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# Palladium(II) organic synthetic methodology

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# Palladium(II) organic synthetic methodology

by

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# DEDICATION

I would like to dedicate this accomplishment to my family, the Greens and most of all Pooter and Bubba Bridgman.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| aq | Aqueous |
| Ar | Aryl |
| br | Broad |
| Bu | Butyl |
| d | Doublet |
| DBN | 1,5-Diazabicyclo[4.3.0]non-5-ene |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| dd | Doublet of doublets |
| ddd | Double doublet of doublets |
| DDQ | 2,3-Dichloro-5,6-dicyanoquinone |
| ddt | Double doublet of triplets |
| DMA | *N,N*-Dimethylacetamide |
| DMF | *N,N*-Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| DPPE | 1,2-bis(Diphenylphosphino)ethane |
| dt | Doublet of triplets |
| eq | Equation |
| equiv. | Equivalents |
| Et | Ethyl |
| g | Grams |
| GC | Gas chromatography |
| HMPA | Hexamethylphosphoramide |
| HRMS | High resolution mass spectrometry |

| | |
|---|---|
| IR | Infrared |
| LAH | Lithium aluminum hydride |
| LDA | Lithium diisopropylamide |
| M | Molar |
| m | Multiplet |
| mg | Milligrams |
| mL | Milliliters |
| mol | Moles |
| mmol | Millimoles |
| m/z | Mass to charge ratio |
| NMR | Nuclear magnetic resonance |
| Ph | Phenyl |
| Pr | Propyl |
| rt | Room temperature |
| q | Quartet |
| s | Singlet |
| t | Triplet |
| TBAF | tetra-*n*-Butylammonium fluoride |
| TBDMS | *t*-Butyldimethylsilyl |
| Tf | Trifluoromethanesulfonyl |
| THF | Tetrahydrofuran |
| TIPS | Triisopropylsilyl |
| TLC | Thin layer chromatography |
| TMS | Trimethylsilyl |
| Ts | *p*-Tolylsulfonyl |

# GENERAL INTRODUCTION

The development of new synthetic methodology utilizing palladium is one of the most exciting areas in organic chemistry today. Recently, a wide variety of palladium-assisted organic reactions have been developed and applied to organic synthesis. These findings have inspired us to develop new palladium-catalyzed methods directed towards the synthesis of functionalized organic compounds. These methods are briefly discussed below.

The research in each paper of this dissertation involves palladium(II)-based organic synthetic methodology. The primary focus of Paper One is the palladium(II)-catalyzed cyclization of alkenoic acids to unsaturated lactones. Existing methods for this synthetic transformation have a variety of shortcomings, one of which is the toxicity of the metals other than palladium used as catalysts. This improved procedure eliminates this hazard, and affords the unsaturated lactones in excellent yields.

The focus of Paper Two is the development of a palladium(II)-catalyzed process for the cyclization of N-substituted olefinic amines. Previous palladium(II)-based approaches have required the use of stoichiometric amounts of palladium or an additional reoxidant other than oxygen if catalytic amounts of palladium are used. This improved method, which eliminates the need for additional reoxidants other than oxygen, allows for the cyclization of olefinic tosylamides in moderate to

excellent yields. In some instances these conditions yield a totally different product than previously reported cyclizations of the same substrate.

The focus of Paper Three is development of the palladium(II)-catalyzed cyclization of 2-allylphenol. Previous palladium(II)-catalyzed cyclizations of this compound have always provided the five-membered ring product, 2-methylbenzofuran, as the only product. Here we have developed a unique set of conditions which allow the exclusive formation of the six-membered ring benzopyran in 41% yield.

In the final paper of this dissertation, we have developed a unique set of conditions which allow for the formation of α,β-unsaturated carbonyl systems from their corresponding enol silyl derivatives. Other palladium(II)-based methodologies for this conversion require a stoichiometric amount of palladium or, if the reaction utilizes only catalytic amounts of palladium, additional reoxidants are needed along with an oxygen atmosphere. Our improved procedure requires no additional reoxidants, other than oxygen, to reoxidize Pd(0) formed *in situ* back to Pd(II). These new reaction conditions allow for the formation of α,β-unsaturated carbonyl systems in moderate to excellent yields.

## Explanation of Dissertation Format

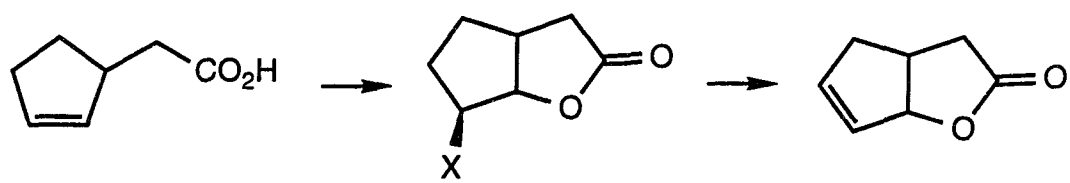
This dissertation consists of four papers, each paper suitable for publication, along with a General Summary following the papers. The doctoral candidate was primarily responsible for the research and writing of these papers.

# PAPER I. THE PALLADIUM(II)-CATALYZED INTRAMOLECULAR CYCLIZATION OF ALKENOIC ACIDS

# INTRODUCTION

The cyclization of alkenoic acids to unsaturated lactones is a very valuable synthetic transformation most commonly effected by two step processes involving either halolactonization-dehydrohalogenation[1] (Scheme 1; X = Br, I),

Scheme 1

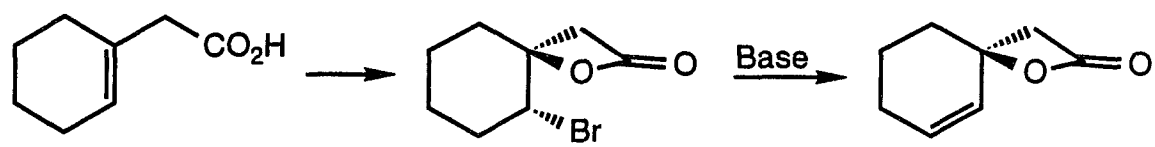



selenolactonization-selenoxide elimination[1c,1d,1g,2] (Scheme 1; X = SeR) or sulfenolactonization-sulfoxide elimination (Scheme 1; X = SR).[2b,2g,3] In order to understand the concept of these reactions, these procedures are examined in more detail.

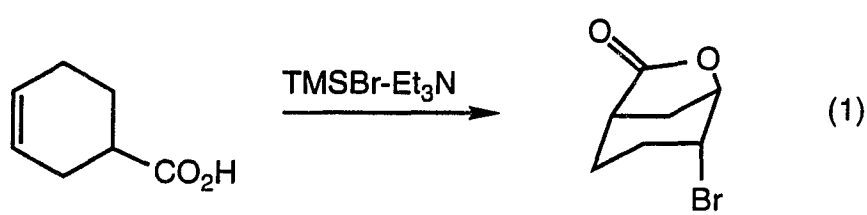
The bromolactonization of unsaturated acids originated from the work of Fittig and Stobbe as early as the late 1800's.[4] Since that time, there have been several publications which have incorporated lactonization using bromine or a bromine equivalent.[5] For example, bromolactonization of 1-cyclohexeneacetic acid has provided the corresponding β-bromospirolactone (Scheme 2) using either 3-bromo-

5-isobutyl-5-methylhydantoin, 3-bromo-5,5-dimethylhydantoin, N-bromophthalimide, 1,3-dibromo-5,5-dimethylhydantoin, N-bromosuccinimide, or $Br_2$.[5a-5c,5g-5j] These β-bromolactones can be easily converted to the unsaturated lactone with the addition of a base to initiate an E2 elimination (Scheme 2).

Scheme 2



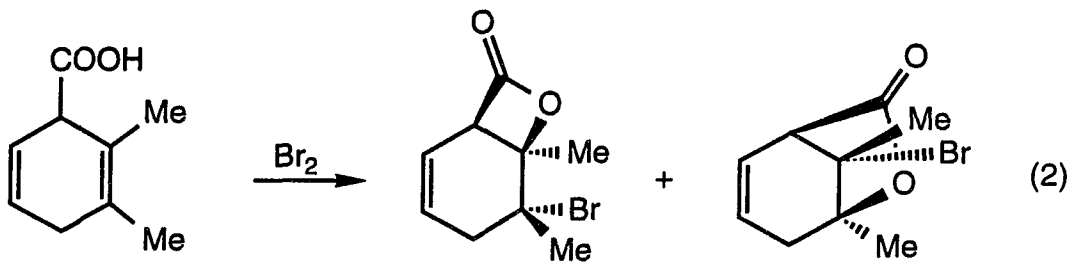

A novel bromolactonization procedure using a DMSO-trimethylsilyl bromide-amine system developed by Iwata and co-workers has also shown great success in the formation of bromolactones.[5e] For example, 3-cyclohexenecarboxylic acid yields the following bicyclic lactone in 70% yield (eq 1).



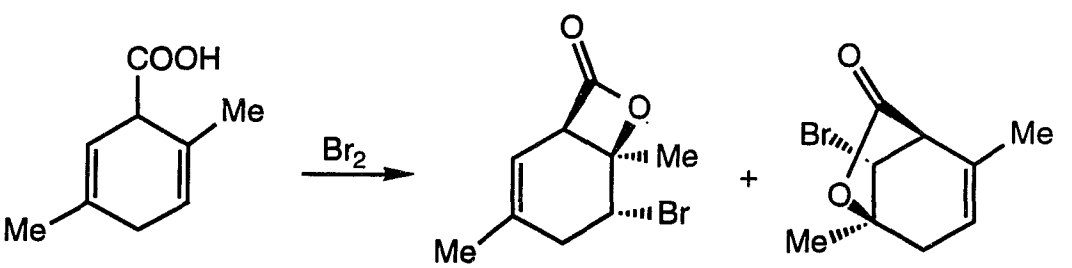

(1)

Barnett and Needham have reported the effect that methyl substituents have in directing the bromolactonization of 1,4-dihydrobenzoic acids.[6] Cyclization onto the more substituted carbon demonstrates that intermediate bromonium ions have a

greater degree of carbonium ion character at the more substituted carbon atoms (eqs 2 and 3).




(2)

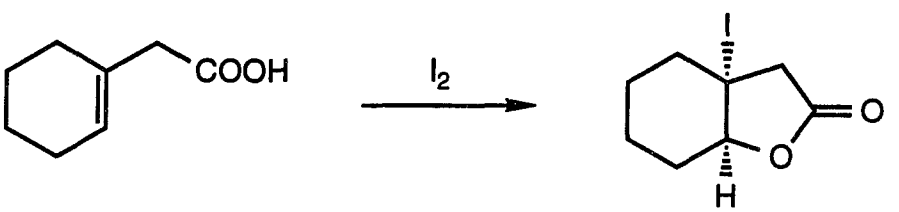



(3)

There have been several other examples reported in the literature of the cyclization of additional alkenoic acids using these bromolactonization methodologies.[5,6]

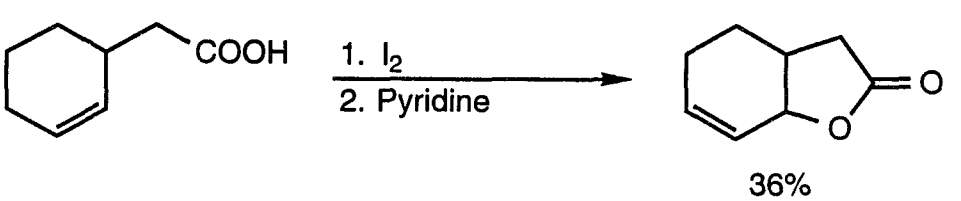
Iodolactonization, which appears to be the more accepted of the two halolactonization methods has also proven quite successful. The conversion of β,γ- or γ,δ-unsaturated acids to iodolactones was first developed by Bougault.[1j-m] His general procedure involved dissolving unsaturated acids in aqueous sodium bicarbonate, followed by treatment of the resultant solution with a mixture of iodine in aqueous potassium iodide which allows the iodolactone to separate from the

reaction medium. Bougault was able to cyclize 1-cyclohexeneacetic acid to provide the 5-membered ring lactone using this procedure (eq 4), whereas bromolactonization has provided the 4-membered ring spirolactone (Scheme 2). By manipulation of the reaction conditions, iodolactonization of 1-cyclohexeneacetic acid has been shown to provide the 4-membered ring spirolactone as well.[1i] This result implies that choosing the appropriate conditions and not the difference in halogens is the reason for the different regioselectivity.




(4)

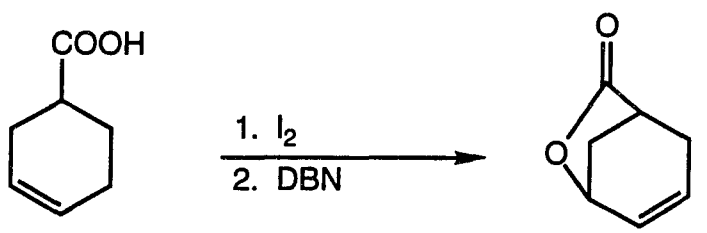
As in the case of bromolactonization, dehydrohalogenation of the intermediate iodolactone can also be effected by subjecting the iodolactone to an appropriate base. In 1959, Klein reported that the iodolactonization-dehydroiodination of 2-cyclohexeneacetic acid affords the unsaturated lactone in 36% yield (eq 5).[1a]




36%

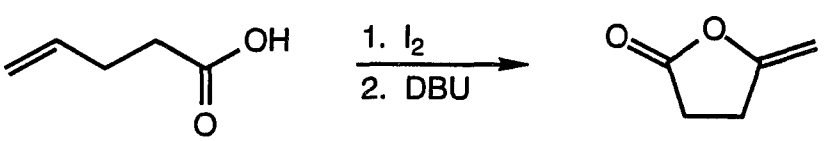
(5)

As part of an enantioconvergent approach to prostanoid synthesis developed by Trost, 3-cyclohexenecarboxylic acid was converted via iodolactonization to the unsaturated lactone (eq 6).[7]



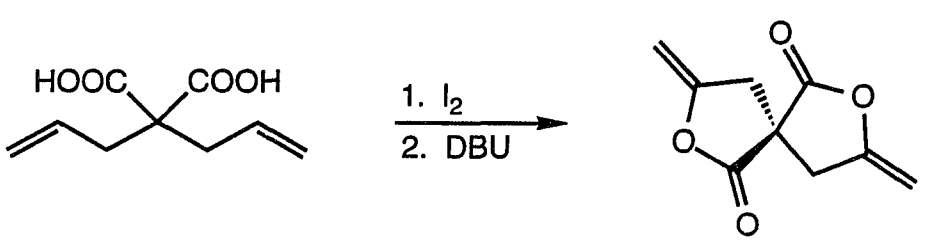

(6)

Jager and Gunther have synthesized γ-methylene-butyrolactones from 4-pentenoic acids via iodolactonization-dehydroiodination, by subjecting the intermediate iodolactone to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (eq 7).[8]



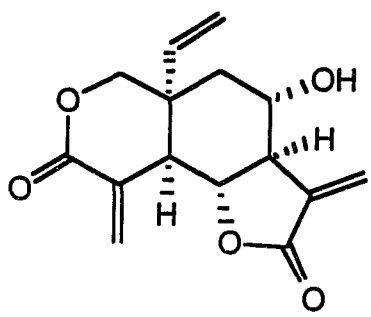

(7)

The following spiro-bis-γ-methylenebutyrolactone has been prepared in a similar fashion from the corresponding dicarboxylic acid (eq 8).[8]

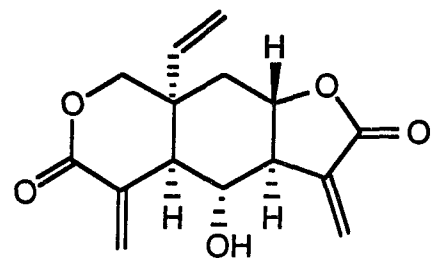



(8)

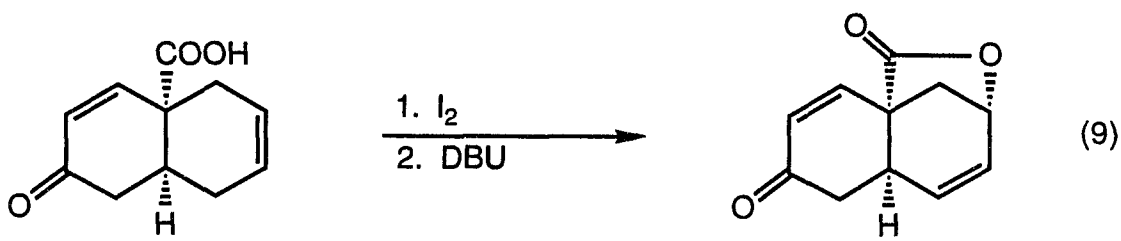
The process of iodolactonization followed by dehydroiodination was successfully employed in the total synthesis of the tumour inhibitors (±)-vernolepin and (±)-vernomenin. These syntheses involved preparation of the corresponding acid and its' conversion to the iodolactone, followed by treatment with DBU, smoothly affording the dienone lactone required for the synthesis of these tumour inhibitors (eq 9).[9]



vernolepin



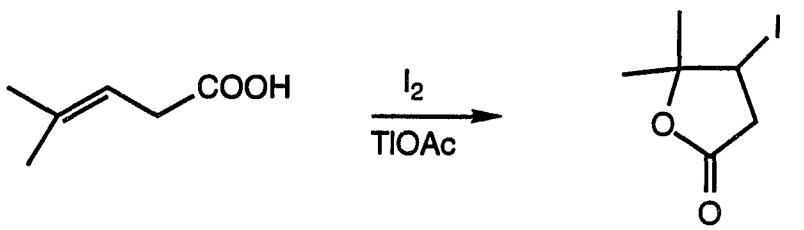
vernomenin




(9)

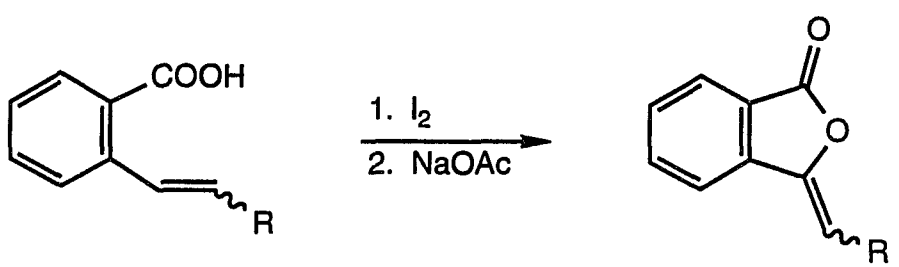
A convenient procedure for iodolactonization under neutral conditions was developed by Cambie and co-workers in which iodine was added to an unsaturated thallium(I) carboxylate in ether at 20°C.[10] The products formed using these

conditions are those of predominantly kinetic control. The following example illustrates the use of Cambie's procedure (eq 10).



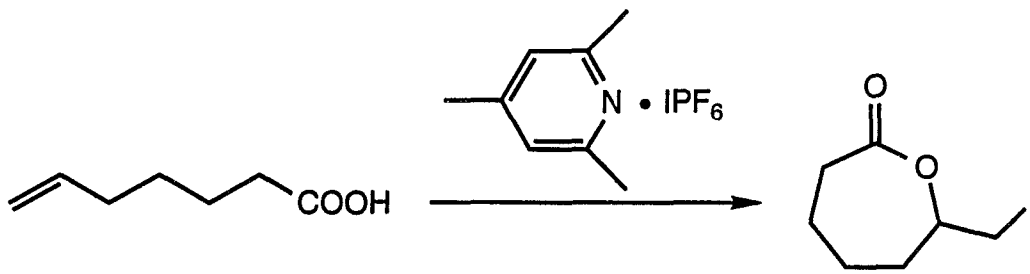

(10)

Mali and co-workers have used iodolactonization as a pathway in their synthesis of naturally-occurring 3-alkylidenephthalides.[11] The strategy involved consists of exposing 2-(1-alkenyl)benzoic acids to iodolactonization-dehydroiodination conditions (eq 11).




(11)

More recently, Simont and Rousseau have reported an iodolactonization procedure which allows for the formation of 7-, 8-, 9-, 10- and 11-membered ring iodolactones. For example, the 7-membered ring iodolactone was formed in 76% yield (eq 12).[12]



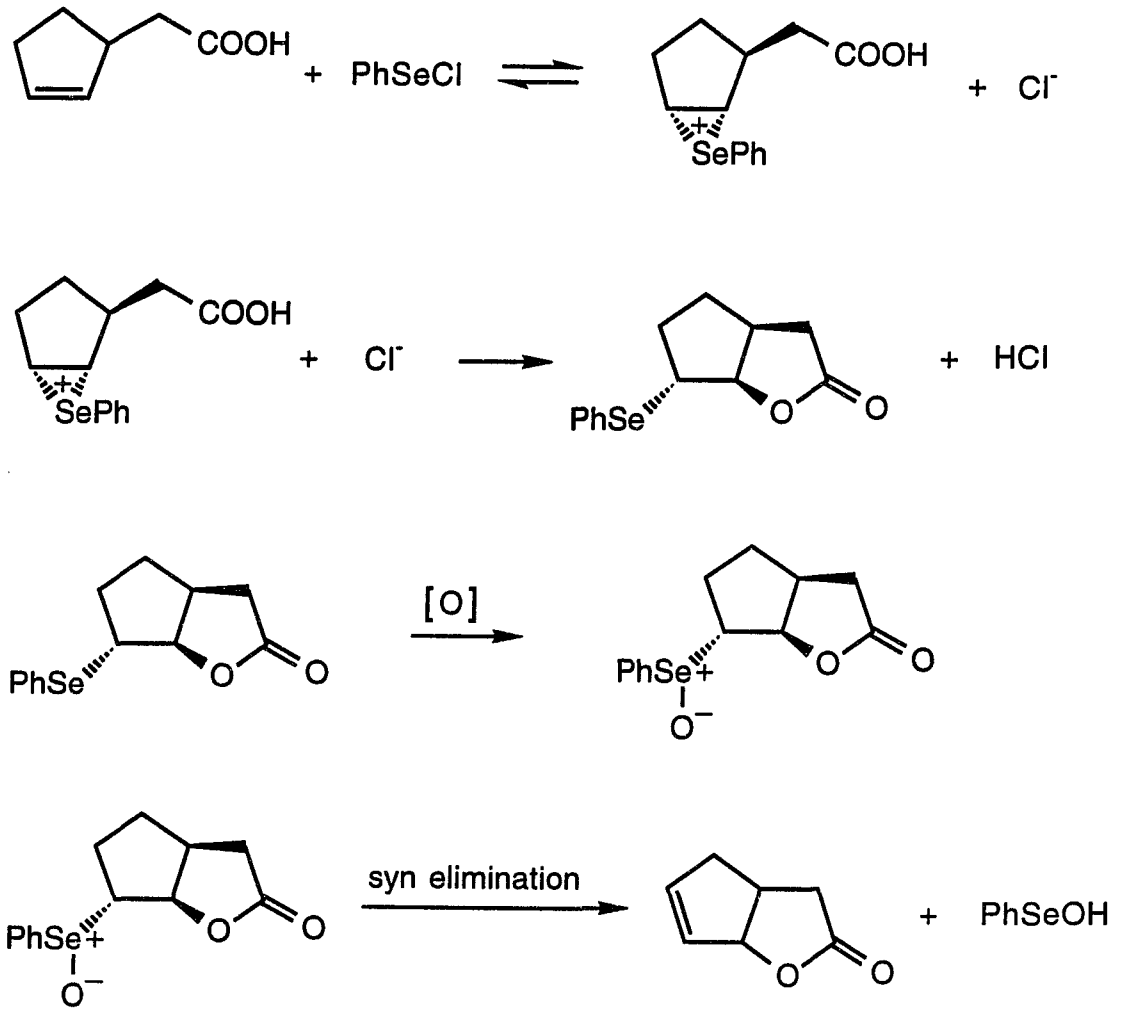

(12)

As mentioned previously, another electrophilic lactonization tool developed has been that of selenolactonization, as well as sulfenolactonization.[2b] Since selenolactonization is the most widely used method of the two, focus will be given to this process. The first reagent to be used in connection with selenolactonization was the commercially available phenylselenenyl chloride.[2d] Since this finding, a number of other selenium reagents have also been used, such as phenylselenenyl bromide, N-phenylselenophthalimide, N-phenylselenosuccinimide and phenylselenenic acid.[2d]

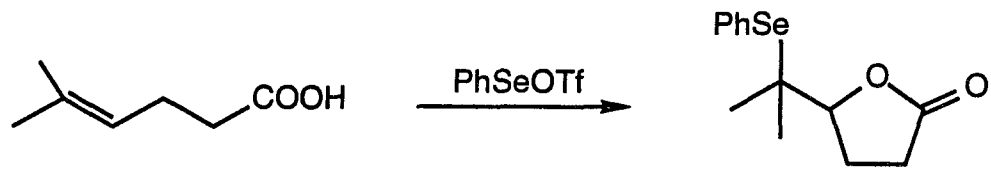
The proposed mechanism involved in the formation of unsaturated lactones via selenolactonization-oxidation of alkenoic acids is shown in Scheme 3.

The initial step of this facile cyclization is presumed to be the reversible electrophilic addition of the phenylselenonium ion to the double bond of the alkenoic acid, leading to the reactive electron deficient intermediate. This intermediate subsequently undergoes an intramolecular attack by the nucleophile, furnishing the observed phenylselenolactone. Elimination occurs upon subjecting this product to an oxidizing agent, yielding the desired unsaturated lactone. A number of alkenoic acids have been cyclized using this methodology.[2b,2d,2n,2m,2q]

Scheme 3

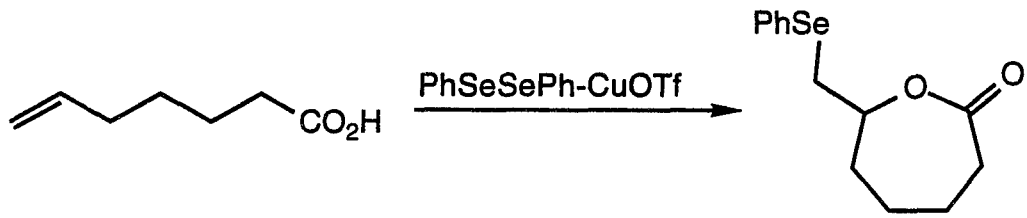

COOH
+ PhSeCl
COOH
SePh
+ Cl⁻
COOH
SePh
+ Cl⁻
PhSe
O
O
+ HCl
PhSe
O
O
[O]
PhSe+
O⁻
O
O
PhSe+
O⁻
O
O
syn elimination
O
O
+ PhSeOH

Murata and Suzuki developed the superelectrophilic benzeneselenenyl triflate to promote selenolactonization.[2n] For example, 5-methyl-4-hexenoic acid was cyclized to provide only the 5-membered ring selenolactone (eq 13).



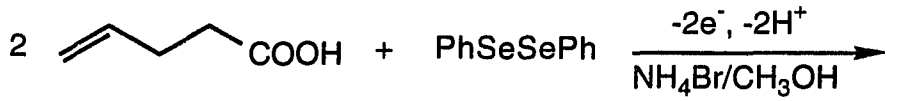

(13)

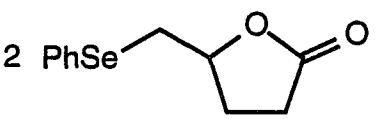
In 1991, Miyachi and co-workers developed a binary reagent PhSeSePh-CuOTf as a useful phenylselenylating agent.[2q] Through this methodology, 6-heptenoic acid was cyclized to the 7-membered ring phenylselenolactone in 37% yield (eq 14).




(14)

Konstantinovic, Vukicevic and Mihailovic have performed phenylselenolactonization in one step by electrolysis of unsaturated carboxylic acids and diphenyl diselenide in methanol containing ammonium bromide (eq 15).[2m]

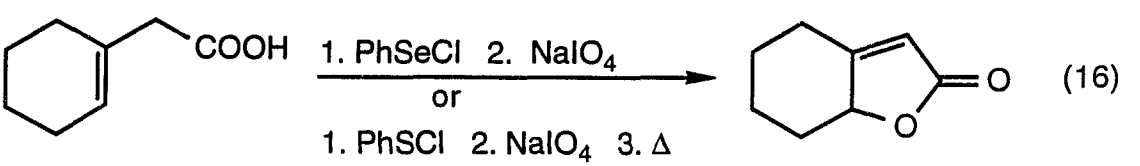



(15)

In general with selenolactonization, the ring closure occurs at the carbon able to sustain the most carbonium ion character, although subsequent rearrangements are possible. It also appears that 5-membered ring lactones are preferred over the corresponding 4- and 6-membered ring lactones and the 7-membered ring lactone is preferred over the corresponding 8-membered ring lactone.[2d]

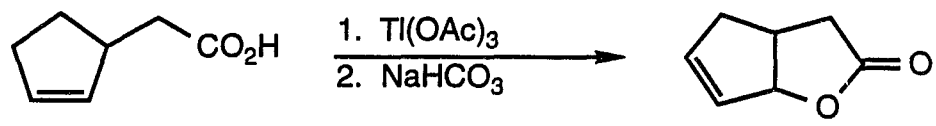
Nicolaou and co-workers have shown that phenylsulfenolactonization accomplishes similar results as phenylselenolactonization toward the formation of unsaturated lactones.[2b] Cyclization of 1-cyclohexeneacetic acid via either phenylseleno- or phenylsulfenolactonization provides the same unsaturated lactone in comparable yields (eq 16).




(16)

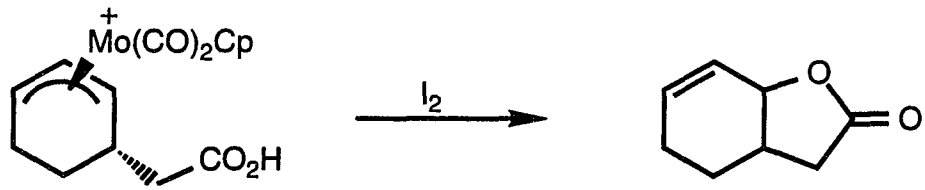
There are several other miscellaneous methods for synthesizing unsaturated lactones. Listed below are just a few of those methods.

Ferraz and Ribeiro have synthesized the following lactone via thallium-induced intramolecular cyclization of 2-cyclopenteneacetic acid (eq 17).[13]




(17)

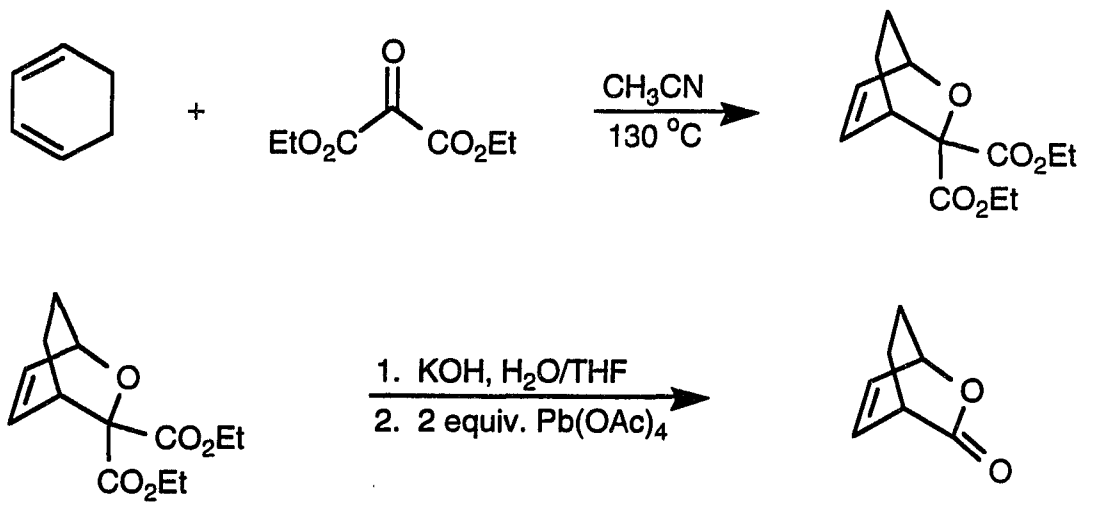
Pearson and co-workers have reported the use of organomolybdenum complexes as a cyclization mediator in the cyclization of alkenoic acids (eq 18).[14]




(18)

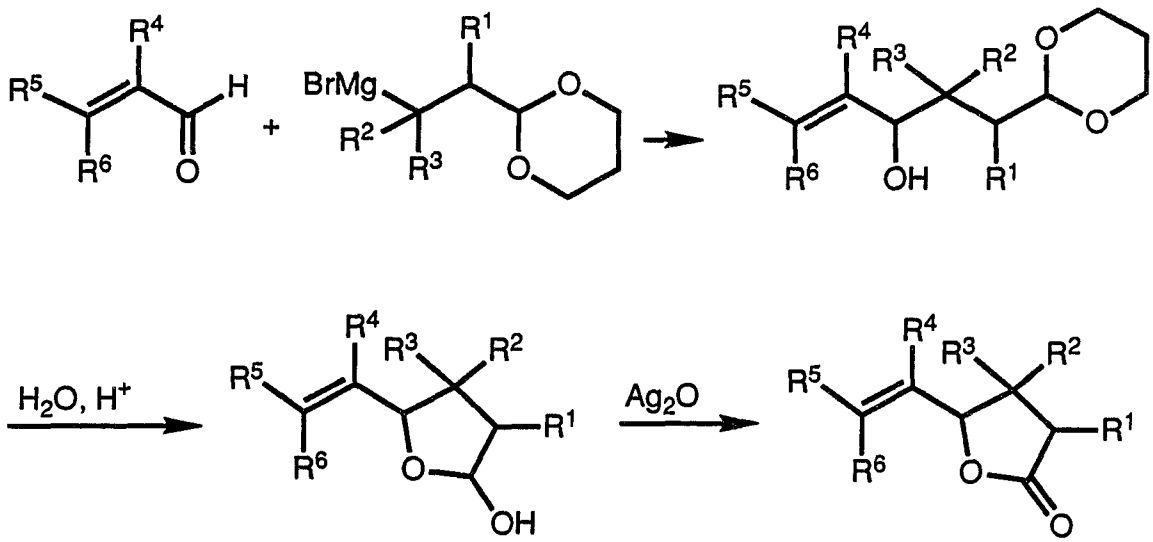
Bonjouklian and Ruden have reported the use of Diels-Alder adducts as intermediates in the synthesis of unsaturated lactones (Scheme 4).[15]

Scheme 4



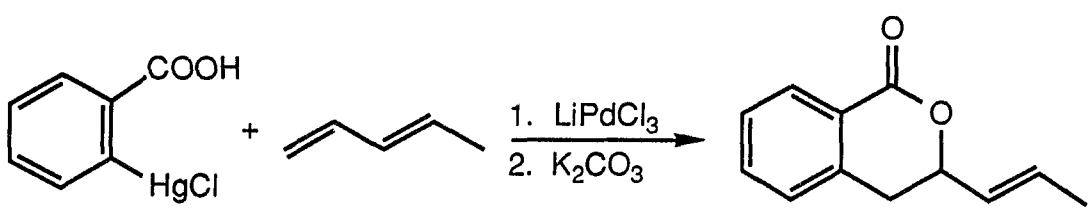

Kawashima and Fujisawa have developed a synthetic method for the preparation of γ-alkenyl-γ-butyrolactones through the use of α,β-unsaturated aldehydes (Scheme 5).[16]

Scheme 5



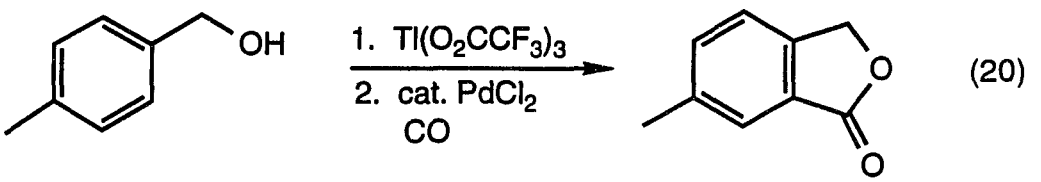

There have also been several approaches to the synthesis of lactones via palladium catalysis.[17-27]

Larock and co-workers have reported that conjugated or nonconjugated dienes or vinylcyclopropanes react with $LiPdCl_3$ and organomercurials bearing a carboxylic acid, phenol, or alcohol functionality to generate π-allylpalladium compounds.[17] Upon the addition of an appropriate base, these intermediates readily undergo intramolecular nucleophilic displacement of palladium by oxygen to give a wide variety of oxygen heterocycles (eq 19).




(19)

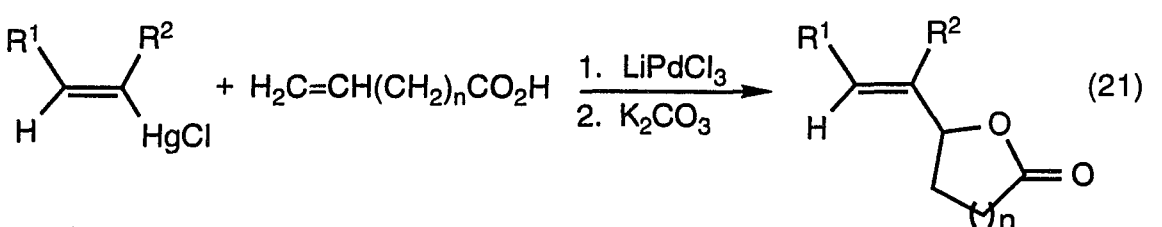
Thallated compounds have also been exploited in the synthesis of heterocyclic products (eq 20).[18] The mechanism of this reaction involves an initial




(20)

transmetallation of the ortho-thallated intermediate by palladium, followed by CO insertion into the arylpalladium bond. Displacement of this acylpalladium species by the alcohol nucleophile provides the lactone product. In this displacement step, Pd(0) is formed only to be reoxidized to Pd(II) by the thallium(III) salt present after transmetallation. Thus, this process requires only a catalytic amount of palladium(II) salts.

Larock and co-workers have also used a similar approach for the synthesis of vinylic 5- and 6-membered ring lactones via transmetallation of organomercurials (eq. 21).[19]

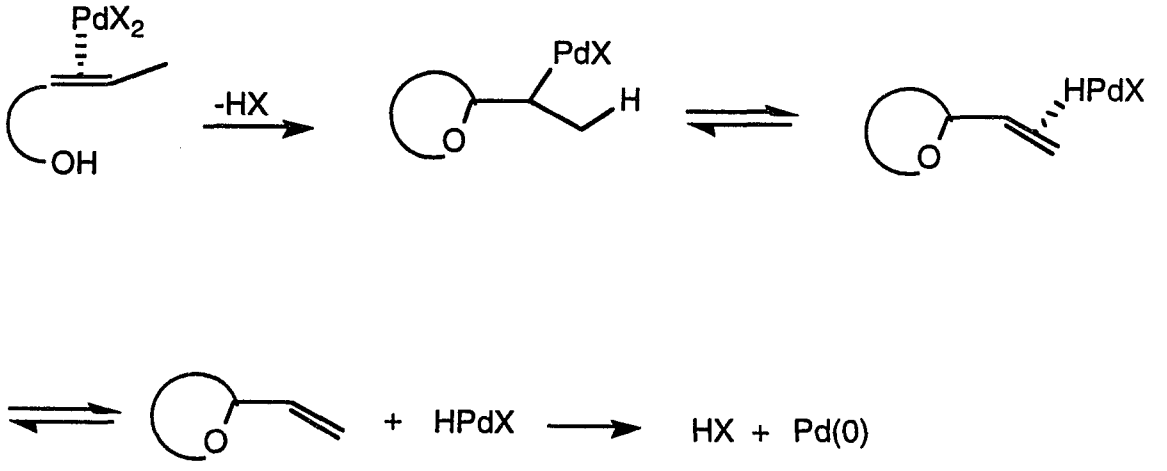



(21)

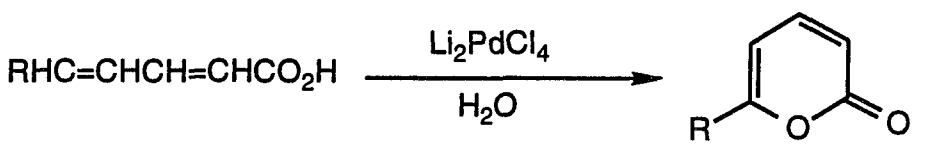
n = 1,2

The fundamental chemistry of palladium(II) can be seen in the oxidation of alkenes by $PdX_2$ (X = Cl or OAc). Izumi and Kasahara have used nucleophiles, such as OH and OAc, which first attack olefins coordinated to the metal, forming a sigma-bonded Pd(II)-intermediate.[20] Subsequent β-hydride elimination of HPdX leads to the final products, and the reductive elimination of the resulting HPdX to give Pd(0) and HX. Intramolecular versions of this reaction become a useful entry to oxygen-containing heterocycles (Scheme 6).[21]

Scheme 6

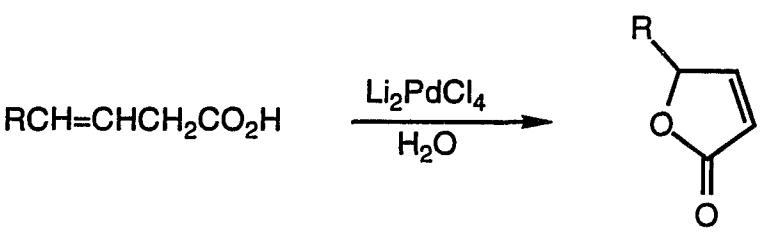


Izumi and Kasahara have employed the reaction of sodium salts of penta-2,4-dienoic acids with lithium chloropalladate in polar solvents, such as water, to form 2-pyrone derivatives (eq 22).[20]

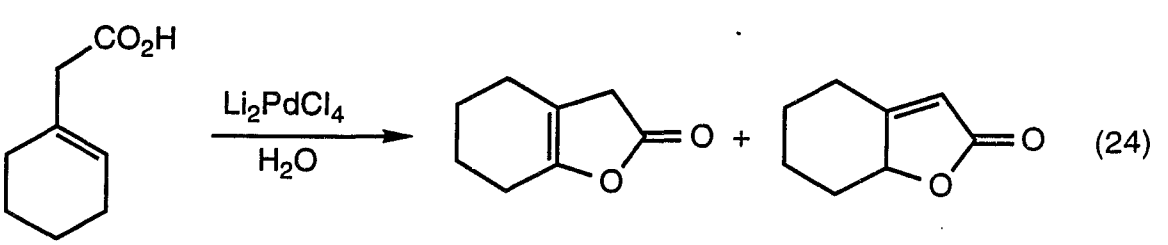



(22)

Kasahara and co-workers have also utilized the reaction of sodium salts of 3- and 4-alkenoic acids with dilithium tetrachloropalladate(II) to prepare an array of butenolide products in low yields (eqs 23 and 24).[22]

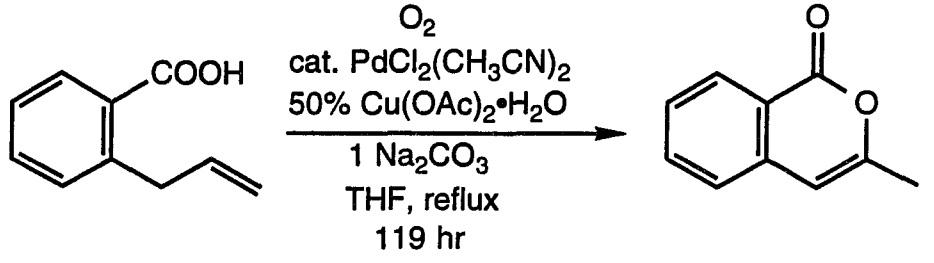



(23)

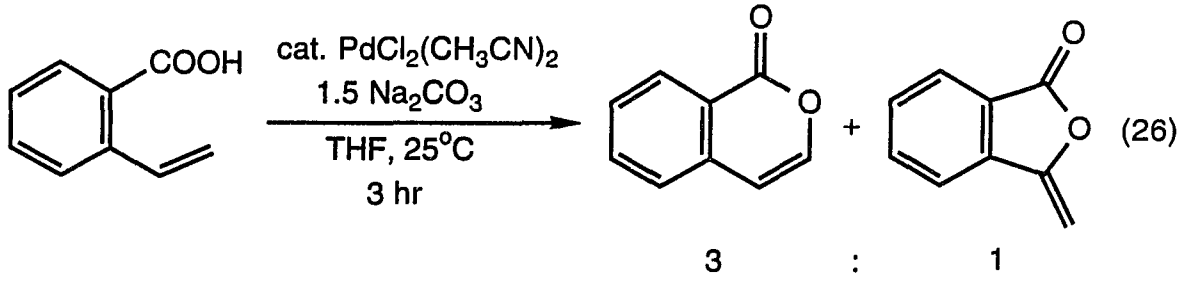



(24)

Hegedus and co-workers have synthesized isocoumarins, phthalides, dihydroisocoumarins and isoquinolines via palladium chloride cyclizations.[23] This reaction involves once again an oxypalladation process (eqs 25 and 26).



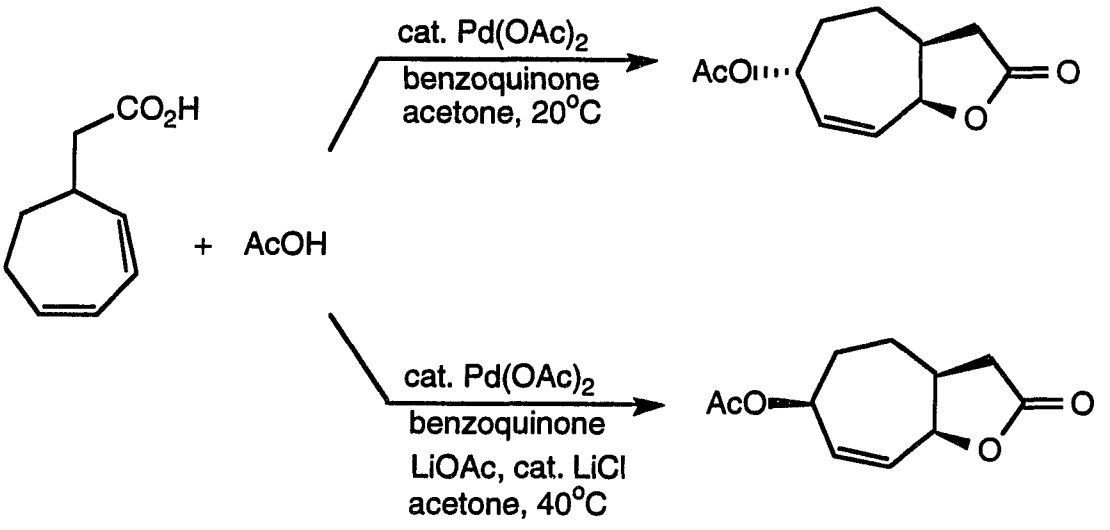

(25)



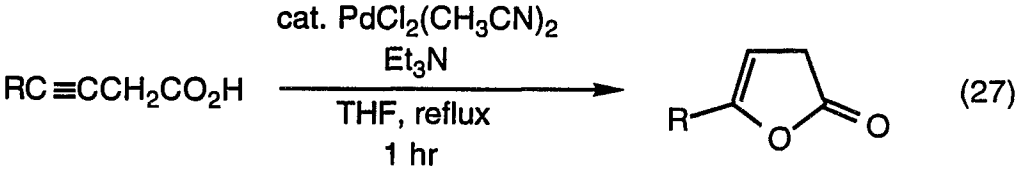

(26)

Bäckvall and co-workers have transformed dienes into γ-lactones via a novel stereocontrolled palladium-catalyzed lactonization reaction involving the formation of a π-allylpalladium intermediate (Scheme 7).[24]

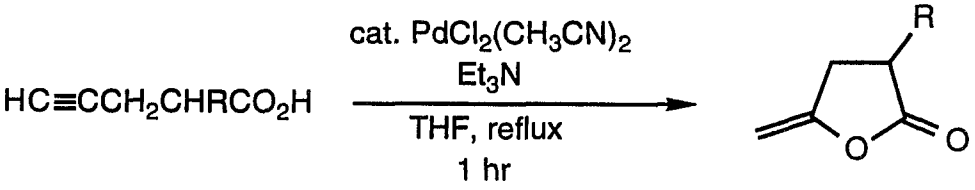
Scheme 7



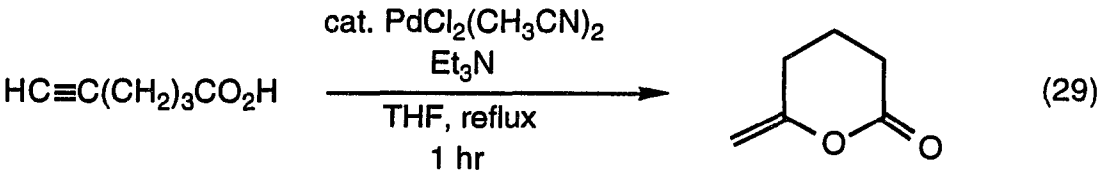

Lambert and co-workers have utilized the catalytic action of palladium(II) and the presence of triethylamine to cyclize 3-, 4- and 5-alkynoic acids to 3-buten-4-olides, 4-penten-4-olides and 5-hexen-5-olides respectively (eqs 27-29).[25]




(27)



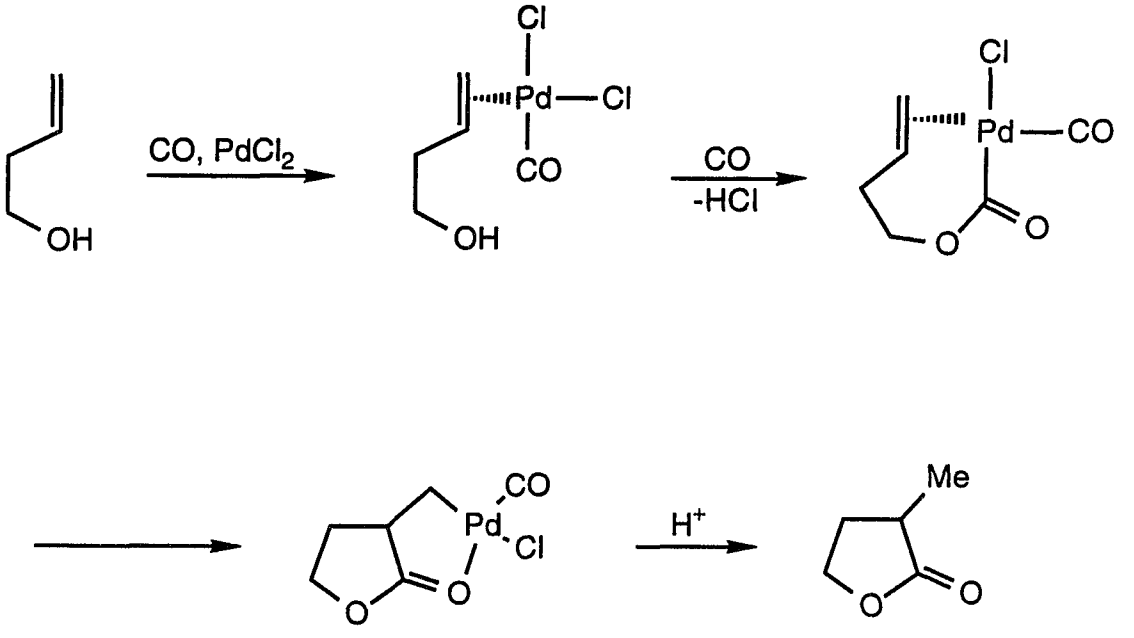

(28)




(29)

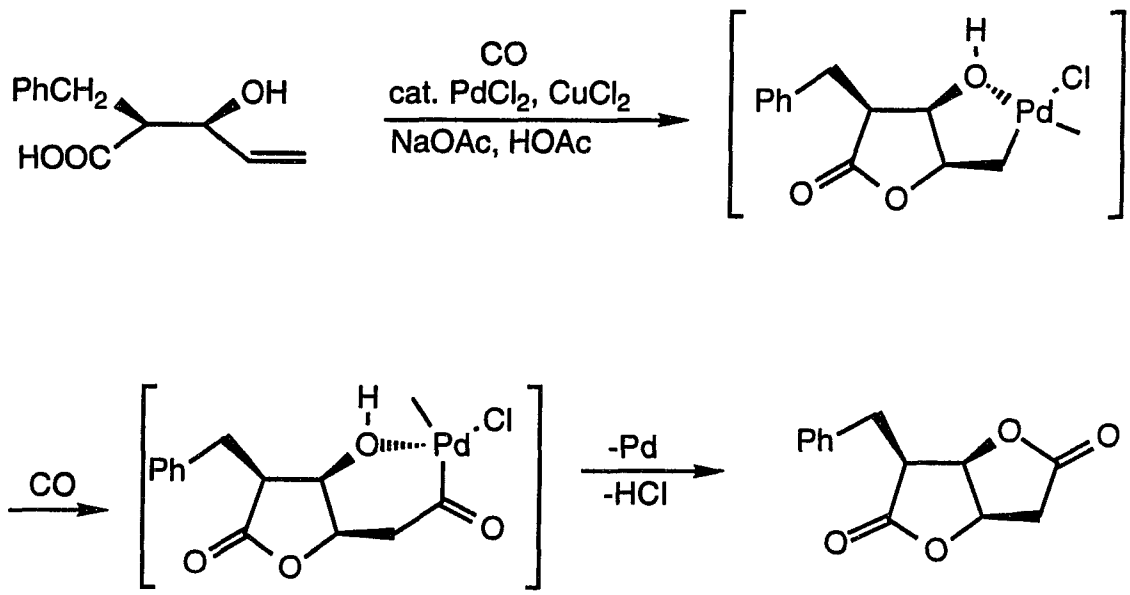
Unsaturated lactones have also been synthesized via insertion of carbon monoxide. In these reactions using a homoallylic alcohol, the OH group first attacks the CO coordinated to Pd(II) to form an alkoxycarbonyl palladium(II) intermediate, which then cyclizes forming a lactone containing a Pd-C bond. Under acidic conditions, protonolysis of this Pd-C bond leads to the α-methyl-γ-butyrolactone. This carbonylation process is known as "intramolecular hydroesterification" (Scheme 8).[20]

Scheme 8

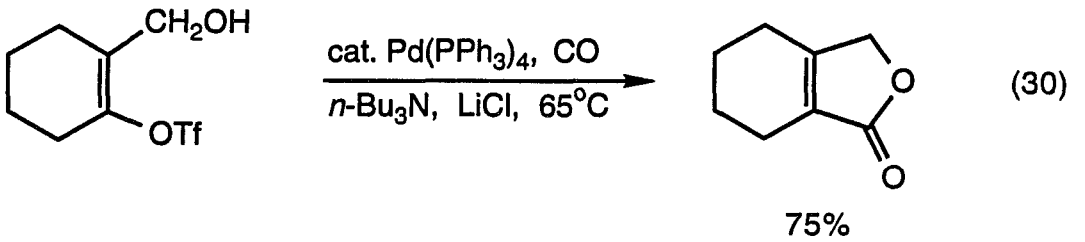


The following bislactone has also been synthesized using a somewhat different version of this CO insertion. In this reaction, acyloxypalladation takes place first, followed by carbonylation (Scheme 9).[26]

Scheme 9




Crisp and Meyer have synthesized substituted α,β-butenolides through palladium-catalyzed carbonylative intramolecular coupling of hydroxy vinyl triflates.[27] Mechanistically, the reaction involves oxidative addition of the vinyl triflate bond to Pd(0), followed by CO insertion to form an intermediate, which then cyclizes to the desired butenolide (eq 30).

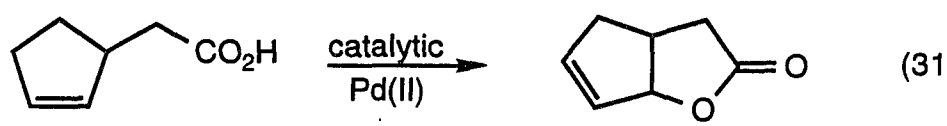



75% (30)

Realizing the importance of unsaturated lactone formation in organic synthesis, we found ourselves compelled to develop a new and improved lactonization method. It appeared that the most efficient route to achieve the formation of unsaturated lactones would entail an acyloxypalladation process. With this idea, we set out to accomplish such a palladium(II)-catalyzed method.

# RESULTS AND DISCUSSION

In this Chapter, the main thrust of my research has involved the formation of unsaturated lactones by the palladium(II)-catalyzed cyclization of alkenoic acids. The initial challenge was to produce the unsaturated lactone (compound **1**) in an excellent yield from the corresponding 2-cyclopenteneacetic acid (eq 31).




(31)

**1**

With this challenge in mind, a variety of solvents were examined along with a stoichiometric amount of palladium acetate. These results are summarized in Table 1.

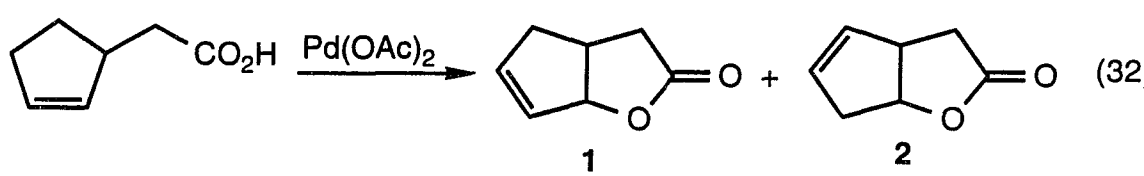
Table 1. Solvent Effects on the Cyclization of 2-Cyclopenteneacetic acid[a]

| Entry | Solvent | Ratio[b] 1 : 2 | % Isolated Yield |
|---|---|---|---|
| 1 | HMPA | 0 : 0 | 0 |
| 2 | DMF | 80 : 20 | 60 |
| 3 | DMA | 83 : 17 | 42 |
| 4 | $CH_3CN$ | 92 : 8 | 53 |
| 5 | DMSO | 100 : 0 | 80 |

[a]The reaction conditions entail stirring 0.5 mmol of 2-cyclopenteneacetic acid, 0.5 mmol of $Pd(OAc)_2$ in 10 ml of the desired solvent for 2 hours at 25°C.

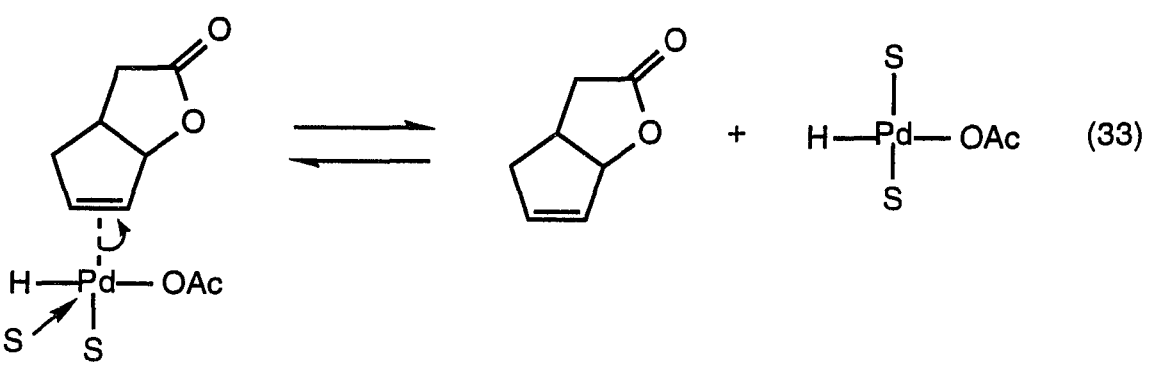
[b]The ratio of products was determined by $^1H$ NMR spectoscopic analysis of the vinylic hydrogens.

The initial problem encountered involved the formation of an additional undesirable isomer, compound **2** (eq 32).




**1** **2** (32)

Entries 1-4 in Table 1 reveal that by changing the solvent system, one can change the ratio of the desired compound to that of the undesired lactone, and even eliminate the undesired product completely. Using HMPA as the solvent, proved to be a total disaster, with no reaction occurring. An explanation of this result entails the coordinating ability of HMPA to palladium. Since HMPA coordinates so readily to palladium, there arises a competition between the palladium coordinating with HMPA versus palladium coordinating with the olefin of the alkenoic acid, the latter being a crucial step if the reaction is to take place. By using $CH_3CN$, DMA or DMF as the solvent, formation of the desired product, as well as formation of the undesired lactone, was observed. However, DMSO as the solvent eliminated the undesired second isomer completely. These results can be understood by examining equation 33 and Scheme 10.



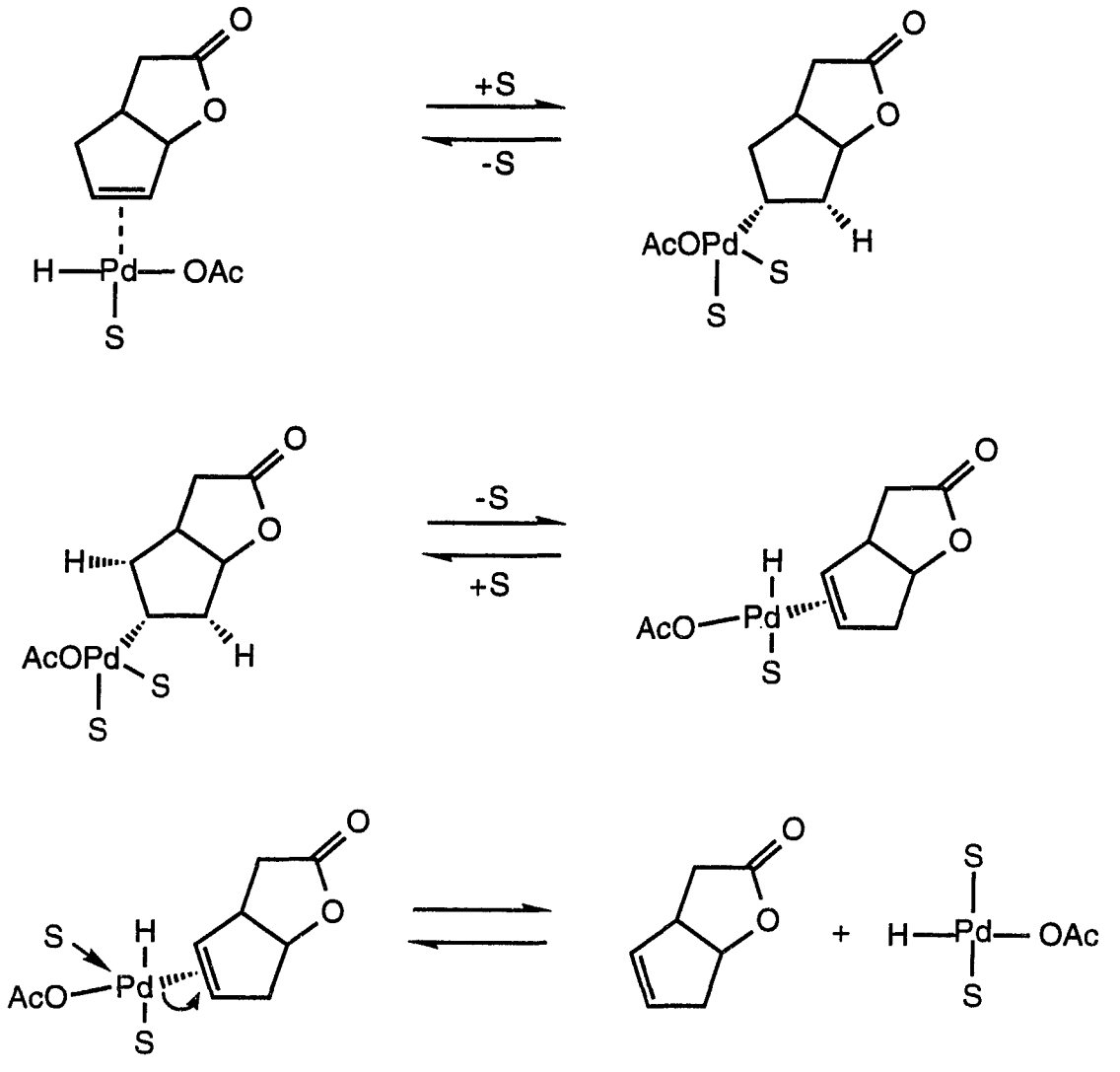

(33)

S = solvent

If the solvent displaces palladium from the $\pi$-complex, as shown in equation 33, readdition of HPdOAc to the olefin will not be allowed to occur. This solvent

displacement gives rise to the desired product. If this displacement does not take place, readdition of the hydridopalladium acetate species to the newly formed olefin can then occur allowing for an additional β-hydride elimination in the opposite direction. Upon displacement of this newly formed π-complex, the undesired product is formed. This concept is represented in Scheme 10.

Scheme 10



As mentioned earlier, from Table 1 it is apparent that DMSO is the solvent of choice. Not only does DMSO eliminate the undesired lactone, it also provides the desired lactone in the best yield. The ability of DMSO to coordinate well enough to palladium to displace the initial hydridopalladium acetate $\pi$-complex, but not coordinate so strongly that the palladium acetate is unable to initially coordinate to the olefin of the alkenoic acid is essential in achieving these desired results.

With the first goal complete of obtaining only the desired isomer, we set out to develop conditions which would employ only catalytic amounts of palladium. Since the development of the Wacker process, which involves the oxidation of ethylene to acetaldehyde via $PdCl_2$ and $H_2O$,[28] a wide variety of organic reactions using palladium(II) salts have been developed.[20,29] In these Wacker-type reactions, Pd(II) is reduced to Pd(0) and hence the reaction is not catalytic. To make these reactions catalytic, Pd(0) must be reoxidized to its' original oxidation state of Pd(II). To achieve this reoxidation, the addition of a reoxidant, such as Cu(II), is needed. In the reoxidation process, Cu(II) is reduced to Cu(I), but in the presence of oxygen the reduced Cu(I) can be reoxidized to Cu(II) thus making the system catalytic in palladium and copper. This can be seen in Scheme 11.

Scheme 11

$$Pd(0) + 2CuX_2 \longrightarrow PdX_2 + 2CuX$$

$$2CuX + 2HX + 0.5O_2 \longrightarrow 2CuX_2 + H_2O$$

With this reoxidation method in mind, an attempt to develop a unique catalytic system for the cyclization of 2-cyclopenteneacetic acid was undertaken. These results are summarized in Table 2.

Table 2. Catalytic Cyclization of 2-Cyclopenteneacetic acid[a]

| Entry | Reoxidant | Equiv. | Base | Equiv. | Time (hr) | % Isolated Yield of **1** |
|---|---|---|---|---|---|---|
| 1 | $Cu(OAc)_2$ | 2 | ---- | --- | 24 | 51 |
| 2 | $Cu(OAc)_2$ | 2 | $Et_3N$ | 1 | 96 | 38 |
| 3 | $Cu(OAc)_2$ | 2 | $Et_3N$ | 2 | 120 | 42 |
| 4 | $Cu(OAc)_2$ | 2 | NaOAc | 2 | 2 | 80 |
| 5 | $Cu(OAc)_2$ | 0.10 | NaOAc | 2 | 21 | 90 |
| 6 | ---------- | --- | NaOAc | 2 | 24 | 86 |
| 7 | ---------- | --- | NaOAc | 0 | 144 | ---- |
| 8 | ---------- | --- | NaOAc | 4 | 24 | 84 |
| 9 | ---------- | --- | KOAc | 2 | 72 | 85 |
| 10 | ---------- | --- | $LiOAc \cdot 2H_2O$ | 2 | 10 | 92 |

[a]The reaction conditions entail stirring 0.5 mmol of 2-cyclopenteneacetic acid, 5 mol% of $Pd(OAc)_2$, the appropriate amount of reoxidant, and the appropriate amount of base in 10 ml of DMSO under an oxygen atmosphere at 25°C.

By decreasing the amount of $Pd(OAc)_2$ to 5 mol% and adding 2 equivalents of $Cu(OAc)_2$, the reaction became catalytic with regards to palladium, although the overall yield is lower than the reaction using a full equivalent of $Pd(OAc)_2$ (entry 1). Entries 2-4 indicate that the addition of a base to the reaction mixture can dramatically effect the rate of reaction. The addition of triethylamine dramatically decreased the reaction rate. The problem associated with amines is that amines tend to coordinate very well to palladium. This coordination can tie up the palladium, limiting the necessary coordination of palladium to the olefin of the alkenoic acid. This is further amplified when the concentration of triethylamine is doubled (entries 2 and 3). Entry 4 reveals that the addition of an inorganic base, such as NaOAc, has the opposite effect of an amine base. The addition of NaOAc to the reaction mixture creates a "hotter" nucleophile, the carboxylate anion of the alkenoic acid, without tying up the palladium, which in turn decreases the reaction time by over 10 times.

As previously shown, the reoxidation of Pd(0) to Pd(II) requires only two equivalents of Cu(II) per one equivalent of Pd(0) (Scheme 10). Entry 5 accomplishes this stoichiometry. As indicated, the yield and reaction rate are quite good. In order to determine if Cu(II) was even needed for the reoxidation of the palladium catalyst, the copper was excluded. Surprisingly, the reaction worked well with a catalytic turnover number greater than 17 (entry 6). There have been other examples where $O_2$ has reoxidized Pd(0) to Pd(II), but they are limited.[30]

Entries 7-10 involve manipulation of the acetate base. For example, entry 7 shows that the addition of NaOAc is necessary for the reaction to proceed at an appreciable rate. With the addition of four equivalents of NaOAc, the results did not improve (entry 8). Using KOAc as the base decreased the rate of reaction by

approximately three fold (entry 9), but the use of LiOAc•2$H_2O$ increased the reaction rate by approximately 2 times (entry 10).

From the results of entry 10, additional experiments were examined in order to determine whether the LiOAc or the addition of $H_2O$ was responsible for the dramatic increase in the rate of the reaction. These results are summarized in Table 3.

The experiment described in entry 1 involved the addition of 4 equivalents of $H_2O$ to create a NaOAc reaction equivalent to that of LiOAc•2$H_2O$. These results show that indeed the addition of water increases the reaction rate. Note that the reaction of KOAc which initially took 72 hours without the addition of $H_2O$ takes only 11 hours with the addition of 4 equivalents of $H_2O$ to the reaction mixture (entry 5). Entry 2 establishes that a 9:1 mixture of DMSO/$H_2O$ accomplishes the same effect as using 4 equivalents of $H_2O$. Using a 1:1 mixture of DMSO/$H_2O$ as the solvent system still provided an excellent yield, but lower than the 9:1 DMSO/$H_2O$ solvent system (entry 3). By removing the DMSO from the solvent system completely, and using only $H_2O$ as the solvent, no reaction was observed to occur (entry 4). The result of entry 6 indicates that using a 9:1 DMSO/$H_2O$ solvent system with the LiOAc•2$H_2O$ base, decreases not only the rate of the reaction, but also the yield as compared to using only DMSO as the solvent with LiOAc•2$H_2O$ as the base (entry 10, Table 2). These results illustrate that the addition of water to the reaction mixture in moderate amounts can have a dramatic increase in the rate of the reaction without reducing the yield. It should also be noted that when the reaction is run in pure water as the solvent, no cyclization is observed to occur.

Table 3. Effects of Water on the Cyclization of 2-Cyclopenteneacetic acid[a]

| Entry | Base | Solvent | Time (hr) | %Isolated Yield |
|---|---|---|---|---|
| 1 | NaOAc | DMSO + 4 equiv. $H_2O$ | 12 | 84 |
| 2 | NaOAc | 9:1 DMSO/$H_2O$ | 11 | 87 |
| 3 | NaOAc | 1:1 DMSO/$H_2O$ | 11 | 80 |
| 4 | NaOAc | $H_2O$ | 72 | -- |
| 5 | KOAc | DMSO + 4 equiv. $H_2O$ | 11 | 82 |
| 6 | LiOAc•2$H_2O$ | 9:1 DMSO/$H_2O$ | 15 | 74 |

[a]The reaction conditions entail stirring 0.5 mmol of 2-cyclopenteneacetic acid, 5 mol% of $Pd(OAc)_2$, 1.0 mmol of NaOAc and 10 ml of DMSO under an oxygen atmosphere at 25°C.

In conclusion, a novel catalyst system has been developed for the cyclization of 2-cyclopenteneacetic acid using 5 mol% of $Pd(OAc)_2$, 2 equivalents of NaOAc, 1 atmosphere of $O_2$ and a DMSO or DMSO/$H_2O$ solvent system. Note that oxygen alone is remarkably efficient in reoxidizing palladium under these reaction conditions.

From these preliminary experiments, three basic experimental procedures were obtained for effecting the cyclization of 2-cyclopenteneacetic acid to the corresponding unsaturated lactone. These are method A (5 mol% of $Pd(OAc)_2$, 2 equiv. of NaOAc, 10 ml of DMSO, $O_2$ balloon for 24 hrs. at 25°C), method B (5 mol% of $Pd(OAc)_2$, 2 equiv. of NaOAc, 9:1 DMSO/$H_2O$, $O_2$ balloon for 12 hrs. at 25°C), and method C (5 mol% of $Pd(OAc)_2$, 2 equiv. of $LiOAc{\bullet}2H_2O$, 10 ml of DMSO, $O_2$ balloon for 12 hrs. at 25°C). Using these three methods, monocyclic, fused and bridged bicyclic, and spirocyclic lactones bearing 5- or 6-membered rings are all readily formed in excellent yields using mono-, di-, and trisubstituted alkenoic acids as shown in Table 4.

The experiments described in entries 1-9 of Table 4 yield the expected 5-membered ring lactone product. While 3-(1-cyclohexenyl)propanoic acid (entries 5-8) has the possibility of closing to either the 5- or 6-membered ring lactone, only the 5-membered ring lactone is formed. Apparently the formation of the 5-membered ring product is kinetically, as well as thermodynamically, favored. This is apparently due to the carbonium ion character developed in the intermediate $\pi$-complex, which is more efficiently stabilized in the tertiary position. The alkenoic acids illustrated in entries 9-14 also provide only the 5-membered ring lactone products.

As mentioned earlier, *E*-4-hexenoic acid reacts with $Li_2PdCl_4$ to afford the butenolide product (eq 23).[22] Under our conditions, *E*-4-hexenoic acid affords only the vinyl valerolactone (entry 9).

The results for entries 10 and 11 compare the results for *E* and *Z* isomers of 4-decenoic acid. From these results one can conclude that the product is dictated by the stability of the product and not the stereochemistry of the starting material.

Table 4. Palladium(II)-Catalyzed Cyclization of Alkenoic Acids

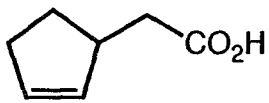
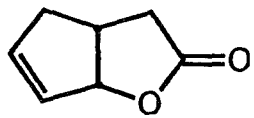
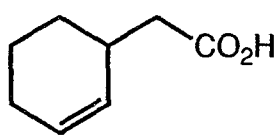
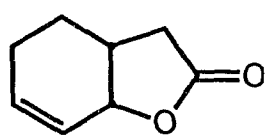
| Entry | Alkenoic Acid | Method[a] | Time (hr), Temp. ($^{o}$C) | Product(s)[b] | % Isolated Yield |
|---|---|---|---|---|---|
| 1 |  | A | 24, 25 |  | 86 |
| 2 | | B | 11, 25 | | 87 |
| 3 | | C | 11, 25 | | 92 |
| 4 |  | A | 24, 25 |  | 90 |

Table 4. (cont'd)

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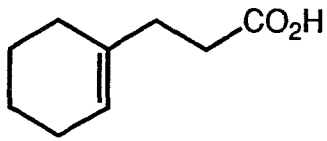
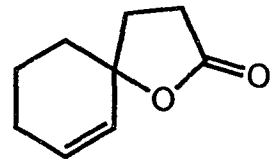
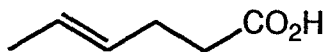
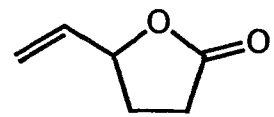
|---|---|---|---|---|---|
| 5 |  | A | 120, 25 |  | -- |
| 6 | | A | 24, 80 | | 91 |
| 7 | | B | 60, 25 | | 77 |
| 8 | | C | 96, 25 | | -- |
| 9 |  | A | 48, 25 |  | 81 |

Table 4. (cont'd)

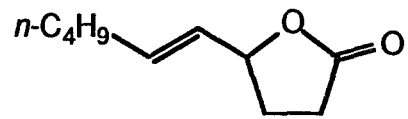
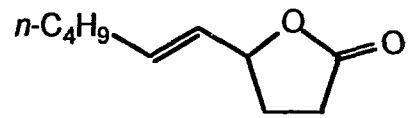
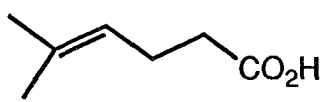
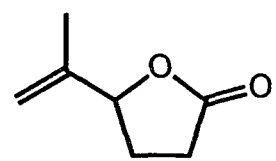
| | | | | | |
|---|---|---|---|---|---|
| 10 | *E*-*n*-$C_5H_{11}CH{=}CH(CH_2)_2CO_2H$ | A | 48, 25 |  | 78 |
| 11 | *Z*-*n*-$C_5H_{11}CH{=}CH(CH_2)_2CO_2H$ | A | 72, 25 |  | 81 |
| 12 |  | A | 168, 25 |  | 82 |
| 13 | | B | 168, 25 | | 69 |
| 14 | | C | 168, 25 | | 67 |

Table 4. (cont'd)

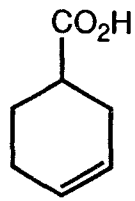
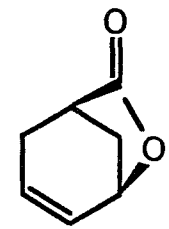
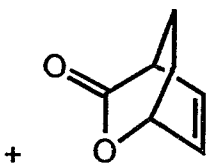
| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 15 |  | A | 240, 25 |  | + |  | -- |
| 16 | | A | 240, 65 | | | | -- |
| 17 | | A | 36, 80 | 3 | : | 1 | 56 |
| 18 | | B | 72, 25 | | | | -- |
| 19 | | B | 48, 80 | 3 | : | 1 | 54 |
| 20 | | C | 72, 25 | | | | -- |
| 21 | | C | 48, 80 | 3 | : | 1 | 63 |

Table 4. (cont'd)

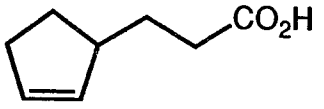
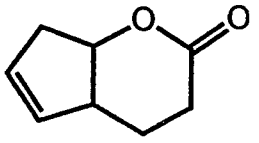
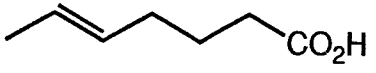
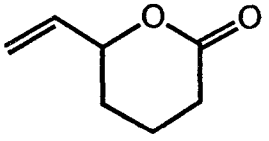
| | | | | | |
|---|---|---|---|---|---|
| 22 |  | A | 24, 80 |  | 87 |
| 23 | | B | 72, 24 | | 88 |
| 24 |  | A | 48, 80 |  | 68 |

Table 4. (cont'd)

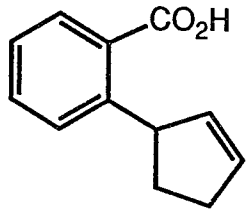
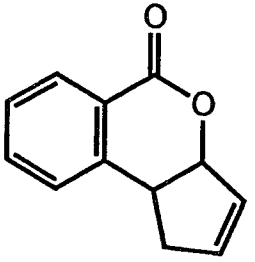
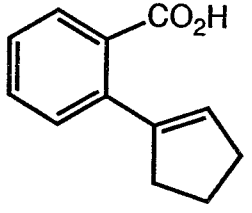
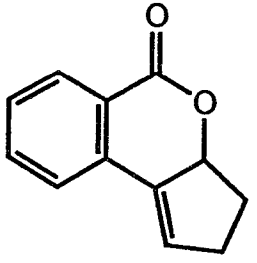
| | | | | | |
|---|---|---|---|---|---|
| 25 |  | A | 72, 25 |  | 82 |
| 26 |  | A | 72, 25 |  | 80 |

Table 4. (cont'd)

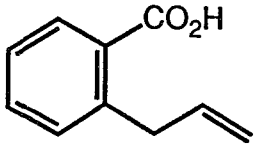
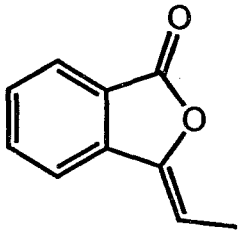
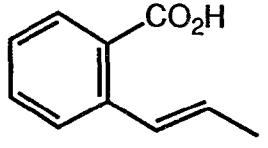
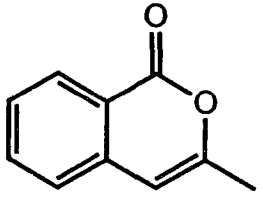
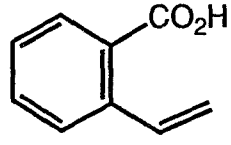
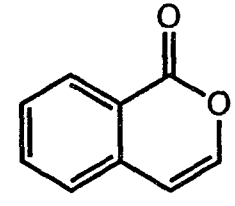
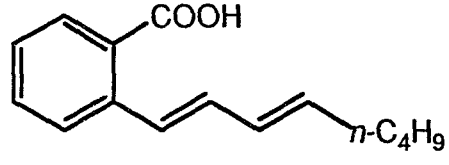
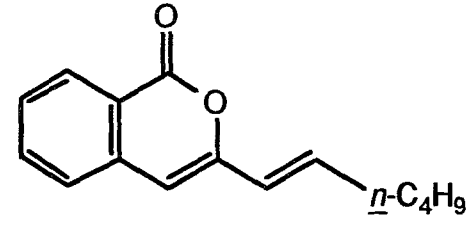
| | | | | | |
|---|---|---|---|---|---|
| 27 |  | A | 72,80 |  | 83 |
| 28 |  | A | 48,80 |  | 78 |

Table 4. (cont'd)

| | | | | | |
|---|---|---|---|---|---|
| 29 |  | A | 48, 25 |  | 90 |
| 30 |  | A | 48,25 |  and inseparable unknown | 80 |

[a]The reaction methods are described on page 35.

[b]The ratio of products was determined by $^1$H NMR spectral analysis of the vinylic hydrogens.

In the proposed mechanism ( see Scheme 13 on page 48 ), the intermediate sigma-alkylpalladium species is bonded to an $sp^3$ carbon. This allows for free rotation around a carbon-carbon single bond. The most stable conformation which still allows for β-hydride elimination is that leading to the *E*-alkenyl lactone.

While previous work on the halo-, seleno- and sulfenolactonization of 3-cyclohexenecarboxylic acid (eq 6) afforded only the 5-membered ring lactone,[2b] our method cyclized this substrate to a mixture of the 5- and 6-membered ring lactones (entries 15-21 of Table 4).

The results of entries 22-24 establish that not only can 5-membered ring lactones be formed, but 6-membered ring lactones can also be prepared successfully.

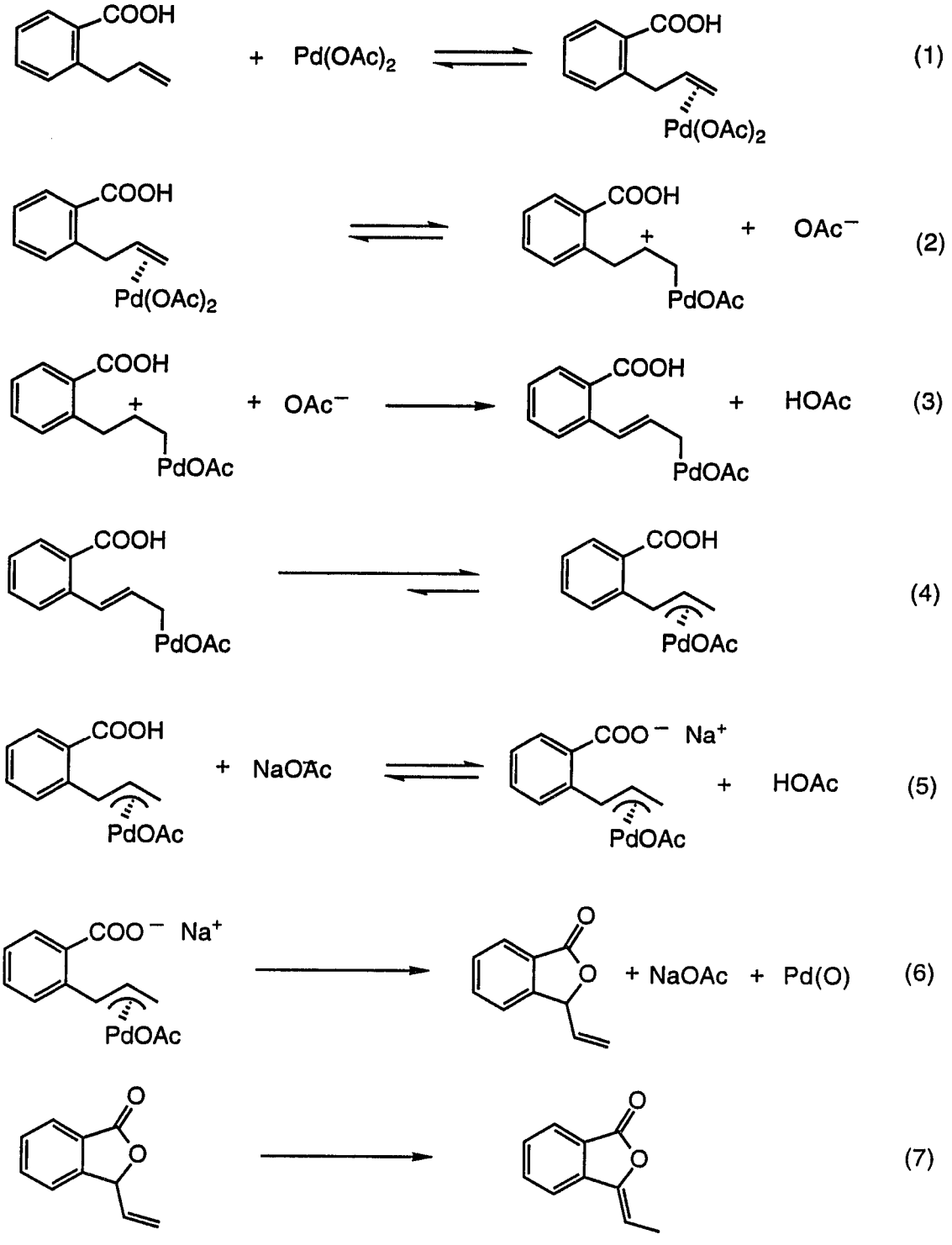
Some *o*-substituted benzoic acids have also been subjected to our cyclization conditions. For example, 2-(2-cyclopentenyl)benzoic acid and 2-(1-cyclopentenyl)benzoic acid both yield dihydroisocoumarin products (entries 25 and 26). It is important to notice that entry 26 has the possibility of closing to the 5-membered ring product, but instead closes only to the 6-membered ring product. Apparently, due to the considerable amount of ring strain associated with closing this substrate to the 5-membered ring product versus the 6-membered ring product, cyclization only to the 6-membered ring occurred.

The cyclization of *o*-allylbenzoic acid yielded what was to our surprise the *Z*-alkylidenephthalide in excellent yield (entry 27). As previously shown, Hegedus and co-workers[23] cyclized this substrate to 3-methylisocoumarin using either stoichiometric amounts of $PdCl_2 \cdot 2CH_3CN$ plus $Na_2CO_3$, or 2% $PdCl_2 \cdot 2CH_3CN$ in the presence of $Cu(OAc)_2 \cdot H_2O$, $Na_2CO_3$ and molecular oxygen in a THF solvent (eq 25). Our method appears to be a particularly useful route to the naturally-

occurring 3-alkylidenephthalide ring system.[31] Formation of the phthalide product suggests that perhaps the starting acid was first isomerizing to *o*-(1-propenyl)benzoic acid. However, cyclization of the latter substrate afforded only 3-methylisocoumarin (entry 28).

The mechanism of formation of the phthalide product is presently unknown. It is presumed that phthalide formation is occurring through a π-allylpalladium species as shown in Scheme 12. The mechanism proposed for the formation of this possible π-allylpalladium intermediate involves the presence of palladium acetate, which can coordinate with the olefin of the benzoic acid to form a π-complex (1). The formation of this π-complex delocalizes the electron density of the olefin. If the palladium is allowed to remove enough electron density to create a free carbocation (2), loss of a benzylic proton can occur leading to the formation of a sigma-allylpalladium species (3). This collapses to a π-allylpalladium intermediate (4). π-Allylpalladium species are known to undergo displacement of palladium by nucleophiles. With the formation of the carboxylate anion, a nucleophile is established within the molecule (5). The nucleophile performs an intramolecular attack on this π-allylpalladium complex to provide the initial lactone (6). This lactone apparently isomerizes into conjugation with the aromatic ring *in situ* to yield the final product (7). With our solvent DMSO being more polar than the THF solvent used by Hegedus[23] in a similar cyclization of this same substrate, a more polar intermediate, such as the free carbocation, can be established; whereas THF, a much less polar solvent, would not allow for such a polar intermediate. The pathway proposed for the cyclization via the less polar intermediate would entail an acyloxypalladation mechanism similar to Scheme 13.

Scheme 12


COOH
+ Pd(OAc)2
Pd(OAc)2
(1)
COOH
Pd(OAc)2
COOH
+
+ OAc−
PdOAc
(2)
COOH
+
PdOAc
+ OAc−
COOH
+ HOAc
PdOAc
(3)
COOH
PdOAc
COOH
PdOAc
(4)
COOH
PdOAc
+ NaOAc
COO− Na+
+ HOAc
PdOAc
(5)
COO− Na+
PdOAc
O
O
+ NaOAc + Pd(O)
(6)
O
O
O
O
(7)

Since 2-vinylbenzoic acid cyclized readily under Hegedus and co-workers' conditions to afford a 3:1 mixture of isocoumarin to 3-methylene phthalide,[23] we examined the cyclization of this substrate as well. The isocoumarin was our sole product (entry 29 of Table 4).

With these differing results, it is quite clear that the mechanism of our palladium acetate-catalyzed process is significantly different from that of the palladium chloride based methodologies reported previously. The general mechanism proposed for these reactions is shown in Scheme 13. This proposed mechanism involves the establishment of an equilibrium between the initial carboxylic acid and the sodium carboxylate ion (1). As shown earlier, in the presence of palladium acetate a π-complex can be formed with the olefin of the alkenoic acid (2). The formation of this π-complex delocalizes the electron density allowing the olefin to be attacked by a neighboring nucleophile. With the formation of the carboxylate anion, a nucleophile is established within the molecule. This nucleophile performs an intramolecular attack on the π-palladium complex to render a lactone containing a sigma-alkylpalladium species (3). Since sigma-alkylpalladium species are very unstable, unless a stabilizing ligand is present, a syn β-hydride elimination occurs (4). This elimination leads to the formation of a second π-complex containing a hydridopalladium acetate. Upon decomposition of this latest π-complex, the final desired product is obtained along with a hydridopalladium acetate (5), which undergoes reductive elimination to form Pd(0) and acetic acid (6). In the presence of molecular oxygen, Pd(0) is reoxidized to Pd(II) (7).

With every success, there are often failures. Table 5 attempts to summarize these failures.

Scheme 13

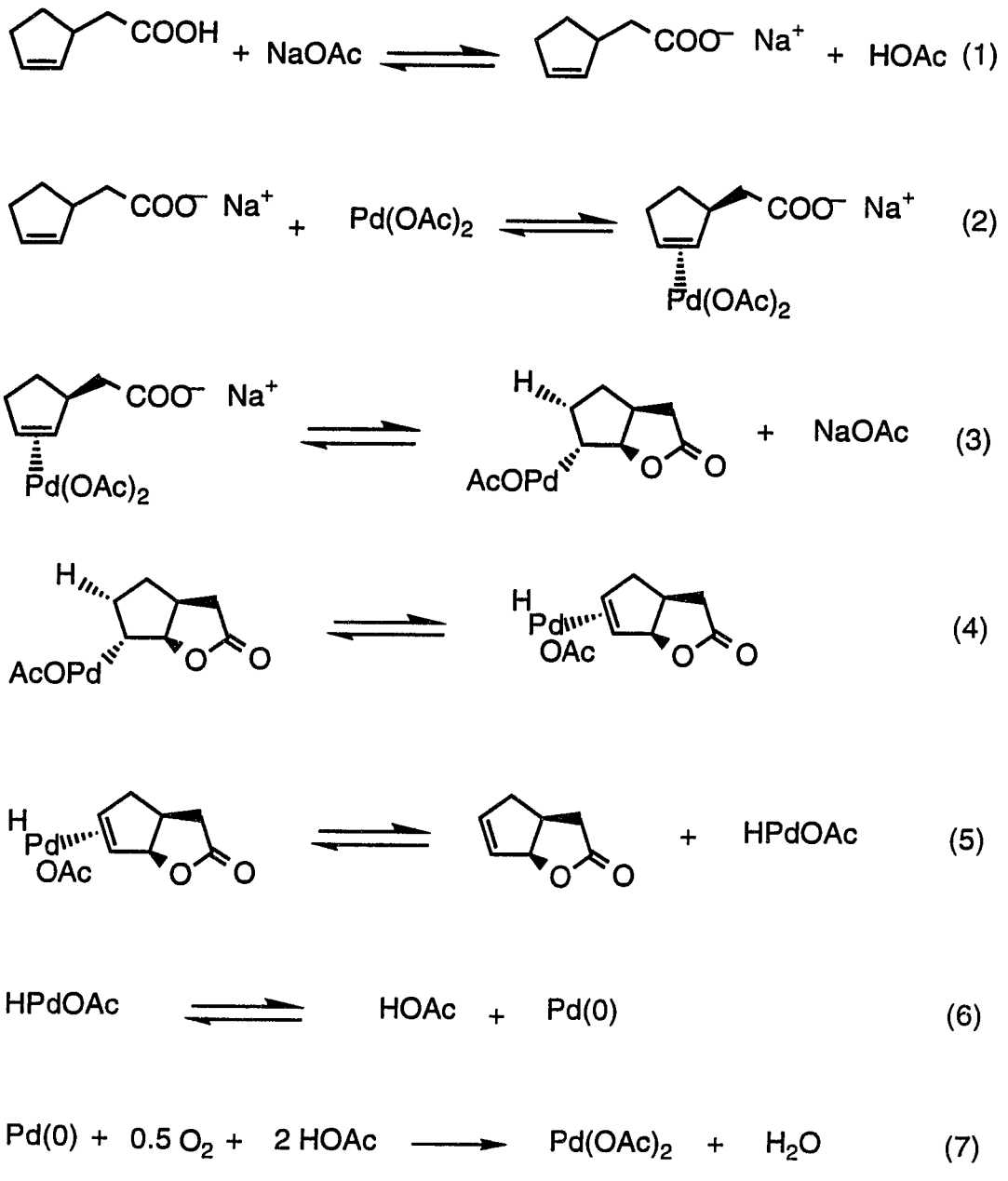

COOH
+ NaOAc
COO⁻ Na⁺
+ HOAc (1)
COO⁻ Na⁺
+ Pd(OAc)2
COO⁻ Na⁺
Pd(OAc)2 (2)
COO⁻ Na⁺
Pd(OAc)2
H
AcOPd
O
O
+ NaOAc (3)
H
AcOPd
O
O
H
Pd
OAc
O
O (4)
H
Pd
OAc
O
O
+ HPdOAc (5)
HPdOAc
HOAc + Pd(0) (6)
Pd(0) + 0.5 O2 + 2 HOAc
Pd(OAc)2 + H2O (7)

Table 5. Substrates Which Failed to Cyclize[a]

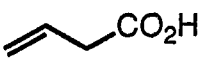
| Entry | Alkenoic Acid | Method | Time (hr), Temp. (°C) |
|---|---|---|---|
| 1 |  | A | 72, 25 |
| 2 | | A | 72, 80 |
| 3 | | B | 72, 25 |
| 4 | | B | 72, 80 |
| 5 | | C | 72, 25 |
| 6 | | C | 72, 80 |

Table 5. (cont'd)

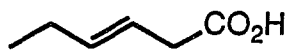
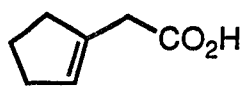
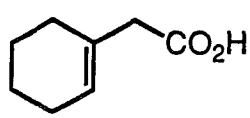
| | | | |
|---|---|---|---|
| 7 |  | A | 72, 25 |
| 8 | | A | 72, 80 |
| 9 |  | A | 72, 25 |
| 10 | | A | 72, 80 |
| 11 |  | A | 72, 25 |
| 12 | | A | 72, 80 |

Table 5. (cont'd)

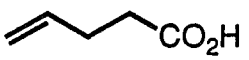
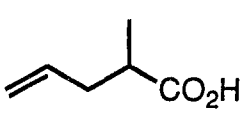
| | | | |
|---|---|---|---|
| 13 |  | A | 72, 25 |
| 14 | | A | 72, 80 |
| 15 | | B | 72, 25 |
| 16 | | B | 72, 80 |
| 17 | | C | 72, 25 |
| 18 | | C | 72, 80 |
| 19 |  | A | 72, 25 |
| 20 | | A | 72, 80 |

Table 5. (cont'd)

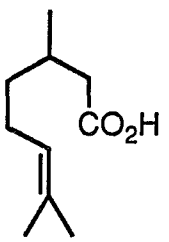
| | | | |
|---|---|---|---|
| 21 |  | A | 72, 25 |
| 22 | | A | 72, 80 |
| 23 | | A | 72, 100 |
| 24 |  | A | 72, 25 |
| 25 | | A | 72, 80 |
| 26 | | A | 72, 100 |

Table 5. (cont'd)

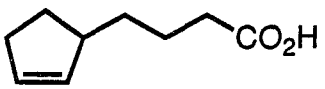
| | | | |
|---|---|---|---|
| 27 |  | A | 72, 25 |
| 28 | | A | 72, 80 |
| 29 | | A | 72, 100 |
| 30 | | B | 72, 25 |
| 31 | | B | 72, 80 |
| 32 | | C | 72, 25 |
| 33 | | C | 72, 80 |

Table 5. (cont'd)

| | | | |
|---|---|---|---|
| 34 |  | A | 72, 25 |
| 35 | | A | 72, 80 |
| 36 | | B | 72, 25 |
| 37 | | B | 72, 80 |
| 38 | | C | 72, 25 |
| 39 | | C | 72, 80 |

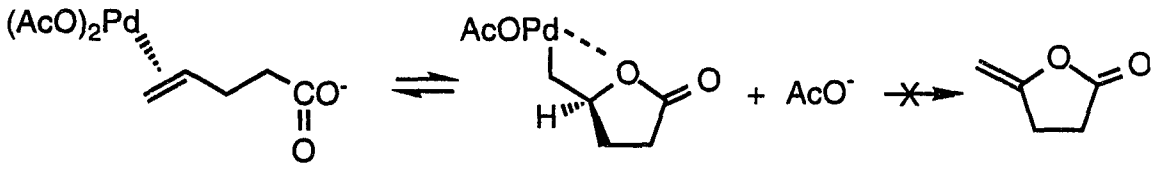
[a]The reaction methods are described on page 35.

The substrates described in entries 1-12 could either cyclize to give the 4- or 5-membered ring product. Although 3- and 4-alkenoic acids have previously been cyclized by $Li_2PdCl_4$ to the corresponding butenolides,[22] no cyclization has been observed using our conditions. While the 5-endo-trig halo-[1a] and selenolactonization[2b] of 1-cyclopenteneacetic acid and 1-cyclohexeneacetic acid have been successful, our palladium-catalyzed cyclization of these systems fails, presumably due to the strain present in the organopalladium intermediate and the reversibility of the acyloxypalladation reaction.[32]

The alkenoic acids illustrated in entries 13-20 have the option of cyclizing to either a 5- or 6-membered ring lactone. Since similar substrates cyclize to yield the 5-membered ring products under our conditions (entries 9-14, Table 4), apparently the ring closure is not the problem.

Scheme 14 helps diagram a coordination effect which could possibly explain this result. If closure occurs leading to the terminal sigma-alkylpalladium species, the palladium could coordinate to the lone pair of electrons on the nearby oxygen. This could in turn increase the dihedral angle of the syn-β-hydrogen relative to the palladium sufficiently that β-hydride elimination would not be allowed to occur. This would allow a free acetate to attack the sigma-alkylpalladium species and return the intermediate back to the original starting materials. Under these circumstances no syn β-hydride is ever available for syn elimination.

Scheme 14




The final entries 21-39 of Table 5 reveal that 7- and 12-membered ring lactones apparently cannot be formed using this methodology.

# CONCLUSION

While literature has shown that alkenoic acids can be cyclized to unsaturated lactones by palladium(II)-catalyzed methodology, our methods A, B, and C are far superior. As mentioned earlier, the literature procedures require the use of a stoichiometric amount of palladium, or, if the reaction utilizes only a catalytic amount of palladium, additional reoxidants are needed along with an oxygen atmosphere in order to reoxidize the Pd(0) formed during the reaction back to Pd(II). Our palladium(II) methodology requires only the use of catalytic amounts of palladium and has no need for any additional reoxidants other than oxygen to reoxidize the Pd(0) formed *in situ* to Pd(II).

As far as comparing our three methods, one does not seem to be vastly superior to the others. The two methods B and C, which incorporate LiOAc•$2H_2O$ or a 9:1 DMSO/$H_2O$ solvent system do have the advantage of an increased reaction rate, but do not significantly effect the yield.

It is important to note, however, that our palladium(II)-catalyzed cyclization methodology has similar yields as compared to those reported by Hegedus,[23] and significantly better yields than Kasahara's stoichiometric cyclization conditions.[22] In some instances, cyclization of identical substrates using either Hegedus' or Kasahara's palladium(II)-cyclization procedures versus our conditions, allow formation of totally different products (eqs 23 and 25).

In conclusion, acyclic and cyclic, aliphatic or aromatic 4- or 5-alkenoic acids cyclize in high yield to 5- or 6-membered unsaturated lactones using 5 mol% of $Pd(OAc)_2$, 2 equivalents of NaOAc or $LiOAc{\bullet}H_2O$, 1 atmosphere of $O_2$ and a DMSO or DMSO/$H_2O$ solvent system. As mentioned earlier, formation of larger rings failed.

# EXPERIMENTAL SECTION

## Equipment

All NMR spectra were recorded on a Nicolet NT-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75 MHz for carbon nuclei). Infrared spectra were obtained on an IBM IR/98 FT-IR. Mass spectral data were obtained on a Kratos high resolution mass spectrometer.

## Reagents

2-Cyclopenteneacetic acid and 2-bromostyrene were obtained from Aldrich Chemical Co. Methanesulfonyl chloride, DMF, DMA, $CH_3CN$, HMPA and DMSO were all obtained from Fisher Scientific. *E*-4-Hexenoic acid, was obtained from MTM Research Chemicals and 3-cyclohexenecarboxylic acid was obtained from Chemical Dynamics Corporation. 1-Cyclohexeneacetic acid and *Z*-4-hexenoic acid were obtained from Johnson Matthey, Inc. Kawaken Fine Chemicals Co., Ltd. and Johnson Matthey, Inc. generously provided the palladium acetate.

## Preparation of Alkenoic Acids

The preparation of 2-cyclohexeneacetic acid followed the procedure reported by Blomquist and co-workers.[33]

The preparation of 3-(1-cyclohexenyl)propanoic acid involved an LAH reduction of the commercially available 1-cyclohexeneacetic acid to the corresponding alcohol. The 1-cyclohexeneacetic acid (13.3 mmol, 1.5 g) dissolved in anhydrous THF (35 ml) was added (under nitrogen) dropwise to LAH (16 ml of a 1 M THF solution). After stirring overnight, the reaction mixture was quenched with $H_2O$, followed by 10% HCl until the pH was <7. The alcohol was extracted with ether, dried ($MgSO_4$) and the crude product subjected to methanesulfonation. Methanesulfonyl chloride (18 mmol, 1.4 ml) was added to a solution of the previously prepared alcohol in THF (75 ml) containing $Et_3N$ (21 mmol, 3.0 ml), and allowed to stir 3 hours. The mixture was filtered and the filtrate extracted with diethyl ether. The ether fractions were combined, dried ($MgSO_4$) and concentrated to provide the the crude product. This crude mesylate was then stirred at reflux overnight in a solution of acetone (125 ml) and NaI (53 mmol, 7.8 g). After refluxing, the reaction mixture was filtered and the filtrate washed with aqueous sodium bisulfite to remove the excess iodide and dried ($MgSO_4$) to provide the crude alkenyl iodide. The iodide was then displaced by stirring it in a solution of NaCN (13.3 mmol, 0.65g) in DMSO (30 ml) at 100°C. After stirring for 2 days at 100°C, the reaction mixture was diluted with satd aq NaCl and the mixture extracted with diethyl ether. The ether fractions were combined, dried ($MgSO_4$) and concentrated to obtain the crude product. The crude nitrile was then refluxed for 5 days in a solution of KOH (266 mmol, 14.8 g) in 75 ml $H_2O$/75 ml EtOH. The crude product was subjected to an acid-base extraction

and dried to yield the crude product. The product was purified by flash chromatography on silica gel. The overall yield from 1-cyclohexeneacetic acid was 35%: IR (neat) 2920, 1710 $cm^{-1}$; $^1H$ NMR $\delta$ 1.50-1.66 (m, 4H, $CH_2CH_2$), 1.90-2.00 (m, 4H, $CH_2C{=}CCH_2$), 2.26 (t, J = 7.5 Hz, 2H, $C(O)CCH_2$), 2.46 (t, J = 6.9 Hz, 2H, $C(O)CH_2$), 5.43 (br s , 1H, vinyl); $^{13}C$ NMR $\delta$ 22.4, 22.9, 25.2, 28.3, 32.6, 32.7, 121.7, 135.7, 180.1; HRMS m/z ($M^+$) calcd for $C_9H_{14}O_2$ 154.09938, found 154.09911.

The preparation of *E*-4-decenoic acid followed the procedure reported by Ireland and co-workers.[34]

The preparation of *Z*-4-decenoic acid involved a Jones oxidation of the corresponding aldehyde.[35] The $^1H$ NMR spectrum was identical with that previously reported by Levin and Warren.[36]

The preparation of 5-methyl-4-hexenoic acid involved an ester enolate alkylation of 1-bromo-3-methyl-2-butene using the following procedure. n-Butyllithium (20 mmol, 8.0 ml) was added to a previously prepared solution of diisopropylamine (20 mmol, 2.8 ml) and THF (5 ml) cooled to -78°C. After the solution was warmed to 0°C for 5 minutes and recooled to -78°C, EtOAc (20 mmol, 2.0 ml) was added dropwise. This solution was transferred by cannula to a solution of 1-bromo-3-methyl-2-butene (10 mmol, 3 ml) and THF (20 ml) and allowed to stir for 3 hours. The resulting solution was quenched with acetic acid. The reaction mixture was then diluted with $H_2O$, washed with 20% $K_2CO_3$ and saturated NaCl, and dried ($MgSO_4$) to provide the crude ester product. The crude product was then purified by flash chromatography on silica gel to provide in 54% yield ethyl 5-methyl-4-hexenoate: $^1H$ NMR ($CDCl_3$) $\delta$ 1.25 (t, 3H, J = 7.2 Hz, $OCCH_3$), 1.62 (s, 3H, $=CCH_3$), 1.67 (s, 3H, $=CCH_3$), 2.24-2.38 (m, 4H, $CH_2CH_2$), 5.09 (s, 1H, vinyl). The

ethyl ester (5 mmol, 0.78 g) was then refluxed overnight with KOH (35 mmol, 1.96 g) in 5 ml $H_2O$/20 ml EtOH and the product worked up through an acid-base extraction and dried ($MgSO_4$). The product was purified by flash chromatography on silica gel to provide in 70% yield 5-methyl-4-hexenoic acid. The $^1H$ NMR spectrum was identical with that previously reported by Mori and co-workers.[37]

The preparation of 3-(2-cyclopentenyl)propanoic acid followed the procedure reported by Abdel-Moety and Mangold.[38]

The preparation of *E*-5-heptenoic acid followed the procedure of 3-(1-cyclohexenyl)propanoic acid starting with *E*-4-hexenoic acid: IR (neat) 2940, 1710 $cm^{-1}$; $^1H$ NMR δ 1.60-1.75 (m, 5H, $CH_3$ and $C(O)CCH_2$), 1.97-2.08 (m, 2H, $C=CCH_2$), 2.34 (t ,J = 7.2 Hz, 2H, $C(O)CH_2$), 5.32-5.55 (m, 2H, vinyl); $^{13}C$ NMR δ 18.0, 27.9, 29.6, 80.2, 116.8, 136.0, 171.1; HRMS m/z ($M^+$) calcd for $C_7H_{12}O_2$ 128.08373, found 128.08359.

2-(2-Cyclopentenyl)benzoic acid was prepared via hydrolysis of ethyl 2-(2-cyclopentenyl)benzoate, which was prepared following the procedure reported by Baker[39]: IR ($CDCl_3$) 2950, 1696 $cm^{-1}$; $^1H$ NMR δ 1.60-1.72 (m, 1H, $ArCCH_2$), 2.40-2.50 (m, 2H, $C=CCH_2$), 2.55-2.66 (m, 1H, $ArCCH_2$), 4.80-4.87 (m, 1H, ArCH), 5.73-5.79 (m, 1H, vinyl), 5.96-6.01 (m, 1H, vinyl), 7.24 -7.37 (m, 2H, ArH), 7.49 ( td, J = 7.5, 1.2 Hz, 1H, ArH), 8.00 (dd, J = 7.8, 1.5 Hz, 1H, ArH); $^{13}C$ NMR δ 33.9, 34.0, 47.7, 125.9, 128.1, 128.2, 131.1, 132.6, 133.1, 134.0, 149.0, 173.5; HRMS m/z ($M^+$) calcd for $C_{12}H_{12}O_2$ 188.08373, found 188.08399.

The preparation of 2-(1-cyclopentenyl)benzoic acid involved subjecting the previously prepared 2-(2-cyclopentenyl)benzoic acid (7.5 mmol, 1.62 g) to a solution of KOH (75 mmol, 4.25 g) and DMSO (10 ml) at 120°C for 2 days and working the reaction up by an acid-base extraction. The product was purified by flash

chromatography on silica gel: yield 48%; IR ($CDCl_3$) 2950, 1690 $cm^{-1}$; $^1H$ NMR δ 1.99-2.08 (m, 2H, $C{=}CCCH_2$), 2.46-2.54 (m, 2H, $C{=}CCH_2$), 2.64-2.71 (m, 2H, $C{=}CCH_2$), 5.73-5.75 (m, 1H, vinyl), 7.27-7.33 (m, 2H, ArH), 7.46 (td, J = 7.5, 1.5 Hz, 1H, ArH), 7.90 (d, J = 7.8 Hz, 1H, ArH); $^{13}C$ NMR δ 24.4, 33.5, 36.6, 126.8, 128.7, 129.7, 129.8, 130.3, 132.2, 140.8, 144.1, 174.2; HRMS m/z ($M^+$) calcd for $C_{12}H_{12}O_2$ 188.08373, found 188.08399.

*o*-Allylbenzoic acid was prepared by refluxing for 6 hours a solution of *o*-allylbromobenzene (10 mmol, 1.97 g) (prepared via reference 40) and Mg (11 mmol, 0.27 g) in THF (15 ml), followed by the bubbling of $CO_2$ into the solution at room temperature. The product was worked up by an acid-base extraction. The crude product was then purified by flash chromatography on silica gel: yield 60%. The $^1H$ NMR spectrum was identical with that previously reported by Hegedus and co-workers.[23]

The preparation of 2-(1-propenyl)benzoic acid involved subjecting *o*-allylbenzoic acid (3.5 mmol, 0.45 g) to a solution of KOH (140 mmol, 7.8 g) and DMSO (25 ml) and stirring at 120°C for 1.5 days. The reaction mixture was then washed with diethyl ether, acidified HCl (25%), extracted with diethyl ether and dried ($MgSO_4$) to yield the crude product. The crude product was purified by flash chromatography on silica gel: yield 48 %; IR ($CDCl_3$) 3430, 2963, 1695 $cm^{-1}$; $^1H$ NMR δ 1.97 (dd, J = 6.3, 1.2 Hz, 3 H, $CH_3$), 6.20 (dq, J = 15.3, 6.6 Hz, 1 H, vinyl), 7.30-7.33 (m, 2 H, ArH and vinyl), 7.52 (t, J = 7.5 Hz, 1 H, ArH), 7.56 (t, J = 7.2 Hz, 1 H, ArH), 8.39 (d, J = 7.8 Hz, 1 H, ArH); $^{13}C$ NMR δ 18.87, 126.56, 126.72, 127.48, 129.03, 129.80, 131.34, 132.88, 140.61, 173.21; HRMS m/z ($M^+$) calcd for $C_{10}H_{10}O_2$ 162.06808, found 162.0617.

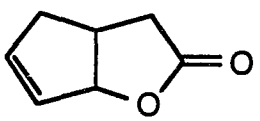
The preparation of 2-vinylbenzoic acid involved bubbling $CO_2$ into a solution of the corresponding aryllithium reagent prepared from *n*-butyllithium (7.8 mmol, 3.9 ml), THF (125 ml) and 2-bromostyrene (7.8 mmol, 1.42 g) at -78°C. The desired acid was then purified by an acid-base extraction: yield 64%; IR ($CDCl_3$) 3070, 1693 $cm^{-1}$; $^1H$ NMR δ 5.39 (d, J = 10.8 Hz, 1H, vinyl), 5.67 (d, J = 17.4 Hz, 1H, vinyl), 7.37 (t, J = 7.2 Hz, 1H, ArH), 7.55 (t, J = 7.2 Hz, 1H, ArH), 7.58-7.64 (m, 2H, ArH and ArCH), 8.05 (d, J = 7.8 Hz, 1H, ArH); $^{13}C$ NMR δ 116.8, 127.2, 127.5, 127.6, 131.3, 133.2, 136.1, 141.0, 173.2; HRMS m/z ($M^+$) calcd for $C_9H_8O_2$ 148.05243, found 148.05240.

## General Procedures for the Palladium(II)-Catalyzed Reactions

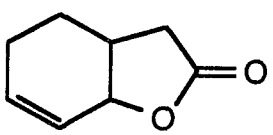
Method A: The alkenoic acid (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), NaOAc (1.0 mmol, 82 mg) and DMSO (10 ml) were stirred under an $O_2$ atmosphere at the designated temperature. After completion, the reaction mixture was diluted with satd aq $NH_4Cl$ and the mixture extracted with diethyl ether. The ether fractions were combined, dried ($MgSO_4$), concentrated and the product purified by flash chromatography on silica gel. The following lactones were prepared using this procedure.

Method B: The alkenoic acid (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), NaOAc (1.0 mmol, 82 mg) and 9:1 DMSO/$H_2O$ (10 ml) were stirred under an $O_2$ atmosphere at the designated temperature. After completion, the reaction mixture was diluted with satd aq $NH_4Cl$ and the mixture extracted with diethyl ether. The ether fractions were combined, dried ($MgSO_4$), concentrated and the product purified by flash chromatography on silica gel.

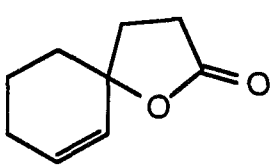
Method C: The alkenoic acid (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), $LiOAc•H_2O$ (1.0 mmol, 66 mg) and DMSO (10 ml) were stirred under an $O_2$ atmosphere at the designated temperature. After completion, the reaction mixture was diluted with satd aq $NH_4Cl$ and the mixture extracted with diethyl ether. The ether fractions were combined, dried ($MgSO_4$), concentrated and the product purified by flash chromatography on silica gel.



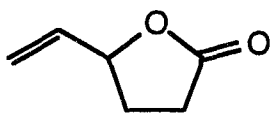
IR (neat) 1770 (C=O) $cm^{-1}$; $^1H$ NMR δ 2.27 (m, 2H, $C{=}CCH_2$), 2.81 (m, 2H, $C(O)CH_2$), 3.15 (m, 1H, $CH_2C\underline{H}CH_2$), 5.52 (d, 1H, J = 7.5 Hz, OCH), 5.87 (m, 1H, vinyl), 6.09 (m, 1H, vinyl); $^{13}C$ NMR δ 35.0, 35.9, 39.6, 89.6, 128.9, 136.9, 177.1; HRMS m/z ($M^+$) calcd for $C_7H_8O_2$ 124.05243, found 124.05256.



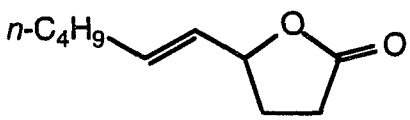
IR (neat) 1775 (C=O) $cm^{-1}$; $^1H$ NMR δ 1.42 (m, 1H, $C{=}CCCH_2$), 1.70 (m, 1H, $C{=}CCCH_2$), 2.05 (m, 2H, $C{=}CCH_2$ and $CH_2C\underline{H}CH_2$), 2.27 (dd, 1H, J = 17.4, 3.6 Hz, $C(O)CH_2$), 2.55 (m, 1H, $C{=}CCH_2$), 2.70 (dd, 1H, J = 17.4, 8.1 Hz, $C(O)CH_2$), 4.76 (t, 1H, J = 4.2 Hz, OCH), 5.82 (ddt, 1H, J = 10.2, 3.9, 2.1 Hz, vinyl), 6.07 (m, 1H, vinyl); $^{13}C$ NMR δ 22.5, 22.8, 33.3, 34.9, 75.3, 122.9, 134.0, 176.4; HRMS m/z ($M^+$) calcd for $C_8H_{10}O_2$ 138.06808, found 138.06812.



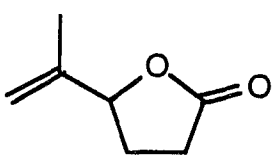
IR (neat) 1765 (C=O) $cm^{-1}$; $^1H$ NMR δ 1.60-2.07 (m, 6H, $C=CCH_2CH_2CH_2$), 2.12 (t, 2H, J = 8.4 Hz, $C(O)CCH_2$), 2.62 (t, 2H, J = 8.4 Hz, $C(O)CH_2$), 5.65 (dt, 1H, J = 10.2, 1.8 Hz, vinyl), 5.97 (dt, 1H, J = 10.2, 3.6 Hz, vinyl); $^{13}C$ NMR δ 19.3, 24.5, 28.7, 33.9, 34.4, 89.5, 128.3, 132.5, 176.7; HRMS m/z ($M^+$) calcd for $C_9H_{12}O_2$ 152.08373, found 152.08343.



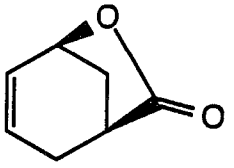
IR (neat) 1775 (C=O) $cm^{-1}$; $^1H$ NMR δ 2.02 (m, 1H, $OCCH_2$), 2.35-2.58 (m, 3H, $C(O)CH_2$ and $OCCH_2$), 4.95 (qt, 1H, J = 7.2, 1.2 Hz, OCH), 5.26 (dt, 1H, J = 10.5, 1.2 Hz, vinyl), 5.37 (dt, 1H, J = 16.8, 1.2 Hz, vinyl), 5.90 (ddd, 1H, J = 16.8, 10.5, 6.0 Hz, vinyl); $^{13}C$ NMR δ 28.3, 80.5, 117.4, 135.5, 176.9 (minus 1 peak due to overlap); HRMS m/z ($M^+$) calcd for $C_6H_8O_2$ 112.05243, found 112.05219.



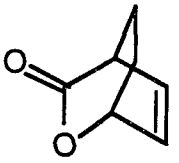
IR (neat) 1770 (C=O) $cm^{-1}$; $^1H$ NMR δ 0.82 (t, 3H, J = 6.9 Hz, $CH_3$), 1.27 (m, 4H, $CH_2CH_2$), 1.85-2.05 (m, 3H, $C=CCH_2$ and $C(O)CCH_2$), 2.30 (m, 1H, $C(O)CCH_2$), 2.40-2.58 (m, 2H, $C(O)CH_2$), 4.82 ( q, 1H, J = 7.2 Hz, OCH), 5.43 (ddd, 1H, J = 15.3, 7.2, 1.2 Hz, vinyl), 5.73 (dt, J = 15.3, 6.9 Hz, 1H, vinyl); $^{13}C$ NMR δ 13.9, 22.2, 28.8, 28.9, 30.9, 31.8, 81.2, 127.4, 135.7, 177.1; HRMS m/z ($M^+$) calcd for $C_{10}H_{16}O_2$ 168.11503, found 168.11527.



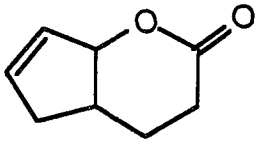
IR (neat) 1770 (C=O) $cm^{-1}$; $^1H$ NMR δ 1.77 (s, 3H, $CH_3$), 2.04 (m, 1H, $OCCH_2$), 2.38 (m, 1H, $OCCH_2$), 2.55 (m, 2H, $C(O)CH_2$), 4.87 (t, 1H, J = 7.2 Hz, OCH), 4.94 (d, 1H, J = 0.6 Hz, vinyl), 5.01 (d, 1H, J = 0.6 Hz, vinyl); $^{13}C$ NMR δ 17.5, 26.9, 28.5, 82.5, 112.3, 141.9, 177.0; HRMS m/z ($M^+$) calcd for $C_7H_{10}O_2$ 126.06808, found 126.06832.



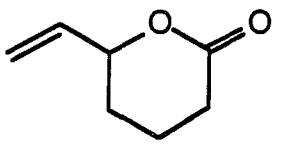
The $^1H$ NMR spectrum was identical with that previously reported by Martin and co-workers.[41]



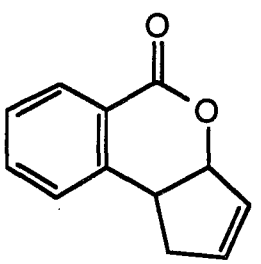
The $^1H$ NMR spectrum was identical with that previously reported by Bonjouklian and Ruden.[15]



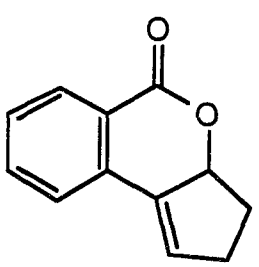
IR (neat) 1730 (C=O) $cm^{-1}$; $^1H$ NMR δ 1.65 (m, 1H, $C(O)CCH_2$), 2.10 (m, 1H, $C(O)CCH_2$), 2.26 (m, 1H, $CH_2C\underline{H}CH_2$), 2.40 (m, 2H, $C{=}CCH_2$), 2.73 (m, 2H, $C(O)CH_2$), 5.42 (m, 1H, OCH), 5.82 (m, 1H, vinyl), 6.09 (m, 1H, vinyl); $^{13}C$ NMR δ 24.6, 28.8, 32.9, 38.6, 86.2, 129.2, 136.2, 172.6; HRMS m/z ($M^+$) calcd for $C_8H_{10}O_2$ 138.06808, found 138.06803. The stereochemistry of the ring juncture was not established.



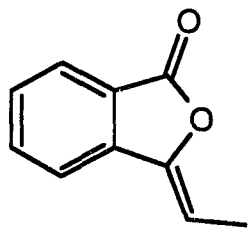
IR (neat) 1735 (C=O) $cm^{-1}$; $^1H$ NMR δ 1.60-2.10 (m, 4H, $C(O)CCH_2CH_2$), 2.55 (m, 2H, $C(O)CH_2$), 4.83 (m, 1H, OCH), 5.25 (dt, 1H, J = 10.5, 1.2 Hz, vinyl), 5.35 (dt, 1H, J = 17.1, 1.2 Hz, vinyl), 5.83 (ddd, 1H, J = 17.1, 10.5, 5.4 Hz, vinyl); $^{13}C$ NMR δ 18.1, 27.9, 29.6, 80.2, 116.8, 136.0, 171.1; HRMS m/z ($M^+$) calcd for $C_7H_{10}O_2$ 126.06808, found 126.06788.



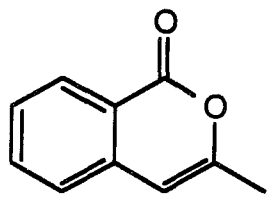
IR ($CDCl_3$) 1715 (C=O) $cm^{-1}$; $^1H$ NMR δ 2.50 (m, 1H, $C=CCH_2$), 2.85 (m, 1H, $C=CCH_2$), 3.51 (q, 1H, J = 7.5 Hz, ArCH), 5.54 (dt, 1H, J = 6.3, 1.8 Hz, OCH), 6.10 (m, 1H, vinyl), 6.32 (m, 1H, vinyl), 7.23-7.45 (m, 2H, Ar), 7.55 (t, 1H, J = 7.2 Hz, Ar), 8.15 (d, 1H, J = 7.5 Hz, Ar); $^{13}C$ NMR δ 38.6, 40.2, 84.2, 122.8, 127.6, 128.1, 130.0, 130.5, 133.9, 138.9, 140.6, 164.0; HRMS m/z ($M^+$) calcd for $C_{12}H_{10}O_2$ 186.06808, found 186.06839.



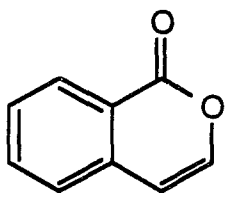
IR ($CDCl_3$) 1715 (C=O) $cm^{-1}$; $^1H$ NMR δ 2.39 (m, 1H, $OCCH_2$), 2.49 (m, 1H, $OCCH_2$), 2.67 (m, 1H, $C=CCH_2$), 2.78 (m, 1H, $C=CCH_2$), 5.61 (m, 1H, OCH), 6.33 (m, 1H, vinyl), 7.34 (d, 1H, J = 7.5 Hz, Ar), 7.51 (t, 1H, J = 7.5 Hz, Ar), 7.66 (t, 1H, J = 7.5 Hz, Ar), 7.88 (d, 1H, J = 7.5 Hz, Ar); $^{13}C$ NMR δ 32.0, 36.6, 98.1, 121.8, 125.3, 125.9, 129.1, 130.6, 134.3, 139.5, 152.7, 169.9; HRMS m/z ($M^+$) calcd for $C_{12}H_{10}O_2$ 186.06808, found 186.06849.



The $^1H$ NMR spectrum was identical with that previously reported by Mali and co-workers.[11]



The $^1H$ NMR spectrum was identical with that previously reported by Lin and co-workers.[42]



The $^1H$ NMR spectrum was identical with that previously reported by Narasimhan and Mali.[43]

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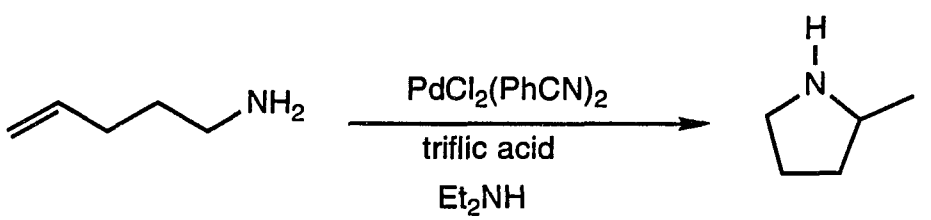
# PAPER II. SYNTHESIS OF UNSATURATED NITROGEN HETEROCYCLES VIA PALLADIUM(II)-CATALYZED CYCLIZATION OF OLEFINIC TOSYLAMIDES

# INTRODUCTION

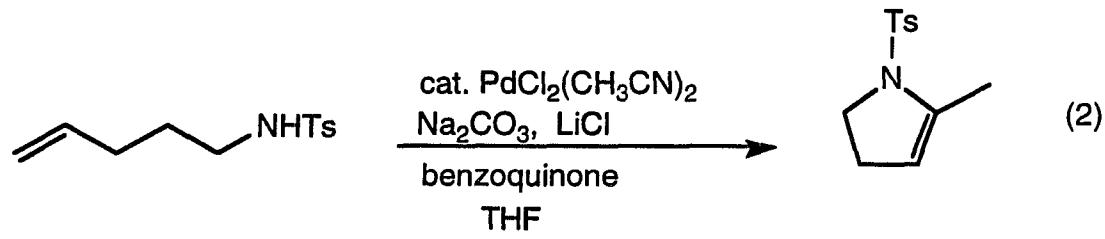
In recent years palladium-promoted amination of olefins has been shown to be a particularly useful method for the synthesis of nitrogen-containing heterocycles. These palladium-assisted methods employ either Pd(0)- or Pd(II)-based methodology. Since the work of the author is based on Pd(II) methodology, this will be discussed in detail.

Pugin and Venanzi have shown that trifluoromethanesulphonate salts of 4- and 5-alkenylamines cyclize in the presence of $PdCl_2(PhCN)_2$ and a nitrogen base to the corresponding pyrrolidines and methylpiperidine respectively.[1] For example 4-pentenylamine cyclizes to 2-methylpyrrolidine under these conditions (eq 1).

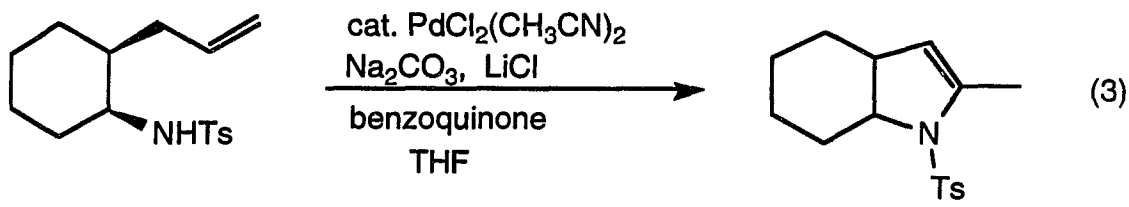



(1)

Hegedus and McKearin have used Pd(II)-catalyzed intramolecular amination for the cyclization of ω-olefinic tosylamides to a variety of nitrogen heterocycles.[2] Equations 2 and 3 show examples of this methodology.



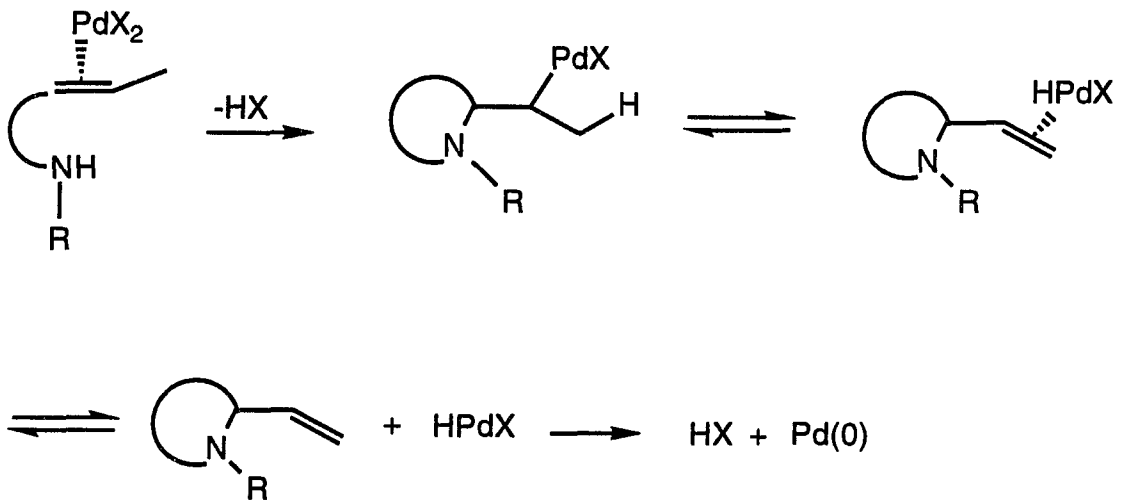

(2)



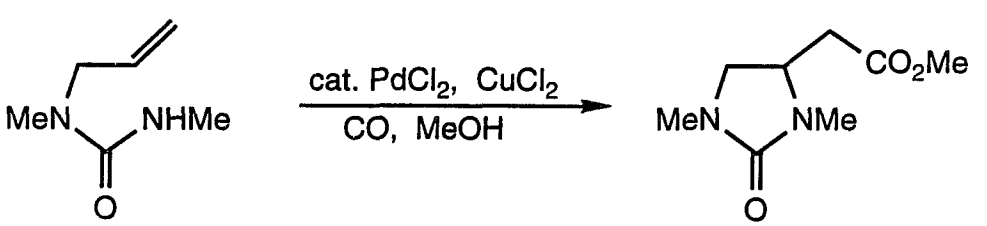

(3)

The fundamental mechanism of this type of aminopalladation can be seen in Scheme 1. The nucleophile (N) first attacks the olefin coordinated to the metal, forming a sigma-bonded Pd(II)-intermediate. Subsequent β-hydride elimination of HPdX leads to the final cyclization product, and reductive elimination of the resulting HPdX affords Pd(0) and HX. Intramolecular versions of this reaction have become a useful method for the synthesis of nitrogen-containing heterocycles.

Scheme 1

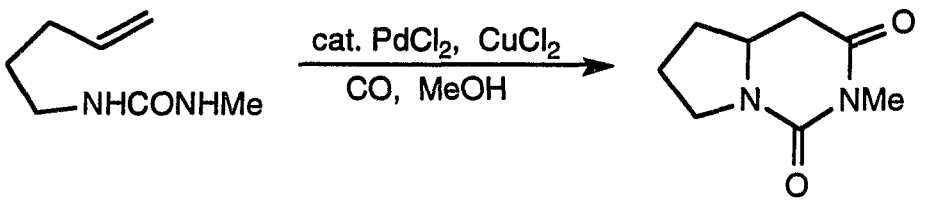



Tamaru and co-workers have employed substituted ureas (which are known to be ambident nucleophiles) as a nitrogen nucleophile for the palladium(II)-catalyzed aminocarbonylation of unsaturated amines.[3] Under his reaction conditions, a number of N-2-propenyl-, N-3-butenyl, N-4-pentenyl and N-5-hexenylureas undergo palladium(II)-catalyzed aminocarbonylation. An example of this reaction is shown below (eq 4).



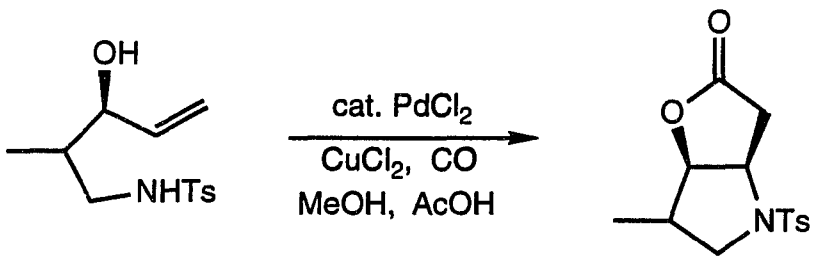

(4)

Tamaru and co-workers have also employed the same approach for the palladium(II)-catalyzed aminocarbonylation of unsaturated carbamates (eq 5).[4]



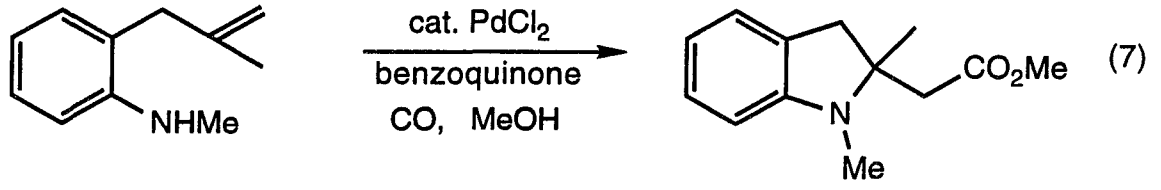

(5)

Tamaru and co-workers have taken the art of CO insertion a step further in the palladium(II)-catalyzed intramolecular aminocarbonylation of 3-hydroxy-4-pentenylamines and 4-hydroxy-5-hexenylamines (eq 6).[5]

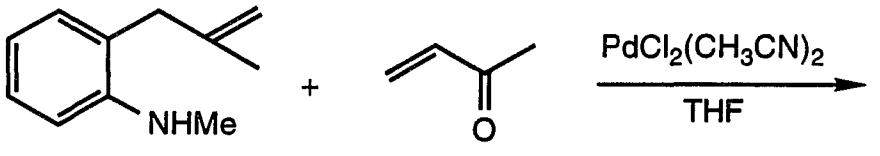


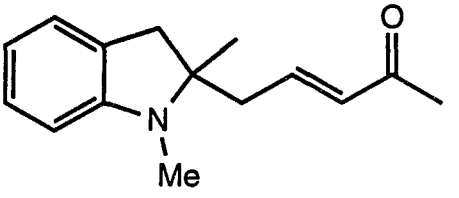

(6)

Hegedus and co-workers have also developed palladium(II)-assisted cyclization-insertion reactions in the synthesis of aromatic heterocycles.[6] Hegedus found that not only was carbon monoxide able to insert into the sigma-alkylpalladium bond, but α,β-unsaturated ketones could insert as well (eqs 7 and 8).



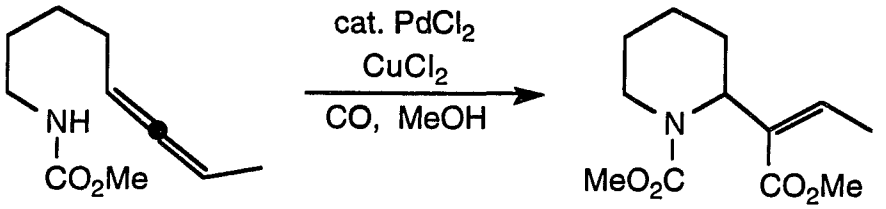

(7)



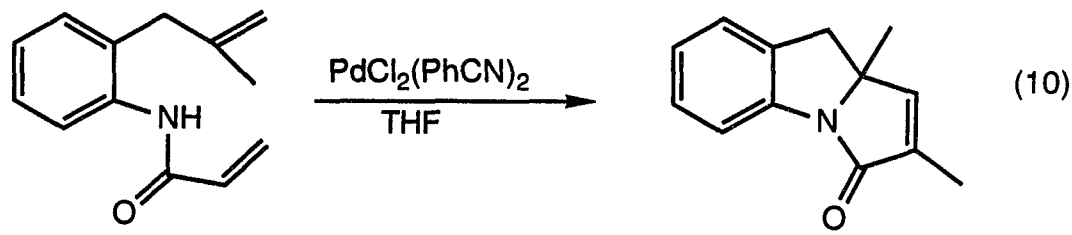

(8)

Lathbury and co-workers have performed palladium(II)-catalyzed intramolecular aminocarbonylation on allenes (eq 9).[7] In addition, Fox and co-workers have implemented this methodology in the enantioselective synthesis of Pumiliotoxin 251D.[7b]




(9)

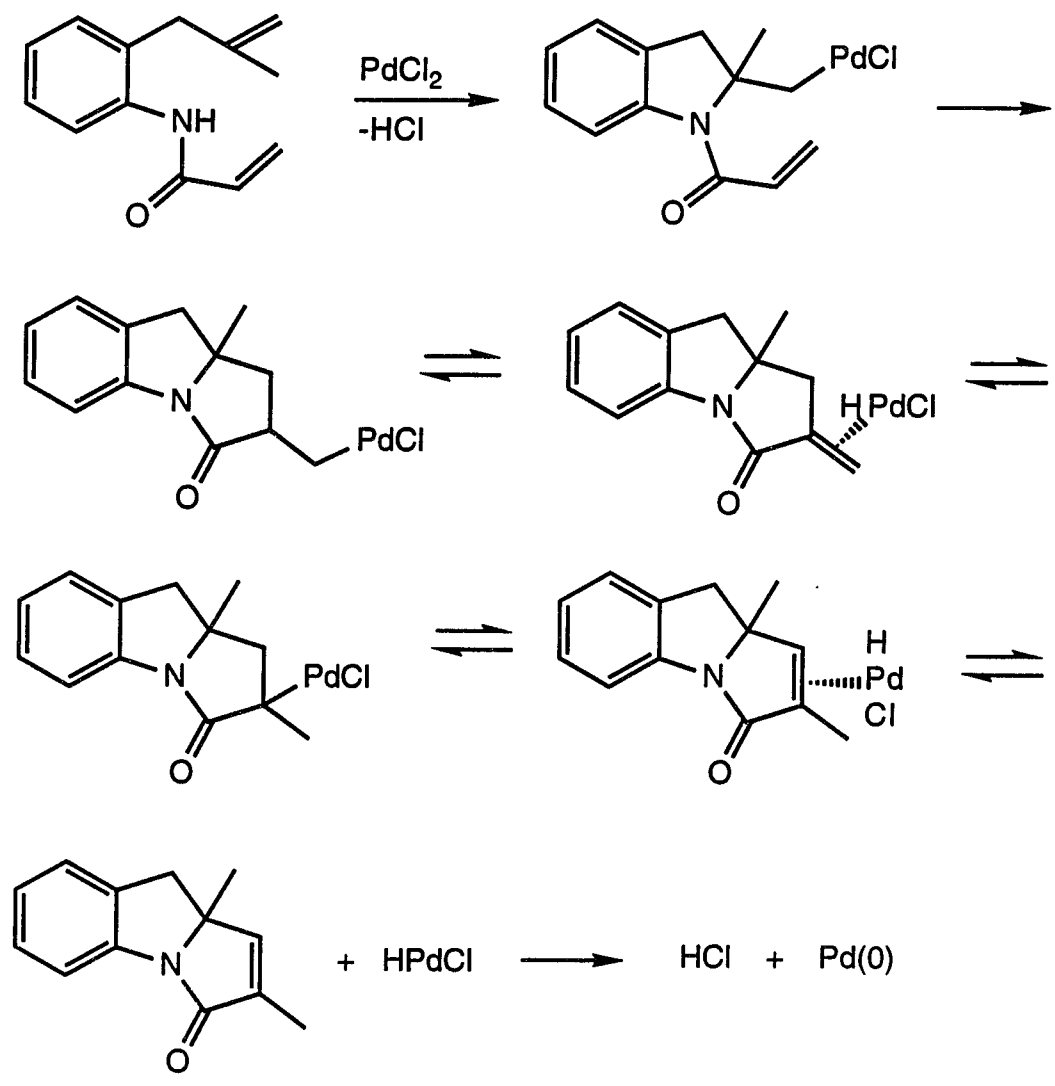
Danishefsky and Taniyama[8] have performed an intramolecular version of the Hegedus process previously shown in equation 8 (eq 10).



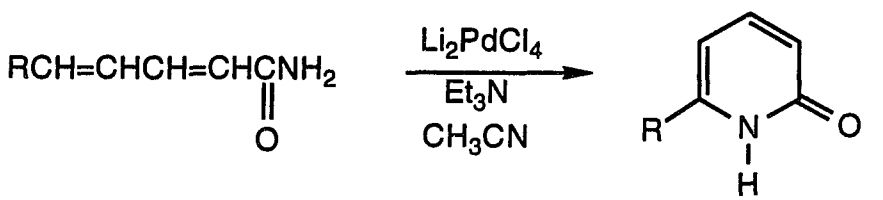

(10)

This insertion reaction (eq 10) proceeds through the expected aminopalladation step to provide a terminal sigma-alkylpalladium species. Subsequent olefin insertion and subsequent β-hydride eliminations provides the final product. Reductive elimination of the resulting HPdCl affords Pd(0) and HCl. This can be more easily understood by examining Scheme 2.

Scheme 2

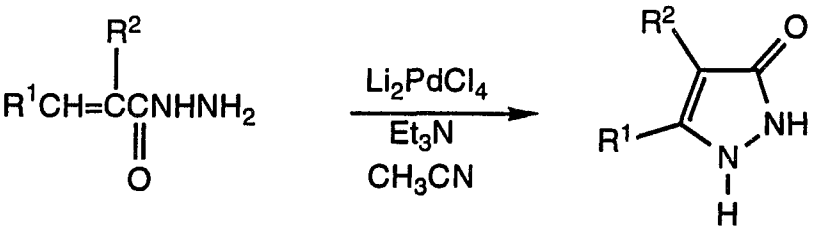


Kasahara and Saito have developed an aminopalladation methodology for the synthesis of 2-pyridones from the corresponding 2,4-pentadienamides (eq 11).[9]



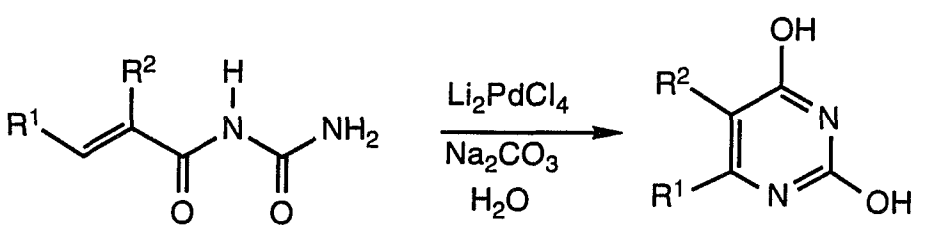

(11)

Kasahara has also utilized similar reaction conditions for the synthesis of 3-pyrazolones from α,β-unsaturated acid hydrazides (eq 12).[10]



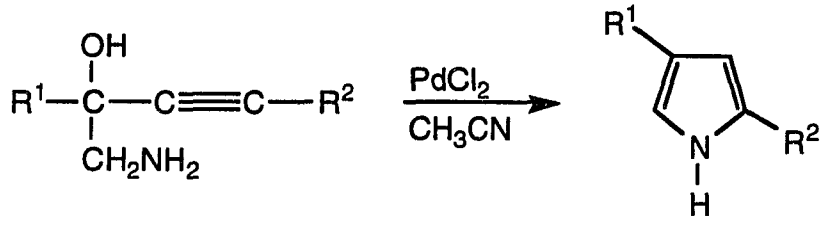

(12)

Kasahara and Fukuda have reported a palladium(II)-catalyzed synthesis of substituted uracils using unsaturated acyl ureas (eq 13).[11]




(13)

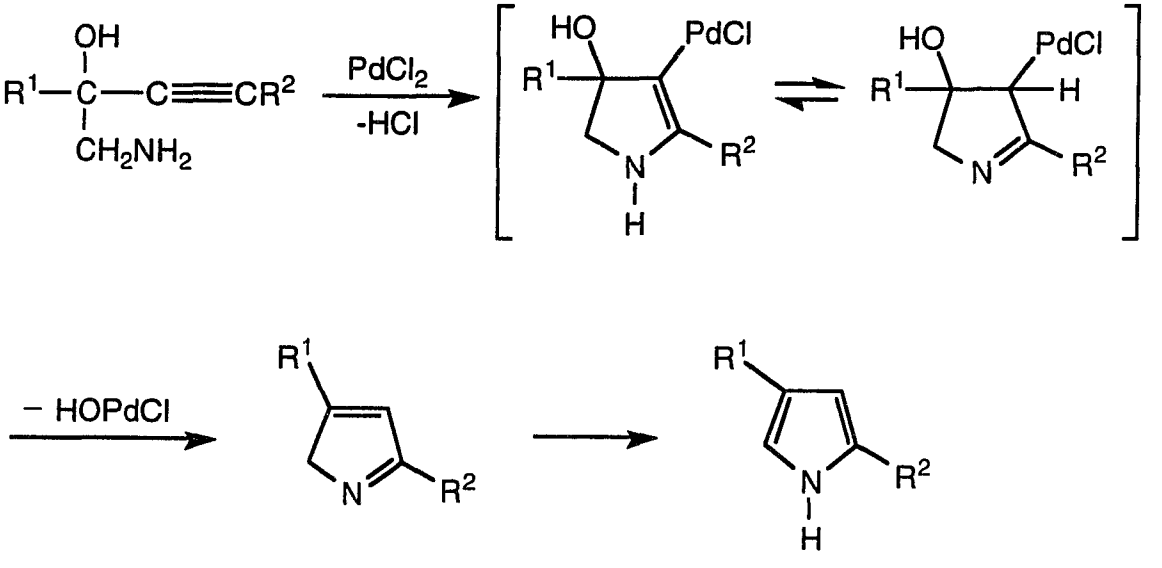
Utimoto and co-workers have prepared pyrrole derivatives by the catalytic action of palladium(II) on the corresponding 1-amino-3-alkyn-2-ols (eq 14).[12]




(14)

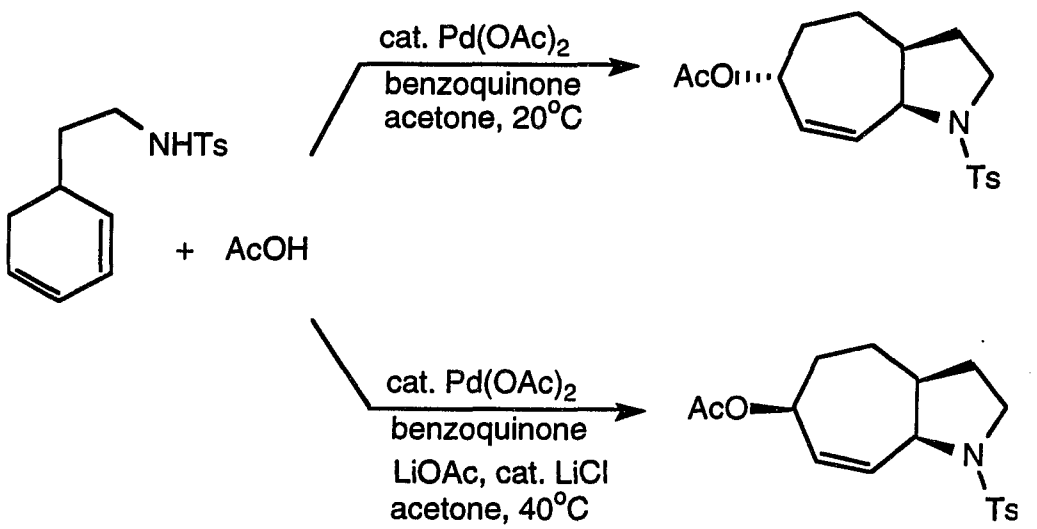
The mechanism proposed by Utimoto proceeds via aminopalladation, followed by a β-hydroxy elimination. This intermediate product undergoes a hydrogen shift to yield the final substituted pyrrole. This can be seen in Scheme 3.

Scheme 3

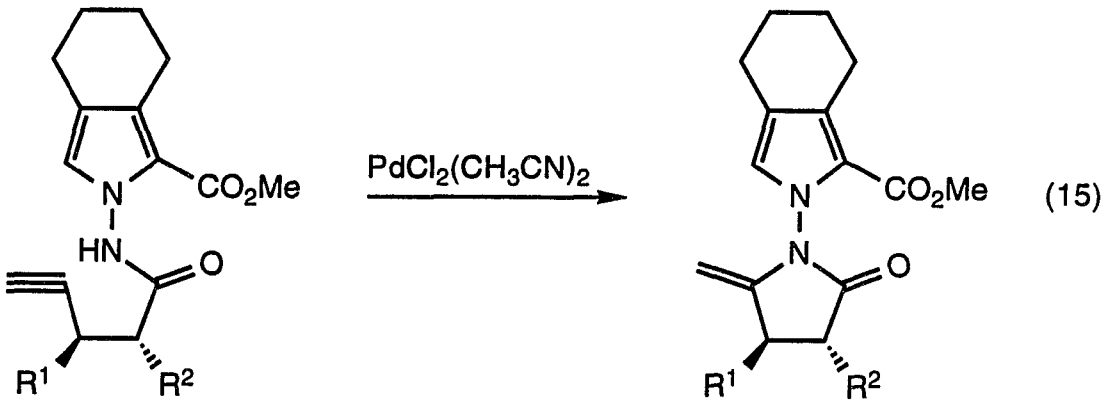


Bäckvall and Andersson have developed a palladium(II)-catalyzed cyclization reaction of amido dienes (Scheme 4),[13] which they have utilized in the synthesis of α- and γ-lycorane.[13a]

Scheme 4

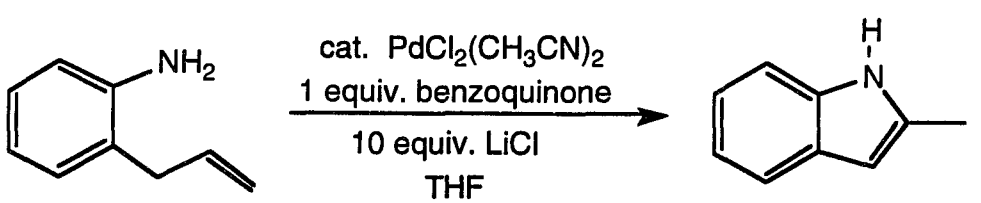



Jacobi and Rajeswari have incorporated a palladium(II)-catalyzed cyclization in their synthesis of a key intermediate involved in their synthesis of homochiral dihydropyrromethenones (eq 15).[14]

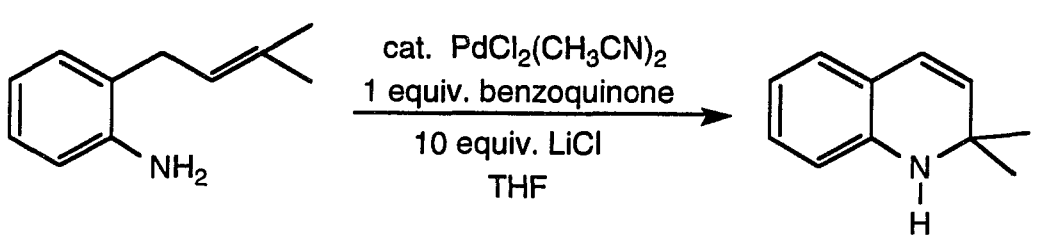



(15)

Hegedus and co-workers have cyclized a variety of *o*-allylanilines to indoles using palladium (eqs 16 and 17).[15]

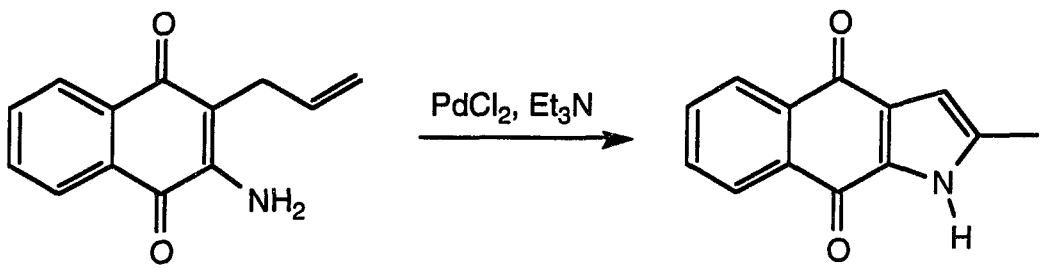



(16)

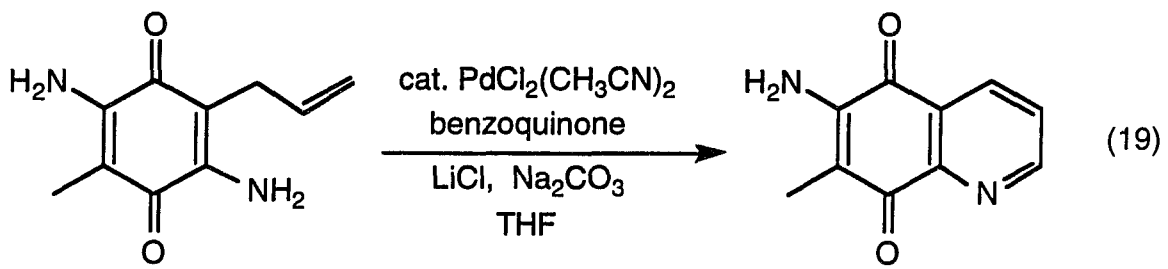



(17)

Aminoquinones undergo analogous cyclizations (eqs 18 and 19).[16]



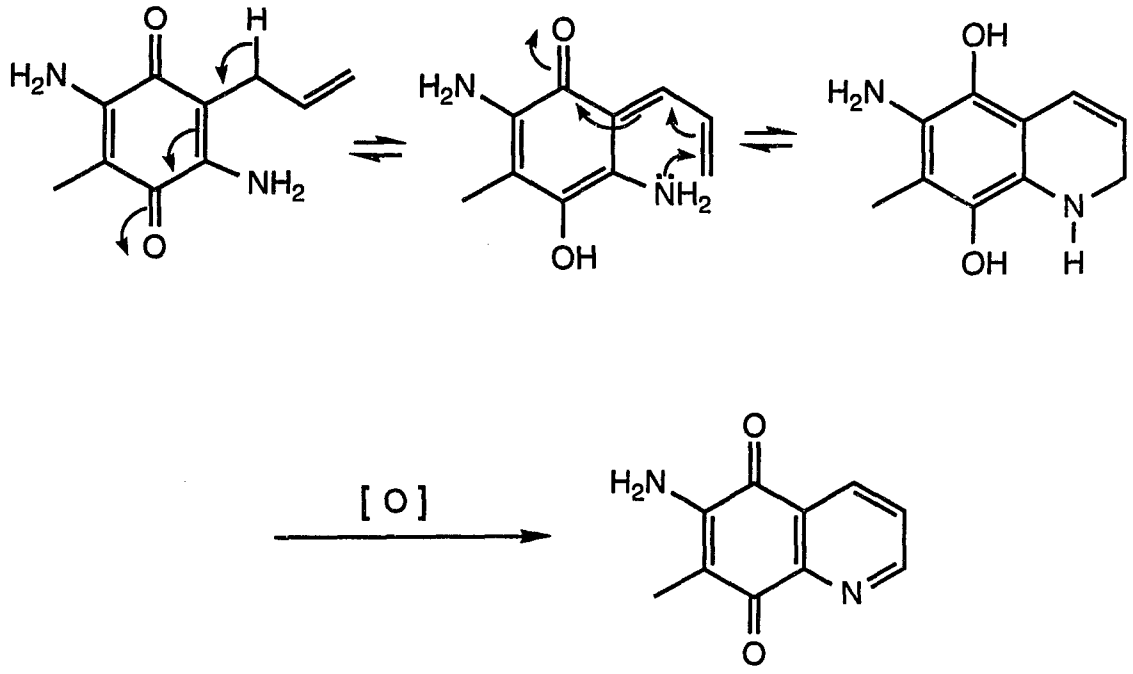

(18)



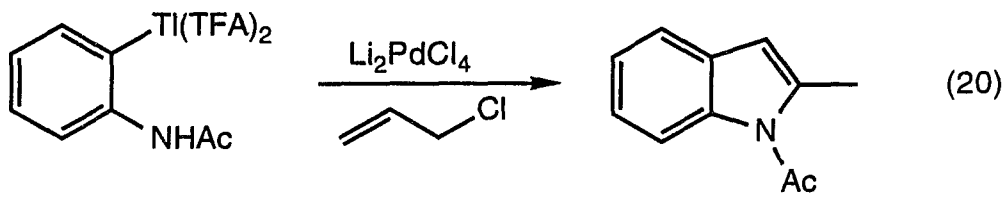

(19)

It is important to notice that equation 19 does not give the predicted 5-membered ring product, but instead provides the 6-membered ring product. A reasonable route for this oxidative cyclization is shown in Scheme 5 and involves a simple enolization-Michael addition-oxidation process.[16c]

Scheme 5




Larock and co-workers have utilized a one pot, two step palladium(II) process in the synthesis of indoles (eq 20).[17] The first part of this process

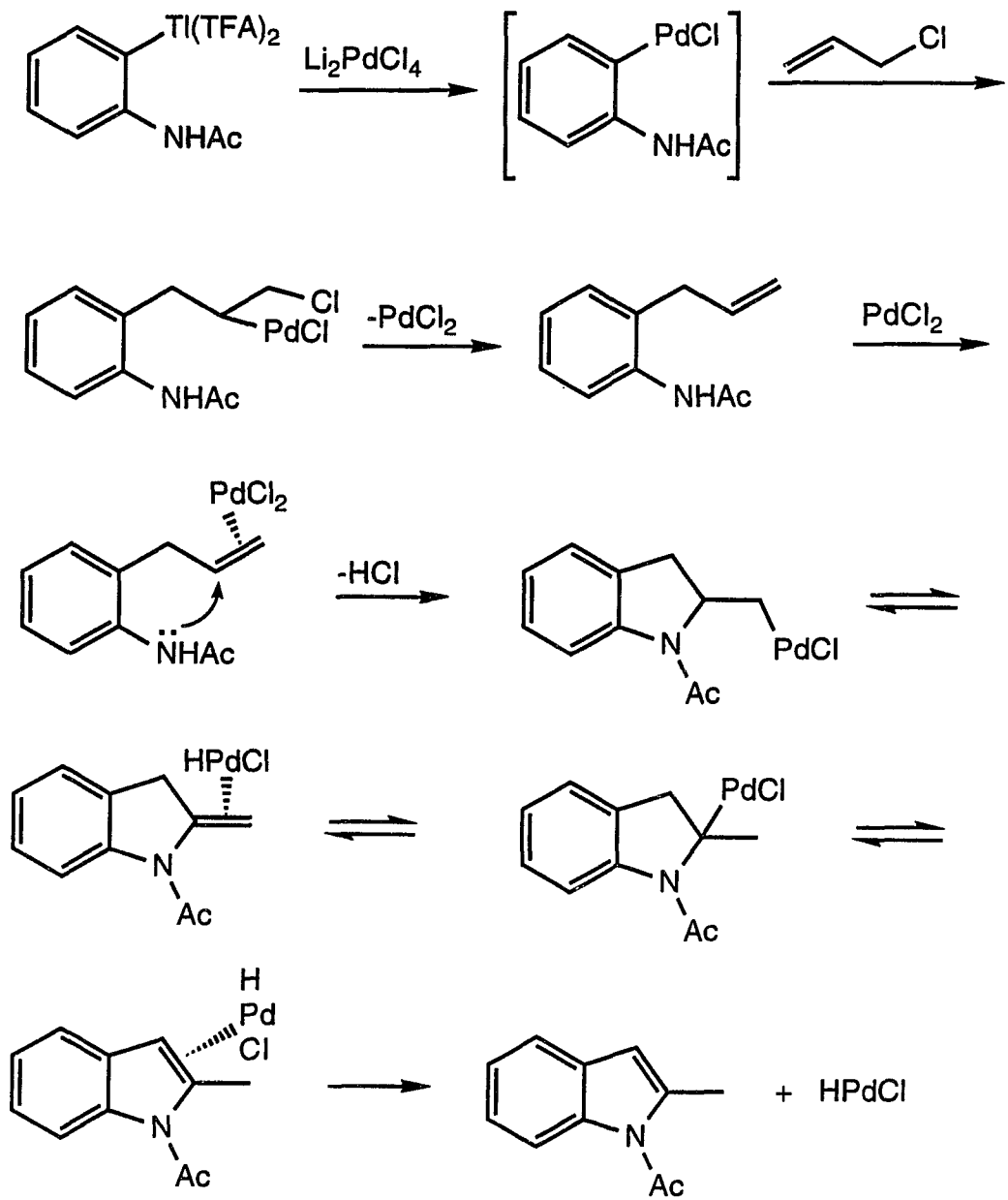



(20)

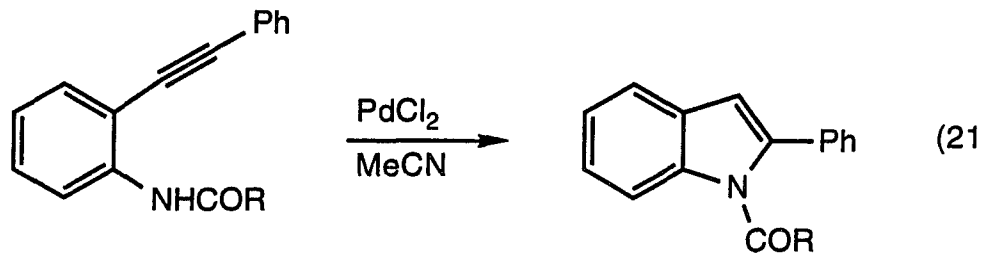
involves transmetallation of thallium by palladium, followed by insertion of the allyl chloride and elimination of $PdCl_2$ to provide the intermediate allylaniline. The

second part of this process, entails aminopalladation on the olefin of the allylaniline by the nitrogen nucleophile. The mechanism involved is shown in Scheme 6.

Scheme 6



The cyclization of aryl acetylenes has also been used in the synthesis of indoles.[18-20] For example, Taylor and co-workers have developed an aminopalladation approach via aryl acetylenes for the synthesis of indoles (eq 21).[18]

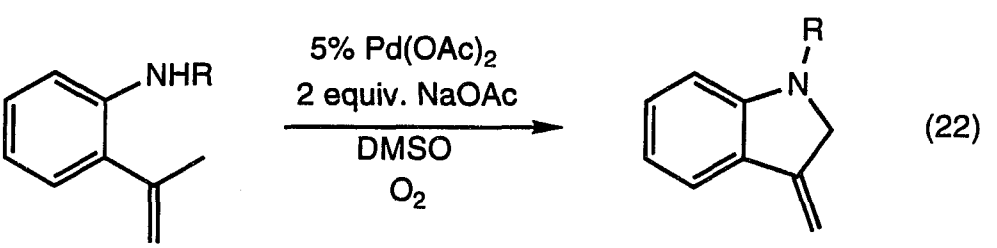



(21)

Previously reported palladium(II)-based methodologies for the cyclization of alkenylamines require the use of a stoichiometric amount of a palladium(II) salt, or additional reoxidants other than oxygen to reoxidize Pd(0) formed *in situ* back to Pd(II). We felt that our unique palladium(II)-catalyzed cyclization procedure for the cyclization of alkenoic acids, which eliminates the need for additional reoxidants other than oxygen, could successfully be employed in the cyclization of unsaturated amines.

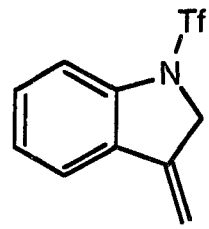
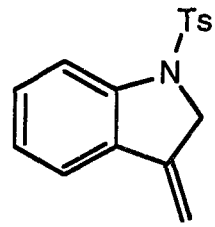
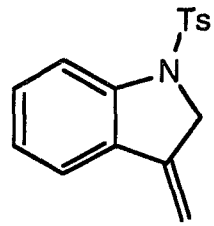
# RESULTS AND DISCUSSION

As previously shown, numerous five- and six-membered ring nitrogen heterocycles have been prepared from olefinic amines by palladium(II)-based methodology. In this chapter, it was our goal to improve upon this methodology. With this goal in mind, a number of N-substituted-2-isopropenylanilines were subjected to the standard reaction conditions A for the cyclization of alkenoic acids used previously in Paper 1 (eq 22). These results are summarized in Table 1.




(22)

Table 1. Substituent Effects on the Cyclization of 2-Isopropenylanilines[a]

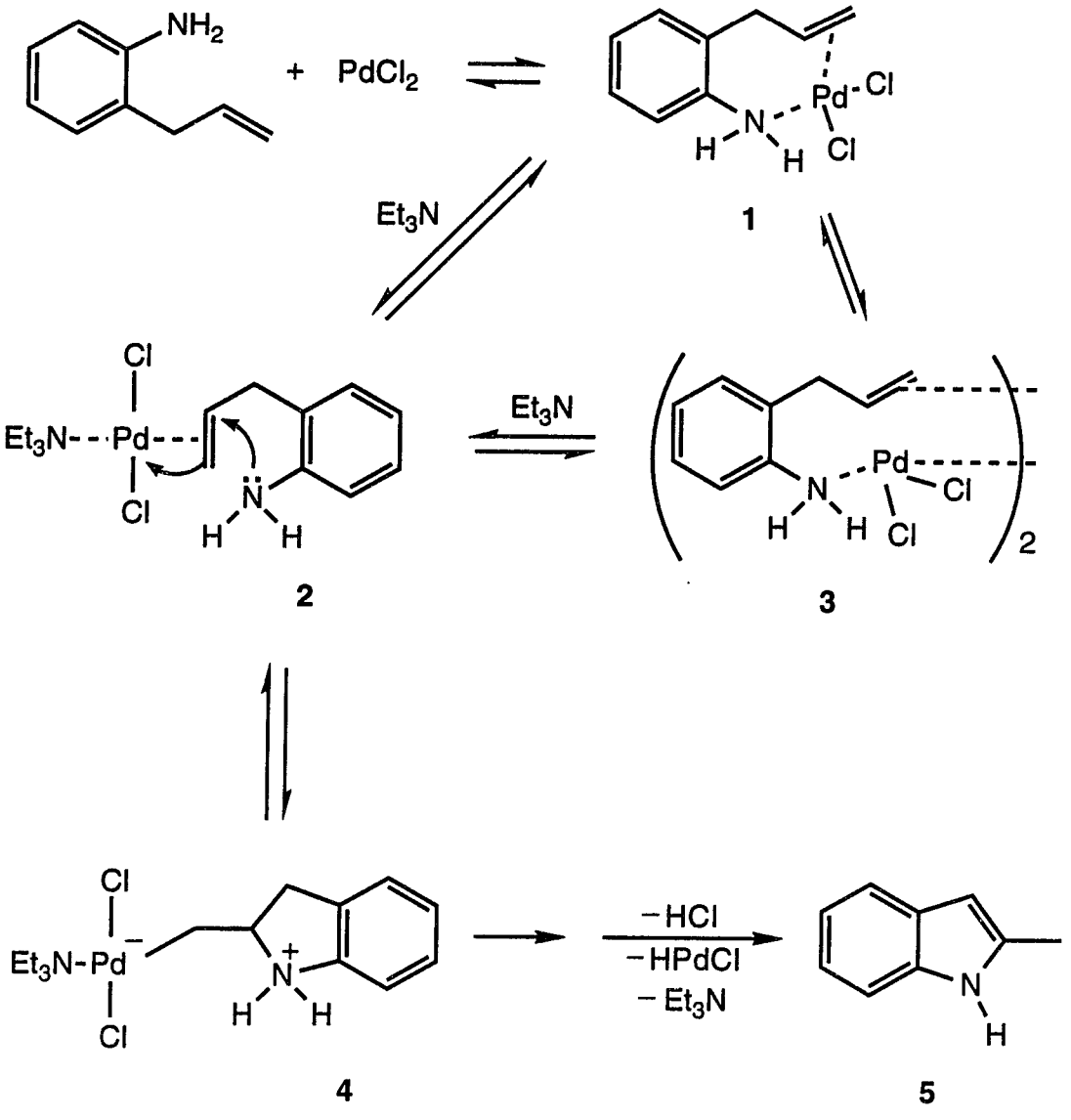
| Entry | R | Time (hr), Temp. (°C) | Product | % Isolated Yield |
|---|---|---|---|---|
| 1 | H | 72, 25 | Starting Material | --- |
| 2 | H | 72, 80 | Starting Material | --- |
| 3 | Ac | 72, 25 | Starting Material | --- |
| 4 | Tf | 72, 25 |  | 46 |
| 5 | Ts | 72, 25 |  | 58 |
| 6 | Ts | 24,25 |  | 32 |

[a]The reaction conditions entail 0.25 mmol of the amide, 5 mol% of $Pd(OAc)_2$, 2 equiv. of NaOAc and 5 ml of DMSO under 1 atm. $O_2$.

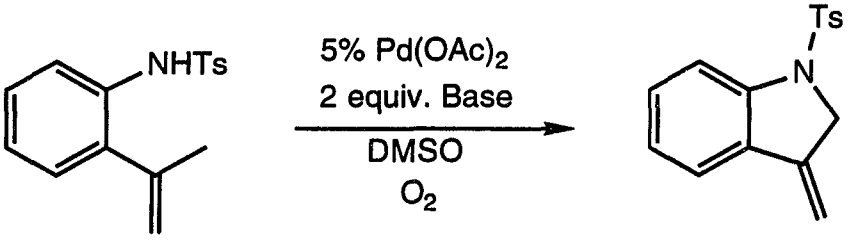
The results of entries 1 and 2 indicate that the free amine fails to cyclize under these conditions. Hegedus and co-workers also had difficulty cyclizing free amines.[16b] It was proposed that in the case of *o*-allylaniline the equilibrium shown in Scheme 7 was established. Hegedus determined that in the absence of triethylamine, the stable complex **3** is formed. Since the amino group is coordinated to the palladium, the amine cannot attack the olefin. The addition of triethylamine leads to displacement of the weakly basic aromatic amine, generating complex **2**, which allows for amination of the coordinated olefin. Attack on the coordinated olefin by the aromatic amine results in the sigma-alkylpalladium complex **4**, which upon the loss of HCl, β-hydride elimination, and rearrangement provides HPdCl and the final product **5**. With these earlier findings, it is quite possible that the free amine of entries 1 and 2 is having the same coordination effect in our system.

Since the addition of triethylamine to the cyclization of alkenoic acids decreased the rate of reaction under our conditions (entry 2, Table 2 of Chapter 1), a different route was chosen to accomplish the cyclization of amines. This route involved the addition of a substituent to the amine in order to change the basicity of the nitrogen. By the addition of an electron-withdrawing substituent to the nitrogen, the amine hydrogen becomes more acidic. In the presence of a base, a better nucleophile is established from the formation of the conjugate base of the amine. Introducing an acetyl substituent does not appear to have a strong enough electron-withdrawing effect to generate the desired nitrogen anion for nucleophilic attack (entry 3). However, the triflate substituent proved to be successful, giving the desired product in 46% yield (entry 4). This was improved by changing to a tosyl substituent (entry 5). The result of entry 6 revealed that the reaction was not complete after 24 hours. This result would account for the decreased yield.

Scheme 7


NH2
+ PdCl2
Pd
Cl
N
H
H
Cl
1
Et3N
Et3N
Et3N
Cl
Et3N
Pd
Cl
N
H
H
2
Pd
Cl
N
H
H
Cl
2
3
Cl
Et3N
Pd
Cl
N
H
H
4
−HCl
−HPdCl
− Et3N
N
H
5

With these results, a variety of bases were examined (eq 23). These results are shown in Table 2.




(23)

Table 2. Base Effects on the Cyclization of N-Tosyl-2-isopropenylaniline[a]

| Entry | Base | Time (hr) | % Isolated Yield |
|---|---|---|---|
| 1 | --- | 72 | --- |
| 2 | NaOAc | 72 | 58 |
| 3 | $Na_2CO_3$ | 72 | 49 |
| 4 | $NaHCO_3$ | 72 | 50 |
| 5 | $LiOAc•2H_2O$ | 24 | 56 |

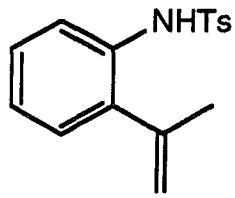
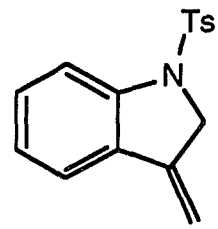
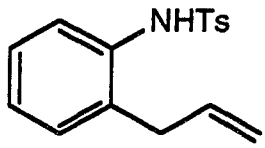
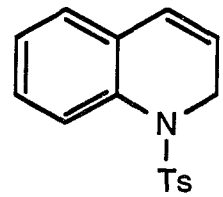
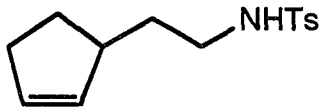
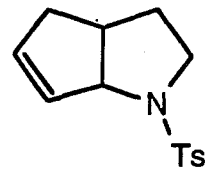
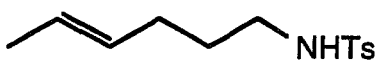
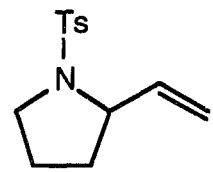
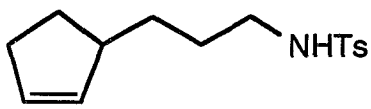
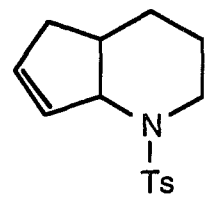
[a]The reaction conditions entail 0.25 mmol of the tosylamide, 5 mol% of $Pd(OAc)_2$, 2 equiv. of the appropriate base and 5 ml of DMSO under 1 atm. $O_2$.

From the results of Table 2, it is apparent that a base must be present in order for the reaction to proceed, but the type of inorganic base used does not seem to be crucial (entries 1-4). The use of $LiOAc{\bullet}2H_2O$ as the base increased the rate of reaction without decreasing the yield (entry 5), as it did with the cyclization of alkenoic acids (entry 10, Table 2 of Chapter 1). What is not shown in Table 2 is that by using NaOAc and replacing DMSO with a 9:1 DMSO/$H_2O$ solvent system provides the same result as entry 5.

The results of Table 2 establish that the same standard reaction conditions A, which proved successful in the cyclization of alkenoic acids, can also be employed in the cyclization of olefinic tosylamides. Using these standard reaction conditions A, monocyclic and fused nitrogen heterocycles have been synthesized from a variety of olefinic tosylamides in moderate to excellent yields as shown in Table 3.

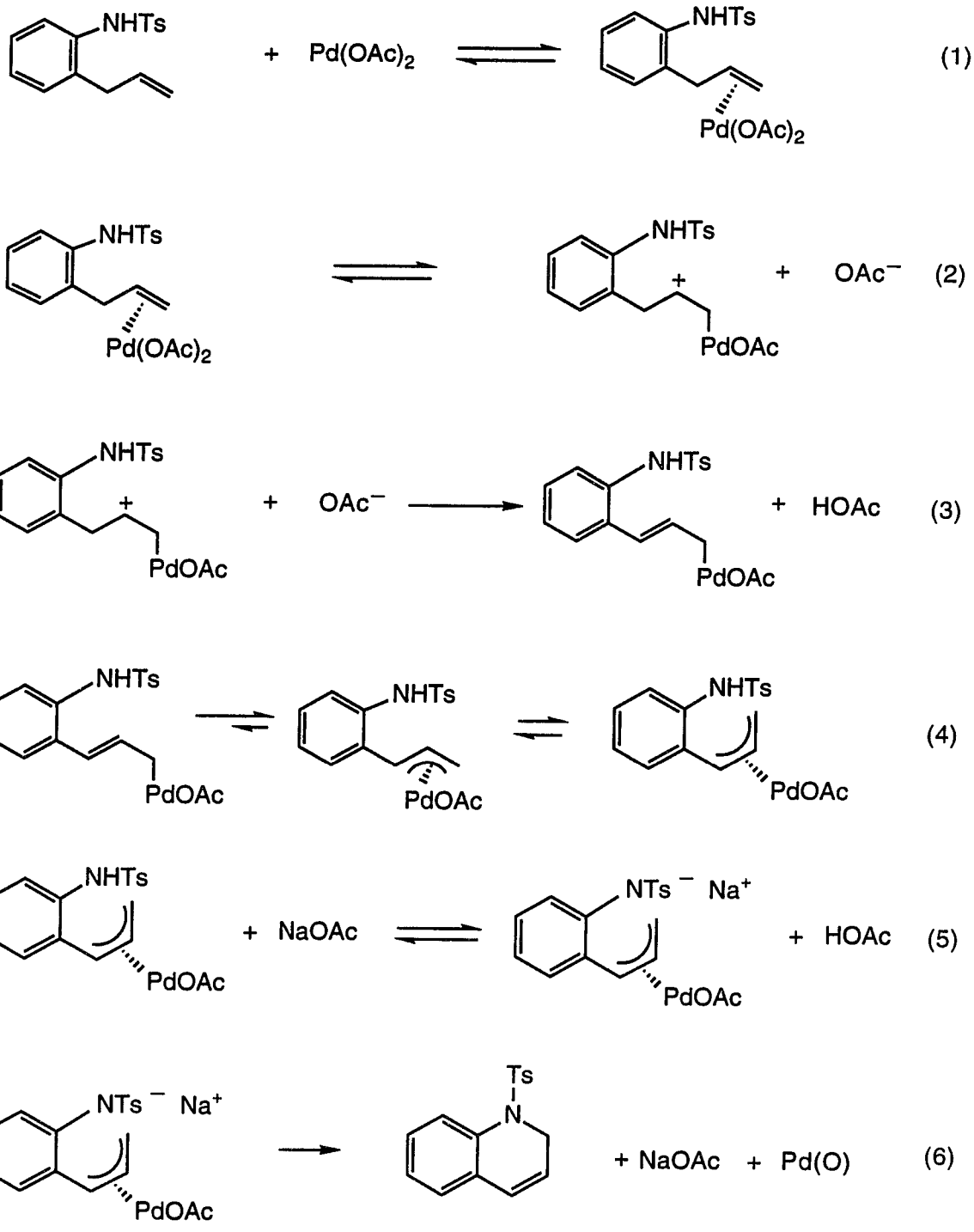
As previously shown, N-tosyl-2-isopropenylaniline cyclized to form the expected five-membered ring heterocycle (entry 1). The cyclization of N-tosyl-2-allylaniline unexpectedly yielded N-tosyl-1,2-dihydroquinoline in excellent yield (entry 2). As previously shown, Hegedus and co-workers cyclized *o*-allylaniline to 2-methylindole using a catalytic amount of $PdCl_2(MeCN)_2$, benzoquinone and LiCl in a THF solvent (eq 16).[15] The formation of the quinoline product under our conditions suggests that perhaps the reaction is taking place through a different mechanism. It is presumed that the formation of the six-membered ring product is occurring through a $\pi$-allylpalladium species as shown in Scheme 8.

Table 3. Palladium(II)-Catalyzed Cyclization of Olefinic Tosylamides[a]

| Entry | Olefinic Tosylamide | Time (hr), Temp. (°C) | Product | % Isolated Yield |
|---|---|---|---|---|
| 1 |  | 72, 25 |  | 58 |
| 2 |  | 72, 80 |  | 86 |
| 3 |  | 72, 25 |  | 86 |
| 4 |  | 72, 25 |  | 93 |
| 5 |  | 96, 80 |  | 82 |

[a]The reaction conditions entail 0.25 mmol of the tosylamide, 5 mol% of $Pd(OAc)_2$, 2 equiv. of NaOAc and 5 ml of DMSO under 1 atm. $O_2$.

Scheme 8

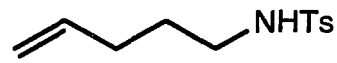

NHTs
+ Pd(OAc)2
NHTs
Pd(OAc)2
(1)
NHTs
Pd(OAc)2
NHTs
+
PdOAc
+ OAc−
(2)
NHTs
+
PdOAc
+ OAc−
NHTs
+ HOAc
PdOAc
(3)
NHTs
PdOAc
NHTs
PdOAc
NHTs
PdOAc
(4)
NHTs
PdOAc
+ NaOAc
NTs − Na+
PdOAc
+ HOAc
(5)
NTs − Na+
PdOAc
Ts
N
+ NaOAc + Pd(O)
(6)

The mechanism proposed for the formation of this possible π-allylpalladium intermediate involves the presence of palladium acetate, which can coordinate with the olefin of the tosylamide to form a π-complex ( step 1). The formation of this π-complex delocalizes the electron density of the olefin. If the palladium is allowed to remove enough electron density to create a free carbocation (2), loss of a benzylic proton can occur leading to the formation of a sigma-allylpalladium species (3). This collapses to a π-allylpalladium intermediate (4). π-Allylpalladium species are known to undergo displacement of palladium by nucleophiles. With the formation of the anion, a nucleophile is established within the molecule (5). This nucleophile performs an intramolecular attack on the terminal end of the π-allylpalladium complex to provide the dihydroquinoline (6). With our solvent DMSO being more polar than the THF solvent used by Hegedus for the cyclization of *o*-allylaniline to 2-methylindole, a more polar intermediate, such as the free carbocation, can be established; whereas THF, a much less polar solvent, would not allow for such a polar intermediate. The pathway proposed for the *o*-allylaniline cyclization via the less polar intermediate would entail an aminopalladation mechanism similar to Scheme 1.

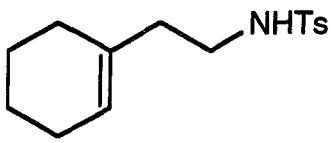
The results of entries 3 and 4 indicate that five-membered ring heterocycles can be efficiently synthesized from the corresponding cyclic and acyclic 4-alkenyl tosylamides. It is apparent that six-membered ring heterocycles can also be formed through this methodology (entries 2 and 5), although this seems limited as revealed in entries 5 and 6 of Table 4. Hegedus and co-workers found they were unable to catalytically cyclize non-aromatic alkenyl tosylamides to the corresponding 6-membered ring heterocycles.

There are a few tosylamides which failed to cyclize. These can be seen below:

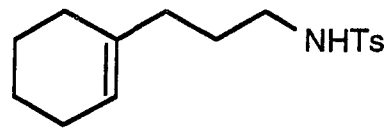

**6**



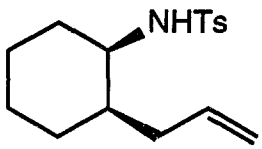

**7**




**8**




**9**




**10**


**11**

Although 3- and 4-alkenyl tosylamides have previously been cyclized by $PdCl_2$ to the corresponding pyrrolidines and pyrrolines,[16] no cyclization has been observed using our conditions (compounds **6-8**). An attempt to synthesize a spiro-heterocycle from N-tosyl-3-(1-cyclohexenyl)propylamine also failed (compound **9**). This is probably due to the increased steric hindrance of the trisubstituted olefin. Hegedus and McKearin were able to cyclize *cis*-N-tosyl-2-(2-propenyl)cyclohexylamine (compound **10**), but when this substrate was subjected to our conditions, no product was detected. Instead a number of unidentified products were noted. An attempt to cyclize N-tosyl-5-heptenylamine (compound **11**) to the six-membered ring failed. It seems reasonable to conclude that the nucleophile is

not in as close proximity to the C-C double bond as in the case of N-tosyl-(2-cyclopentenyl)propylamine (entry 5, Table 3) for closure to occur to the six-membered ring.

It is important to remember that when comparing our procedure to that of Hegedus, not only does our method offer the advantage of eliminating excess reoxidants, but in some cases gives rise to totally different products. Hegedus' conditions on the other hand, offer similar yields and allow for the cyclization of terminal olefinic tosylamides where our conditions do not. In short, our methodology offers a more cost efficient approach, but has its' limitations; whereas, Hegedus' methodology could possibly be more applicable to the formation of nitrogen-containing heterocycles.

# CONCLUSION

As shown earlier, there have been many palladium(II)-based methods developed for the synthesis of nitrogen-containing heterocycles. We have developed a unique set of conditions which allow for the formation of these nitrogen-containing heterocycles in moderate to excellent yield. Previous literature procedures require the use of a stoichiometric amount of a palladium(II) salt, or if the reaction utilizes only a catalytic amount of palladium, additional reoxidants are needed, along with an oxygen atmosphere, in order to reoxidize the Pd(0) formed during the reaction back to Pd(II). The advantage of our palladium(II) methodology is that it requires only the use of catalytic amounts of palladium and has no need for any additional reoxidants other than oxygen to reoxidize the Pd(0) formed *in situ* back to Pd(II).

In conclusion, acyclic and cyclic, aliphatic or aromatic 4- or 5-olefinic tosylamides cyclize in moderate to high yield to 5- or 6-membered unsaturated nitrogen heterocycles using 5 mol% $Pd(OAc)_2$, 2 equivalents of NaOAc, 1 atmosphere of $O_2$ and a DMSO solvent system. As mentioned earlier, these conditions do have limitations and are not general for all alkenyl tosylamides, especially those involving the formation of 6-membered ring nitrogen heterocycles.

# EXPERIMENTAL SECTION

## Equipment

All NMR spectra were recorded on a Nicolet NT-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75 MHz for carbon nuclei). Infrared spectra were obtained on an IBM IR/98 FT-IR. Mass spectral data were obtained on a Kratos high resolution mass spectrometer.

## Reagents

2-Cyclopenteneacetic acid, 2-isopropenylaniline and triflic anhydride were obtained from Aldrich Chemical Co. EtOAc, $MgSO_4$, THF, thionyl chloride, pyridine, tosyl chloride and DMSO were all obtained from Fisher Scientific. *E*-4-Hexenoic acid was obtained from MTM Research Chemicals. Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. generously provided the palladium acetate.

## Preparation of Olefinic Tosylamides

The preparation of N-tosyl-2-isopropenylaniline involved the addition of tosyl chloride (20 mmol, 3.81 g) to a solution of 2-isopropenylaniline (20 mmol, 2.66 g) in pyridine (6.4 ml). The reaction was cooled, diluted with diethyl ether and washed with 5% aqueous HCl. The organic phase was dried ($MgSO_4$) and the solvent removed under vacuum to yield the desired tosylamide: yield 72%; mp 77-79°C; IR ($CDCl_3$) 3325 (NH), 3067-2918 (CH), 1337 ($SO_2$) $cm^{-1}$; $^1H$ NMR $\delta$ 1.67 (s, 3H,C=$CCH_3$), 2.33 (s, 3H, $ArCH_3$), 4.66 (s, 1H, vinyl), 5.24 (s, 1H, vinyl), 6.9-7.25 (m, 6H, ArH), 7.60-7.65 (m, 3H, ArH and NH); $^{13}C$ NMR $\delta$ 21.3, 24.2, 116.9, 120.4, 124.2, 127.0, 127.8, 129.4, 132.6, 134.6, 136.0, 141.7, 143.7 (minus 1 peak due to overlap); HRMS m/z ($M^+$) calcd for $C_{16}H_{17}NO_2S$ 287.09800, found 287.09778.

The preparation of N-trifyl-2-isopropenylaniline involved the addition of a solution of triflic anhydride (10 mmol, 1.7 ml) and $CH_2Cl_2$ (10 ml) to a mixture of 2-isopropenylaniline (20 mmol, 2.72 ml) and $CH_2Cl_2$ (30 ml) cooled to 0°C. After stirring the reaction mixture for 1 hour at room temperature, the mixture was washed with 10% HCl and $H_2O$, dried ($MgSO_4$) and concentrated under vacuum to afford the corresponding triflamide: yield 72%; IR (neat) 3302 (NH), 2976-3300 (CH), 1369 ($SO_2$) $cm^{-1}$; $^1H$ NMR $\delta$ 2.04-2.11 (t, J = 0.9 Hz, 3H, C=$CCH_3$), 5.00 (s, 1H, vinyl) 5.44 (t, J = 1.5 Hz, 1H, vinyl), 7.17-7.33 (m, 4H, ArH and NH), 7.57 (d, J = 8.1 Hz, 1H, ArH); $^{13}C$ NMR $\delta$ 24.28, 117.80, 121.42, 126.27, 128.21, 128.44, 130.43, 136.28, 141.74 (minus $CF_3$ carbon); HRMS m/z ($M^+$) calcd for $C_{10}H_{10}NO_2SF_3$ 265.03844, found 265.03797.

The preparation of N-tosyl-2-allylaniline followed the procedure reported by Inada and co-workers.[21]

The preparation of N-2-(2-cyclopentenyl)ethylamine involved preparation of the tosyl derivative from the corresponding free amine, which was prepared by the reduction of 2-cyclopenteneacetamide. The preparation of 2-cyclopenteneacetamide involved refluxing a solution of 2-cyclopenteneacetic acid (50 mmol, 6.0 ml) and thionyl chloride (103 mmol, 7.5 ml) for 4 hours. The excess thionyl chloride was evaporated and the residue was added to concentrated $NH_4OH$ (40 ml) cooled to 0°C. After stirring the reaction mixture for 30 minutes, the solid was filtered off and washed with $H_2O$. The crude product was dissolved in EtOAc, subjected to decolorizing carbon, filtered and the EtOAc removed to give the desired product in 77% yield. The $^1H$ NMR spectrum was identical with that previously reported by Knapp and Gibson.[22]

The preparation of 2-(2-cyclopentenyl)ethylamine involved subjecting 2-cyclopenteneacetamide (15 mmol, 1.88 g) dissolved in anhydrous THF (37 ml) to a slurry of LAH (31.5 mmol, 31.5 ml of a 1.0 M THF solution). After refluxing the reaction mixture for 3 days, the mixture was treated with EtOAc (1 ml) and 10% NaOH (4 ml) and then filtered. The filtrate combined with washings of the precipitate was dried ($MgSO_4$) and concentrated to give the amine: yield 68%; $^1H$ NMR δ 1.30-1.70 (m, 3H, aliphatic), 1.83 (s, 2H, $NH_2$), 1.98-2.12 (m, 1H, aliphatic), 2.20-2.42 (m, 2H, $C{=}CCH_2$), 2.64-2.77 (m, 3H, $NCH_2$ and C=CCH), 5.63-5.69 (m, 1H, vinyl), 5.69-5.75 (m, 1H, vinyl).

The preparation of N-tosyl-2-(2-cyclopentenyl)ethylamine followed the procedure reported earlier for the tosylation of 2-isopropenylaniline. IR ($CDCl_3$) 3282 (NH), 2928-2873 (CH), 1326 ($SO_2$) $cm^{-1}$; $^1H$ NMR δ 1.15-1.70 (m, 4H, aliphatic), 1.85-2.05 (m, 1H, allylic), 2.20-2.30 (m, 2H, allylic), 2.42 (s, 3H, $ArCH_3$), 2.56-2.70 (m, 1H, NH), 2.94 (ddd, J = 6.6, 6.6, 6.6 Hz, 2H, $NCH_2$), 5.50-5.58 (m, 1H,

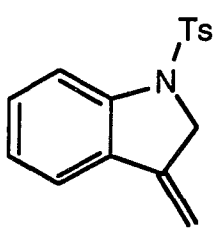
vinyl), 5.64-5.74 (m, 1H, vinyl), 7.30 (d, J = 8.1 Hz, 2H, ArH), 7.78 (d, J = 8.1 Hz, 2H, ArH); $^{13}C$ NMR δ 21.34, 29.27, 31.10, 35.37, 41.70, 42.52, 126.85, 129.49, 130.80, 133.66, 136.62, 143.14; HRMS m/z ($M^+$) calcd for $C_{14}H_{19}NO_2S$ 265.11365, found 265.10478.

The preparation of *E*- N-tosyl-4-hexenylamine from *E*-4-hexenoic acid followed the procedure reported for the synthesis of N-tosyl-(2-cyclopentenyl)ethylamine: IR (neat) 3228 (NH), 3022-2855 (CH), 1326 ($SO_2$) $cm^{-1}$; $^1H$ NMR δ 1.39-1.61 (m, 5H, aliphatic) 1.90-2.00 (m, 2H,C=C$CH_2$), 2.42 (s, 3H, Ar$CH_3$), 2.91 (ddd, J = 6.6, 6.6, 6.6 Hz, 2H, N$CH_2$), 5.00 (t, J = 6.3 Hz, 1H, NH), 5.20-5.40 (m, 2H, vinyl), 7.30 (d, J = 8.1 Hz, 2H, ArH), 7.76 (d, J = 8.1 Hz, 2H, ArH); $^{13}C$ NMR δ 17.82, 21.43, 29.13, 29.40, 42.55, 125.89, 126.99, 129.54, 129.60, 136.88, 143.14; HRMS m/z ($M^+$) calcd for $C_{13}H_{19}NO_2S$ 253.11365, found 253.11383.

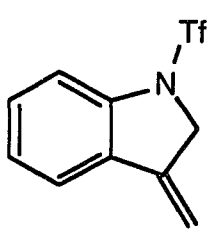
The preparation of N-tosyl-3-(2-cyclopentenyl)propylamine involved preparation of the tosyl derivative from the corresponding free amine. The amine was obtained from an LAH reduction (same procedure used for the reduction of 2-cyclopenteneacetamide) of the corresponding nitrile, which was prepared following the procedure reported by Abdel-Moety and Mangold[23]: IR (neat) 3281 (NH), 2930-2871 (CH), 1325 ($SO_2$) $cm^{-1}$; $^1H$ NMR δ 1.10-1.51 (m, 5H, aliphatic), 1.85-2.05 (m, 1H, aliphatic), 2.14-2.80 (m, 2H, aliphatic), 2.41 (s, 3H, Ar$CH_3$), 2.45-2.55 (m, 1H, aliphatic), 2.90 (ddd, J = 6.9, 6.9, 6.9 Hz, 2H, N$CH_2$), 5.10 (bs, 1H, NH), 5.53-5.56 (m, 1H, vinyl), 5.64-5.68 (m, 1H, vinyl), 7.29 (d, J = 8.1 Hz, 2H, ArH), 7.76 (d, J = 8.1 Hz, 2H, ArH); $^{13}C$ NMR δ 21.38, 27.74, 29.50, 31.81, 32.71, 43.29, 44.85, 127.00, 129.52, 130.40, 134.36, 136.86, 143.10; HRMS m/z ($M^+$) calcd for $C_{15}H_{21}NO_2S$ 279.12930, found 279.12897.

General Procedure for the Palladium(II)-Catalyzed Reactions

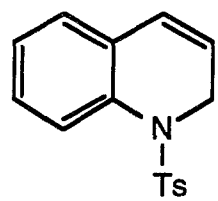
The olefinic tosylamide (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), NaOAc (1.0 mmol, 82 mg) and DMSO (10 ml) were stirred under an $O_2$ atmosphere at the designated temperature. After completion, the reaction mixture was diluted with satd aq $NH_4Cl$ and the mixture extracted with diethyl ether. The ether fractions were combined, dried ($MgSO_4$), concentrated and the product purified by flash chromatography on silica gel. The following nitrogen heterocycles were prepared following this procedure.



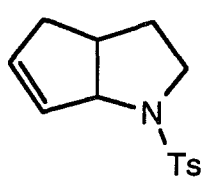

IR (neat) 3152 (CH), 3065 (CH), 2924-2871 (CH), 1362 ($SO_2$) $cm^{-1}$; $^1H$ NMR δ 2.34 (s, 3H, $ArCH_3$), 4.51-4.55 (t, J = 2.7 Hz, 2H, $CH_2$), 4.95-4.99 (t, J = 2.1 Hz, 1H, vinyl), 5.35-5.38 (t, J = 2.4 Hz, 1H, vinyl), 7.00 (t, J = 7.5 Hz, 1H, ArH), 7.15-7.37 (m, 4H, ArH), 7.65-7.74 (m, 3H, ArH); $^{13}C$ NMR δ 21.50, 54.77, 102.20, 114.96, 120.89, 123.59, 127.13, 129.58, 129.70, 130.04, 133.81, 140.00, 144.20, 144.40; HRMS m/z ($M^+$) calcd for $C_{16}H_{15}NO_2S$ 285.08235, found 285.08233.



IR (neat) 3077-3054 (ArH), 2958-2870 (CH) $cm^{-1}$; $^1H$ NMR δ 4.79 (s, 2H, $CH_2$), 5.13 (t, J = 2.4 Hz, 1H, vinyl), 5.60 (t, J = 3.0 Hz, 1H, vinyl), 7.13 (t, J = 7.5 Hz, 1H, ArH), 7.26 (t, J = 8.1 Hz, 1H, ArH), 7.48 (d, J = 8.4 Hz, 2H, ArH). $^{13}C$ NMR δ 55.77, 103.67, 114.52, 121.21, 124.97, 128.41, 130.26, 138.34, 141.96 (minus $CF_3$ carbon); HRMS m/z ($M^+$) calcd for $C_9H_8N$ 130.06567, found 130.06556. Note that the actual formula is $C_{10}H_8NO_2SF_3$. There was no peak seen at this molecular weight. It appears that the triflate group is cleaved during the ionization process.

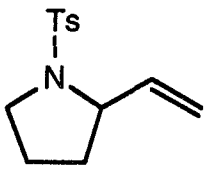



IR ($CDCl_3$) 3062 (ArH), 2956-2855 (CH), 1351 ($SO_2$) $cm^{-1}$; $^1H$ NMR δ 2.32 (s, 3H, $ArCH_3$), 4.43 (dd, J = 1.8, 4.2 Hz, 2H, $CH_2$), 5.56 (m, 1H, vinyl), 6.01 (d, J = 9.6 Hz, 1H, vinyl), 6.92 (dt, J = 2.1, 7.5 Hz, 1H, ArH), 7.05-7.31 (m, 6H, ArH), 7.70 (d, J = 7.5 Hz, 1H, ArH); $^{13}C$ NMR δ 21.52, 45.86, 123.92, 125.82, 126.41, 126.60, 128.80, 127.24, 127.93, 128.99, 129.49, 134.91, 136.27, 143.29; HRMS m/z ($M^+$) calcd for $C_{16}H_{15}NO_2S$ 285.08235, found 285.08240.

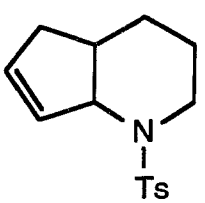



IR ($CDCl_3$) 2925-2854 (CH), 1337 ($SO_2$) $cm^{-1}$; $^1H$ NMR δ 1.40-1.60 (m, 2H, aliphatic), 1.75-1.95 (dt, J = 1.8, 16.8 Hz, 1H, aliphatic), 2.08-2.20 (m, 1H, aliphatic), 2.40-2.70 (m, 4H, aliphatic and $ArCH_3$), 3.00-3.12 (m, 1H, $NCH_2$), 3.30-3.45 (m, 1H, $NCH_2$), 4.55 (d, J = 8.1 Hz, 1H, NCH), 5.70-5.76 (m, 1H, vinyl), 5.79-5.84 (m, 1H, vinyl), 7.31 (d, J = 8.1 Hz, 2H, ArH), 7.73 (d, J = 8.1 Hz, 2H, ArH); $^{13}C$ NMR δ 21.42,

32.28, 37.87, 39.75, 48.15, 69.95, 127.44, 129.48, 131.06, 131.81, 134.52, 143.16; HRMS m/z ($M^+$) calcd for $C_{14}H_{17}NO_2S$ 263.09800, found 263.09800.




IR ($CDCl_3$) 2978-2875 (CH), 1341 ($SO_2$) $cm^{-1}$; $^1H$ NMR δ 1.57-1.84 (m, 4H, $CH_2CH_2$), 2.41 (s, 3H, $CH_3$), 3.17-3.25 (m, 1H, $NCH_2$), 3.39-3.47 (m, 1H, $NCH_2$), 4.08-4.14 (m, 1H, C=CCH), 5.10 (d, J = 10.2 Hz, 1H, vinyl), 5.26 (d, J = 16.8 Hz, 1H, vinyl), 5.80 (ddd, J = 16.8, 10.2, 6.0 Hz, 1H, vinyl), 7.29 (d, J = 8.1 Hz, 2H, ArH), 7.70 (d, J = 8.1 Hz, 2H, ArH); $^{13}C$ NMR δ 21.50, 23.68, 32.22, 48.74, 61.85, 115.17, 127.42, 129.50, 134.99, 138.61, 143.18; HRMS m/z ($M^+$) calcd for $C_{13}H_{17}NO_2S$ 251.09800, found 251.09811.




IR (neat) 2972-2870 (CH), 1341 ($SO_2$) $cm^{-1}$; $^1H$ NMR δ 1.1-1.65 (m, 4H, aliphatic), 1.93 (d, J = 13.5 Hz, 1H, aliphatic), 2.20-2.46 (m, 5H, $ArCH_3$ and aliphatic), 2.70-2.83 (m, 1H, $NCH_2$), 3.71-3.82 (m, 1H, $NCH_2$), 4.83-4.91 (m, 1H, C=CCHN), 5.29-5.34 (m, 1H, vinyl), 5.74-5.80 (m, 1H, vinyl), 7.29 (d, J = 7.8 Hz, 2H, ArH), 7.71 (d, J = 8.4 Hz, 2H, ArH); $^{13}C$ NMR δ 21.57, 22.98, 26.39, 35.41, 37.77, 41.91, 61.76, 127.10, 129.65, 132.88, 137.88, 142.98 (minus 1 peak due to overlap); HRMS m/z ($M^+$) calcd for $C_{15}H_{19}NO_2S$ 277.11365, found 277.11389.

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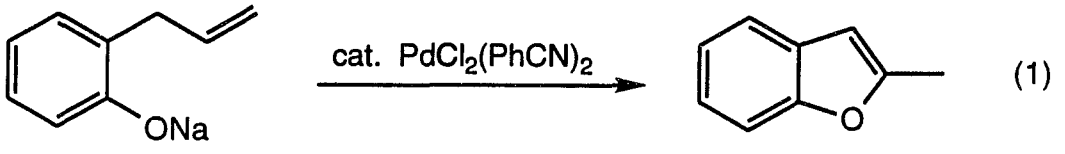
# PAPER III. SYNTHESIS OF BENZOPYRAN VIA PALLADIUM(II)-CATALYZED CYCLIZATION OF 2-ALLYLPHENOL

# INTRODUCTION

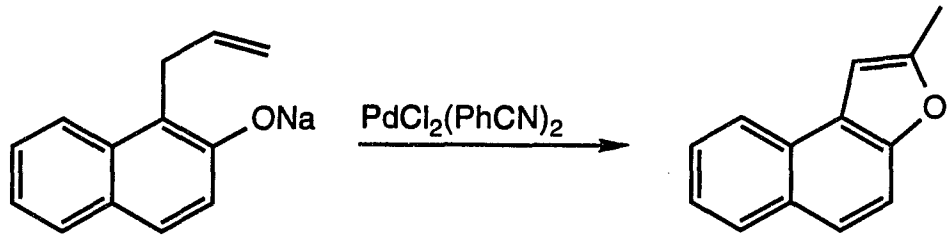
The discovery of the Wacker process has not only led to the palladium(II)-catalyzed intramolecular cyclization of carboxylic acids and amines, but also intramolecular cyclization of unsaturated alcohols[1] and alkenylphenols.[2] The focus of this chapter will be on the palladium(II)-catalyzed cyclization of *o*-allylphenol.

The first direct process for the synthesis of 2-substituted benzofurans from allylic phenols using palladium was developed in 1973 by Hosokawa and co-workers.[3] This synthesis entails palladium(II)-catalyzed intramolecular cyclization from the corresponding 2-allylphenol. Stoichiometric, as well as catalytic, amounts of palladium have also been applied to the cyclization of a number of phenols.[4] The catalytic cyclization of 2-allylphenol provided 2-methylbenzofuran in 34% yield (eq 1).[4c]




34% (1)

Using a stoichiometric amount of palladium(II) salt, Hosokawa cyclized 1-allyl-2-naphthol (eq 2) and 2-allyl-1-naphthol in excellent yield.[3]

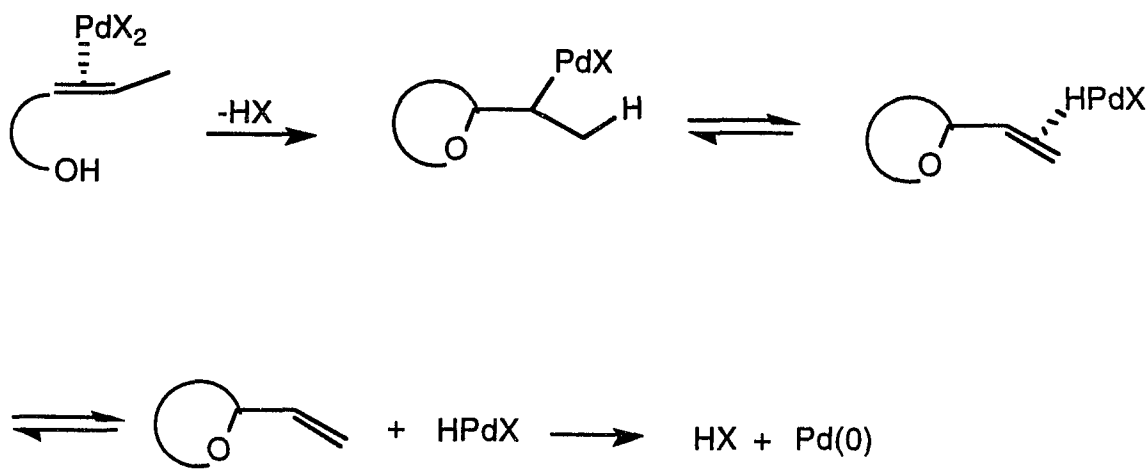



(2)

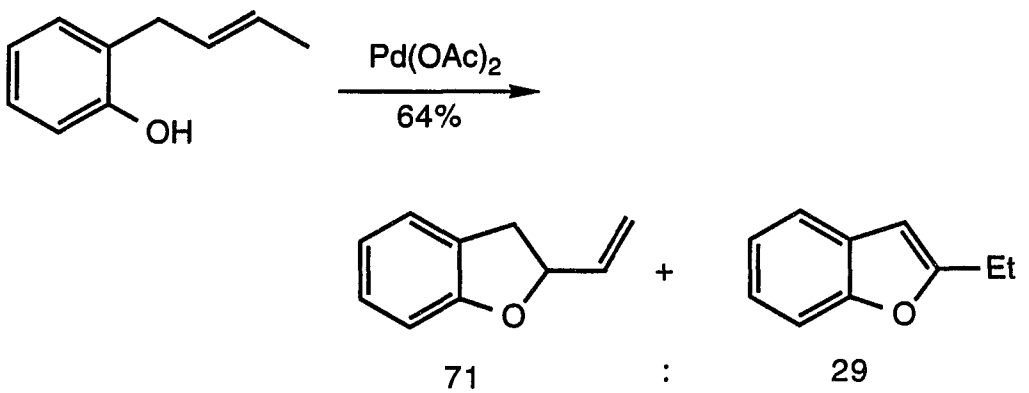
42%

The proposed mechanism for this oxypalladation process is shown in Scheme 1. In this mechanism, the oxygen nucleophile first attacks the olefin coordinated to the metal forming a sigma-bonded Pd(II)-intermediate. Subsequent β-hydride elimination of HPdX leads to the final products. The resulting HPdX reductively eliminates to give Pd(O) and HX.

Scheme 1

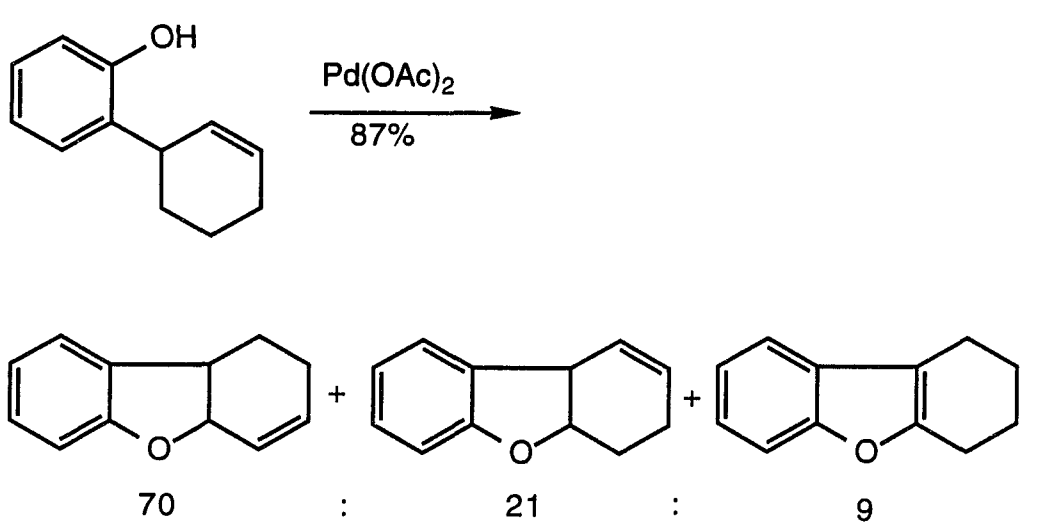


In 1976, Hosokawa and co-workers expanded this methodology to the intramolecular cyclization of 2-(2-butenyl)phenol (eq 3). This reaction involves attack by the oxygen atom of the phenoxy group at the 2-position of the allylic side chain to give 2 different five-membered ring products.[4a]



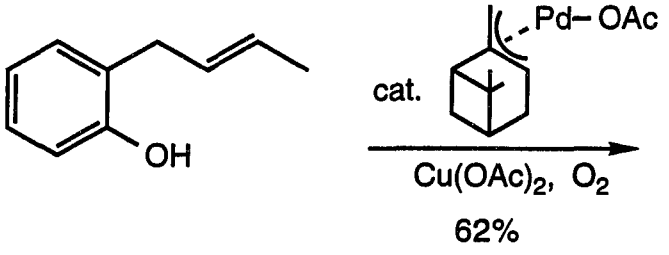

(3)

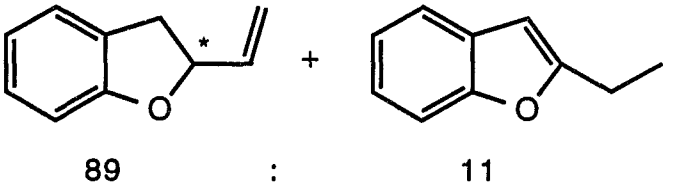
In 1978, Hosokawa and co-workers examined the palladium(II)-catalyzed intramolecular cyclization of 2-(2-cyclohexenyl)phenol and 2-(2-cyclopentenyl)phenol. For example, the cyclization of 2-(2-cyclohexenyl)phenol gives rise to the following isomeric products (eq 4).[5]




(4)

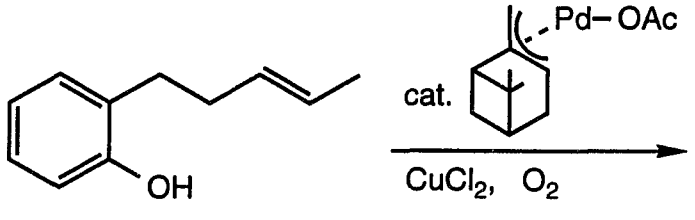
The palladium(II)-catalyzed asymmetric cyclization of 2-allylphenol to optically active 2,3-dihydro-2-vinylbenzofuran has been achieved in 12% optical yield along with 2-ethylbenzofuran by using a catalytic amount of $[(\eta^3$ -pinene)PdOAc$]_2$ (eq 5).[6a]



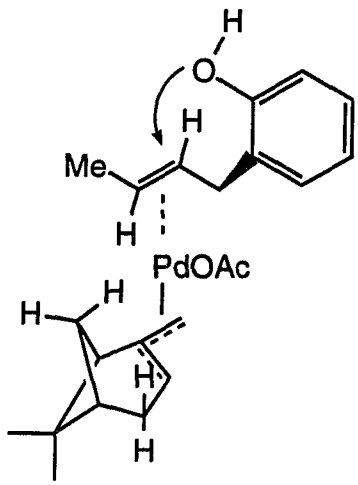

(5)

An analogous cyclization has also been carried out on 2-(3-pentenyl)phenol (eq 6).[6b]



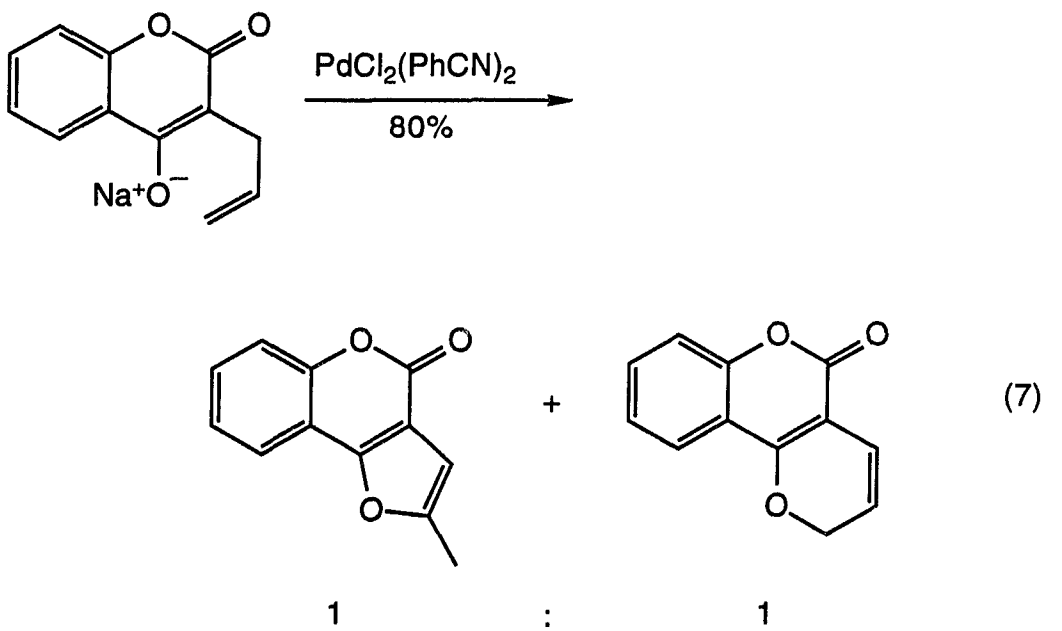

(6)

The enantioselectivity of this reaction occurs from the palladium coordinating to the least sterically hindered side of the olefin, followed by attack of the phenoxy group. The intermediate **1** involved is shown below.



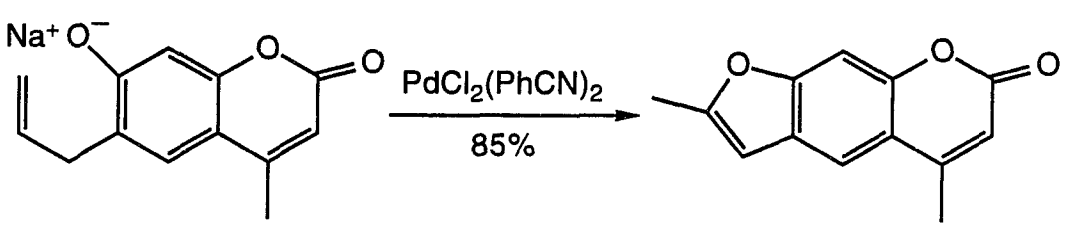

**1**

Kumar and co-workers have utilized the methodology developed by Hosokawa in the synthesis of 2-methyl-4H-furo[3,2-c][1]benzopyran-4-ones and 2H,5H-pyrano[3,2-c][1]benzopyran-5-ones (eq 7).[7]



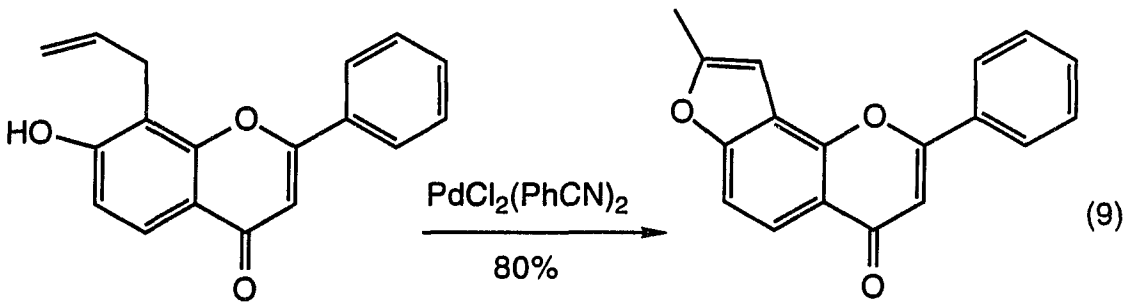

(7)

Kumar and co-workers have also applied this methodology to the synthesis of α-methylfurocoumarins (eq 8).[8]




(8)

Krupadanam and co-workers have also incorporated the palladium(II)-based methodology developed by Hosokawa in the synthesis of methylfuroflavones (eq 9).[9]

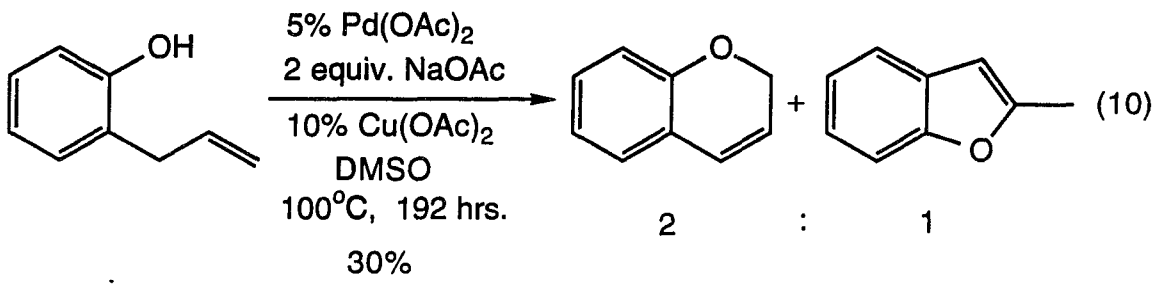



(9)

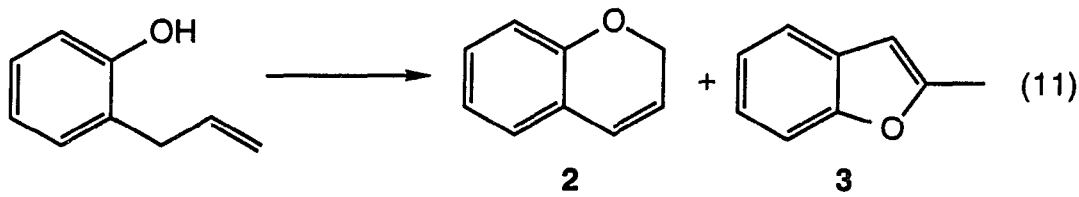
As shown earlier, palladium(II)-catalyzed cyclizations of 2-allylphenols occur in moderate yield. The reported conditions require the use of a stoichiometric amount of palladium, or, if the reaction utilizes only catalytic amounts of palladium, additional reoxidants are needed along with an oxygen atmosphere to reoxidize Pd(0) formed during the reaction back to Pd(II). It was thought that our unique standard cyclization conditions A, could be applied to the cyclization of 2-allylphenols. It was also noticed that previously reported palladium(II)-based cyclizations of 2-allylphenol generally did not afford benzopyran products which we thought might be accessible using our catalyst system.

## RESULTS AND DISCUSSION

In this chapter the goal was to apply the palladium(II)-catalyzed intramolecular methodology developed in the first two papers of this thesis to the cyclization of 2-allylphenol. From the previously reported literature, 2-allylphenol cyclized to the five-membered ring 2-methylbenzofuran product exclusively.[3,4c] From our preliminary results, we found that not only was the six-membered ring benzopyran product formed along with the five-membered ring 2-methylbenzofuran product, but the six-membered benzopyran was the major product. The ratio of benzopyran to the benzofuran was 2 to 1 (eq 10).




With these surprising results, it became desirable to find conditions which would exclusively provide the benzopyran product. With these thoughts in mind, a number of experiments were carried out (according to eq 11). These results are summarized in Table 1.




**2** **3**

Table 1. Optimization Conditions for the Palladium(II)-Catalyzed Cyclization of 2-Allylphenol [a]

| Entry | Solvent | Base | Time (hr), Temp. (°C) | Ratio[b] **2 : 3** | % Isolated Yield |
|---|---|---|---|---|---|
| 1 | DMSO | NaOAc | 48, 25 | --- | --- |
| 2 | DMSO | NaOAc | 48, 100 | --- | --- |
| 3 | DMSO | NaOAc | 48, 120 | --- | --- |
| 4 | $CH_2Cl_2$ | NaOAc | 72, 25 | --- | --- |
| 5 | $CH_3CN$ | NaOAc | 96, 25 | 0 : 1 | 41 |
| 6 | THF | NaOAc | 72, 25 | --- | --- |
| 7 | DMSO | $F_3CCO_2Na$ | 72, 25 | --- | --- |

Table 1. (cont'd)

| | | | | | |
|---|---|---|---|---|---|
| 8 | DMSO | $LiOAc•2H_2O$ | 72, 25 | --- | --- |
| 9 | DMSO | $LiOAc•2H_2O$ | 15, 80 | 2 : 1 | 49 |
| 10 | DMSO | $LiOAc•2H_2O$ | 24, 80 | 2 : 1 | 52 |
| 11 | 9:1 DMSO/ $H_2O$ | NaOAc | 72, 25 | --- | --- |
| 12 | 9:1 DMSO/ $H_2O$ | NaOAc | 24, 80 | 2 : 1 | 51 |
| 13 | 9:1 DMSO/ $H_2O$ | KOAc | 24, 80 | 2 : 1 | 55 |
| 14 | 9:1 DMSO/ $H_2O$ | $NaHCO_3$ | 24, 80 | 1 : 0 | 35 |
| 15 | 9:1 DMSO/ $H_2O$ | $Na_2CO_3$ | 24, 80 | 1 : 0 | 41 |

[a]The reaction conditions entail stirring 0.5 mmol of 2-allylphenol, 5 mol% of $Pd(OAc)_2$, 2 equivalents of the appropriate base, and 10 ml of the appropriate solvent under an oxygen atmosphere for the designated time and temperature.

[b]The ratio was determined by $^1H$ NMR spectroscopic analysis of the vinylic hydrogens.

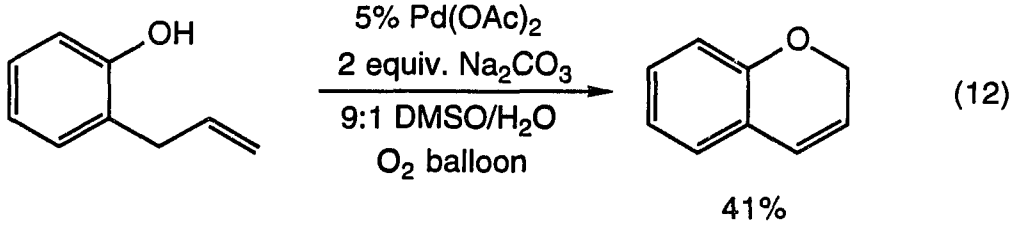
The results of Table 1 indicate that the solvent conditions seem to be the most influential parameter involved in initiating the cyclization of 2-allylphenol. For example, entries 1-3 established that DMSO alone is not a suitable solvent for the cyclization of 2-allylphenol. It is also apparent that $CH_2Cl_2$ has no beneficial effect on the cyclization (entry 4). The use of $CH_3CN$ as the solvent did assist in the cyclization of 2-allylphenol, however, not to the desired six-membered ring benzopyran product, but instead cyclization provided only the five-membered ring 2-methylbenzofuran product (entry 5). THF also failed to promote the cyclization of 2-allylphenol (entry 6). The result of entry 7 indicated that $F_3CCO_2Na$ also was not the base of choice. With the use of $LiOAc{\bullet}2H_2O$ at 25°C, there appeared to be formation of a product according to analysis of the reaction mixture by thin layer chromatography, but not enough product was formed to isolate (entry 8). When the temperature was elevated to 80°C for 15 hours, cyclization occurred, providing a 2 to 1 ratio of the compounds **2** and **3** (entry 9). Extending the reaction time to allow completion of the reaction, slightly increased the yield (entry 10). The results of entries 11 and 12 established that a 9:1 DMSO/$H_2O$ solvent system could accomplish the same result as entries 9 and 10. The use of KOAc as the base coupled with the 9:1 DMSO/$H_2O$ solvent system provided basically the same result as entry 10 (entry 13). The use of carbonate bases provided the desired six-membered ring benzopyran product in moderate yield with only trace amounts of the undesired five-membered ring 2-methylbenzofuran product (entries 14 and 15).

The mechanism for the formation of the five-membered ring 2-methylbenzofuran follows the accepted oxypalladation sequence shown in Scheme 1. The mechanism for the formation of the six-membered ring benzopyran product is

believed to proceed through the formation of a π-allylpalladium intermediate as shown in Scheme 8, page 98.

# CONCLUSION

As previously reported in the literature, the cyclization of 2-allylphenol using either a stoichiometric or catalytic amount of palladium provided only 2-methylbenzofuran in 31-34% yield.[3,4c] Here we have developed a unique set of conditions which allow the exclusive formation of benzopyran in 41% yield (eq 12). To our knowledge this is the only palladium-based methodology which demonstrates this regioselectivity.




(12)

# EXPERIMENTAL SECTION

## Equipment

All NMR spectra were recorded on a Nicolet NT-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75 MHz for carbon nuclei). Infrared spectra were obtained on an IBM IR/98 FT-IR. Mass spectral data were obtained on a Kratos high resolution mass spectrometer.

## Reagents

2-Allylphenol was obtained from Aldrich Chemical Co. $CH_2Cl_2$, $CH_3CN$ and DMSO were all obtained from Fisher Scientific. Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. generously provided the palladium acetate.

## General Procedure for the Palladium(II)-Catalyzed Reactions

The 2-allylphenol (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol, 5.6 mg), the appropriate base (1.0 mmol) and solvent (10 ml) were stirred under an $O_2$ atmosphere at the designated temperature. After completion, the reaction mixture

was diluted with satd aq $NH_4Cl$ and the mixture extracted with diethyl ether. The ether fractions were combined, dried ($MgSO_4$), concentrated and the product purified by flash chromatography on silica gel (elution with 15:1 hexane / EtOAc).

The 2-methylbenzofuran $^1H$ NMR spectrum was identical with that previously reported by Okuyama and Fueno.[10]

The preparation of benzopyran followed the general cyclization procedure. IR ($CDCl_3$) 3072 (CH), 2900-2981 (CH) $cm^{-1}$; $^1H$ NMR $\delta$ 4.81 (dd, J = 3.6, 2.1 Hz, 2H, $CH_2$), 5.75 (dt, J = 9.9, 3.6 Hz, 1H, vinyl), 6.41 (d, J = 9.9 Hz, 1H, vinyl), 6.76 (d, J = 8.1 Hz, 1H, ArH), 6.85 (td, J = 7.5, 1.2 Hz, 1H, ArH), 6.94 (dd, J = 7.5, 1.8 Hz, 1H, ArH), 7.08 (td, J = 7.8, 1.5 Hz, 1H, ArH); $^{13}C$ NMR $\delta$ 65.4, 115.6, 121.2, 121.9, 122.3, 124.5, 126.5, 129.1, 154.0; HRMS m/z (M-1) calcd for $C_9H_7O$ 131.04969, found 131.04957.

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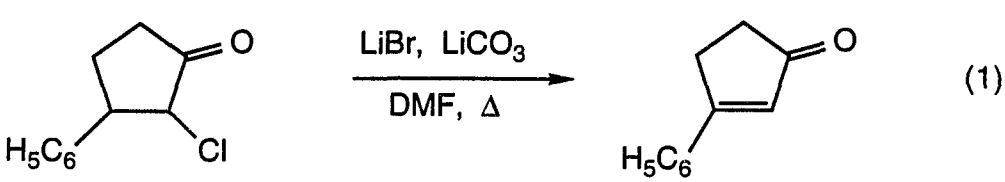
# PAPER IV. SYNTHESIS OF α,β-UNSATURATED CARBONYL SYSTEMS VIA PALLADIUM(II)-CATALYSIS

# INTRODUCTION

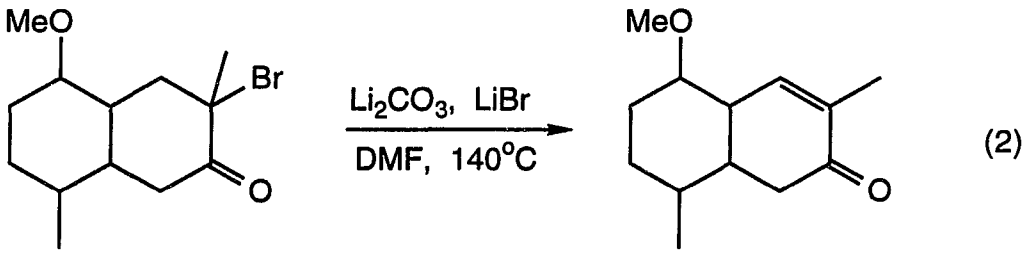
Since α,β-unsaturated carbonyl systems are so prevalent in natural products, it is of no surprise that there is a large demand to obtain these systems synthetically. A great deal of time and effort has already been spent in the development of useful synthetic methodology, providing several modes of construction in the literature today. Traditional methodology includes α-halogenation-dehydrohalogenation of carbonyl compounds and direct dehydrogenation with various reagents such as selenium, sulfur and palladium.

We will first take a close look at the formation of α,β-unsaturated carbonyl systems by bromination-dehydrobromination. Green and Depres have shown this to be a particularly useful method in the synthesis of the following conjugated system (eq 1).[1]



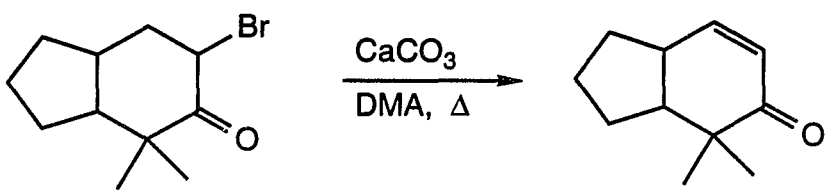

(1)

Vidari and co-workers have also used this methodology in the synthesis of quassin (eq 2).[2]



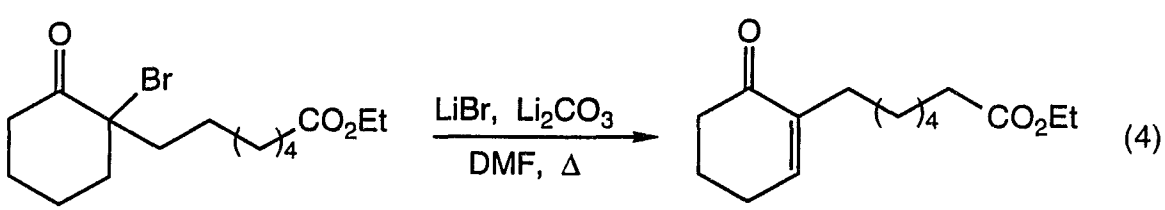

(2)

Marshall and co-workers have also utilized halogenation-dehydrohalogenation in the synthesis of hydroazulenes (eq 3).[3]



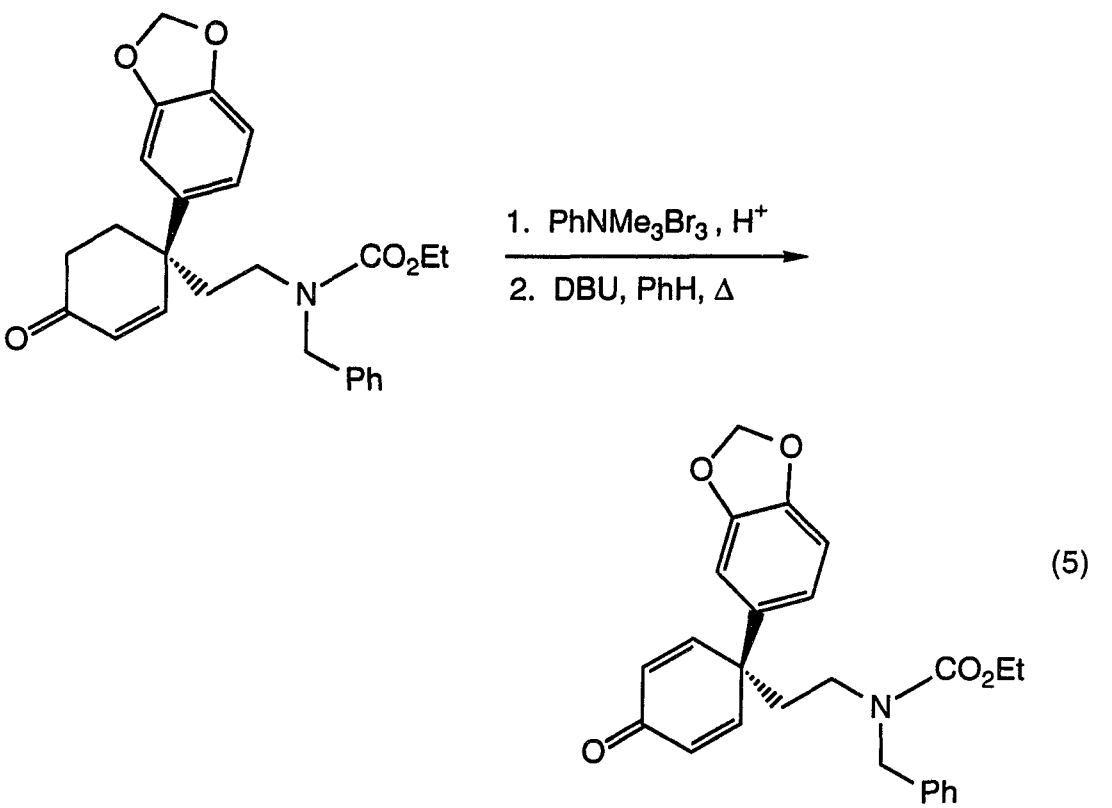

(3)

Floyd and Weiss have incorporated this methodology in the synthesis of homoprostaglandins (eq 4).[4]




(4)

Martin and Campbell have used this methodology in the synthesis of crinine and buphanisine (eq 5).[5]



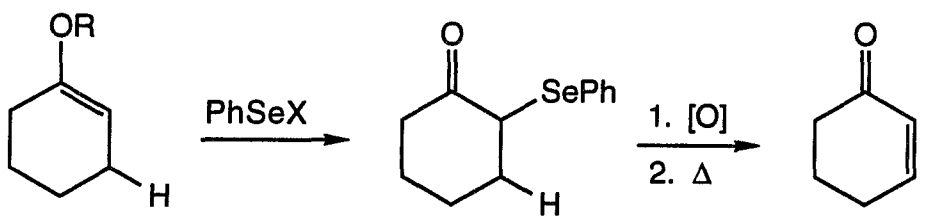

(5)

As mentioned earlier, selenium chemistry is another viable means of obtaining α,β-unsaturated carbonyl systems. The application of organoselenium chemistry to this area was first explored by Sharpless[6] and Reich.[7] As a result, a useful synthetic method evolved which makes this type of transformation the most widely used application of organoselenium reagents.[6b]

The methodology involved in these reactions consists of treating the enolic form of the carbonyl substrate with an electrophilic organoselenium reagent and subsequently oxidizing the resulting α-organoseleno carbonyl compound to the

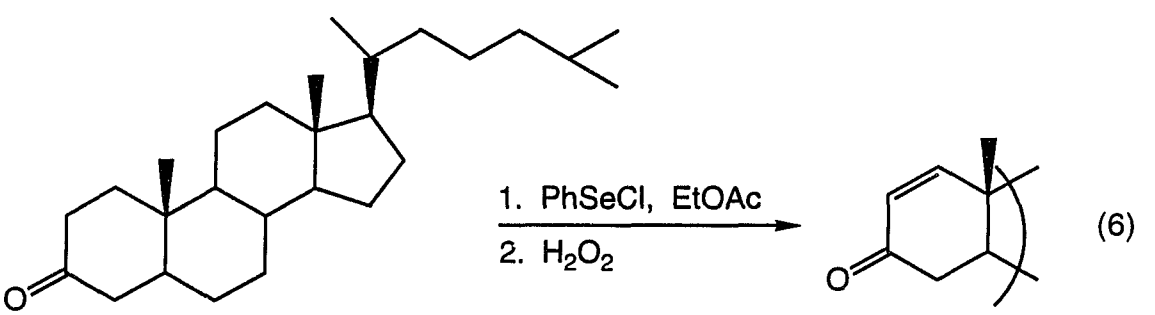
corresponding selenoxide, which undergoes syn elimination to form the corresponding α,β-unsaturated carbonyl product (Scheme 1).

Scheme 1



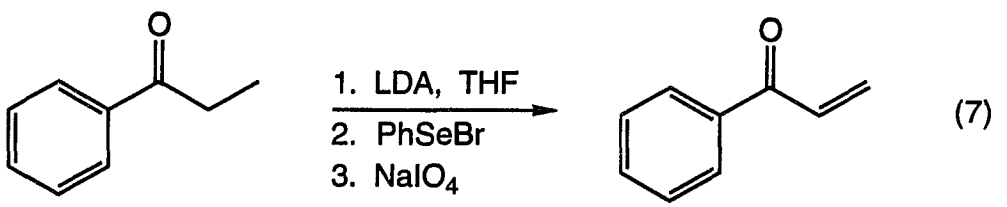

R = H, Li, Na, K, Cu, Zr, Al, Ac, $SiMe_3$ or Me

Highly enolizable ketones can be selenenylated directly by treatment with PhSeCl in a EtOAc solution. Sharpless and co-workers have developed this methodology in the transformation of 3-cholestanone to the corresponding enone (eq 6).[6]



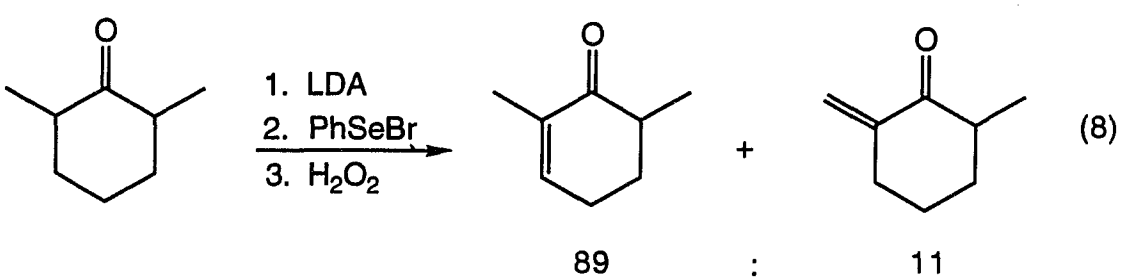

(6)

Reich and co-workers[7] have developed a method based on their observation that lithium enolates react rapidly and cleanly with benzeneselenenyl halides to give α-phenylselenocarbonyl compounds and the fact that aliphatic selenoxides readily undergo β-elimination to provide olefins. This method is further illustrated for the conversion of propiophenone to acrylophenone (eq 7).[7]



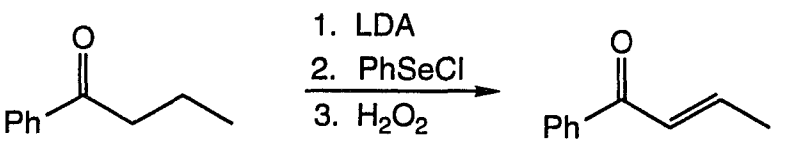

(7)

Reich has also applied this methodology in the transformation of 2,6-dimethylcyclohexanone to the corresponding mixture of enones (eq 8),[7]



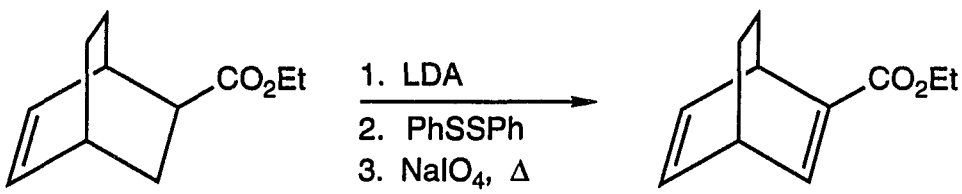

(8)

and towards the synthesis of aryl enones (eq 9).[8]



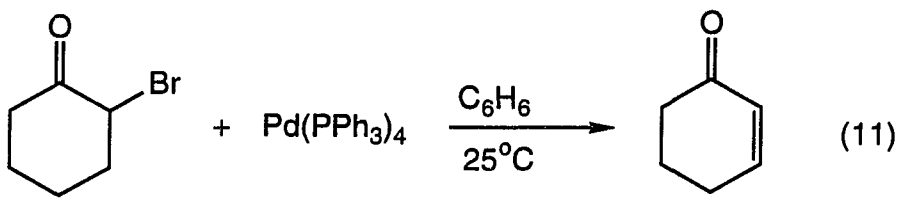

(9)

Similar chemistry has been accomplished via α-sulfenylation. Trost and co-workers have developed this methodology in the synthesis of α,β-unsaturated esters (eq 10).[9,10]




(10)

The formation of α,β-unsaturated carbonyl systems has also been accomplished by palladium chemistry. Townsend and co-workers have used the dehydrobromination of α-bromo ketones with tetrakis(triphenylphosphine)-palladium(0) to provide α,β-unsaturated ketones.[11] The conversion of 2-bromocyclohexanone to 2-cyclohexenone occurs in 70% yield (eq 11) Some catalysis occurs if *p*-benzoquinone is added, but rates and yields decrease under the catalytic conditions if less than 25-50 mol% of palladium is used.

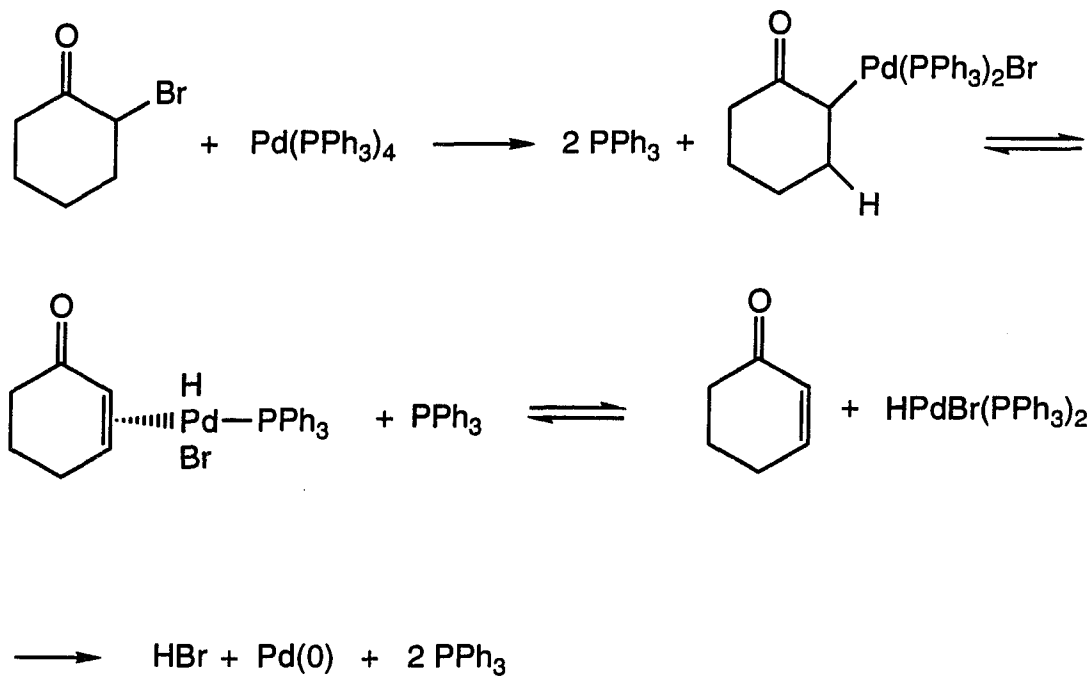



(11)

The advantage of this palladium(0)-based methodology over debromination of similar substrates is that base sensitive substrates can easily be converted to α,β-unsaturated ketones. The disadvantage is that palladium is a far more expensive reagent.

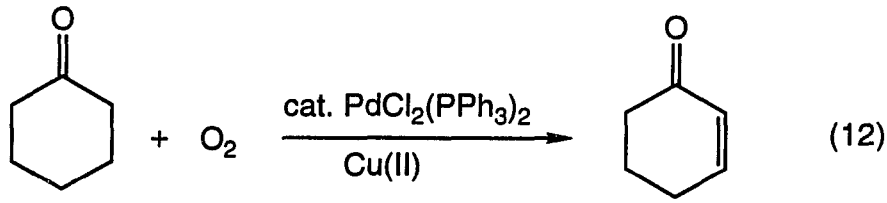
The mechanism suggested for this process is shown in Scheme 2.

Scheme 2




It is believed that Pd(0) undergoes a facile oxidative addition of the α-bromoketone, just as Pd(0) complexes do with other organic halides. The resulting species β-hydride eliminates to expel HPdBr along with the corresponding enone. Reductive elimination of $HPdBr(PPh_3)_2$ affords Pd(0), HBr and triphenylphosphine.

Theissen has developed a procedure for the dehydrogenation of saturated ketones and aldehydes to their α,β-unsaturated counterparts by using catalytic amounts of $PdCl_2(PPh_3)_2$ and either Cu(II) or hydroquinone as co-catalysts, and air or $O_2$ as reoxidants and the substrate as solvent (eq 12).[12] This dehydrogenation procedure has the advantage of simplicity, but has the disadvantage of low yields as well as the lack of regiospecificity in the case of unsymetrical ketones.

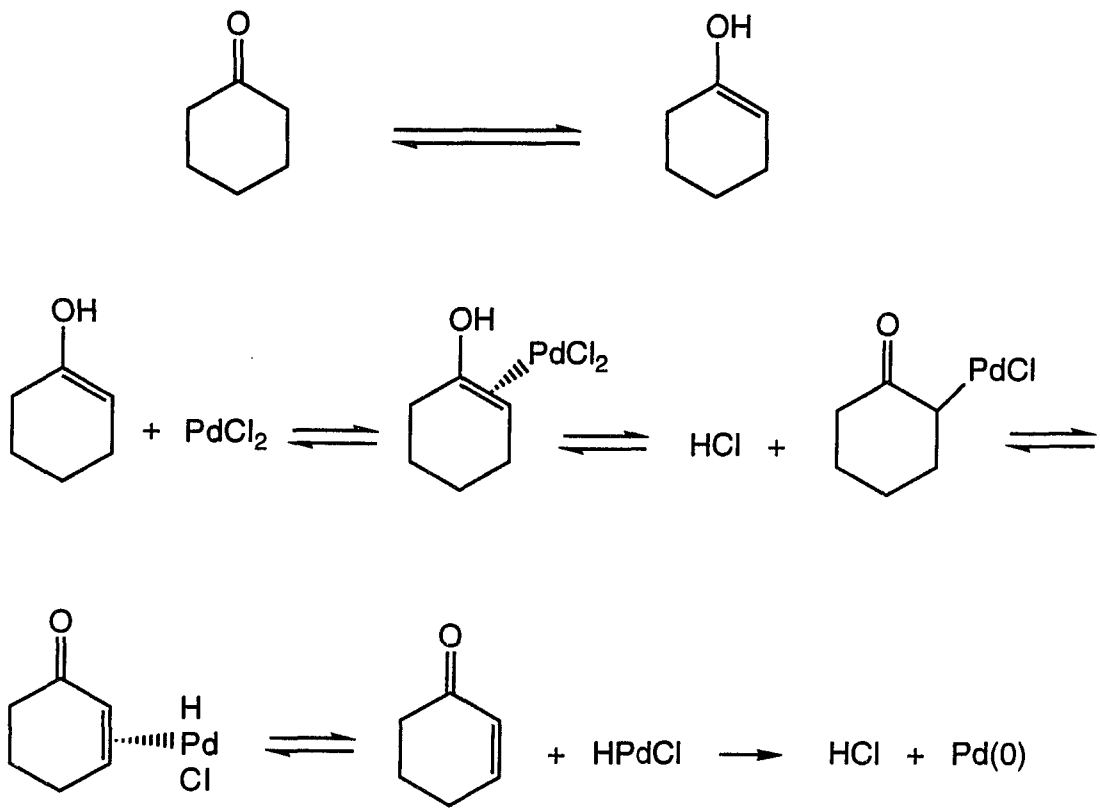



(12)

80% yield of enone
at 30% conversion

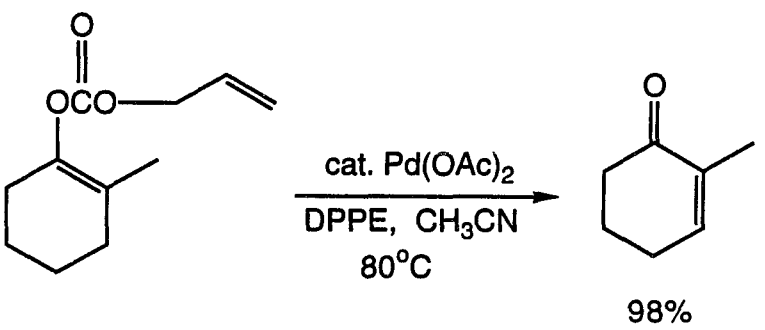
The mechanism of this reaction involves the initial enolization of cyclohexanone, followed by formation of the π-palladium complex, which rearranges to the σ-alkylpalladium species as shown in Scheme 3. The desired α,β-unsaturated

Scheme 3.



ketone is provided upon β-hydride elimination and decomposition of the second π-complex.

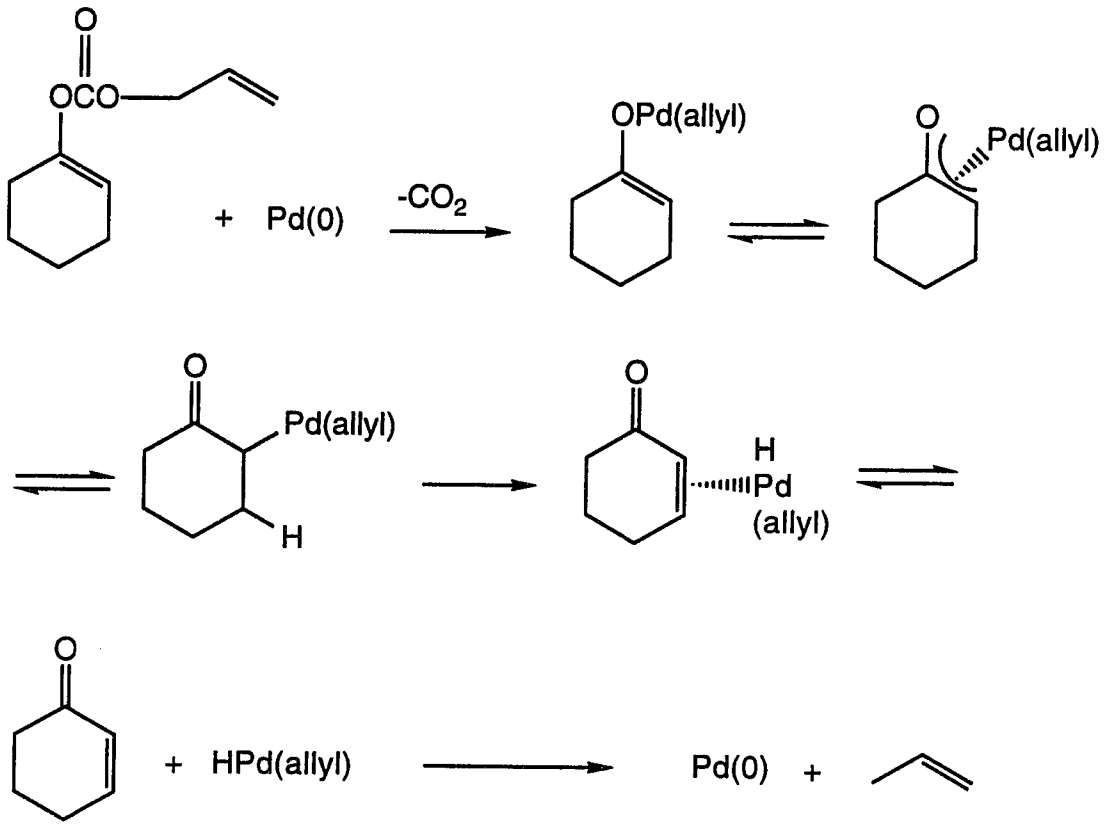
Another variation of dehydrogenation, involves the reaction of allyl enol carbonates with $Pd(OAc)_2$ and DPPE (eq 13).[13]



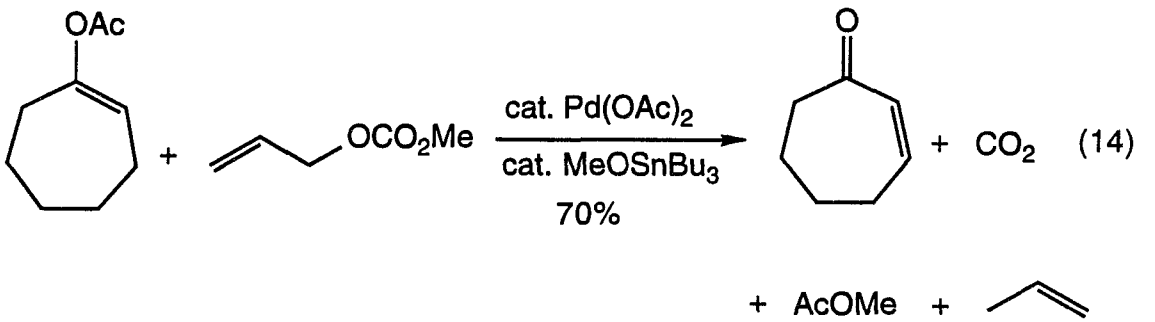

(13)

Shimizu and co-workers suggest that perhaps the mechanism involves oxidative addition of Pd(0) to the allyl carbonate moiety leading to the formation of an oxy π-allylpalladium complex. Upon rearrangement and β-hydride elimination, the α,β-unsaturated ketone is formed as shown in Scheme 4.

Scheme 4

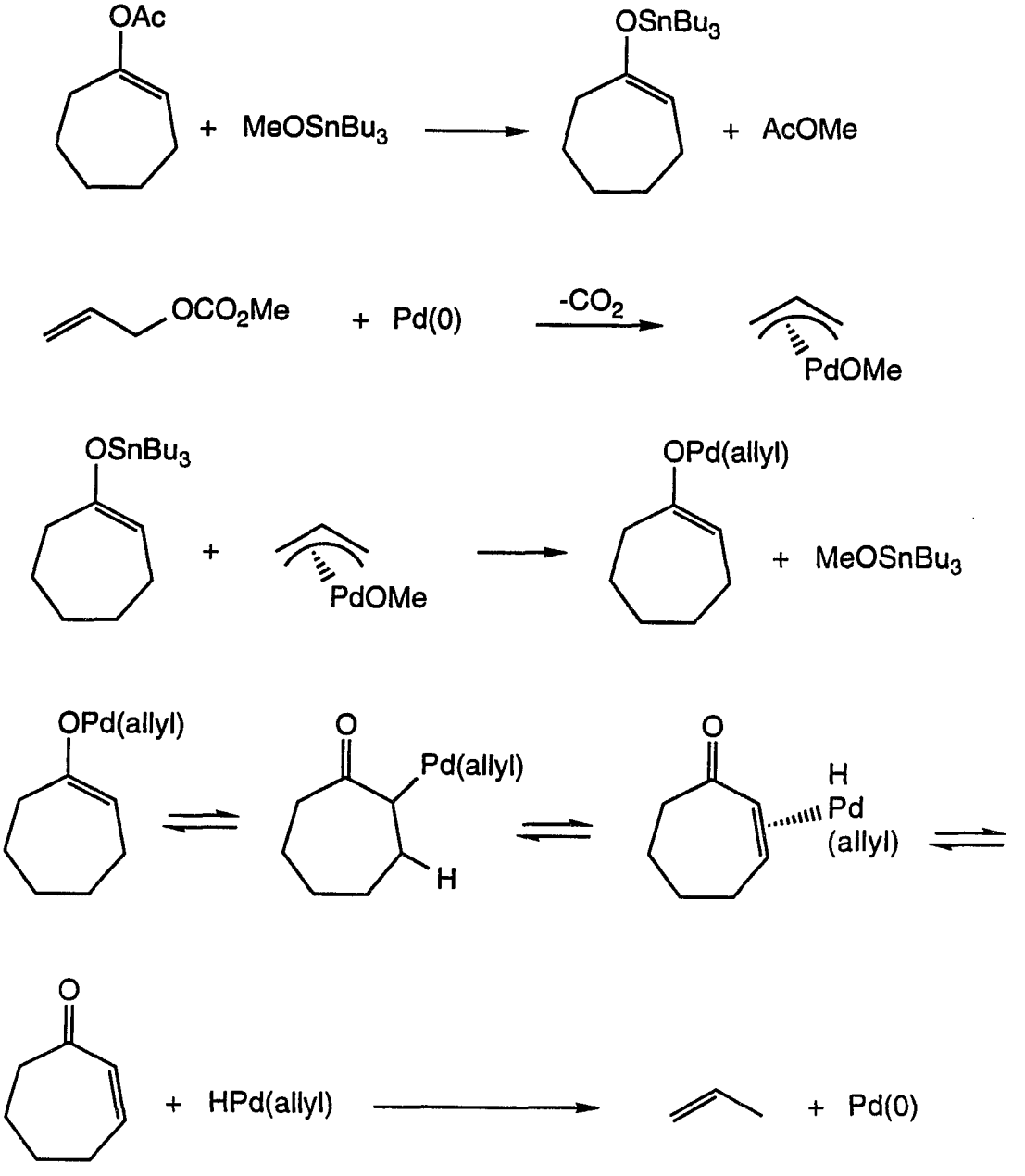

O
OCO
+ Pd(0)
-CO2
OPd(allyl)
O
Pd(allyl)
O
Pd(allyl)
H
O
H
Pd
(allyl)
O
+ HPd(allyl)
Pd(0) +

Tsuji and co-workers have taken an enol acetate approach to the synthesis of enones (eq 14).[14]

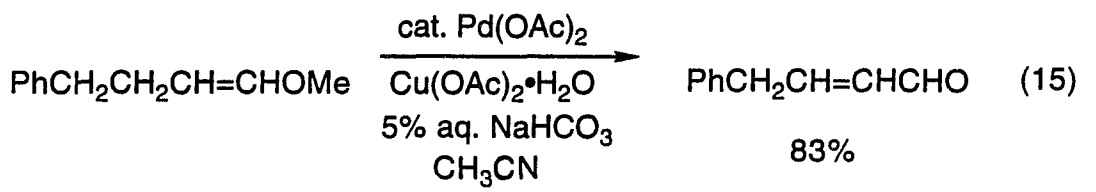



This unique bimetallic catalysis can be explained mechanistically by Scheme 5, whereby a tin enolate, provided by the reaction of an enol acetate with a tin alkoxide, transmetallates with a π-allylpalladium complex formed by the oxidative addtition of allyl methyl carbonate to Pd(0). This gives a palladium enolate and regenerates the tin alkoxide, making the reaction catalytic with regard to the tin compound. Finally, β-hydride elimination affords the enone and regenerates the Pd(0) catalyst.

Scheme 5

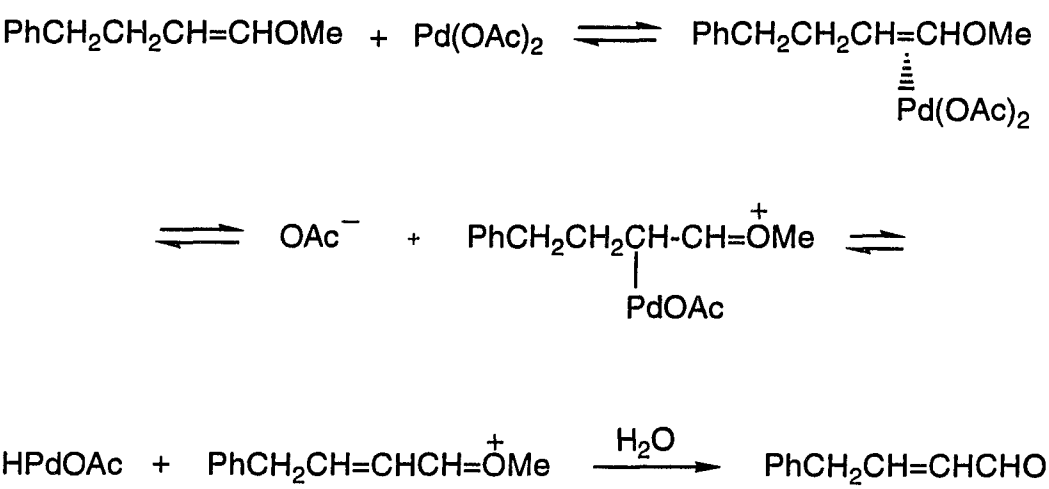

OAc
+ MeOSnBu3
OSnBu3
+ AcOMe
OCO2Me
+ Pd(0)
-CO2
PdOMe
OSnBu3
+
PdOMe
OPd(allyl)
+ MeOSnBu3
OPd(allyl)
O
Pd(allyl)
H
O
H
Pd
(allyl)
O
+ HPd(allyl)
+ Pd(0)

Takayama and co-workers have developed a convenient method for converting methyl enol ethers to the corresponding α,β-unsaturated enones via Pd(II)-promoted oxidation (eq 15).[15]



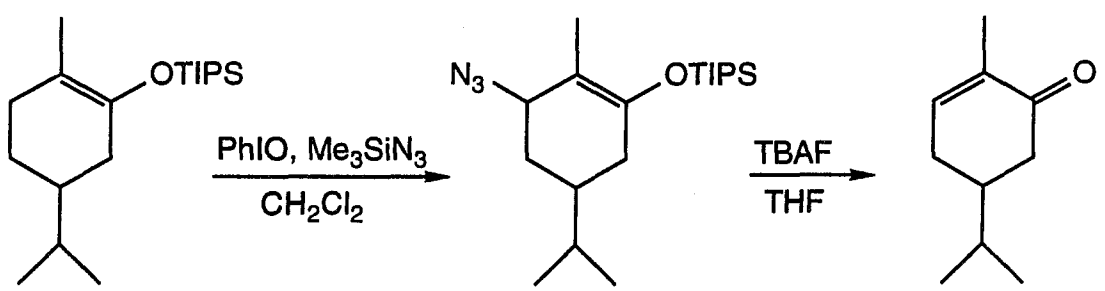

Mechanistically, the reaction is projected to proceed differently than the other enol derivatives previously shown. After coordination of palladium to the olefin and formation of the σ-alkylpalladium complex, β-hydride elimination occurs. Hydrolysis of the enol ether provides the final α,β-unsaturated aldehyde. This can be seen in Scheme 6.

Scheme 6



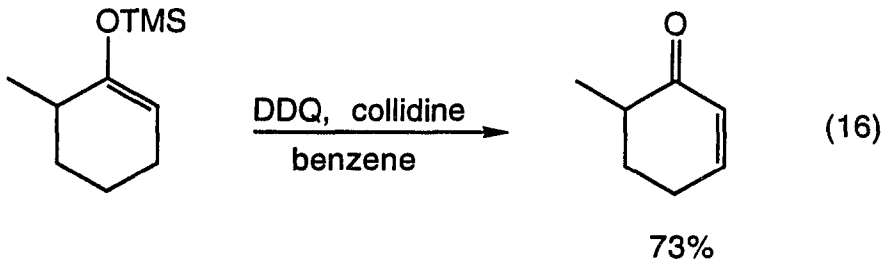
Trialkylsilyl enol ethers have also been utilized in the synthesis of α,β-unsaturated ketones. Magnus and co-workers have reported the unprecedented direct β-azidonation of triisopropylsilyl enol ethers (TIPS) using the reagent combination PhIO, $Me_3SiN_3$ and $CH_2Cl_2$. Elimination of the intermediate β-azido triisopropylsilyl enol ether with tetra-*n*-butylammonium fluoride provides the desired enone (Scheme 7).[16] It is important to note that the regiospecificity of this elimination is controlled by this methodology, whereas the existing methodology applied to this substrate could eliminate to provide either the exocyclic or the endocyclic enone.

Scheme 7




overall yield 66%

Ketone-enone conversions via enol silyl enol ethers have also been accomplished by DDQ (2,3-dichloro-5,6-dicyanoquinone).[17] Fleming and Paterson have used DDQ methodology in the synthesis of carvone (eq 16).[17a]

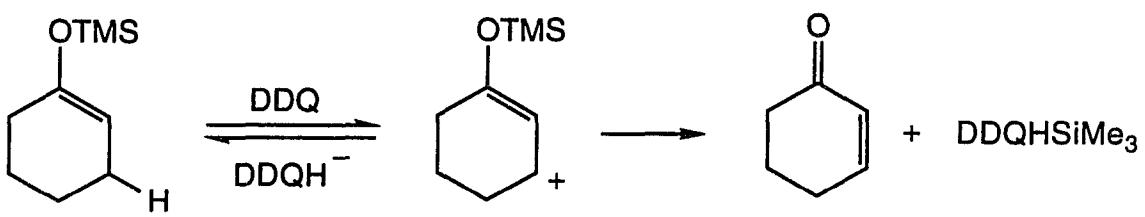



(16)

73%

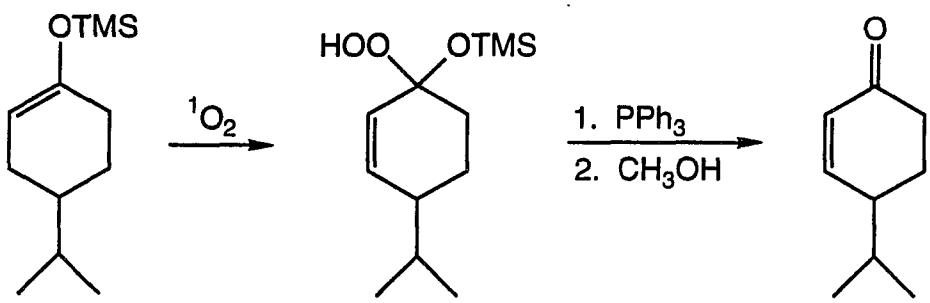
Formation of the enone is believed to be initiated by hydrogen abstraction from the allylic position of the corresponding enol as shown in Scheme 8.

Scheme 8




Friedrich and Lutz have incorporated a singlet oxygen approach for the conversion of enol silyl ethers to the corresponding α,β-unsaturated ketones as shown in Scheme 9.[18]

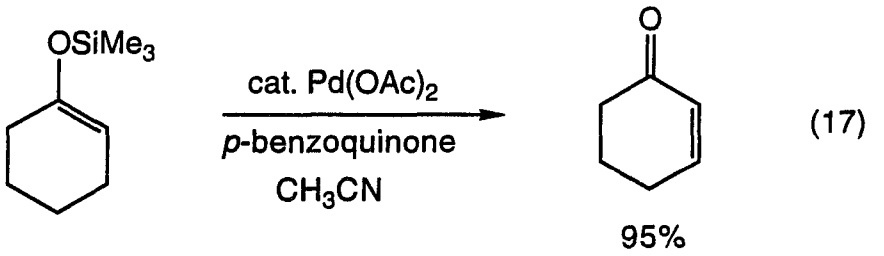
Scheme 9




overall yield 67%

The final methodology presented in this introduction more closely resembles the research presented in the following Results and Discussion of this chapter. This methodology entails the conversion of enol silyl ethers to the corresponding carbonyl compounds via palladium(II)-based methodology. In 1978, Ito, Hirao and Saegusa developed the synthesis of α,β-unsaturated carbonyl compounds using either a stoichiometric or catalytic amounts of $Pd(OAc)_2$ from the dehydrosilation of enol silyl ethers.[19] In this study, the following enol silyl ether was converted into cyclohexenone in 95% yield by using 0.5 equivalents of $Pd(OAc)_2$, 0.5 equivalents of *p*-benzoquinone and $CH_3CN$ (eq 17).

This palladium(II)-approach for the conversion of enol silyl ethers offers comparable yields to that of the selenium-based methodology with the advantages that palladium is much less toxic than selenium and can be used in catalytic amounts.

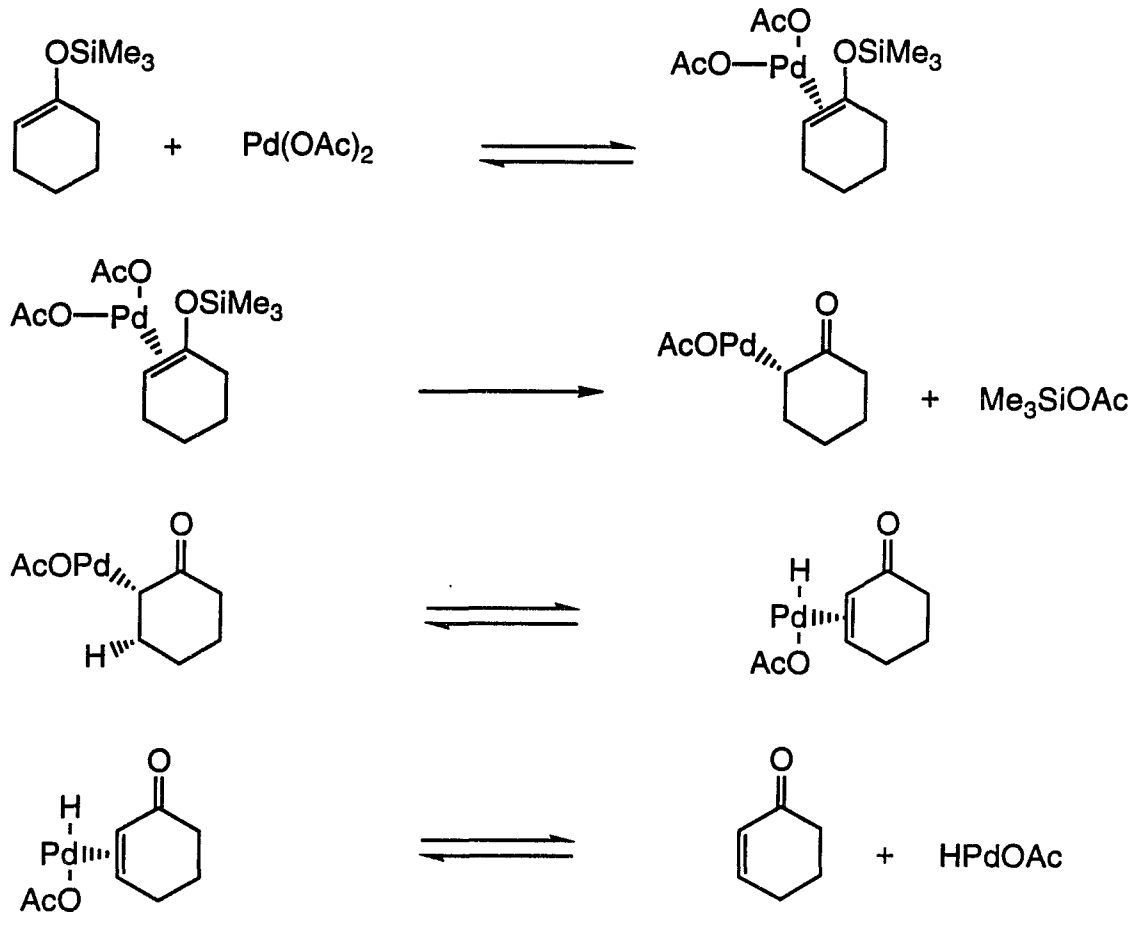


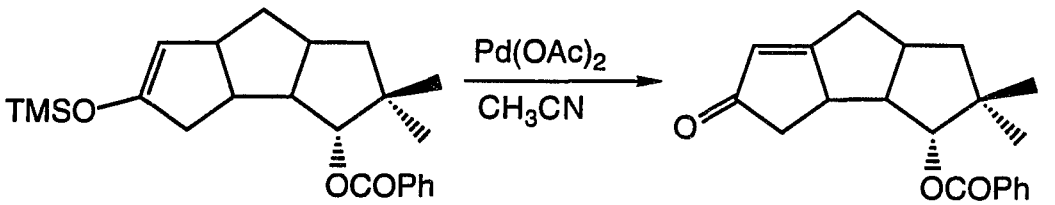

(17)

Formation of the enone is believed to follow the mechanism shown in Scheme 10, in which coordination of palladium to the olefin forms a π-palladium complex, which rearranges to the σ-alkylpalladium species. This σ-species undergoes β-hydride elimination to create a second π-complex, which decomposes to afford the desired product and HPdOAc, which reductively eliminates to HOAc and Pd(0). This Pd(0) is reoxidized by *p*-benzoquinone to regenerate Pd(II), thus making the reaction catalytic in palladium.

Since Saegusa's finding, a number of syntheses have incorporated these conditions using either a stoichiometric, or greater than a stoichiometric amount of $Pd(OAc)_2$ for the transformation of enol silyl ethers to their corresponding ketones.[20] For example, Hijfte and co-workers have utilized 1.1 equivalents of $Pd(OAc)_2$ in the synthesis of hypnophilin and coriolin (eq 18).[20a]

Scheme 10

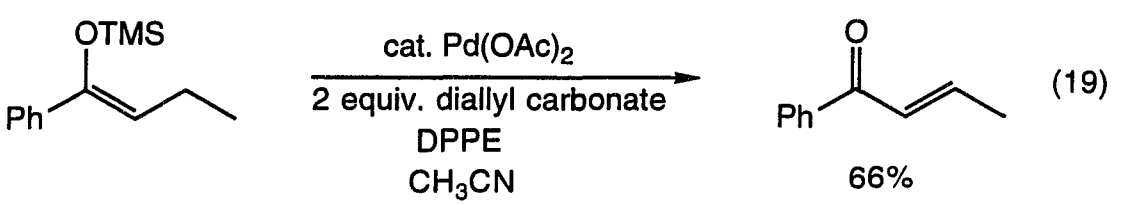

OSiMe3
+
Pd(OAc)2
AcO
AcO—Pd
OSiMe3
AcO
AcO—Pd
OSiMe3
AcOPd
O
+
Me3SiOAc
AcOPd
O
H
H
Pd
AcO
O
H
Pd
AcO
O
O
+
HPdOAc




(18)

91% yield based on recovered starting material

Tsuji and co-workers have also utilized enol silyl ethers in the synthesis of α,β-unsaturated carbonyl compounds.[13a,21] Silyl enol ethers are easily converted to enones using 5-10% palladium acetate, diallyl carbonate as the reoxidant, DPPE and $CH_3CN$ (eq 19). Tsuji's suggested mechanism involves the same transmetallation route as shown in Scheme 5.



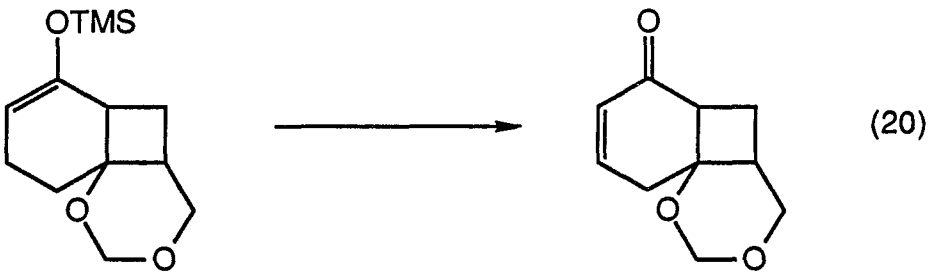

(19)

Having developed a unique palladium(II)-catalyst system which has the advantage of eliminating the need for additional reoxidants other than oxygen to reoxidize Pd(0) formed during the reaction back to Pd(II), it appeared that this system could be applied to the conversion of enol silyl ethers to the corresponding α,β-unsaturated compounds.

## RESULTS AND DISCUSSION

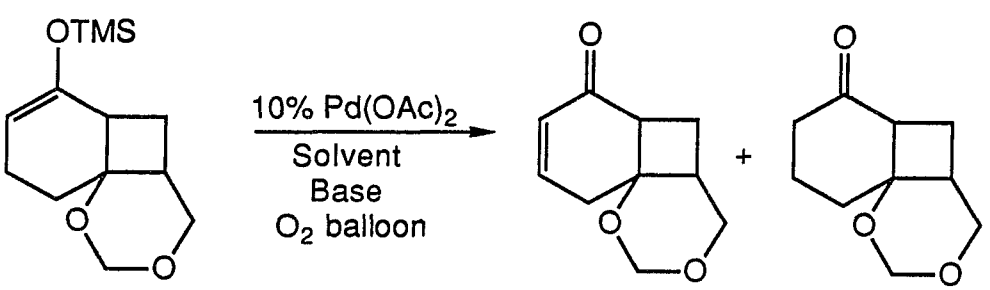
As shown earlier, the two major transformations of carbonyl compounds to the corresponding α,β-unsaturated counterparts involve selenium and palladium methodology. Since the toxicity of palladium is much less than selenium, palladium was the reagent of choice. In the past palladium has been used in either stoichiometric amounts or catalytically. Using catalytic amounts of palladium requires costly or inconvenient reoxidants, such as benzoquinone, copper salts, or allyl carbonates. We are pleased to report a procedure for the formation of α,β-unsaturated carbonyl systems which requires only catalytic amounts of palladium and uses only molecular oxygen as the reoxidant. This finding provides the most cost efficient, and environmentally sound methodology to date for the conversion of carbonyl compounds to their corresponding α,β-unsaturated counterparts.

Our initial study involved the conversion of the following enol silyl ether to the desired α,β-unsaturated ketone (eq 20). This had proven to be a most difficult transformation via catalytic palladium(II) and the use of reoxidants, such as benzoquinone, copper salts, or allyl carbonates. A stoichiometric amount of $Pd(OAc)_2$ converted the enol silyl ether to the corresponding enone in 90% yield.[20b]




(20)

Employing an array of conditions (as seen in Table 1), we were able to develop a set of parameters which effectively enabled the formation of the desired unsaturated ketone. Initially 10% $Pd(OAc)_2$, two equiv. of NaOAc and a variety of solvents, such as $CH_3CN$, DMSO and 9:1 DMSO/$H_2O$ under an oxygen atmosphere proved unsuccessful (entries 1-3). Omitting NaOAc produced the desired product, and best results were obtained using anhydrous DMSO as the solvent (entries 5-8). The results of entries 9 and 10 indicate that decreasing the amount of $Pd(OAc)_2$ to 3% increased the amount of the undesired saturated ketone, even when this decrease in catalyst was accompanied by decreasing the amount of solvent by one half.




**1** **2** **3**

Table 1. Catalytic Transformation of the Enol Silyl Ether **1** to the Corresponding α,β-Unsaturated Ketone **2**[a]

| Entry | Solvent | Time (h), Temp. (°C) | Base | % Isolated Yield | Ratio[b] **2:3** |
|---|---|---|---|---|---|
| 1 | $CH_3CN$ | 72, 25 | NaOAc | -- | --- |
| 2 | DMSO | 24, 25 | NaOAc | -- | --- |
| 3 | 9:1 DMSO/ $H_2O$ | 24, 25 | NaOAc | -- | --- |
| 4 | $CH_3CN$ | 72, 25 | --- | -- | --- |
| 5 | DMSO | 72, 25 | --- | 86 | 1:0 |
| 6 | 9:1 DMSO/ $H_2O$ | 72, 25 | --- | 70 | 1:1 |
| 7 | DMSO | 16, 80 | --- | 80 | 1:0 |
| 8 | 9:1 DMSO/ $H_2O$ | 16, 80 | --- | --[e] | 1:1 |
| 9 | DMSO | 16, 80 | --- | --[e] | 1:2[c] |
| 10 | DMSO | 24, 80 | --- | --[e] | 1:2[d] |

[a]The reaction conditions entail 0.25 mmol of enol silyl ether, 2 equiv. of base where indicated, 10 mol% of $Pd(OAc)_2$ and 5 ml of solvent.

[b]The ratio of products was determined by gas chromatography.

Table 1. (cont'd)

[c]The reaction used 3 mol% $Pd(OAc)_2$ in place of 10 mol% $Pd(OAc)_2$.

[d]The reaction used 3 mol% $Pd(OAc)_2$ in place of 10 mol% $Pd(OAc)_2$ and 2.5 ml of DMSO instead of 5 ml of DMSO.

[e]The products were not isolated due to an unacceptable amount of saturated ketone.

These results reveal that the conversion of **1** to **2** can be accomplished using 10 mol% $Pd(OAc)_2$ and DMSO. Using these conditions, additional substrates have been transformed to their corresponding α,β-unsaturated carbonyl systems as shown in Table 2.

As previously shown, entry 1 illustrates that a complicated enol silyl ether can be transformed to the corresponding unsaturated ketone in excellent yield. The results of entry 2 indicate that *trans*-1-phenyl-2-buten-1-one can also be prepared through this methodology with good results. The conversion of entry 3 to 2,6-dimethyl-2-cyclohexen-1-one afforded the desired endocyclic as well as the exocyclic enone products in a 12 to 1 ratio. These enones were accompanied by an equal amount of the saturated 2,6-dimethylcyclohexanone (not shown in Table 2). At 25°C no reaction occurred. The decrease in reactivity of the trisubstituted olefin appears to be directly related to the increase in steric hindrance. The conversion shown in entry 4 of a silyl enol acetal to the corresponding unsaturated ester occurred in low yield along with a 49% yield of the saturated ester.

Table 2. Conversion of Enol Silyl Ethers to the Corresponding α,β-Unsaturated Carbonyl Systems[a]

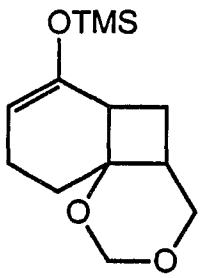
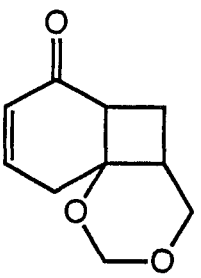
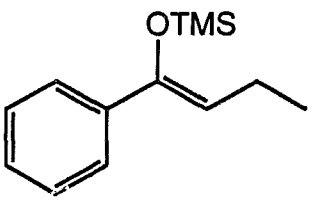
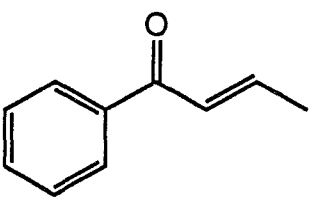
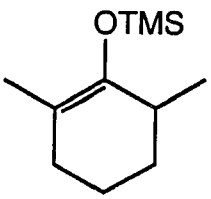
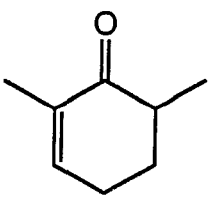
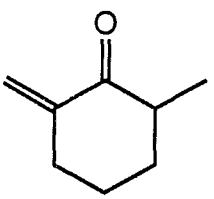
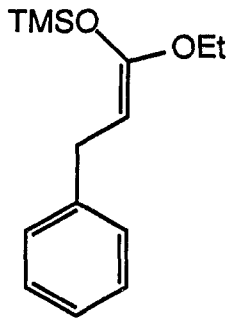
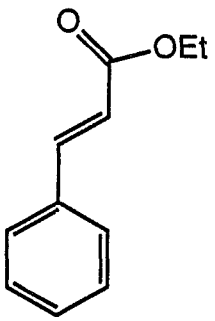
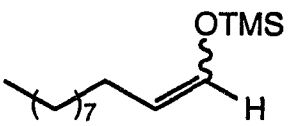
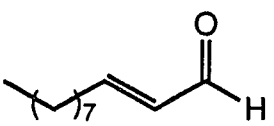
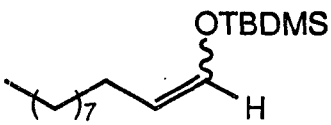
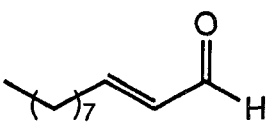
| Entry | Substrate | Time (hr), Temp. (°C) | Product | % Isolated Yield |
|---|---|---|---|---|
| 1 |  | 72, 25 |  | 86 |
| 2 |  | 72, 25 |  | 74 |
| 3 |  | 12, 80 |  and  | 45[b] |

Table 2. (cont'd)

| | | | | |
|---|---|---|---|---|
| 4 |  | 72, 25 |  | 40[c] |
| 5 |  | 72, 25 |  | 86 |
| 6 |  | 84, 25 |  | 82 |

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[a]The reaction conditions entail 0.25 mmol of enol silyl ether, 10 mol% of $Pd(OAc)_2$ and 5 ml of DMSO.

[b]The ratio of products was determined by $^1H$ NMR spectroscopic analysis of the vinylic hydrogens to indicate a 12 to 1 ratio of the endocyclic to exocyclic product. The unsaturated products were isolated alongside a 45% yield of the saturated ketone.

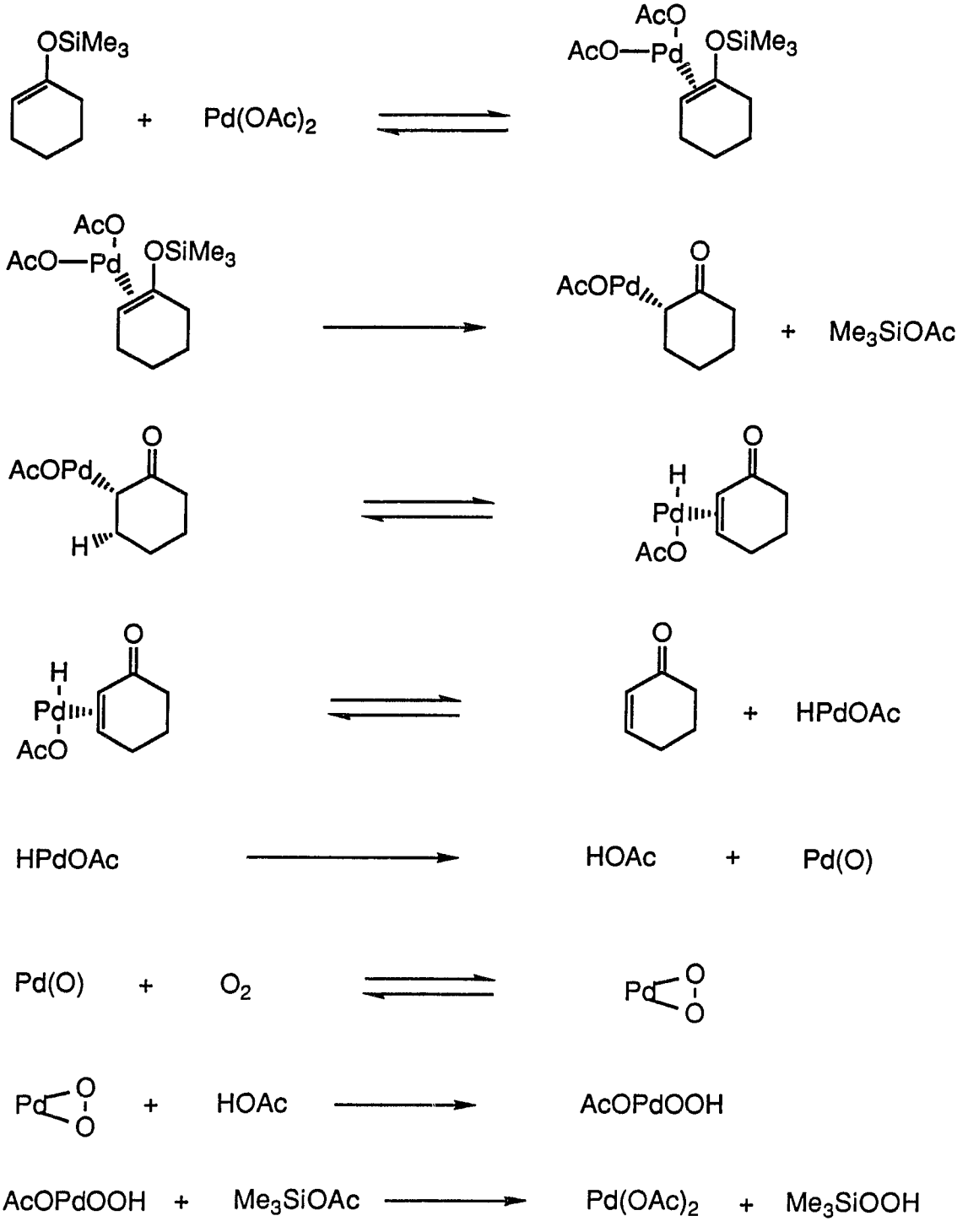
[c]The desired α,β-unsaturated ester was isolated alongside a 49% yield of the saturated ester.

The results of entries 5 and 6 reveal that the trimethylsilyl enol ether, as well as the *t*-butyldimethylsilyl enol ether, work well in the conversion of the enol silyl ether of undecanal to the corresponding α,β-unsaturated aldehyde. The proposed mechanism for the formation of these α,β-unsaturated carbonyl systems using our methodology is shown in Scheme 11.

The proposed mechanism suggests the initial formation of a π-complex which rearranges to provide the σ-complex and trimethylsilyl acetate. Upon rearrangement, β-hydride elimination and decomposition of the newly formed π-complex, the desired α,β-unsaturated ketone and HPdOAc are provided. The reductive elimination of HPdOAc to the corresponding Pd(0) and HOAc allows $O_2$ to reoxidize Pd(0) to $PdO_2$.[22] In the presence of HOAc, HOOPdOAc is formed. This hydroperoxypalladium acetate can transmetallate with trimethylsilyl acetate to restore the original $Pd(OAc)_2$.

It is also possible that the mechanism of transformation involves an initial transmetallation to provide a π-allylpalladium enolate intermediate, followed by rearrangement and β-hydride elimination of the resulting σ-alkylpalladium species to afford the desired α,β-unsaturated ketone (as shown in Scheme 5).

Scheme 11


OSiMe3
+ Pd(OAc)2
AcO
AcO—Pd
OSiMe3
AcOPd
O
+ Me3SiOAc
H
Pd
AcO
HPdOAc
HOAc + Pd(O)
Pd(O) + O2
O
O
Pd
+ HOAc
AcOPdOOH
AcOPdOOH + Me3SiOAc
Pd(OAc)2 + Me3SiOOH

# CONCLUSION

As reported earlier, there have been several methods developed for the synthesis of α,β-unsaturated carbonyl systems. We have developed a unique set of conditions which allow for the formation of these systems in moderate to excellent yield. The advantage of our palladium(II)-based methodology over the previously accepted selenium-based methodology, is that our methodology requires only a catalytic amount of palladium acetate; in addition, palladium is much less toxic than selenium.

Our advantage over other palladium(II)-based methodologies is that they require a stoichiometric amount of palladium, or, if the reaction utilizes only a catalytic amount of palladium, additional reoxidants, such as benzoquinone, copper salts and allyl carbonates are needed along with an oxygen atmosphere in order to reoxidize the Pd(0) formed during the reaction back to Pd(II). Our procedure requires no additional reoxidants, other than oxygen, to reoxidize the Pd(0) formed *in situ* to regenerate Pd(II), which could prove to be a more cost efficient transformation for industrial application.

In general, ketones and aldehydes are efficiently transformed via their enol silyl ether counterparts into α,β-unsaturated carbonyl compounds by 10 mol% of $Pd(OAc)_2$, DMSO and an oxygen atmosphere.

# EXPERIMENTAL SECTION

## Equipment

All NMR spectra were recorded on a Nicolet NT-300 spectrometer (operating at 300 MHz for hydrogen nuclei and 75 MHz for carbon nuclei). Infrared spectra were obtained on an IBM IR/98 FT-IR. Mass spectral data were obtained on a Kratos high resolution mass spectrometer.

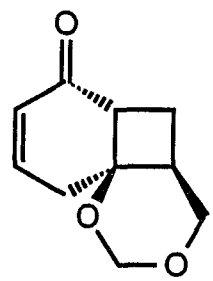
## Reagents

All enol silyl ethers were obtained from the Kraus group. EtOAc, NaOAc, $MgSO_4$, $CH_3CN$ and DMSO were all obtained from Fisher Scientific. Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. generously provided the palladium acetate.

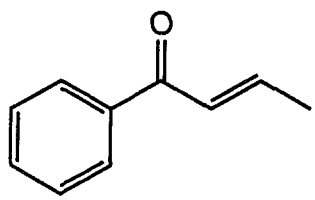
## General Procedure for the Palladium(II)-Catalyzed Reactions

The appropriate enol silyl ether (0.25 mmol) was added to a solution of $Pd(OAc)_2$ (0.025 mmol, 5.6 mg) and DMSO (5 ml). The reaction mixture was

placed under an oxygen atmosphere via balloon and allowed to stir at the designated time and temperature. The reaction mixture was diluted with saturated aqueous ammonium chloride and the mixture extracted with diethyl ether. The ether fractions were combined, dried ($MgSO_4$) and concentrated under vacuum to yield the crude product. The crude product was purified by flash chromatography on silica gel.

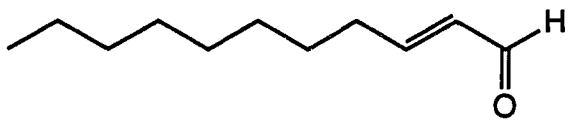


IR (neat) 1655 (C=O) $cm^{-1}$; $^1H$ NMR δ 2.07 (m, 1H, OCCH), 2.38-2.50 (m, 2H, CHC<u>H2</u>CH), 2.77-2.96 (m, 3H, C(O)CH and $C{=}CCH_2$), 3.75-3.77 (m, 2H, $OCH_2C$), 4.69 (d, J = 6.6 Hz, 1H, $OCH_2O$), 4.96 (d, J = 6.9 Hz, 1H, $OCH_2O$), 6.15 (ddd, J = 10.5, 3.0, 1.8 Hz, 1H, vinyl), 6.87 (ddd, J = 10.2, 5.4, 3.0 Hz, 1H, vinyl); $^{13}C$ NMR δ 26.2, 31.8, 34.6, 65.5, 46.8, 76.0, 88.6, 129.3, 145.8, 200.8; HRMS m/z ($M^+$) calcd for $C_{10}H_{12}O_3$ 180.07864, found 180.07854.

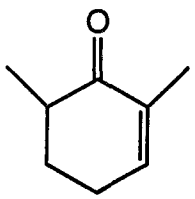


IR (neat) 3059 (ArH), 2963-2853 (CH), 1683 (C=O) $cm^{-1}$; $^1H$ NMR δ 1.87 (dd, J = 6.9, 1.2 Hz, 3H, $CH_3$), 6.78 (dd, J = 15.6, 1.5 Hz, 1H, vinyl), 6.95 (dq, J = 15.6, 6.6 Hz, 1H, vinyl), 7.33 (t, J = 6.9 Hz, 2H, ArH), 7.42 (tt, J = 7.5, 1.2 Hz, 1H, ArH), 7.8 (dd, J = 8.1, 0.9 Hz, 2H, ArH); $^{13}C$ NMR δ 18.6, 127.4, 128.4, 132.5,

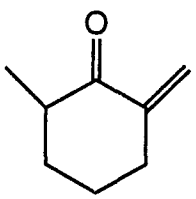
137.8, 145.0, 190.7 (minus 1 peak due to overlap); HRMS m/z ($M^+$) calcd for $C_{10}H_{10}O$ 146.07317, found 146.07301



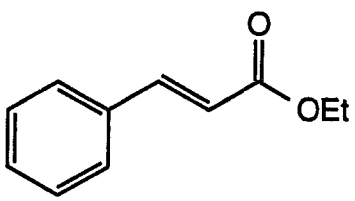
IR (neat) 3026-2809 (CH), 1694 (C=O) $cm^{-1}$; $^1H$ NMR δ 0.88 (t, J = 6.9 Hz, 3H, $CH_3$), 1.27 (m, 10H, $CH_2$), 1.50 (m, 2H, $CH_2$), 2.33 (ddd, J = 6.9, 6.9, 6.9 Hz, 2H, $C=CCH_2$), 6.12 (ddd, J = 15.6, 7.8, 0.9 Hz, 1H, vinyl), 6.58 (dt, J = 15.6, 6.6 Hz, 1H, vinyl), 9.50 (d, J = 8.1 Hz, 1H, C(O)H); $^{13}C$ NMR δ 14.04, 22.59, 27.79, 29.11, 29.25, 31.73, 32.68, 132.84, 158.99, 194.11 (minus 1 peak due to overlap); HRMS m/z ($M^+$) calcd for $C_{11}H_{20}O$ 168.15142, found 168.15095.



This compound was obtained as a mixture with the exocyclic isomer and the corresponding saturated compound. The products were worked up with a minimum amount of ether, dried ($MgSO_4$) and the solvent removed by distillation. A crude $^1H$ NMR spectrum was acquired to determine the presence of the desired product. The key olefinic peak was a singlet at δ 6.88. Purity was determined by GC.



This compound was obtained as a mixture with the previously mentioned isomer and the corresponding saturated compound. The products were worked up with a minimum amount of ether, dried ($MgSO_4$) and the solvent removed by distillation. A crude $^1H$ NMR spectrum was acquired to determine the presence of the product. The key olefinic peaks were two singlets at δ 5.91 and 5.29. Purity was determined by GC.




The compound was obtained as a mixture with the corresponding saturated compound. $^1H$ NMR δ 1.21 (t, J = 7.2 Hz, 3H, $CH_3$), 4.15 (q, J = 7.2 Hz, 2H, $CH_2$), 6.31 (d, J = 16.2 Hz, 1H, vinyl), 7.00-7.70 (m, 6H, ArH and vinyl).

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# GENERAL SUMMARY

In this dissertation, the power of palladium(II)-catalysis in organic synthesis has been demonstrated. The first three papers of the dissertation illustrate that alkenoic acids, olefinic tosylamides and allylphenol all readily cyclize to their corresponding unsaturated heterocycles in moderate to excellent yield using a unique set of palladium(II)-based conditions. In all these cases, the usual palladium(II)-based methodology requires a stoichiometric amount of palladium or, if the reaction utilizes only a catalytic amount of palladium, additional reoxidants are needed along with an oxygen atmosphere in order to reoxidize Pd(0) formed during the reaction back to Pd(II). It is important to note that our conditions eliminate the use of reoxidants other than oxygen. Since these reaction conditions eliminate the need for any additional reoxidants other than oxygen, this allows for a very simple, cost efficient, environmentally sound cyclization procedure.

In Paper IV of this dissertation, the transformation of enol silyl ethers and acetals to the corresponding $\alpha,\beta$-unsaturated aldehyde, ketones and ester have been explored. A set of reaction conditions, using only 10 mol% of $Pd(OAc)_2$ and DMSO under an oxygen atmosphere, have been developed which once again eliminates the need for an additional reoxidant other than oxygen.

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