et_3N, pentane, 0°C, 50 min; then 25°C, 30 min	41	100:0	28:72
4	1.5 PhLi	3 Et_3N, pentane, 0°C, 50 min; then 25°C, 30 min	59	87:13	77:23
5	2 Ph_2CuLi	ether, -50°C, 1 hr	55	89:11	60:40
6	1.1 $Ph_2CuCNLi_2$	THF, -45°C, 1.5 hr	35	83:17	63:37

[a]The isolated product was a mixture of compounds 8, 9 and

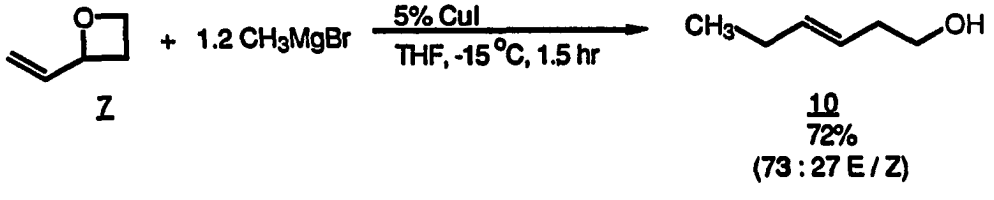
.

used were similar to those shown in equations 6.1-6.4 and Table 6.1. The results summarized in Table 6.3 show that the highest yield of compounds 8 and 9 was obtained when compound 7 was allowed to react with phenylmagnesium bromide in the presence of a catalytic amount of cuprous iodide (see entry 1 in Table 6.3). Unfortunately, compounds 8 and 9 could not be separated by flash column chromatography. Compound 8 was

formed regioselectively, however, when one equivalent of phenyllithium and two equivalents of triethylamine were used in the reaction (see entry 3 in Table 6.3). The other organometallic reagents studied yielded mixtures of regioisomers in approximately the same ratio.

The E-isomer of compound 8 was favored most strongly when compound 7 was treated with 1.5 equivalents of phenyllithium in the presence of three equivalents of triethylamine (see entry 4 in Table 6.3). This result was unexpected because when vinylic epoxides were allowed to react with organolithium reagents in the presence of a base, the Z-isomer of the corresponding allylic alcohol was produced preferentially (see eq. 6.1).[26] As predicted, however, the Z-isomer of compound 8 predominated when compound 7 was treated with one equivalent of phenyllithium and two equivalents of triethylamine (see entry 3 in Table 6.3).

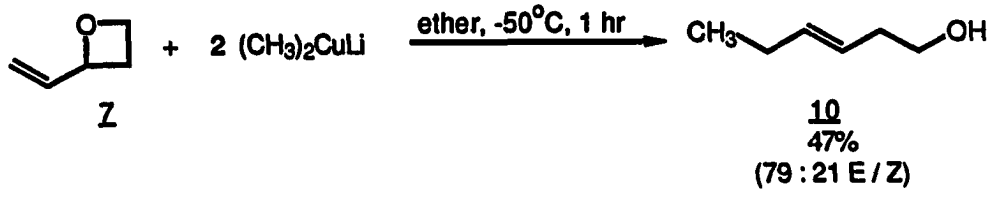
Compound 7 was also allowed to react with various methylcopper reagents (eqs. 6.12 and 6.13). The reactions



7

10
72%
(73 : 27 E / Z)

(6.12)



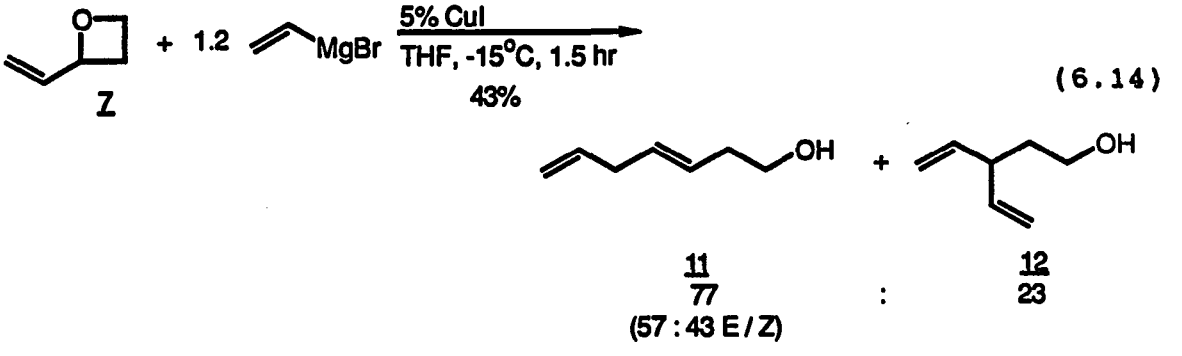
7

10
47%
(79 : 21 E / Z)

(6.13)

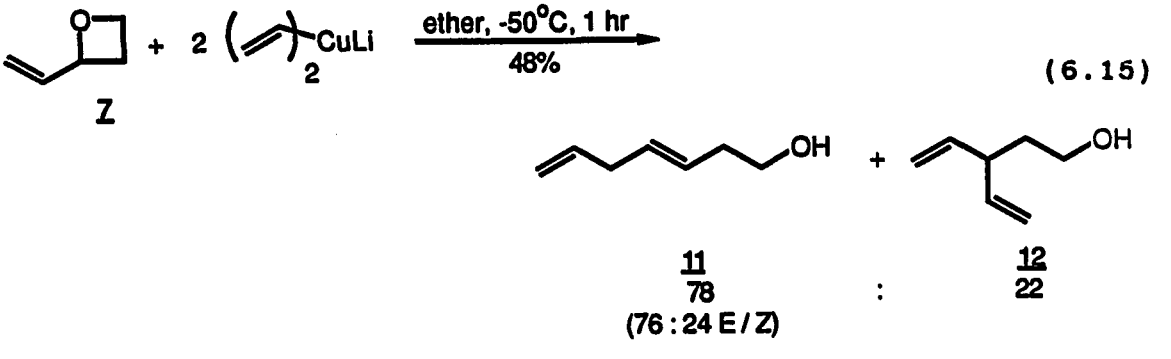
were run using the best conditions observed for the reaction of compound 1 with these reagents (see Table 6.2). Unlike the reactions of compound 7 with phenylcopper reagents (see Table 6.3), the reactions shown in equations 6.12 and 6.13 yielded the corresponding homoallylic alcohol, compound 10, as the sole regioisomer. The highest yield of compound 10 was obtained when compound 7 was treated with methylmagnesium bromide and a catalytic amount of cuprous iodide. However, the E-isomer of compound 10 was more strongly favored when dimethylcopper lithium was used as the organometallic reagent.

The reactions of compound 7 with vinylcopper reagents were also explored (eqs. 6.14 and 6.15). In both of the



(6.14)

11 : 12
77 : 23
(57 : 43 E / Z)

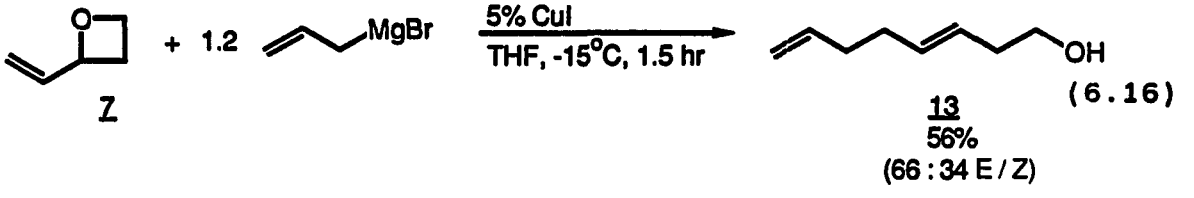


(6.15)

11 : 12
78 : 22
(76 : 24 E / Z)

reactions studied, the ring-opened product was produced as an inseparable mixture of regioisomers. The regioselectivity of the reaction did not seem to depend on which vinylcopper reagent was utilized. However, the yield of compounds 11 and 12 was the greatest and the E-isomer of compound 11 was more strongly favored when compound 7 was treated with divinylcopper lithium.

Compound 7 was also allowed to react with allylmagnesium bromide in the presence of a catalytic amount of cuprous iodide (eq. 6.16). This reaction produced the corresponding



7

13
56%
(66 : 34 E / Z)

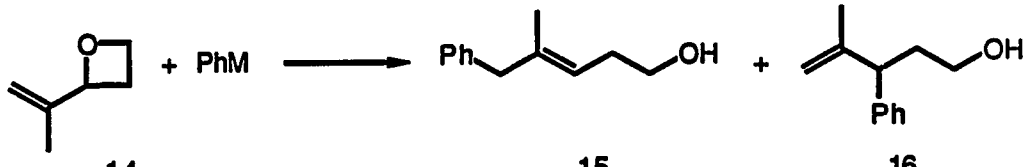
(6.16)

homoallylic alcohol, compound 13, regioselectively but as a mixture of stereoisomers.

The results presented in this section have shown that homoallylic alcohols can be produced regioselectively in modest to good yields when compound 7 was treated with methylcopper or allylcopper reagents. The reactions of compound 7 with phenylcopper or vinylcopper reagents produced inseparable mixtures of regioisomers. In all cases studied, the homoallylic alcohols were formed as mixtures of stereoisomers. Conditions could generally be found for the reaction, however, where the E- to Z-isomer ratio of the corresponding homoallylic alcohol was greater than 75:25.

Additions to 2-methyl-3,5-epoxy-1-pentene

Compound 14, 2-methyl-3,5-epoxy-1-pentene, was synthesized using a procedure similar to the one Portnyagin and Pak reported for the preparation of compound 7.[99] The preparation of compound 14 was discussed in Chapter II (see eq. 2.19). Compound 14 was treated with phenyllithium and various phenylcopper reagents (Table 6.4). The reactions



(6.17)

14 15 (E and Z) 16

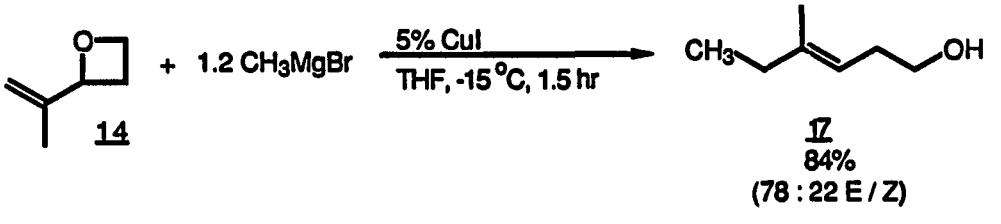
Table 6.4. Additions of phenyllithium and phenylcopper reagents to compound 14

Entry	Organometallic reagent	Conditions	% Yield 15 and 16	15/16 Ratio	E/Z Ratio of 15
1	5% CuI, 1.2 PhMgBr	THF, -15°C, 1.5 hr	67	95:5	84:16
2	1.0 PhLi	2 Et_3N, pentane, 0°C, 50 min; then 25°C, 30 min	58	95:5	75:25
3	1.5 PhLi	3 Et_3N, pentane, 0°C, 50 min; then 25°C, 30 min	20	94:6	77:23
4	2 Ph_2CuLi	ether, -50°C, 1 hr	59	95:5	69:31

were run under conditions similar to those shown in equations 6.1, 6.2 and 6.4. The results illustrated in Table 6.4 show that the highest yield of compounds 15 and 16 was obtained when compound 14 was allowed to react with phenylmagnesium bromide and a catalytic amount of cuprous iodide (see entry 1 in Table 6.4). In all reactions studied, compounds 15 and 16 were isolated as an inseparable mixture. The regioselectivity of the reaction did not seem to depend upon the organometallic reagent used.

The E-isomer of compound 15 most strongly predominated when the reaction was run using phenylmagnesium bromide and a catalytic amount of cuprous iodide (see entry 1 in Table 6.4). The E-isomer of compound 15 was formed preferentially in all of the reactions studied, even if the reaction was run in the presence of phenyllithium and triethylamine (see entries 2 and 3 in Table 6.4). This result was unexpected because when the reactions of organolithium reagents with vinylic epoxides were run in the presence of a base, the Z-isomers of the corresponding allylic alcohols were strongly favored (see eq. 6.1).[26]

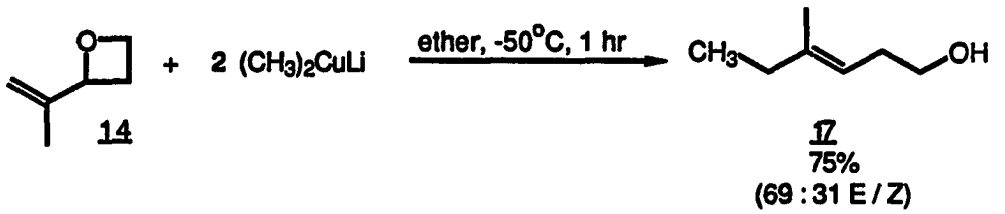
The reactions of compound 14 with methylcopper reagents were also studied (eqs. 6.18 and 6.19). The reactions were



14

17
84%
(78 : 22 E / Z)

(6.18)



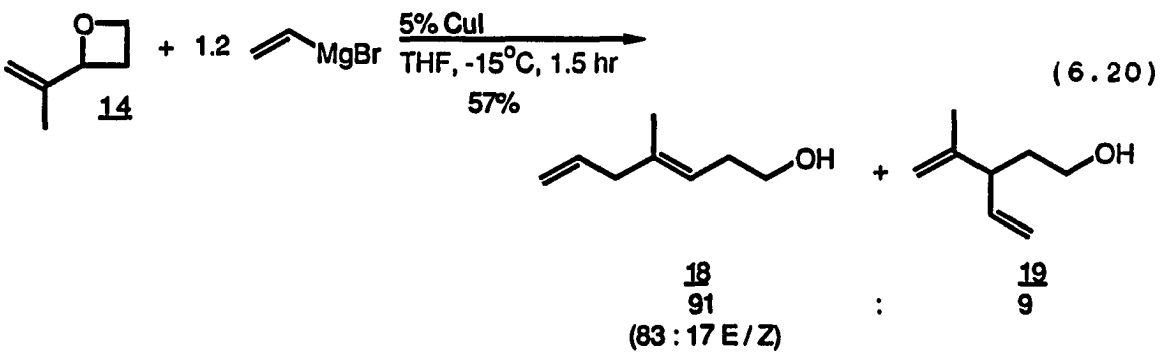
14

17
75%
(69 : 31 E / Z)

(6.19)

run using the best conditions observed for the reaction of compound 1 with these reagents (see Table 6.2). Unlike the previously studied reactions of compound 14 with phenylcopper reagents (see Table 6.4), the reactions shown in equations 6.18 and 6.19 yielded a single regioisomer. Compound 17 was produced in the highest yield with the highest selectivity for the E-isomer, when compound 14 was treated with methylmagnesium bromide and a catalytic amount of cuprous iodide.

Compound 14 was also allowed to react with vinylcopper reagents (eqs. 6.20 and 6.21). An inseparable mixture of



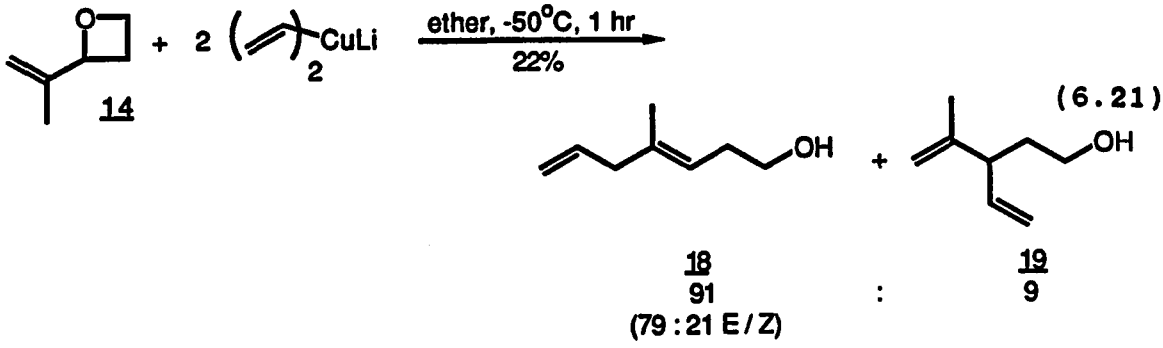
14

18
91
(83 : 17 E / Z)

:

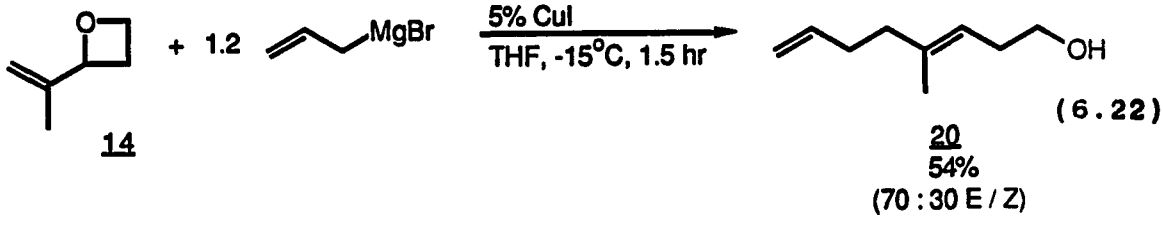
19
9

(6.20)



regioisomers, compounds 18 and 19, was isolated from both of the reactions studied. The ratio of the two regioisomers and E- and Z-isomer ratio of compound 18 did not seem to depend upon which vinylcopper reagent was utilized in the reaction. A higher yield of compounds 18 and 19 was obtained, however, when the reaction was run using vinylmagnesium bromide and a catalytic amount of cuprous iodide.

The reaction of compound 14 with allylmagnesium bromide in the presence of a catalytic amount of cuprous iodide was also studied (eq. 6.22). Compound 20 was synthesized



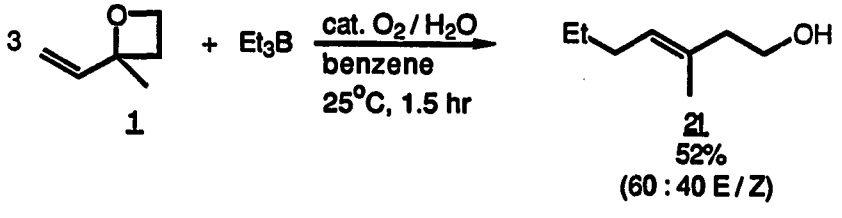
regioselectively as a mixture of stereoisomers when this reaction was run.

The results presented in this section show that homoallylic alcohols can be synthesized in modest to good yields as mixtures of stereoisomers when compound 14 was allowed to react with organolithium and -copper reagents. The

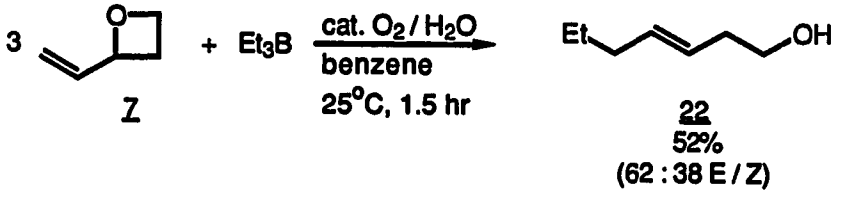
E- to Z-isomer ratio of the homoallylic alcohols formed was generally greater than 70:30. The homoallylic alcohols were produced regioselectively when compound 14 was treated with methylcopper or allylcopper reagents. Mixtures of regioisomers were formed, however, when phenyllithium, phenylcopper or vinylcopper reagents were used in the reaction, although the regioisomeric ratio was always greater than 90:10.

Additions of Organoboron Reagents to Vinylic Oxetanes

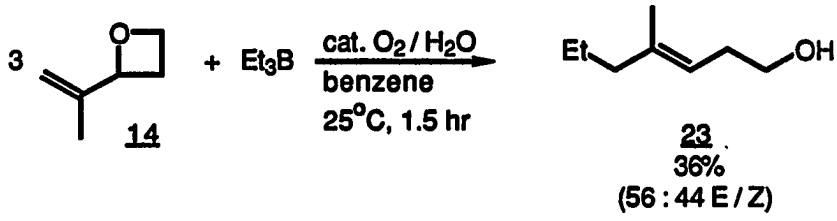
The reactions of compounds 1, 7 and 14 with triethylborane in the presence of oxygen were studied. The reactions were run under conditions similar to those shown in equation 6.5. As one can see from the results illustrated in equations 6.23-6.25, homoallylic alcohols can be prepared



1 → 21, 52% (60 : 40 E / Z) (6.23)



7 → 22, 52% (62 : 38 E / Z) (6.24)



14

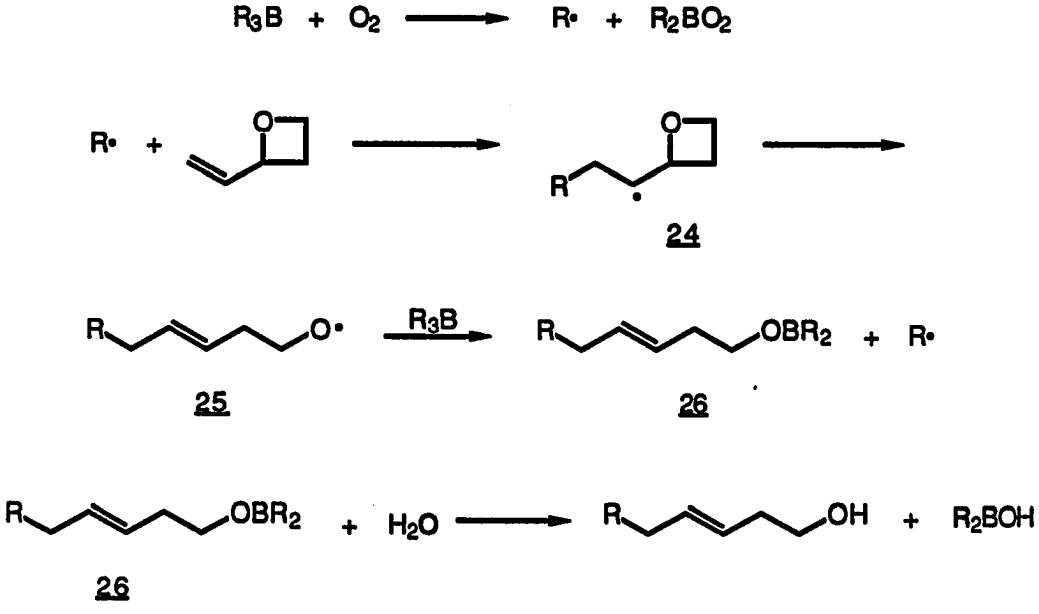
23
36%
(56 : 44 E / Z)

(6.25)

regioselectively in moderate yields when vinylic oxetanes are treated with organoboron reagents and a catalytic amount of oxygen. Unfortunately, these reactions exhibit poor stereoselectivity.

A possible mechanism is shown in Scheme 6.1 which explains how the homoallylic alcohols are formed in these reactions. While no experiments have been run to attempt to

Scheme 6.1



support (or disprove) this mechanism, an analogous mechanism has been proposed to explain how vinylic epoxides react with organoboranes in the presence of a catalytic amount of

oxygen.[53] Trialkylboranes will react with oxygen to generate an alkyl radical. The alkyl radical thus formed adds to the double bond of the vinylic oxetane to yield intermediate radical 24, which then rearranges with opening of the oxetane ring to form intermediate 25. Alkoxy radical 25 reacts with the trialkylborane to yield borinate 26, displacing an alkyl radical which continues the chain. Hydrolysis of the intermediate borinate produces the observed homoallylic alcohol. A free-radical mechanism has been proposed for this reaction because Suzuki and co-workers have reported that the reaction of butadiene monoepoxide with an organoborane will not proceed in the absence of oxygen or in the presence of free-radical scavengers.[53] They have also found that typical free-radical initiators, such as di-t-butylperoxide and azobisisobutyronitrile, as well as oxygen, are effective in promoting the reaction.

Conclusion

It has been shown that homoallylic alcohols can be formed in good yield by allowing vinylic oxetanes to react with various organolithium, -copper and -boron reagents. The reactions are the first observed examples of vinylic oxetanes reacting with these types of organometallic reagents. The reactions of compound 1 form homoallylic alcohols regioselectively. The regioselectivity of the reactions of compounds 7 and 14, however, depends upon the organometallic

reagent used. Unlike the reactions of the corresponding vinylic epoxides, these reactions exhibit only modest stereoselectivity.

Experimental

Spectral data and analysis

All proton and carbon nuclear magnetic resonance spectra were recorded on a Nicolet NT-300 spectrometer at 300 and 75.5 MHz respectively. All infrared spectra were recorded on a Beckmann 4250 spectrophotometer. Exact mass spectral data were recorded on a Kratos MS-50 spectrometer. Elemental analyses were performed by Galbraith Laboratories.

Oxetanes

Compounds 1 and 7 were prepared according to the procedure reported by Portnyagin and Pak.[99] Compound 14 was synthesized by a method similar to the one Portnyagin and Pak used for the preparation of compound 7.[99] The synthesis of compound 14 was discussed in Chapter II.

General procedure for the addition of organomagnesium reagents to vinylic oxetanes in the presence of a catalytic amount of cuprous iodide (procedure A)

A solution of 1.2 equivalents (0.60 mmol) of the appropriate organomagnesium reagent was added slowly to a mixture of 1.0 equivalent (0.50 mmol) of the vinylic oxetane

to be studied and 0.05 equivalents (0.025 mmol) of cuprous iodide in 2 ml of dry THF, maintained at -15°C. The solution was allowed to stir under nitrogen for 1.5 hr at -15°C. The reaction mixture was then hydrolyzed with 1 ml of saturated ammonium chloride. The two layers were separated and the aqueous layer was washed with ether (2 X 5 ml). The combined ether layers were washed with a 17% aqueous ammonium hydroxide solution (1 ml), saturated sodium chloride (1 ml) and dried over anhydrous magnesium sulfate. After removal of the solvents, the residue was purified by flash column chromatography on silica gel.

General procedure for the addition of dialkylcopper lithium reagents to vinylic oxetanes (procedure B)

To a slurry of 2.0 equivalents (1.0 mmol) of cuprous iodide in 2 ml of dry ether, maintained at -50°C, was added 4 equivalents (2.0 mmol) of the appropriate organolithium reagent. The solution was allowed to stir under nitrogen for 15 min at -50°C. Then 1.0 equivalent (0.50 mmol) of the vinylic oxetane to be studied, dissolved in 0.4 ml of ether, was added to the dark brown homocuprate solution. After 1 hr, the reaction was quenched with 5 ml of a 3% aqueous ammonium hydroxide solution, warmed to room temperature and stirred for 20 min. The two layers were separated and the aqueous layer was extracted with ether (2 X 5 ml). The combined ether layers were dried over anhydrous magnesium sulfate. After

removal of the solvents, the residue was purified by flash column chromatography on silica gel.

Spectral data for homoallylic alcohols prepared by the general procedures for the addition of organocopper reagents to vinylic oxetanes

E- and Z-3-Methyl-5-phenyl-3-penten-1-ol (2) Compound 2 was synthesized in 79% yield (66:34 E/Z), when compound 1 was allowed to react with phenylmagnesium bromide and a catalytic amount of cuprous iodide using procedure A.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the alcohol group. The ^{1}H NMR and IR spectra of a mixture of the E- and Z-isomers of compound 2 have previously been reported in the literature.[124] E-isomer: ^{1}H NMR ($CDCl_3$) δ 1.68 (s, 3 H, CH_3), 2.23 (t, 2 H, J = 6.3 Hz, $=CCH_2$), 3.32 (d, 2 H, J = 7.2 Hz, $PhCH_2$), 3.63 (t, 2 H, J = 6.3 Hz, $HOCH_2$), 5.39 (t, 1 H, J = 7.2 Hz, =CH), 6.98-7.30 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 15.9, 34.1, 42.6, 60.4, 126.0, 126.4, 128.2, 128.3, 132.5, 141.2. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ 1.71 (s, 3 H, CH_3), 2.37 (t, 2 H, J = 6.3 Hz, $=CCH_2$), 5.46 (t, 1 H, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ 23.4, 34.3, 35.1, 60.6, 125.8, 126.5, 132.3, 141.3.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3070, 3040

(vinyl, aryl C-H), 2980, 2930, 2890 (aliphatic C-H), 1605, 1495, 1455, 1380, 1050, 735, 700 cm^{-1}; mass spectrum m/e 176.12021 (calculated for $C_{12}H_{16}O$ = 176.12012). Anal. calcd for $C_{12}H_{16}O$: C, 81.81; H, 9.09. Found: C, 78.92; H, 9.19.

E- and Z-3-Methyl-3-hexen-1-ol (4) Compound 4 was prepared in 83% yield (56:44 E/Z), when compound 1 was treated with methylmagnesium bromide and a catalytic amount of cuprous iodide using procedure A. Compound 4 was purified by flash column chromatography on silica gel followed by bulb-to-bulb distillation: bp 56°C/14 mm Hg (lit.[125] bp 63.5-64.5°C/8 mm Hg).

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the alcohol group. The ^1H NMR spectrum of a mixture of the E- and Z-isomers of compound 4 has previously been reported in the literature.[126] E-isomer: ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 7.5 Hz, $CH_2C\underline{H}_3$), 1.61 (s, 3 H, $=CCH_3$), 2.02 (dq, 2 H, J = 6.9 Hz, J = 7.5 Hz, $CH_3C\underline{H}_2$), 2.23 (t, 2 H, J = 6.3 Hz, $=CCH_2$), 3.64 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 5.23 (t, 1 H, J = 6.9 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 14.3, 15.6, 21.3, 42.7, 60.2, 130.0, 130.4. Z-isomer: ^1H NMR ($CDCl_3$) same as the E-isomer except δ 0.93 (t, 3 H, J = 7.5 Hz, $CH_2C\underline{H}_3$), 1.70 (s, 3 H, $=CCH_3$), 2.31 (t, 2 H, J = 6.6 Hz, $=CCH_2$), 5.31 (t, 1 H, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ 14.6, 21.2, 23.4, 35.1, 60.7, 130.6.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 2960, 2930, 2880 (aliphatic C-H), 1465, 1450, 1445, 1435, 1380, 1040, 1005 cm^{-1}; mass spectrum m/e 114.10448 (calculated for $C_7H_{14}O$ = 114.10447).

E- and Z-3-Methyl-3,6-heptadien-1-ol (5) Compound 5 was synthesized in 68% yield (65:35 E/Z), when compound 1 was allowed to react with vinylmagnesium bromide and a catalytic amount of cuprous iodide using procedure A. Compound 5 was purified by flash column chromatography on silica gel followed by bulb-to-bulb distillation: bp 62°C/15 mm Hg.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the vinylic hydrogen. E-isomer: ^1H NMR ($CDCl_3$) δ1.45 (br s, 1 H, OH), 1.63 (s, 3 H, CH_3), 2.27 (t, 2 H, J = 6.3 Hz, $=CCH_2$), 2.77 (dd, 2 H, J = 7.2 Hz, J = 6.3 Hz, $=CHC\underline{H}_2CH=$), 3.67 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 4.95 (dd, 1 H, J = 10.2 Hz, J = 1.8 Hz, $=CH_2$ cis), 5.00 (dd, 1 H, J = 17.1 Hz, J = 1.8 Hz, $=CH_2$ trans), 5.27 (t, 1 H, J = 7.2 Hz, C=CH), 5.78 (ddt, J = 17.1 Hz, J = 10.2 Hz, J = 6.3 Hz, $H_2C=C\underline{H}$); ^{13}C NMR ($CDCl_3$) δ15.8, 32.4, 42.7, 60.3, 114.6, 124.7, 132.7, 136.9. Z-isomer: ^1H NMR ($CDCl_3$) same as the E-isomer except δ1.74 (s, 3 H, CH_3), 2.32 (t, 2 H, J = 6.6 Hz, $=CCH_2$), 5.35 (t, 1 H, J = 7.2 Hz, C=CH), 5.79 (ddt, 1 H, J = 16.8 Hz, J = 10.2 Hz, J = 6.0 Hz, $H_2C=C\underline{H}$); ^{13}C NMR ($CDCl_3$) δ 23.5, 32.2, 35.1, 60.6, 122.2, 125.2, 132.6,

137.4.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3082 (vinyl C-H), 2976, 2935 (aliphatic C-H), 1666, 1637 (C=C), 1433, 1383, 1045, 995, 910, 735 cm^{-1}; mass spectrum m/e 126.10471 (calculated for $C_8H_{14}O$ = 126.10447).

E- and Z-3-Methyl-3,7-octadien-1-ol (6) Compound 6 was synthesized in 55% yield (58:42 E/Z), when compound 1 was allowed to react with allylmagnesium bromide and a catalytic amount of cuprous iodide using procedure A. Compound 6 was purified by flash column chromatography on silica gel followed by bulb-to-bulb distillation: bp 43°C/8 mm Hg (lit.[127] 130°C/22 mm Hg).

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic methyl hydrogens. The ^1H NMR spectrum of a mixture of the E- and Z-isomers of compound 6 has previously been reported in the literature.[127] E-isomer: ^1H NMR ($CDCl_3$) δ 1.51 (br s, 1 H, OH), 1.61 (s, 3 H, CH_3), 2.11 (m, 4 H, $H_2C{=}CHC\underline{H}_2$ and $C{=}CHC\underline{H}_2$), 2.23 (t, 2 H, J = 6.3 Hz, $=CCH_2$), 3.63 (m, 2 H, $HOC\underline{H}_2$), 4.94 (d, 1 H, J = 11.1 Hz, $=CH_2$ cis), 4.99 (d, 1 H, J = 17.4 Hz, $=CH_2$ trans), 5.21 (t, 1 H, J = 7.8 Hz, C=CH), 5.78 (ddt, 1 H, J = 17.4 Hz, J = 11.1 Hz, J = 6.6 Hz, $H_2C{=}C\underline{H}$); ^{13}C NMR ($CDCl_3$) δ 15.8, 27.4, 33.8, 42.6, 60.0, 114.7, 127.6, 131.6, 138.4. Z-isomer: ^1H NMR ($CDCl_3$) same as the E-isomer

except δ1.70 (s, 3 H, CH_3), 2.31 (t, 2 H, J = 6.6 Hz, $=CCH_2$), 5.08 (d, 1 H, J = 11.1 Hz, $=CH_2$ cis), 5.09 (d, 1 H, J = 15.0 Hz, $=CH_2$ trans), 5.30 (t, 1 H, J = 6.0 Hz, C=CH), 5.79 (ddt, 1 H, J = 15.0 Hz, J = 11.1 Hz, J = 6.9 Hz, $H_2C=C\underline{H}$); ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ23.4, 34.1, 35.1, 60.6, 127.2, 131.5, 138.3.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3085 (vinyl C-H), 2970, 2930, 2890 (aliphatic C-H), 1645 (C=C), 1445, 1420, 1385, 1050, 1000, 912, 735 cm^{-1}; mass spectrum m/e 122.10954 (M - H_2O) (calculated for C_9H_{14} = 122.10956).

<u>E- and Z-5-Phenyl-3-penten-1-ol (8) and 3-phenyl-4-penten-1-ol (9)</u> Compounds <u>8</u> and <u>9</u> were synthesized in 67% yield as an inseparable mixture (85:15 <u>8</u>/<u>9</u>), when compound <u>7</u> was allowed to react with phenylmagnesium bromide and a catalytic amount of cuprous iodide using procedure A. Compound <u>8</u> was produced as a mixture of stereoisomers (47:53 E/Z).

The ratio of compound <u>8</u> to compound <u>9</u> was determined by integration of the 300 MHz NMR spectral peaks corresponding to the vinylic hydrogens. The E- and Z-isomer ratio of compound <u>8</u> was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the aryl group. The ^1H NMR spectrum of a mixture of the E- and Z-isomers of compound <u>8</u> has previously been reported in the

literature.[128] The ^{1}H NMR and IR spectra of the E-isomer of compound 8 can also be found in the literature.[129] The E-isomer of compound 8: ^{1}H NMR ($CDCl_3$) δ1.50 (br s, 1 H, OH), 2.33 (dt, 2 H, J = 6.3 Hz, J = 6.6 Hz, $HOCH_2C\underline{H}_2$), 3.36 (d, 2 H, J = 6.6 Hz, $PhCH_2$), 3.65 (t, 2 H, J = 6.6 Hz, $HOC\underline{H}_2$), 5.49 (dt, 1 H, J = 15.0 Hz, J = 6.3 Hz, $HOCH_2CH_2C\underline{H}$=), 5.72 (dt, 1 H, J = 15.0 Hz, J = 6.6 Hz, $PhCH_2C\underline{H}$=), 7.12-7.32 (m, 5 H, Ph). The Z-isomer of compound 8: ^{1}H NMR ($CDCl_3$) same as the E-isomer of compound 8 except δ2.45 (dt, 2 H, J = 6.3 Hz, J = 6.6 Hz, $HOCH_2C\underline{H}_2$), 3.42 (d, 2 H, J = 7.5 Hz, $PhCH_2$), 3.67 (t, 2 H, J = 6.6 Hz, $HOC\underline{H}_2$), cis vinyl protons buried under trans protons. Compound 9: ^{1}H NMR ($CDCl_3$) signals buried under compound 8 except δ2.01 (dt, 2 H, J = 6.0 Hz, J = 6.6 Hz, $HOCH_2C\underline{H}_2$), 3.64 (m, 3 H, $HOC\underline{H}_2$ and PhCH), 5.09 (dd, 1 H, J = 10.2 Hz, J = 1.5 Hz, $=CH_2$ cis), 5.11 (dd, J = 17.1 Hz, J = 1.5 Hz, $=CH_2$ trans), 6.01 (m, 1 H, =CH-).

The following spectral data were taken from a mixture of compounds 8 and 9: ^{13}C NMR ($CDCl_3$) δ30.8, 33.6, 35.8, 37.9, 39.0, 46.1, 60.6, 62.0, 62.1, 114.2, 125.9, 126.2, 127.5, 128.2, 128.3, 128.4, 130.9, 131.9, 140.4, 140.7, 141.7, 143.6, 5 carbons the same or not seen; IR (neat) 3200-3600 (OH), 3080, 3060, 3030 (vinyl, aryl C-H), 2930, 2880 (aliphatic C-H), 1600, 1495, 1455, 1430, 1045, 1030, 970, 910, 735, 695 cm^{-1}. Anal. calcd for $C_{11}H_{14}O$: C, 81.48; H, 8.64. Found: C, 81.01; H, 8.96.

E- and Z-3-Hexen-1-ol (10) Compound 10 was synthesized in 72% yield (73:27 E/Z), when compound 7 was allowed to react with methylmagnesium bromide and a catalytic amount of cuprous iodide using procedure A. Compound 10 was purified by flash column chromatography on silica gel followed by bulb-to-bulb distillation: bp 47°C/12 mm Hg. The E- and Z-isomers of compound 10 can be purchased from Aldrich.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the alcohol group. E-isomer: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 7.5 Hz, CH_3), 2.01 (dq, 2 H, J = 6.9 Hz, J = 7.5 Hz, $CH_3C\underline{H}_2$), 2.23 (dt, 2 H, J = 6.3 Hz, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 3.60 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 5.35 (dt, 1 H, J = 15.3 Hz, J = 6.9 Hz, $CH_3CH_2C\underline{H}$=), 5.57 (dt, 1 H, J = 15.3 Hz, J = 6.3 Hz, $HOCH_2CH_2C\underline{H}$=); ^{13}C NMR ($CDCl_3$) δ 13.8, 25.7, 36.0, 62.1, 124.8, 135.7. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ 0.96 (t, 3 H, J = 7.5 Hz, CH_3), 2.30 (dt, 2 H, J = 6.6 Hz, J = 6.6 Hz, $HOCH_2C\underline{H}_2$), cis vinyl protons buried under trans protons; ^{13}C NMR ($CDCl_3$) δ 14.3, 20.7, 30.8, 62.4, 124.5, 135.1.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3009 (vinyl C-H), 2964, 2933, 2875 (aliphatic C-H), 1639 (C=C), 1462, 1441, 1375, 1186, 1128, 1047, 968, 908, 865 cm^{-1}; mass spectrum m/e 100.08859 (calculated for $C_6H_{12}O$ = 100.08882).

E- and Z-3,6-Heptadien-1-ol (11) and 3-ethenyl-4-penten-1-ol (12) Compounds 11 and 12 were synthesized in 48% yield as an inseparable mixture (78:22 11/12), when compound 7 was treated with divinylcopper lithium using procedure B. Compound 11 was produced as a mixture of stereoisomers (76:24 E/Z). The mixture of compounds 11 and 12 was purified by flash column chromatography on silica gel followed by bulb-to-bulb distillation: bp 48°C/25 mm Hg (lit. bp compound 11[130] 79-82°C/17 mm Hg, bp compound 12[131] 53-56°C/6 mm Hg). Compound 11 has been employed in the synthesis of pseudomonic acids A and C.[132,133] Compound 12 was used to synthesize vitamin D_3.[134]

The ratio of compound 11 to compound 12 and the E- and Z-isomer ratio of compound 11 were determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearest the alcohol group. The ^1H NMR[130,133] and IR[133] spectra of a mixture of the E- and Z-isomers of compound 11 have previously been reported in the literature. The ^1H NMR[135,136] and IR[135] spectra of compound 12 can also be found in the literature. The E-isomer of compound 11: ^1H NMR ($CDCl_3$) δ1.40 (br s, 1 H, OH), 2.28 (dt, 2 H, J = 6.9 Hz, J = 5.7 Hz, $HOCH_2C\underline{H}_2$), 2.77 (dd, 2 H, J = 6.3 Hz, J = 6.3 Hz, $=CHC\underline{H}_2CH=$), 3.70 (m, 2 H, $HOC\underline{H}_2$), 5.02 (dd, 1 H, J = 16.8 Hz, J = 1.8 Hz, $=CH_2$ trans), 5.03 (dd, 1 H, J = 10.5 Hz, J = 1.8 Hz, $=CH_2$ cis), 5.46 (dt, 1 H, J = 15.6 Hz, J = 6.9 Hz,

$HOCH_2CH_2C\underline{H}$=), 5.76 (dt, 1 H, J = 15.6 Hz, J = 6.3 Hz, $HOCH_2CH_2CH{=}C\underline{H}$), 5.81 (ddt, 1 H, J = 16.8 Hz, J = 10.5 Hz, J = 6.3 Hz, $H_2C{=}C\underline{H}$). The Z-isomer of compound 11: ^{1}H NMR ($CDCl_3$) same as the E-isomer of compound 11 except δ 2.33 (dt, 2 H, J = 6.6 Hz, J = 6.9 Hz, $HOCH_2C\underline{H}_2$), 2.82 (dd, 2 H, J = 6.3 Hz, J = 6.3 Hz, $=CHC\underline{H}_2CH=$), 4.98 (dd, 1 H, J = 10.8 Hz, J = 1.5 Hz, $=CH_2$ cis), 4.99 (dd, 1 H, J = 17.1 Hz, J = 1.5 Hz, $=CH_2$ trans), cis vinyl protons buried under trans protons. Compound 12: ^{1}H NMR ($CDCl_3$) signals buried under compound 11 except δ 1.68 (dt, 2 H, J = 6.9 Hz, J = 6.9 Hz, $HOCH_2C\underline{H}_2$), 2.89 (m, 1 H, $=CHC\underline{H}$), 5.07 (m, 4 H, $=CH_2$ cis and trans), 5.71 (ddd, 2 H, J = 17.4 Hz, J = 10.2 Hz, J = 7.5 Hz, =CH-).

The following spectral data were taken from a mixture of compounds 11 and 12: ^{13}C NMR ($CDCl_3$) δ 30.8, 31.6, 36.0, 37.1, 37.8, 44.7, 60.9, 62.1, 62.2, 114.7, 114.8, 115.1, 126.5, 127.2, 130.0, 131.2, 136.7, 136.9, 140.7; IR (neat) 3200-3600 (OH), 3082, 3011 (vinyl C-H), 2935 (aliphatic C-H), 1637 (C=C), 1431, 1047, 995, 970, 910, 735, 648 cm^{-1}; mass spectrum m/e 112.08903 (calculated for $C_7H_{12}O$ = 112.08882).

E- and Z-3,7-Octadien-1-ol (13) Compound 13 was synthesized in 56% yield (66:34 E/Z), when compound 7 was treated with allylmagnesium bromide and a catalytic amount of cuprous iodide using procedure A. Compound 13 was purified by flash column chromatography on silica gel followed by bulb-to-bulb distillation: bp 42°C/16 mm Hg.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearest the alcohol group. E-isomer: ^{1}H NMR ($CDCl_3$) δ1.67 (br s, 1 H, OH), 2.12 (m, 4 H, $H_2C{=}CHC\underline{H}_2$ and $H_2C{=}CHCH_2C\underline{H}_2$), 2.25 (dt, 2 H, J = 6.9 Hz, J = 6.6 Hz, $HOCH_2C\underline{H}_2$), 3.60 (t, 2 H, J = 6.6 Hz, $HOC\underline{H}_2$), 4.96 (dd, 1 H, J = 10.2 Hz, J = 0.6 Hz, $=CH_2$ cis), 4.99 (dd, 1 H, J = 15.3 Hz, J = 0.6 Hz, $=CH_2$ trans), 5.38 (dt, 1 H, J = 15.6 Hz, J = 6.9 Hz, $HOCH_2CH_2C\underline{H}=$), 5.53 (dt, 1 H, J = 15.6 Hz, J = 6.0 Hz, $HOCH_2CH_2CH{=}C\underline{H}$), 5.79 (ddt, 1 H, J = 15.3 Hz, J = 10.2 Hz, J = 5.1 Hz, $H_2C{=}C\underline{H}$); ^{13}C NMR ($CDCl_3$) δ26.8, 33.6, 36.0, 62.0, 114.8, 126.5, 133.3, 138.3. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ1.48 (br s, 1 H, OH), 2.32 (dt, 2 H, J = 6.9 Hz, J = 6.6 Hz, $HOCH_2C\underline{H}_2$), 3.63 (t, 2 H, J = 6.6 Hz, $HOC\underline{H}_2$), 5.01 (dd, 1 H, J = 15.6 Hz, J = 1.5 Hz, $=CH_2$ trans), cis vinyl protons buried under trans protons; ^{13}C NMR ($CDCl_3$) δ30.9, 32.0, 33.8, 62.3, 114.9, 125.7, 132.3. 138.2.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3085, 3010 (vinyl C-H), 2985, 2935, 2850 (aliphatic C-H), 1642 (C=C), 1445, 1435, 1418, 1050, 995, 972, 910, 740 cm^{-1}; mass spectrum m/e 126.10449 (calculated for $C_8H_{14}O$ = 126.10447).

E- and Z-4-Methyl-5-phenyl-3-penten-1-ol (15) and 4-methyl-3-phenyl-4-penten-1-ol (16) Compounds 15 and 16 were synthesized in 67% yield as an inseparable mixture (95:5 15/16), when compound 14 was allowed to react with phenylmagnesium bromide and a catalytic amount of cuprous iodide using procedure A. Compound 15 was produced as a mixture of stereoisomers (84:16 E/Z).

The ratio of compound 15 to compound 16 was determined by integration of the 300 MHz NMR spectral peaks corresponding to the vinylic hydrogens. The E- and Z-isomer ratio of compound 15 was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens next to the aryl group. The E-isomer of compound 15: ^{1}H NMR ($CDCl_3$) δ 1.41 (br s, 1 H, OH), 1.65 (s, 3 H, CH_3), 2.39 (dt, 2 H, J = 7.2 Hz, J = 6.3 Hz, $=CHC\underline{H}_2$), 3.38 (s, 2 H, $PhC\underline{H}_2$), 3.72 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 5.32 (t, 1 H, J = 7.2 Hz, =CH), 7.20-7.37 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ16.0, 31.6, 46.3, 62.3, 121.9, 125.9, 128.2, 128.8, 137.6, 140.0. The Z-isomer of compound 15: ^{1}H NMR ($CDCl_3$) same as the E-isomer of compound 15 except δ 1.72 (s, 3 H, CH_3), 2.51 (dt, 2 H, J = 7.5 Hz, J = 6.6 Hz, $=CHC\underline{H}_2$), 3.47 (s, 2 H, $PhC\underline{H}_2$), 5.38 (t, 1 H, J = 7.5 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 23.5, 31.7, 37.9, 62.5, 122.2, 125.9, 128.3, 128.4, 136.9, 139.8. Compound 16: ^{1}H NMR ($CDCl_3$) signals buried under compound 15 except δ1.61 (s, 3 H, CH_3), 2.17 (dt, 2 H, J = 6.9 Hz, J = 6.9 Hz, $HOCH_2C\underline{H}_2$), 4.92 (s, 1 H,

$=CH_2$), 5.01 (s, 1 H, $=CH_2$); ^{13}C NMR ($CDCl_3$) signals buried under compound 15 or not seen except δ 21.0, 35.7, 48.9, 61.0, 110.4, 126.3, 127.8, 129.1, 139.9.

The following spectral data were taken from a mixture of compounds 15 and 16: IR (neat) 3200-3600 (OH), 3103, 3084, 3062, 3026 (vinyl, aryl C-H), 2914 (aliphatic C-H), 1602, 1495, 1452, 1383, 1336, 1092, 1047, 910, 874, 733, 700 cm^{-1}. Anal. calcd for $C_{12}H_{16}O$: C, 81.81; H, 9.09. Found: C, 81.56; H, 9.11.

E- and Z-4-Methyl-3-hexen-1-ol (17) Compound 17 was synthesized in 84% yield (78:22 E/Z), when compound 14 was treated with methylmagnesium bromide and a catalytic amount of cuprous iodide using procedure A. Compound 17 was purified by flash column chromatography on silica gel followed by bulb-to-bulb distillation: bp 61°C/14 mm Hg (lit.[137] bp 66°C/15 mm Hg). The Z-isomer of compound 17 has been used in the synthesis of cecropia juvenile hormones[138,139] and the pheromone of the pharaoh ant.[140,141]

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic methyl hydrogens. The ^1H NMR,[130,142] ^{13}C NMR[143] and IR[142,144] spectra of a mixture of the E- and Z-isomers of compound 17 have been reported in the literature. The ^1H NMR[138,139,145] and ^{13}C NMR[145] spectra of the Z-isomer of compound 17 can also be found in the literature. E-isomer: ^1H NMR ($CDCl_3$) δ 0.98

(t, 3 H, J = 7.2 Hz, $CH_2\underline{CH}_3$), 1.55 (br s, 1 H, OH), 1.63 (s, 3 H, $=CCH_3$), 2.00 (q, 2 H, J = 7.2 Hz, $CH_3\underline{CH}_2$), 2.28 (dt, 2 H, J = 7.2 Hz, J = 6.3 Hz, $=CHC\underline{H}_2$), 3.60 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 5.10 (t, 1 H, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 12.7, 16.2, 31.6, 32.5, 62.6, 118.4, 140.6. Z-isomer: ^1H NMR ($CDCl_3$) same as the E-isomer except δ 1.70 (s, 3 H, $=CCH_3$), cis vinyl proton buried under trans proton; ^{13}C NMR ($CDCl_3$) δ 12.9, 23.0, 24.9, 31.3, 62.7, 119.6, 140.8.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 2964, 2934 (aliphatic C-H), 1668 (C=C), 1458, 1377, 1263, 1219, 1165, 1117, 1047, 876, 847, 785 cm^{-1}; mass spectrum m/e 114.10427 (calculated for $C_7H_{14}O$ = 114.10447).

<u>E- and Z-4-Methyl-3,6-heptadien-1-ol (18) and 3-ethenyl-4-methyl-4-penten-1-ol (19)</u> Compounds <u>18</u> and <u>19</u> were synthesized in 57% yield as an inseparable mixture (91:9 <u>18</u>/<u>19</u>), when compound <u>14</u> was allowed to react with vinylmagnesium bromide and a catalytic amount of cuprous iodide using procedure A. Compound <u>18</u> was produced as a mixture of stereoisomers (83:17 E/Z). The mixture of compounds <u>18</u> and <u>19</u> was purified by flash column chromatography on silica gel followed by bulb-to-bulb distillation: bp 56°C/20 mm Hg (lit. bp compound <u>18</u>[146] 78-79°C/9 mm Hg).

The ratio of compound <u>18</u> to compound <u>19</u> was determined by

integration of the 300 MHz NMR spectral peaks corresponding to the vinylic hydrogens. The E- and Z-isomer ratio of compound 18 was determined by integration of the 300 MHz NMR spectral peaks corresponding to the doubly allylic hydrogens. The ^{1}H NMR spectra of the E-[146] and Z-isomers[147] of compound 18 have previously been reported in the literature. The E-isomer of compound 18: ^{1}H NMR ($CDCl_3$) δ1.48 (br s, 1 H, OH), 1.65 (s, 3 H, CH_3), 2.29 (dt, 2 H, J = 7.2 Hz, J = 6.3 Hz, C=CHC$\underline{H}_2$), 2.74 (d, 2 H, J = 6.9 Hz, =CHC$\underline{H}_2$C=), 3.62 (t, 2 H, J = 6.3 Hz, HOC$\underline{H}_2$), 5.01 (dd, 1 H, J = 10.2 Hz, J = 1.5 Hz, $=CH_2$ cis), 5.02 (dd, 1 H, J = 16.8 Hz, J = 1.5 Hz, $=CH_2$ trans), 5.17 (t, 1 H, J = 7.2 Hz, C=CH), 5.77 (ddt, 1 H, J = 16.8 Hz, J = 10.2 Hz, J = 6.9 Hz, H_2C=C$\underline{H}$). The Z-isomer of compound 18: ^{1}H NMR ($CDCl_3$) same as the E-isomer of compound 18 except δ1.70 (s, 3 H, CH_3), 2.78 (d, 2 H, J = 6.6 Hz, =CHC$\underline{H}_2$C=), cis vinyl protons buried under trans protons. Compound 19: ^{1}H NMR ($CDCl_3$) signals buried under compound 18 except δ1.69 (s, 3 H, CH_3), 2.84 (m, 2 H, =CHC$\underline{H}$C=), 4.77 (s, 1 H, $C=CH_2$), 4.78 (s, 1 H, $C=CH_2$).

The following spectral data were taken from a mixture of compounds 18 and 19: ^{13}C NMR ($CDCl_3$) δ16.3, 20.0, 23.6, 31.5, 31.7, 35.2, 36.5, 37.2, 44.2, 48.1, 61.3, 62.5, 110.8, 114.9, 115.4, 115.9, 120.9, 135.9, 136.6, 136.7, 137.1, 140.7, 2 carbons the same or not seen; IR (neat) 3200-3600 (OH), 3078 (vinyl C-H), 2918 (aliphatic C-H), 1637 (C=C), 1433, 1383,

1047, 995, 912, 874, 654 cm^{-1}; mass spectrum m/e 126.10476 (calculated for $C_8H_{14}O$ = 126.10447).

E- and Z-4-Methyl-3,7-octadien-1-ol (20) Compound 20 was synthesized in 54% yield (70:30 E/Z), when compound 14 was allowed to react with allylmagnesium bromide and a catalytic amount of cuprous iodide using procedure A. Compound 20 was purified by flash column chromatography on silica gel followed by bulb-to-bulb distillation: bp 53°C/9 mm Hg.

The E- and Z-isomer ratio of compound 20 was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic methyl hydrogens. E-isomer: ^1H NMR ($CDCl_3$) δ 1.48 (br s, 1 H, OH), 1.63 (s, 3 H, CH_3), 2.13 (m, 4 H, $H_2C{=}CHC\underline{H}_2$ and $=CCH_2$), 2.27 (dt, 2 H, J = 6.9 Hz, J = 6.3 Hz, $C{=}CHC\underline{H}_2$), 3.60 (m, 2 H, $HOC\underline{H}_2$), 4.94 (dd, 1 H, J = 10.5 Hz, J = 1.8 Hz, $=CH_2$ cis), 4.99 (dd, 1 H, J = 16.8 Hz, J = 1.8 Hz, $=CH_2$ trans), 5.12 (t, 1 H, J = 6.9 Hz, C=CH), 5.78 (ddt, 1 H, J = 16.8 Hz, J = 10.5 Hz, J = 6.6 Hz, $H_2C{=}C\underline{H}$); ^{13}C NMR ($CDCl_3$) δ 16.1, 31.5, 32.2, 39.1, 62.3, 114.5, 120.3, 138.0, 138.5. Z-isomer: ^1H NMR ($CDCl_3$) same as the E-isomer except δ 1.71 (s, 3 H, CH_3), 5.00 (d, 1 H, J = 16.8 Hz, $=CH_2$ trans), 5.02 (d, 1 H, J = 9.0 Hz, $=CH_2$ cis), 5.14 (t, 1 H, J = 6.9 Hz, C=CH); ^{13}C NMR ($CDCl_3$) δ 23.4, 31.4, 31.6, 35.5, 62.5, 114.6, 115.6, 121.1, 138.4

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3075 (vinyl

C-H), 2960, 2925, 2870 (aliphatic C-H), 1635 (C=C), 1445, 1410, 1375, 1040, 990, 905, 730 cm^{-1}; mass spectrum m/e 122.10965 (M - H_2O) (calculated for C_9H_{14} = 122.10956).

General procedure for the addition of triethylborane to vinylic oxetanes

A 25 ml round bottom flask equipped with a side arm inlet containing a rubber septum was fitted with a condenser and magnetic stir bar and flushed with nitrogen. To the flask was added sequentially 1 ml of dry benzene, 1 ml of a 1 M solution of triethylborane in hexanes (1 mmol) and 3 equivalents of the vinylic oxetane to be studied (3 mmol). The mixture was vigorously stirred at 25°C as air was passed into the flask at the rate of 1 ml/min through a syringe needle placed through the rubber septum to a point just above the reaction mixture. After 1.5 hr, 0.3 ml of 3 N sodium hydroxide was added followed by the gradual addition of 0.3 ml of 30% hydrogen peroxide. The mixture was stirred an additional hour at room temperature. The solution was diluted with 25 ml of ether. The reaction mixture was washed with a saturated ferrous sulfate solution (3 x 5 ml), saturated sodium chloride (2 x 5 ml) and dried over anhydrous magnesium sulfate.

Spectral data for homoallyic alcohols prepared by the general procedure for the addition of triethylborane to vinylic oxetanes

E- and Z-3-Methyl-3-hepten-1-ol (21) Compound 21 was prepared in 52% yield (60:40 E/Z), when compound 1 was treated with triethylborane using the general addition procedure. Compound 21 was purified by flash column chromatography on silica gel followed by bulb-to-bulb distillation: bp 67°C/15 mm Hg.

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the alcohol group. E-isomer: ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 7.5 Hz, $CH_2C\underline{H}_3$), 1.34 (tq, 2 H, J = 7.2 Hz, J = 7.5 Hz, $CH_3C\underline{H}_2$), 1.50 (br s, 1 H, OH), 1.60 (s, 3 H, $=CCH_3$), 1.97 (dt, 2 H, J = 7.2 Hz, J = 7.2 Hz, $=CHC\underline{H}_2$), 2.24 (t, 2 H, J = 6.0 Hz, $=CCH_2$), 3.63 (m, 2 H, $HOC\underline{H}_2$), 5.22 (t, 1 H, J = 7.2 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ 13.8, 15.8, 22.9, 30.1, 42.7, 60.2, 128.6, 131.2. Z-isomer: ^{1}H NMR ($CDCl_3$) same as the E-isomer except δ1.69 (s, 3 H, $=CCH_3$), 2.30 (t, 2 H, J = 6.6 Hz, $=CCH_2$), 5.30 (t, 1 H, J = 6.9 Hz, =CH); ^{13}C NMR ($CDCl_3$) same as the E-isomer or not seen except δ 23.2, 23.4, 30.1, 35.1, 60.7, 128.1.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 2970, 2935, 2880 (aliphatic C-H), 1472, 1465, 1457, 1448, 1382, 1045,

1010, 735 cm^{-1}; mass spectrum m/e 128.11990 (calculated for $C_8H_{16}O$ = 128.12012).

E- and Z-3-Hepten-1-ol (22) Compound 22 was synthesized in 52% yield (62:38 E/Z), when compound 7 was allowed to react with triethylborane using the general addition procedure. Compound 22 was purified by flash column chromatography on silica gel followed by bulb-to-bulb distillation: bp 62°C/15 mm Hg (lit.[148] bp 64.5-65°C/8 mm Hg). Compound 22 has been employed in the synthesis of gephyrotoxin-223AB.[149]

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic hydrogens nearer the alcohol group. The ^1H NMR and IR spectra of the Z-isomer of compound 22 have previously been reported in the literature.[150] E-isomer: ^1H NMR ($CDCl_3$) δ 0.87 (t, 3 H, J = 7.5 Hz, CH_3), 1.36 (tq, 2 H, J = 7.2 Hz, J = 7.5 Hz, $CH_3C\underline{H}_2$), 1.63 (br s, 1 H, OH), 1.97 (dt, 2 H, J = 6.6 Hz, J = 7.2 Hz, $CH_3CH_2C\underline{H}_2$), 2.25 (dt, 2 H, J = 6.9 Hz, J = 6.3 Hz, $HOCH_2C\underline{H}_2$), 3.60 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 5.36 (dt, 1 H, J = 15.3 Hz, J = 6.6 Hz, $CH_3CH_2CH_2C\underline{H}$=), 5.52 (dt, 1 H, J = 15.3 Hz, J = 6.9 Hz, $HOCH_2CH_2C\underline{H}$=); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.6, 30.8, 36.0, 62.1, 125.9, 134.0. Z-isomer: ^1H NMR ($CDCl_3$) same as the E-isomer except δ 0.90 (t, 3 H, J = 7.5 Hz, CH_3), 1.84 (br s, 1 H, OH), 2.02 (dt, 2 H, J = 7.2 Hz, J = 7.2 Hz, $CH_3CH_2C\underline{H}_2$), 2.31 (dt, 2 H, J = 7.2 Hz, J = 6.6 Hz, $HOCH_2C\underline{H}_2$),

3.61 (t, 2 H, J = 6.6 Hz, $HOC\underline{H}_2$), cis vinyl protons buried under trans protons; ^{13}C NMR ($CDCl_3$) δ13.8, 22.9, 29.4, 34.8, 62.4, 125.2, 133.2.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 3020 (vinyl C-H), 2970, 2940, 2885 (aliphatic C-H), 1475, 1470, 1460, 1440, 1385, 1055, 978, 740 cm^{-1}; mass spectrum m/e 114.10421 (calculated for $C_7H_{14}O$ = 114.10447).

E- and Z-4-Methyl-3-hepten-1-ol (23) Compound 23 was prepared in 36% yield (56:44 E/Z), when compound 14 was treated with triethylborane using the general addition procedure. Compound 23 was purified by flash column chromatography on silica gel followed by bulb-to-bulb distillation: bp 62°C/15 mm Hg (lit.[151] bp 52°C/1.2 mm Hg).

The E- and Z-isomer ratio was determined by integration of the 300 MHz NMR spectral peaks corresponding to the allylic methyl hydrogens. The ^1H NMR, ^{13}C NMR and IR spectra of the E-[152] and Z-isomers[152,153] of compound 23 have previously been reported in the literature. E-isomer: ^1H NMR ($CDCl_3$) δ 0.85 (t, 3 H, J = 6.9 Hz, $CH_2C\underline{H}_3$), 1.40 (m, 2 H, $CH_3C\underline{H}_2$), 1.53 (br s, 1 H, OH), 1.61 (s, 3 H, $=CCH_3$), 1.97 (t, 2 H, J = 7.5 Hz, $=CCH_2$), 2.28 (dt, 2 H, J = 6.9 Hz, J = 6.3 Hz, $=CHC\underline{H}_2$), 3.60 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), 5.11 (t, 1 H, J = 6.9 Hz, =CH); ^{13}C NMR ($CDCl_3$) δ14.0, 16.1, 21.0, 31.6, 42,0, 62.6, 120.5, 138.9. Z-isomer: ^1H NMR ($CDCl_3$) same as the E-isomer except

δ0.88 (t, 3 H, J = 7.8 Hz, $CH_2C\underline{H}_3$), 1.69 (s, 3 H, $=CCH_3$), 2.01 (t, 2 H, J = 7.5 Hz, $=CCH_2$), 3.59 (t, 2 H, J = 6.3 Hz, $HOC\underline{H}_2$), cis vinyl proton buried under trans proton; ^{13}C NMR ($CDCl_3$) δ13.7, 21.3, 23.5, 31.5, 34.0, 62.7, 119.7, 139.1.

The following spectral data were taken from a mixture of the E- and Z-isomers: IR (neat) 3200-3600 (OH), 2965, 2940, 2880 (aliphatic C-H), 1472, 1465, 1457, 1435, 1380, 1050, 1020, 740 cm^{-1}; mass spectrum m/e 128.11987 (calculated for $C_8H_{16}O$ = 128.12012).

CONCLUSION

The results discussed in this dissertation have shown that homoallylic alcohols can be prepared in high yields when vinylic oxetanes are allowed to react with organometallic reagents. No such reactions of vinylic oxetanes have previously been reported in the literature. The reactions of vinylic oxetanes with carbon nucleophiles in the presence of a palladium(0) catalyst form di- and trisubstituted homoallylic alcohols regio- and stereoselectively. The additions of aryl- and vinylpalladium species to vinylic oxetanes produce homoallylic alcohols regioselectively as mixtures of E- and Z-isomers. Finally, the reactions of vinylic oxetanes with organolithium, -copper and -boron reagents yield mixtures of E- and Z-homoallylic alcohols.

The palladium(0)-catalyzed nucleophilic ring-opening of substituted vinylic epoxides has also been explored. These reactions produce trisubstituted allylic alcohols as mixtures of stereoisomers. Conditions have been found for this reaction, however, where either the E- or Z-isomer of the corresponding allylic alcohol can be formed preferentially.

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