Studies on Palladium-Catalyzed Carbocyclizations of Allene-Substituted Olefins and 1,3-Dienes

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Abstract

This thesis describes the development and mechanistic studies of carbocyclization reactions of allene-substituted olefins and 1,3-dienes, catalyzed by palladium(0) and palladium(II). These reactions result in the formation of \([n,3,0]\) bicyclic systems \((n = 3-5)\) with high stereoselectivity and in good to excellent yields.

The first carbocyclization presented is a novel palladium(0)-catalyzed cycloisomerization of allene-substituted olefins. Mechanistic studies on this reaction made us propose a mechanism where a Pd-hydride species is the active catalyst. Addition of the Pd-hydride to the allene results in the formation of a vinyl-Pd species. Insertion of the olefin into the vinyl-Pd bond forms the C-C bond, and subsequent \(\beta\)-hydride elimination gives the product.

Secondly an efficient aerobic biomimetic system has been developed for a Pd(II)-catalyzed allylic oxidative carbocyclization of allene-substituted olefins.

Additionally, during the studies of palladium-catalyzed carbocyclizations of allene-substituted olefins, it was found that in the absence of palladium a mild thermal ene-reaction occurs. In this manner stereodefined, functionalized bicyclic compounds are obtained with good regioselectivity and in high yields.

The third and fourth carbocyclization developed are a palladium(II)-catalyzed oxidation and a palladium(0)-catalyzed intramolecular telomerization of allene-substituted 1,3-dienes.

A mechanistic study of the palladium(II)-catalyzed oxidation of allene-substituted 1,3-dienes was made, and reaction intermediates could be isolated. The stereochemistry of the reaction intermediates was assigned, and this made it possible to suggest a mechanism for the reaction. The presented mechanism is a \(trans\) carbopalladation of the 1,3-diene, where the allene act as the carbon nucleophile. Due to different stereochemical outcomes of the stoichiometric and catalytic reactions, this mechanism could only explain the stoichiometric reaction. Another mechanism for the catalytic reaction was suggested, which rationalizes both the regio- and stereochemistry of the products.
Abbreviations

Ac  acetyl
Bn  benzyl
BQ  \textit{p}-benzoquinone
\textit{t}-Bu  tertbutyl
dba  dibenzylidene acetone
DCE dichloroethane
DCM dichloromethane
DMF dimethylformamide
Et  ethyl
FePc iron(II) phthalocyanine
AcOH acetic acid
L  ligand
Me methyl
n.d. not determined
NMR nuclear magnetic resonance
NOE nuclear Overhauser effect
Nu nucleophile
Ph phenyl
\textit{i}-Pr isopropyl
Piv pivaloyl or \textit{t}-butylcarbonyl
Tf trifluoromethanesulfonyl
TFA trifluoroacetic acid
THF tetrahydrofuran
TMS trimethylsilyl
List of Publications

This thesis is based on the following papers, referred to in the text by their Roman numerals I-V:

I. **Palladium(0)-Catalyzed Cycloisomerization of Enallenes**

II. **Palladium(II)-Catalyzed Aerobic Allylic Oxidative Carbocyclization of Allene-Substituted Olefins. Immobilization of Oxygen-Activating Catalyst.**
   Julio Piera, Katja Närhi and Jan-E. Bäckvall, *Manuscript.*

III. **An Unexpectedly Mild Thermal Alder-Ene Cyclization of Enallenes**
    Katja Närhi, Johan Franzén and Jan-E. Bäckvall, *Submitted.*

IV. **Palladium-Catalyzed Carbocyclization of Allene-Diene derivatives. Exploring Different Nucleophiles**

V. **Allenes as Carbon Nucleophiles in Intramolecular Attack on (π-1,3-Diene)-palladium Complexes: Evidence for trans Carbopalladation of the 1,3-Diene**

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Table of Contents

1 Introduction ...................................................................................................... 1
  1.1 Some Fundamental Properties and Reactions of Palladium ......................... 1
  1.2 Palladium(0)-Catalyzed Reactions of Unsaturated Hydrocarbons .......... 3
    1.2.1 Palladium(0)-Catalyzed Reactions of Allenes .................................. 5
  1.3 Palladium(II)-Catalyzed Oxidations of Unsaturated Hydrocarbons ......... 7
    1.3.1 Palladium(II)-Catalyzed Carbocyclizations ..................................... 10
    1.3.2 Palladium(II)-Catalyzed Oxidations of Allenes ............................... 10
    1.3.3 Reoxidation of Palladium ................................................................ 11
  1.4 Aim of the thesis ....................................................................................... 12

2 Preparation of Starting Materials ................................................................. 13

3 Palladium(0)-Catalyzed Cycloisomerization of Allene-Substituted Olefins I ............................................................................................................................ 15
  3.1 Reaction Optimization and Results ........................................................... 15
  3.2 Mechanistic Discussion ............................................................................. 20
  3.3 Conclusions ............................................................................................... 23

4 Palladium(II)-Catalyzed Aerobic Allylic Oxidation of Allene-Substituted Olefins II .............................................................................................................. 25
  4.1 Results and Discussion .............................................................................. 26
  4.2 Mechanistic Discussion ............................................................................. 30
  4.3 Conclusions ............................................................................................... 31

5 A Mild Thermal Ene-reaction of Allene-Substituted Olefins III ......................... 33
  5.1 Results and Discussion .............................................................................. 33
  5.2 Conclusions ............................................................................................... 38

Short Summary of Chapters 3-5 ..................................................................... 39

6 Palladium(II)-Catalyzed Carbocyclization of Allene-substituted Dienes IV,51
  6.1 Exploring Different Nucleophiles ............................................................. 41
    6.1.1 Stereochemical Assignment .............................................................. 43
  6.2 Conclusions ............................................................................................... 45

7 Mechanistic Investigation of the Palladium(II)-Catalyzed Carbocyclization of Allene-Substituted Dienes IV,57
  7.1 Isolation of Reaction Intermediates........................................................... 48
    7.1.1 Conclusions ....................................................................................... 50
  7.2 Mechanistic Discussion of the Palladium-mediated Reaction of 1,3-Diene-Allene Derivatives ............................................................... 50
  7.3 Mechanistic Discussion of the Palladium-catalyzed Reaction of 1,3-Diene-Allene Derivatives ............................................................... 51
  7.4 Conclusions ............................................................................................... 53

8 Palladium(0)-Catalyzed Carbocyclization of Allene-substituted Dienes IV ......................................................................................................................... 55
  8.1 Exploring Different Nucleophiles ............................................................. 55
    8.1.1 Stereochemical Assignment of Products ............................................ 56
  8.2 Mechanistic Discussion ............................................................................. 57
  8.3 Conclusions ............................................................................................... 58

Short Summary of Chapters 6-8 ..................................................................... 59
Introduction

The construction of carbon-carbon bonds is of central importance in organic chemistry. Palladium as a catalyst, has contributed considerably to this area, as it is one of the most versatile metals in organic synthesis and offers many possibilities of carbon-carbon bond formation. Palladium-catalyzed reactions have found wide application in both chemical laboratories and industry.\textsuperscript{1-3} The Wacker process, developed in 1956, constitutes a milestone in the history of palladium catalysis, and is the industrial process for production of acetaldehyde.\textsuperscript{4, 5} Soon after this discovery, various palladium-mediated and catalyzed reactions forming carbon-carbon bonds were developed, \textit{e.g.} the Tsuji-Trost-reaction\textsuperscript{6-8} and the Heck reaction.\textsuperscript{9} Since then, the development of palladium-catalyzed reactions has been both extensive and successful.

1.1 Some Fundamental Properties and Reactions of Palladium\textsuperscript{1, 3}

Palladium is a late transition metal and thereby relatively electronegative. It tends to retain its valence electrons and form d\textsuperscript{10} and d\textsuperscript{8} complexes of low oxidation states; 0 and +2. Some features of palladium are its large size that gives it a “soft” character\textsuperscript{10} and its electronegative properties, which allows the formation of relatively stable organopalladium complexes. Palladium has high affinity for nonpolar π-compounds such as alkenes and alkynes, and readily forms π-complexes with these. It also forms strong σ-bonds with nonbonding electron donors such as amines, imines, nitriles, phosphines, phosphites etc. Palladium is, however, relatively unreactive toward polar functional groups such as carbonyl and hydroxy groups, and so Pd-catalyzed reactions can be carried out without protection of these functional groups. Another important feature for catalysis is the small energy difference between the two preferred oxidation states, 0 and +2, which allows for relatively easy and reversible redox processes to occur.

In principal, transition metal-catalyzed reactions can be divided into a number of fundamental reactions, and those of major importance in Pd-catalyzed reactions are described below:

\textit{(i) Oxidative addition reaction:} A molecule A-B adds to Pd(0) and forms a Pd(II)-species (Scheme 1). A covalent bond is cleaved and two new bonds are formed in the process, thus Pd(0) is oxidized to Pd(II). The most common A-B molecules that undergo oxidative addition to Pd(0) are; alkenyl- and arylhalides (R-X) and acylhalides (RCO-X). Other commonly observed A-B systems are allylic compounds (RHC=CHCH\textsubscript{2}-Y, Y = halogen, esters, NO\textsubscript{2}, SO\textsubscript{2}R etc.), aldehydes (RCO-H), sulfonyl halides (RSO\textsubscript{2}-X), H-H, H-SnR\textsubscript{3}, H-SiR\textsubscript{3}, Ar-H and RCO\textsubscript{2}H.

(ii) *Reductive elimination* is the reverse of oxidative addition and involves a loss of two one-electron ligands of *cis* configuration from the Pd(II) center. The ligands are combined to form an elimination product and Pd(II) is reduced to Pd(0) (Scheme 1).

(i) Oxidative addition

$$\text{Pd(0)} + \text{A-B} \rightarrow_{\text{i}} \text{A-Pd(II)-B} \rightarrow_{\text{ii}} \text{Pd(0)} + \text{R-R'}$$

Scheme 1

(ii) Reductive elimination

$$\text{R-Pd(II)} \rightarrow_{\text{ii}} \text{Pd(0)} + \text{R-R'}$$

(iii) *Insertion*: An unsaturated bond inserts into a Pd-R σ-bond (R = C or H). The insertion can be described as the migration of a one-electron ligand from Pd to an unsaturated bond, also coordinated to Pd (Scheme 2). The reaction can occur in two ways: α,β- and α,α-insertion. The α,β-insertion involves unsaturated bonds, like alkenes, alkynes, CO$_2$ and carbonyl groups. The α,α-insertion involves unsaturated bonds, as in CO, SO$_2$, isonitriles and carbenes (Scheme 2).

(iv) *Elimination of β-hydride* is a *syn* elimination of a β-hydride in an alkyl-Pd complex, forming H-Pd-X and an alkene (Scheme 2). β-hydride elimination is the reverse of alkene α,β-insertion into a Pd-H σ-bond.

(iii) Insertion

$$\begin{align*}
\text{Pd-R} & \rightarrow_{\text{α,β-iii}} \text{Pd} & \text{R}' \\
\text{R} & \rightarrow_{\text{α,α-iii}} \text{Pd} & \text{CO} \\
\text{Pd-CO} & \rightarrow_{\text{H}} \text{Pd} & X
\end{align*}$$

Scheme 2

(iv) β-hydride elimination

$$\begin{align*}
\text{X-Pd} & \rightarrow_{\text{α,β-iii}} \text{Pd} & \text{H} \\
\text{R}' & \rightarrow_{\text{iv}} \text{X-Pd} & \text{H}
\end{align*}$$

(v) *Nucleophilic attack on Pd-coordinated ligands*: π-Coordination of unsaturated hydrocarbons, such as alkenes and alkynes, to palladium decreases the electron density of the π-system and makes it electrophilic. Nucleophilic attack on a π-coordinated ligand occurs *anti* to the coordinated palladium, leading to an overall *trans*-addition of palladium and nucleophile over the π-system (Scheme 3).

(v) Nucleophilic attack on Pd-coordinated ligands

$$\begin{align*}
\text{Pd} & \rightarrow_{\text{Nu}} \text{Pd} & \text{Nu} \\
\text{Pd} & \rightarrow_{\text{Nu}} \text{Pd} & \text{Nu}
\end{align*}$$

Scheme 3
1.2 Palladium(0)-Catalyzed Reactions of Unsaturated Hydrocarbons

The oxidative addition reaction of halides to Pd(0), is one of the key steps in many Pd(0)-catalyzed reactions. One example is the Heck reaction, which is a coupling reaction of aryl or alkenyl halides with alkenes (Scheme 4). This is a powerful method to create C-C bonds, and is widely applied in both inter- and intramolecular variants (Scheme 4). The intramolecular version is a well-established strategy to create carbocycles (Scheme 4b).

The main steps in the Heck reactions are: (i) oxidative addition of R-X (R = alkenyl or aryl, X = halogen, OTf etc.) to Pd(0), giving a σ-carbon Pd intermediate, (ii) an insertion of the olefin into the Pd-C σ-bond, and (iii) a β-hydride elimination to form the product and H-Pd(II)-X. The latter undergoes reductive elimination to form H-X and Pd(0), which closes the catalytic cycle (Scheme 4).

Another reaction, where oxidative addition is the key step, is the Pd(0)-catalyzed allylic substitution. Allylic compounds (e.g. allylic esters) make an oxidative addition to Pd(0) to form a (π-allyl)Pd complex, which then can be attacked by various nucleophiles (Scheme 5). Pd(0)-catalyzed allylic substitutions that create a C-C bond, by the use of a stabilized carbon nucleophile, were developed independently by the groups of Tsuji and Trost, which is why this reaction often is called the Tsuji-Trost reaction.

The Pd(0)-catalyzed allylic substitution has been widely applied in both inter- and intramolecular variants. For example, to create carbocycles, a (π-allyl)Pd complex is formed, which can then be attacked by various nucleophiles to form new C-C bonds.
complex formed by oxidative addition of an allylic compound to Pd(0), can react either by attack of an intramolecular carbon nucleophile, or by an intramolecular α,β-insertion of an olefin into the (π-allyl)Pd bond (Scheme 6).

Scheme 6. Intramolecular Pd(0)-catalyzed allylic substitutions.

Pd(0)-catalyzed linear dimerization and telomerization of conjugated dienes, is a well known way of creating C-C bonds, either forming the linear dimerization product \( \text{a} \), or in the presence of a nucleophile, the telomer products \( \text{b} \) and \( \text{c} \) (Scheme 7). These reactions are believed to proceed via a palladacycle that is formed by oxidative cycloaddition. The palladacycle that is formed is a bis-allyl-Pd complex, that may occur in several isomeric forms, as the allyl moieties can be \( \eta^3,\eta^3 \)-, \( \eta^3,\eta^1 \)- or \( \eta^1,\eta^1 \)-coordinated to the metal. Generally a \( \eta^1,\eta^1 \)-Pd complex reacts with nucleophiles because of its electrophilic character. However, studies have shown that bis-\( \eta^3,\eta^1 \)-allyl-Pd complexes readily react with electrophiles. The dimerization/telomerization reaction shown in Scheme 7 is proposed to go via the bis-\( \eta^3,\eta^1 \)-allyl-Pd intermediate, where the \( \eta^1 \)-allyl moiety reacts with a proton in the \( \gamma \)-position. Subsequently the remaining \( \pi \)-allyl-Pd complex is either undergoing a β-hydride elimination to give product \( \text{a} \), or is attacked by a nucleophile to give the product \( \text{b} \) and \( \text{c} \).

Scheme 7. Pd(0)-catalyzed dimerization and telomerization of butadiene.

The intramolecular version of the dimerization/telomerization of conjugated dienes, produces carbocycles (Scheme 8). These reaction is also believed to
proceed via the intermediacy of a bis-allyl-Pd complex, formed by oxidative cycloaddition. As in the intermolecular version, this reaction can give a product either in the presence or in the absence of a nucleophile, by intramolecular telomerization or cycloisomerization.

Scheme 8. Intramolecular telomerization and cycloisomerization of a bis-diene.

The intramolecular cycloisomerization/telomerization reaction in Scheme 8 is proposed to go via the bis-(η^3,η^1-allyl)Pd intermediate shown in Figure 1, where the η^1-allyl moiety reacts with a proton in the γ-position. Subsequently, the remaining (π-allyl)Pd complex is either undergoing a β-hydride elimination or is attacked by a nucleophile to give the product.

Figure 1. The bis-(η^3,η^1-allyl)Pd intermediate in the intramolecular cycloisomerization/telomerization reaction, in Scheme 8.

Another well-studied reaction for the formation of carbocycles, is the Pd(0)-catalyzed cycloisomerization of enynes and dienes (Scheme 9). The mechanism proposed for these reactions involves initial formation of a Pd-hydride species, which is the active catalyst. Insertion of either an olefin or acetylene into the Pd-hydride bond results in the formation of a vinyl-Pd species. Insertion of the olefin into the vinyl-Pd bond forms the C-C bond, and subsequent β-hydride elimination gives the product (Scheme 9).

Cycloisomerization reactions are not only an efficient way of constructing carbocycles, they are also associated with high atom economy, as no additional reactants are required and no waste products are formed in the process.

Scheme 9. Pd-catalyzed cycloisomerization of a 1,6-enyne or 1,6-diene.

1.2.1 Palladium(0)-Catalyzed Reactions of Allenes

Allenes, as well as olefins, can react with halides of sp^2 carbons and allylic esters via oxidative addition to Pd(0) (Scheme 10). Insertion of an allene into an R-Pd
σ-bond (R = C or H) most often generates a (π-allyl)Pd intermediate via R migration to the middle carbon of the allene.\textsuperscript{29, 30} This intermediate can subsequently react inter- or intramolecularly with a nucleophile to form an allylic product (Scheme 10),\textsuperscript{29-31} or intramolecularly with an olefin, through an α,β-insertion.\textsuperscript{32}

\[
\text{Scheme 10. Insertion of an allene into an R-Pd σ-bond.}
\]

An allene-substituted vinyl/aryl halide or allylic ester can give rise to carbocyclic products in the presence of Pd(0) (Scheme 11).\textsuperscript{29, 33} As in the above Schemes 4b and 6, the reaction starts with a oxidative addition to form an aryl/vinyl-Pd or a (π-allyl)Pd intermediate, but instead of an olefin an allene inserts to form a (π-allyl)Pd intermediate. The latter can then be attacked by a nucleophile to form a product.

\[
\text{Scheme 11. Insertion of an allene into a (π-allyl)Pd complex.}
\]

However, a recent mechanistic investigation by our group, on a similar reaction, shows that allenes are able to act as π-nucleophiles, so instead of \textit{cis} insertion, a \textit{trans} attack by the allene occurs on the (π-allyl)Pd complex shown in Scheme 12.\textsuperscript{34, 35}

\[
\text{Scheme 12. Nucleophilic attack by an allene on a (π-allyl)Pd complex.}
\]

Allenes, as conjugated dienes, can undergo telomerization reactions to give 1,3-dienes, and in the same way as for conjugated dienes (Scheme 7) the reaction proceeds via a palladacycle, which is a bis-allyl-Pd intermediate (Scheme 13).\textsuperscript{36}
In contrast to alkenes and alkynes, allenes have received little attention as components in Pd-catalyzed cycloisomerizations.\textsuperscript{37, 38}

1.3 Palladium(II)-Catalyzed Oxidations of Unsaturated Hydrocarbons

Pd(II) salts are electrophilic and are mostly used as catalysts in oxidation reactions. Pd(II) salts readily form π-complexes with unsaturated hydrocarbons, such as alkenes and alkynes, thereby making these electrophilic and subject to attack by nucleophiles.\textsuperscript{40} Pd(II)-catalyzed oxidations of unsaturated hydrocarbons have received much attention since the discovery and development of the Wacker process (Scheme 14).\textsuperscript{3, 4, 41, 42} The basis of the Wacker process is an electrophilic activation of ethene, by coordination to Pd(II), which decreases the electron density of the π-system and induces a nucleophilic attack by water.

\[ \text{2} \text{Pd(II)} + \text{PdCl}_2 + \text{H}_2\text{O} \rightarrow \text{CuCl}_2 + \text{Pd}_0 + 2\text{HCl} \]

Scheme 14. The Wacker reaction.

The attack on Pd(II)-activated olefins has been extended to other nucleophiles than water, such as ROH, RCO_2H, RNH_2, ‘CH(CO_2R)_2’, resulting in either 1,2-addition or substitution (Scheme 15).\textsuperscript{3}

\[ \text{Nu}_\text{A}/\text{Nu}_\text{B} = \text{H}_2\text{O}, \text{ROH}/\text{RO}^-, \text{RCO}_2\text{H}/\text{RCO}_2^-, \text{RNH}_2, ‘\text{CH(CO}_2\text{R)}’ \]

Scheme 15. Pd(II)-catalyzed addition and substitution of olefins.

Pd-catalyzed reactions involving nucleophilic attack on (π-olefin)- and (π-allyl)Pd complexes are often associated with high stereo- and regioselectivity, and have therefore been extensively studied.\textsuperscript{43, 44} Nucleophilic attack on a (π-olefin) - or (π-allyl)Pd complex proceeds by an external \textit{trans} attack (Scheme 16a). Alternatively, the nucleophile can attack Pd, followed by a \textit{cis} migratory insertion of the π-system into the Pd-Nu bond (Scheme 16b).
The character of the nucleophile often determines whether the reaction proceeds via *trans* attack (Scheme 16a), or via *cis* migration (Scheme 16b). Heteroatoms and stabilized carbon nucleophiles normally attack via the external mode, whereas hydrides and non-stabilized carbon nucleophiles prefer to react via the *cis* migratory insertion pathway.\textsuperscript{16, 17, 45}

When conjugated 1,3-dienes are activated by Pd(II)-salts and attacked by nucleophiles, they most often undergo 1,4-addition reactions.\textsuperscript{44, 46} In the Pd(II)-catalyzed 1,4-diacetoxylation of conjugated dienes, it is possible to direct the reaction toward either 1,4-*trans*- or 1,4-*cis*-diacetoxylation (Scheme 17).\textsuperscript{47, 48}

There are two nucleophilic attacks occurring in this reaction: the first takes place on Pd(II)-activated diene complex A forming (\(\pi\)-allyl)Pd complex B or C. The second nucleophilic attack is either a *trans* attack on the (\(\pi\)-allyl)Pd complex or the nucleophile makes a *cis* migration from palladium. In this reaction it has been shown that nucleophilic attack by acetate can occur through both pathways, depending on the ligands employed. The crucial ligand, which dramatically changes the stereochemical outcome of the reaction, is the chloride ion. In the absence of chloride ligands, a 1,4-*trans*-diacetoxylation takes place, whereas a catalytic amount of chloride ions yield the 1,4-*cis*-diacetoxylation product (Scheme 17).
These results can be explained by considering the bond strength of acetate vs. chloride to Pd. In the absence of chloride ions, the counter ion to Pd is acetate, which migrates from the metal center to the \( \pi \)-allyl.\textsuperscript{49} Addition of catalytic amount of chloride ions, which bind strongly to Pd(II), results in a displacement of acetate by chloride on the palladium atom, and hence only \textit{trans} attack by the acetate can take place. The migration of acetate from palladium to carbon, is believed to proceed via an \((\eta^1\text{-allyl})\)Pd complex, where it is not the oxygen coordinated to the palladium that attacks the allyl carbon, but instead the carbonyl oxygen, as shown in figure 2.\textsuperscript{48-50}

\textbf{Figure 2.} Acetate migration via a \((\eta^1\text{-allyl})\)Pd intermediate.

Instead of inducing nucleophilic attack on an olefin, Pd(II) can catalyze oxidative allylic substitution reaction of olefins, in which an alkene possessing an allylic hydrogen is oxidized to e.g. allylic esters. Pd(II) generates a \((\pi\text{-allyl})\)Pd(II) complex via a C-H bond activation, which is then attacked by a carboxylate nucleophile (Scheme 18).\textsuperscript{51}
1.3.1 Palladium(II)-Catalyzed Carbocyclizations

Pd(II)-catalyzed carbocyclizations have not been as widely studied as the Pd(0)-catalyzed carbocyclization reactions. As described above, Pd(II)-catalyzed oxidation reactions often involve nucleophilic attack on alkenes coordinated to Pd(II). Unfortunately incompatibility between the carbon nucleophile and the stoichiometric oxidant and/or Pd(II) complex has precluded the use of carbonions, even stabilized, acting as nucleophiles on π-ligands coordinated to Pd(II) in all but a few cases.\(^{52-56}\) However, Widenhoefer and co-workers have recently developed a Pd(II)-catalyzed oxidative carbocyclization, where olefin-substituted diones or β-keto esters undergo an oxidative carbocyclization (Scheme 19).\(^{52,57}\) The carbon-carbon bond forming step in these reactions is believed to proceed by attack of an enol carbon atom on the olefin that is activated by Pd(II). Other similar examples have recently been reported, where olefin-substituted β-keto amides\(^{56,58}\) or indoles\(^{59,60}\) were used.

Scheme 19. Pd(II)-catalyzed carbocyclization of an olefin substituted dione.

One of the first reported Pd(II)-catalyzed oxidative carbocyclizations, employed 1,5-dienes.\(^{61,62}\) The carbon-carbon bond forming step in these reactions is, however, not believed to be a carbon nucleophilic attack, but an insertion of a double bond into a Pd-C σ-bond, while the Pd-C σ-bond is formed by an attack of an acetate nucleophile on a Pd(II)-activated double bond (Scheme 20).\(^{62}\)

Scheme 20. Pd(II)-catalyzed carbocyclization of a 1,5-diene.

Several Pd(II)-catalyzed oxidative carbocyclizations of various 1,3-dienes have been reported by Bäckvall and coworkers in the past decade; 1,3-dienes with a pendant stabilized carbon nucleophile\(^ {55}\) or allylsilane\(^ {54}\) and acetylene\(^ {63}\) have been shown to cyclize.

1.3.2 Palladium(II)-Catalyzed Oxidations of Allenes

Allenes can be activated by Pd(II) in the same way as olefins, and subsequently be attacked by a nucleophile. Pd(II) coordinates to one of the double bonds and the nucleophile attacks, most often, on the middle carbon of the allene, giving a (π-allyl)Pd complex (Scheme 21).\(^ {29,64}\) The complex can then be attacked by a second external or intramolecular nucleophile to form an alkene product (Scheme 21). In this way a Pd(II)-catalyzed 1,2-functionalization of allenes has
been developed, which allows preparation of various five- and six-membered heterocycles containing vinyl bromides.\textsuperscript{64,65}

\[ \text{NuA} = \text{Br}^-, \text{Cl}^- \]

\[ \text{NuB} = \text{inter- or intramolecular C-, N-, O-, S-nucleophile or Br}^-, \text{Cl}^- \]

**Scheme 21.** Nucleophilic attack on a Pd(II)-activated allene.

### 1.3.3 Reoxidation of Palladium

In Pd(II)-catalyzed oxidation reactions, Pd(II) is reduced to Pd(0), which requires a reoxidant in order to create a catalytic cycle. In the Wacker process CuCl\textsubscript{2}/O\textsubscript{2} is used (Scheme 14), other frequently used reoxidants are organic peroxides, benzoquinone (BQ) and MnO\textsubscript{2}/BQ.\textsuperscript{66} Pd-catalyzed oxidation reactions using molecular oxygen as terminal oxidant have attracted considerable attention lately.\textsuperscript{60,67-69} These reactions are advantageous both from an environmental point of view and for economical reasons. However, molecular oxygen is not always an effective oxidant, when used as the sole reoxidant, and can lead to decomposition of the palladium catalyst into inactive bulk metal. Another way of using molecular oxygen as the terminal oxidant is by mimicking biological oxidations, where several coupled redox catalysts are used as electron-transfer mediators (ETMs), e.g., iron phthalocyanine (FePc), cobalt salen, cobalt salophen.\textsuperscript{70,71} Such coupled catalytic systems have been designed and developed for the Pd(II)-catalyzed 1,4-oxidation of dienes (Scheme 22)\textsuperscript{70,71} and allylic oxidations of olefins.\textsuperscript{71,72}

**Scheme 22.** Triple-catalytic system for the Pd(II)-catalyzed 1,4-oxidation of 1,3-dienes.
1.4 Objectives of the thesis

The aim of the thesis has been to investigate the ability of allene-substituted olefins and 1,3-dienes to give carbocycles in the presence of a catalytic amount of palladium. The first part of the thesis (Chapters 3-5) is based on studies made on Pd-catalyzed and thermally induced intramolecular carbocyclizations of allene-substituted olefin derivatives. The outcome of the reaction using only heat or catalytic amounts of either palladium 0 or 2, is described and discussed.\textsuperscript{1-III} The second part (chapter 6-8) of the thesis is based on studies made on Pd(II)- and Pd(0)-catalyzed intramolecular carbocyclizations of allene-substituted 1,3-diene derivatives.\textsuperscript{IV-V} A mechanistic investigation of the Pd(II)-catalyzed oxidation of allene-substituted dienes is also described and discussed.\textsuperscript{V}
## Preparation of Starting Materials

This thesis deals with intramolecular cyclizations of allene-substituted olefins and 1,3-dienes. The synthesis of these substrates follows the literature and is briefly discussed below.

The allene-substituted olefins 4-6 (also referred to as enallenes) were obtained from the corresponding allylic acetates 1 (Scheme 23a). A Pd(0)-catalyzed allylic substitution of 1 with sodium dimethylmalonate gave 2. Deprotonation of the latter with sodium hydride followed by reaction with disubstituted bromoallene 3 resulted in enallenes 4-6.73 The acyclic enallenes (7) were synthesized in the same way from the corresponding acyclic allylic acetate (Scheme 23b).73

![Scheme 23](image)

The allene-substituted olefins with a carboxyl group in the allylic position (11 and 12), were synthesized from a cyclic 1,3-diene via the chlорoacryoxylation approach (Scheme 24).44, 74 A Pd(II)-catalyzed 1,4-chlорoacryoxylation of the 1,3-diene gave the cis-1,4-substituted olefin 8. Subsequent substitution of the allylic chloride in 8 with dimethyl malonate, either uncatalyzed (SN2) or Pd(0)-catalyzed afforded the trans product 9 or the cis product 10, respectively. These two malonates were subsequently treated with NaH and bromoallene 3 to give 11 and 12, respectively, in good yields.35
Scheme 24

The allene-substituted 1,3-diene substrates 14 were obtained through a Pd(0)-catalyzed elimination reaction of 10 which gave 13, followed by coupling of the bromoallene to give 14 in good yields (Scheme 24). The disubstituted bromoallenes 3 were obtained from the corresponding 1,1-disubstituted propargylic alcohols by treatment with copper bromide in HBr (Scheme 25).

Scheme 25
Palladium(0)-Catalyzed Cycloisomerization of Allene-Substituted Olefins

Transition metal-catalyzed cycloisomerization reactions of enallenes have only been reported for a few transition metals; Ni/Cr, Ru, and Rh. There is only one Pd-catalyzed cycloisomerization reaction of one single enallenic substrate previously reported. We thus set out to investigate this reaction in detail, employing the enallenes prepared in Chapter 2.

3.1 Reaction Optimization and Results

In our first attempt of this reaction, we used enallene 4a and Pd(dba)$_2$ (5 mol%) in acetic acid at room temperature for 5h, as these reaction conditions had been shown to work on allene-substituted 1,3-dienes. This unfortunately resulted in no product formation, and the starting material could be recovered. The temperature was increased to 120 °C using microwave heating, which resulted in a 6:1 regioisomeric mixture of 15a and 16a after 20 minutes in acetic acid (Scheme 26 and Table 1, entry 1). Traces of a third isomer, 17a, could also be detected in the product mixture (Scheme 26).

The reaction time was studied, and it was found that full conversion of 4a was obtained after only 8 minutes at 120 °C, to give 15a and 16a in a 6:1 ratio (entry 2). The amount of Pd(dba)$_2$ was decreased to 2 mol%, which resulted in a less chemoselective reaction; after 1 h at 120 °C, 15a and 16a were obtained in a ratio of 6:1, but with by-products (entry 3). After running the reaction in several different solvents; it was found that a protic solvent seems to be essential for the reaction. When solvents like acetonitrile, dichloroethane and toluene were used, no reaction was observed, and the starting material could be recovered (entries 4-
6). To find out whether the microwave heating had a significant effect on the reaction of 4a, the reaction was carried out with classical (oil-bath) heating, but otherwise under the same reaction conditions. The result obtained was similar to the result obtained with microwave heating.\textsuperscript{79}

In an attempt to improve the regioselectivity of the Pd(0)-catalyzed carbocyclization, the concentration of acid was varied. When 10 mol% of acetic acid in acetonitrile was used, the reaction became slower and less regioselective (entry 7). A similar result was obtained when LiOAc was added to the reaction run in acetic acid (entry 8). Changing the solvent to trifluoroacetic acid (TFA), resulted in a fast consumption of the starting material, but gave a complex mixture of unidentified products (entry 9). The same result was obtained even when a catalytic amount of TFA in toluene was used (entry 10). However, when a catalytic amount of TFA in acetic acid was used, the rate and regioselectivity decreased, compared to the reaction run in acetic acid (compare entries 11 and 2).

As the regioselectivity could not be improved by changing the solvent, we tried to add different ligands to palladium. When an electron-donating ligand, such as ethylene diamine was added a less selective reaction was observed (entry 12). Maleic anhydride, which is an electron-withdrawing ligand, inhibited the reaction, and the starting material could be recovered (entry 13). Addition of triphenylphosphine gave side reactions and only minor amounts of product could be detected (entry 14).

The conclusion from these optimization studies is that the use of 5 mol% Pd(dba)_2 in acetic acid at 120 °C, for 8 minutes, gave the best result with respect to both regioselectivity and conversion.

\textbf{Table 1:} Investigation of the Pd(0)-catalyzed cycloisomerization of 4a.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Additive (mol%)</th>
<th>Time (min)</th>
<th>Conv. (%)</th>
<th>Ratio 15a:16\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOH</td>
<td>-</td>
<td>20</td>
<td>100</td>
<td>6:1</td>
</tr>
<tr>
<td>2</td>
<td>AcOH</td>
<td>-</td>
<td>8</td>
<td>100</td>
<td>6:1</td>
</tr>
<tr>
<td>3\textsuperscript{c}</td>
<td>AcOH</td>
<td>-</td>
<td>60</td>
<td>100</td>
<td>6:1 (and by-products)</td>
</tr>
<tr>
<td>4</td>
<td>CH\textsubscript{3}CN</td>
<td>-</td>
<td>8</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>-</td>
<td>8</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>DCE</td>
<td>-</td>
<td>8</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Table 1: Investigation of the Pd(0)-catalyzed cycloisomerization of 4a.

\textsuperscript{b}6:1 (and by-products)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent 1</th>
<th>Solvent 2</th>
<th>Condition</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>CH$_3$CN</td>
<td>AcOH (10)</td>
<td>30/90</td>
<td>3:1</td>
</tr>
<tr>
<td>8</td>
<td>AcOH</td>
<td>LiOAc (1 M)</td>
<td>15/100</td>
<td>4:1</td>
</tr>
<tr>
<td>9$^d$</td>
<td>TFA$^a$</td>
<td>-</td>
<td>8/100</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>10</td>
<td>Toluene</td>
<td>TFA (15)</td>
<td>8/100</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>11</td>
<td>AcOH</td>
<td>TFA (10)</td>
<td>8/50</td>
<td>5:1(and by-products)</td>
</tr>
<tr>
<td>12</td>
<td>AcOH</td>
<td>H$_2$NC$_2$H$_4$NH$_2$ (10)</td>
<td>8/100</td>
<td>4:1</td>
</tr>
<tr>
<td>13</td>
<td>AcOH</td>
<td>Maleic anhydride (10)</td>
<td>8/0</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>AcOH</td>
<td>PPh$_3$</td>
<td>8/90</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

(a) Enallene 4a, Pd(dba)$_2$ (5 mol%) and additive were dissolved in the specific solvent (10 mL/mmol) and heated to 120 °C (microwave heating). (b) The ratio was determined by $^1$H NMR experiments. This mixture also contains traces of 17a. (c) The Pd(dba)$_2$ loading was decreased to 2mol%. (d) 60 °C reaction temperature. (e) Trifluoroacetic acid.

The optimum reaction conditions in the cycloisomerization of 4a (entry 2) gave 15a+16a in a ratio of 88:12$^{80}$ in a total yield of 83% (Table 2, entry 1). The same conditions were then employed on a series of different enallenes summarized in Table 2 and Scheme 27. The methyl, ethyl derivative 4b and the cyclohexyl derivative 4c gave 15b+16b and 15c+16c, respectively, in a ratio of 6:1$^{81}$ and a total yield of 90% (entries 2 and 3). When two methyl groups were present in the allylic position of the cyclohexene ring (4d) no reaction occurred and the starting material was recovered (entry 4).
Scheme 27

The effect of the ring size was studied next, and the reaction of cyclopentene analogue 5, gave 18+19 in a ratio of 78:22 in a total yield of 92% (entry 5). The cyclohexene- and cyclopentene analogues were highly stereoselective in the carbon-carbon bond-forming step and gave only the cis-fused ring system. In contrast to the cyclohexene and cyclopentene analogues, the cycloheptene analogue 6 appears to give a mixture of cis- and trans-fused ring systems (Scheme 28).83

Scheme 28

When subjecting the acyclic enallenes 7a and 7b to the same reaction conditions as above, full conversion of the starting material was not obtained. The catalytic load was therefore increased to 10 mol% and the reaction time to 40 minutes, which resulted in full conversion, and 20+21 and 22+23 were obtained in good yields, respectively (entries 6-7). Using these same reaction conditions for the acyclic substrate with a terminal olefin (7c, entry 8) resulted in regioisomers 24 and 25 in a ratio of 4:1. Compound 25, is however not formed by a Pd(0)-catalyzed cycloisomerization, it is instead believed to be formed by a thermal ene-reaction.84 To reduce the by-product amount, the reaction temperature was decreased to 80 °C, which improved the ratio to 13:3, and gave 24 and 25 in a total yield of 52% (entry 8). The thermal ene-reaction will be discussed in more detail in chapter 5.
Table 2. Pd(0)-catalyzed cycloisomerization of allene-substituted olefins 4, 5 and 7.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Products</th>
<th>Ratio</th>
<th>Yield\textsuperscript{b} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>15a + 16a</td>
<td>88:12\textsuperscript{c}</td>
<td>83\textsuperscript{d}</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>15b + 16b</td>
<td>6:1\textsuperscript{f,g}</td>
<td>90\textsuperscript{e}</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>15c + 16c</td>
<td>6:1\textsuperscript{f}</td>
<td>90\textsuperscript{e}</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>18 + 19</td>
<td>78:22\textsuperscript{c}</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>7a</td>
<td>20 + 21</td>
<td>67:33\textsuperscript{c,h}</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>7b</td>
<td>22 + 23</td>
<td>73:27\textsuperscript{c,h}</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>7c</td>
<td>24 + 25</td>
<td>13:3\textsuperscript{l}</td>
<td>52</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: Pd(0) catalyst, solvent, temperature, time.
\textsuperscript{b} Yield determined by NMR analysis.
\textsuperscript{c} Ratio determined by GC analysis.
\textsuperscript{d} Isolated yield after purification.
\textsuperscript{e} Reaction performed under different conditions.
\textsuperscript{f} Ratio determined by UV-Vis analysis.
\textsuperscript{g} Isolated yield after filtration.
\textsuperscript{h} Reaction performed under irradiation.
\textsuperscript{i} Reaction performed in the presence of air.
\textsuperscript{j} Reaction performed in the presence of light.
\textsuperscript{k} Reaction performed in the presence of oxygen.
3.2 Mechanistic Discussion

Two mechanistic pathways can be considered in the Pd-catalyzed cycloisomerization reaction of enallenes (Scheme 29). These mechanisms are initiated in two different ways: either through oxidative addition of acetic acid to Pd(0), forming a palladium-hydride species (Scheme 29, path A), or through an oxidative cycloaddition producing a palladacycle intermediate C (Scheme 29, path B). With the aim of getting some insight into the mechanism of this reaction, enallenes 4a and 5 were treated with 5 mol% of Pd(dba)$_2$ in deuterated acetic acid-$d_4$, which gave the monodeuterated products 15a-$d_1$+16a-$d_1$ and 18-$d_1$+19-$d_1$, respectively (Scheme 30). Path A would explain the incorporation of the deuterium in the product, with the insertion of the allenic double bond into the Pd(II)-H bond, forming vinyl-Pd species A (Scheme 29). This would be followed by an insertion of the double bond into the Pd-C bond, giving B. Intermediate B would then undergo a β-hydride elimination to give the product.
In pathway B the palladacycle intermediate C, formed by oxidative cycloaddition of the enallene to palladium(0), could undergo isomerization to form intermediate D (path B1). Pathway B1 has been taken in consideration because similar (η¹-allyl)Pd complexes have been studied by Kurosawa et al. and more recently by Szabo et al. and it has been shown that electron-donating groups such as σ-carbon bonded ligands on palladium induce the allyl moiety to be reactive towards electrophiles. Thereby the (η¹-allyl) moiety in intermediate D could react with a proton in the γ-position to give B, which then would lead to the product through β-hydride elimination. This would account for the incorporation of deuterium in the products 15a-d₁ and 18-d₁. Another possibility could be that intermediate C undergoes β-hydride elimination and forms intermediate E, followed by reductive hydride elimination to give the product (path B2). However, path B2 can not explain the incorporation of deuterium in the product, unless E undergoes deuterium exchange with DOAc to give E-d₁, which would undergo a reductive elimination to form the deuterated product. This is, however known to be a slow process when a hydrocarbon is coordinated to palladium.

During the optimization studies it was found that the reaction did not proceed in aprotic solvents, indicating path A as the more likely pathway. This is consistent with the result showing that the reaction rate is dependent of the acetic acid concentration, as an equilibrium shift to the left for the oxidative addition of Pd(0) to acetic acid leads to a decrease in the concentration of the reactive Pd(II)-H species, hence to a slower reaction. (Table 1, compare entries 5 and 6 with 1). However, this would mean that in the presence of TFA (Table 1, entry 9), the reaction would be faster, because the concentration of the Pd(II)-H would be higher. Instead a slower reaction was observed, which is probably due to the lower stability of HPdOOCCF₃ compared to HPdOAc.

The regioisomers formed in the reaction are most likely the result of a fast, reversible β-hydride elimination/re-addition/β-hydride elimination process (Scheme 31). The ratio of the products 15, 16 and 17 is most likely the thermodynamic product distribution.
In the last step in pathway B2, besides the primary products 15 or 18, Pd(0) is formed. Considering the reaction when 4a or 5 was treated with Pd(dba)_2 in deuterated acetic acid, the Pd(0) formed would react with DOAc and give DPdOAc. The latter would coordinate to the double bond and introduce deuterium into the ring that is isomerized (shown for product 18-d_1 in Scheme 32). As mentioned above, when 5 was treated with Pd(dba)_2 in deuterated acetic acid, monodeuterated products 18-d_1+19-d_1 were formed, and no additional deuterium was observed in 19-d_1 by ^1H NMR spectroscopy. This observation makes path B2 less likely.

The fact that no additional deuterium is present in regioisomer 19-d_1 is consistent with the mechanisms proposed in path A and B1. In the final step of both these paths, HPdOAc is formed through a β-hydride elimination, and will initially be coordinated to the product. It can thereby directly perform the isomerization, thus there will be no deuterium incorporated in the ring of 16a-d_1 or 19-d_1. Once
HPdOAc is free in solution, it is expected to exchange with acetic acid, and with deuterated acetic acid it would produce DPdOAc, and coordination to the substrate would close the catalytic cycle. However, there is a significant amount of nondeuterated product $15a$ and $18$ produced when deuterated acetic acid is employed as solvent (Scheme 30). This can be explained with, that some of the HPdOAc, formed in the last step of the mechanism in either path A or B1, re-enters the catalytic cycle, before exchange with deuterated acetic acid occurs. The observation that the reaction only proceeds in protic solvents makes path B1 seem less likely.

3.3 Conclusions

In conclusion, we have developed a novel Pd-catalyzed cycloisomerization of readily available enallenes. This reaction gives stereodefined and functionalized bicyclic compounds or functionalized cyclopentene derivatives, with good regioselectivity and in high yields. Deuterium labeling experiments and the fact that the reaction only works in protic solvents, made us propose a mechanism where a Pd-hydride species is the active catalyst. Addition of the Pd-hydride to the allene results in the formation of a vinyl-Pd species. Insertion of the olefin into the vinyl-Pd bond, forms the C-C bond, and subsequent $\beta$-hydride elimination gives the product (Path A, Scheme 29).
Recently, our group reported that enallenes of type 4 can cyclize oxidatively in the presence of a catalytic amount of Pd(II) and with $p$-benzoquinone (BQ) as stoichiometric oxidant to give 26 (Scheme 33). This reaction is an allylic oxidation with formation of a carbon-carbon bond. This type of reaction is scarce, and was previously only reported with the use of stoichiometric amounts of metal.

In recent years, catalytic Pd(II) oxidations using $O_2$ as the reoxidant of Pd(0) have attracted considerable attention. However, Pd(II)-catalyzed aerobic oxidations that give C-C bonds are still very rare. As mentioned in Chapter 1.3.3, so-called biomimetic systems have been developed for Pd(II)-catalyzed oxidations, enabling the use of $O_2$ as terminal oxidant, with the use of several coupled redox catalysts as electron-transfer mediators (Scheme 22 in Chapter 1.3.3). In the above mentioned reaction, BQ was used as a stoichiometric reoxidant. An objective with the present study was to investigate the possibility to employ a biomimetic system to this Pd(II)-catalyzed reaction of enallenes. The system we wanted to developed is an aerobic oxidation via a multistep electron transfer involving three redox systems; Pd(0)/Pd(II)-BQ/HQ-ML$_m$$_{ox}$/ML$_m$$_{red}$, where ML$_m$ is an oxygen activating macrocyclic metal complex, for example iron(II) phthalocyanine (FePc) (Scheme 34 and figure 3). This system would allow the use of catalytic amounts of Pd(II), BQ and ML$_m$ and $O_2$ as the oxidant. The only stoichiometric waste product would be water.
4.1 Results and Discussion

To find optimum conditions for the aerobic allylic oxidation, enallene 4a was used as the model substrate. The first attempt was to treat 4a with 10 mol% of Pd(O₂CCF₃)₂, 20 mol% of BQ and 10 mol% of FePc under an O₂ atmosphere at room temperature, in two different solvents: THF and dichloroethane (Table 3, entries 1, 2). This resulted in a slow reaction and after 72 h, approximately 30% conversion of 4a to 26a was observed. In an attempt to increase the conversion, the more electron-rich 2,6-dimethoxy-1,4-benzoquinone was used. However, after 48 h reaction at room temperature no product could be observed (entries 3, 4). When the reaction temperature was increased to reflux in THF a dramatic rate improvement was observed, and after 6 h 85% conversion was obtained (Table 3, entry 5).
Table 3. Aerobic allylic oxidation of 4a using the triple catalytic system.\textsuperscript{a}

\begin{align*}
\text{Entry} & \quad \text{Solvent} & \quad \text{Temperature (°C)} & \quad \text{Time (h)} & \quad \text{Conversion(%)\textsuperscript{f}} \\
1 & \text{THF} & \text{rt} & 72 & 28 \\
2 & \text{DCM} & \text{rt} & 72 & 29 \\
3 & \text{THF}\textsuperscript{c} & \text{rt} & 48 & \text{nr} \\
4 & \text{DCM}\textsuperscript{c} & \text{rt} & 48 & \text{nr} \\
5 & \text{THF} & \text{reflux} & 6 & 85 \\
6 & \text{THF}\textsuperscript{b,d} & \text{reflux} & 6 & 42 \\
7 & \text{THF}\textsuperscript{b} & \text{reflux} & 6 & 44 \\
8 & \text{THF}\textsuperscript{b,e} & \text{reflux} & 6 & 63 \\
9 & \text{THF}\textsuperscript{b} & 50 & 6 & 19 \\
10 & \text{Toluene}\textsuperscript{b} & 50 & 6 & 12 \\
11 & \text{Acetonitrile}\textsuperscript{b} & 50 & 6 & 8 \\
12 & \text{Trifluorotoluene}\textsuperscript{b} & 50 & 6 & 10 \\
13 & \text{Toluene}\textsuperscript{b} & 95 & 3 & 100 \\
\end{align*}

\textsuperscript{a}Unless otherwise noted, the reactions were carried out in a 0.3-mmol scale with 10 mol% of Pd(O\textsubscript{2}CCF\textsubscript{3})\textsubscript{2}, 20 mol% of benzoquinone, 10 mol% of FePc in 3 mL of solvent. (b) 5% of Pd(O\textsubscript{2}CCF\textsubscript{3})\textsubscript{2}, 20 mol% of benzoquinone and 5 mol% of FePc were used. (c) 10 mol% of 2,6-dimethoxy-1,4-benzoquinone was used. (d) 5 mL of THF was used. (e) 2 mL of THF was used. (f) Determined by \textsuperscript{1}H NMR spectroscopy.
The Pd and iron phthalocyanine loading was thus decreased to 5 mol%, and after 6 h a 42% conversion of 4a was obtained (entry 6). The concentration effect on the reaction was studied next, and increasing the concentration gave an improved conversion from 42% to 60% after 6 h (entries 7, 8). Different solvents were screened at 50 °C, but the solvent only had a minor effect on conversion (entries 9-12). To decrease the reaction time, the temperature was raised to 95°C in toluene, which gave 26a with full conversion of the starting material after 3 h (entry 13).

As mentioned above, there are other systems where Pd(0) is reoxidized to Pd(II) directly by O₂. Therefore we wanted to make sure that our triple catalytic system was necessary for an efficient reaction; in other words the background reactions of the system in the absence of the ETMs were investigated. We carried out the reaction under three different reaction conditions: (i) without the BQ (ii) without FePc and (iii) without both BQ and FePc. In all three experiments a poor selectivity and low yield of the desired oxidation product was obtained. One of the by-products observed is believed to be formed by the cycloisomerization reaction of enallenes (see Chapter 3). This would be catalyzed by the Pd(II)-hydride species that is formed in the last step of this oxidation reaction (see the mechanistic discussion in Chapter 4.3). The second by-product is believed to be formed by a thermal ene-reaction, a reaction discussed in Chapter 5. These experiments demonstrate that the triple catalytic system is necessary for the Pd(II)-catalyzed oxidative carbocyclization of enallenes to proceed in a selective manner.

The optimum reaction conditions (Table 3, entry 13) were employed on a series of enallenes summarized in Table 4. Enallenes 4a-c and 4e gave products 26a-c and 26e in excellent yields (entries 1-4). The cyclization of 4c gave 26c with Z/E ratio 2:1. This result is different from the result obtained in the non-aerobic version of the reaction, were the E/Z ratio was 4:1. This is probably due to the higher temperature used in the aerobic reaction, which led to the formation of the more thermodynamically stable product as the major isomer.

The effect of the ring size was studied next, and the cyclopentene derivative 5 gave products 27+27' in a ratio of 3:1 and a total yield of 81%. In contrast to the cyclohexene and cyclopentene derivatives that gave cis products the cycloheptene derivative gave a trans product (entry 6). When the cycloheptene derivative was treated under the above optimum reaction conditions, trans-28 was formed in 92% yield (entry 6). The reaction was also performed on acyclic enallenes 7b and 7c, which resulted in compounds 29 and 30, respectively, in good yields (entries 7, 8).

Table 4. Pd(II)-catalyzed aerobic allylic oxidation of 4-7.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="4a" /></td>
<td><img src="image" alt="26a" /></td>
<td>99</td>
</tr>
</tbody>
</table>
(a) Unless otherwise noted, enallenes 4-7 were treated with 5 mol% of Pd(CF$_3$CO$_2$)$_2$, 20 mol% of benzoquinone and 5 mol% of FePc in toluene at 95 °C for 3 h. (b) Isolated yields. (c) 4 h reaction time was required for full conversion. (d) 6 h reaction time was required for full conversion.
4.2 Mechanistic Discussion

The mechanism for the Pd(II)-catalyzed allylic oxidation of allene-substituted olefins has been discussed and investigated in the previously reported non-aerobic version. The mechanistic discussion and conclusions will be summarized herein.

Two mechanisms have been proposed for the Pd(II)-catalyzed cyclization of 4 to 26. Both mechanisms are believed to proceed via a (π-cyclohexene)Pd complex (Scheme 35, Pd-4a) with palladium syn to the pending allene. In path A, the allene in intermediate Pd-4a, is making a nucleophilic attack on palladium, which results in complex A. Subsequent insertion of the olefin into the C_viny1-Pd bond would give B, and a syn β-hydride elimination would give 26a. The other mechanism proposed is via the (π-cyclohexene)Pd complex Pd-4a forming a (π-allyl)Pd complex C by an allylic C-H bond activation. Complex C would then insert the allene into the allyl-Pd bond forming D, and subsequent syn β-hydride elimination would give product 26a (Path B).

Scheme 35

These two suggested mechanistic pathways are based on the results of a reaction performed on deuterium labeled substrate trans-4a-d1. (Scheme 36). In this reaction, retention of deuterium was obtained, which is consistent with both of the suggested mechanisms. Both allylic C-H activation and β-hydride elimination are considered to be syn-selective processes. Thus, it is necessary that palladium binds to the cyclohexene derivative in a syn fashion to the pendant allene in order to get retention of deuterium.

Scheme 36
The formation of product 30 from the acyclic substrate 7c would, however, not be accounted for by the suggested mechanism forming a (π-allyl)Pd complex C according to path B (Scheme 35). However, the formation of 30 is constant with path A. Another experiment that suggests path A as the more likely pathway is when the two isomers 4a and 31 were treated in the same pot with a catalytic amount of Pd(O₂CCF₃)₂ and BQ in THF at reflux for 12 h (Scheme 37), isomer 31 could be recovered unreacted whereas 4a was converted to 26a. This result makes the (π-allyl)Pd complex C less likely.⁹³

Scheme 37

Isomer 27', which was formed in the reaction of 5 (Table 4, entry 5), is believed to be the result of an isomerization, catalyzed by the Pd-hydride that is formed in the last step of the reaction (in both path A and B, scheme 35). This is the same type of isomerization that took place in the Pd(0)-catalyzed cycloisomerization of enallenes discussed in Chapter 3. The same Pd-hydride species is catalyzing the cycloisomerization reaction of the substrate, which was observed when the background reactions were investigated, and is the same cycloisomerization reaction as presented in chapter 3.

4.3 Conclusions

An efficient biomimetic system has been developed for the Pd(II)-catalyzed allylic oxidation of enallenes, forming stereodefined, functionalized bicyclic compounds or functionalized cyclopentene derivatives in high yields.
A Mild Thermal Ene-reaction of Allene-Substituted Olefins

During our work with the Pd(0)-catalyzed cyloisomerization of allene-substituted olefins we found that in the absence of palladium, an intramolecular ene-reaction occurred. Ene-reactions are thermal or Lewis acid-catalyzed pericyclic reactions between an olefin containing an allylic hydrogen (ene) and an electron-deficient multiple bond (enophile) (Scheme 38).

Unactivated olefins are in general very poor enophiles and require rather high temperatures in order to undergo ene-reactions. [2+2] Cycloaddition reactions between allenes and alkenes are well documented. In contrast, only a few reports of thermal ene-reactions between allenes and alkenes have been reported, especially with unactivated alkenes, and these reactions are performed at high temperatures and in most cases with the [2+2] cycloaddition product as a by-product. We therefore investigated this reaction in more detail.

5.1 Results and Discussion

To find the optimum reaction conditions, 4a was used as a model substrate, and different temperatures and solvents were screened (Table 5). In the first attempt 4a was heated at 160 °C in CH$_3$CN for 1 h, which resulted in formation of the ene-reaction product 32a together with a [2+2] cycloaddition product 33a, in a 83:17 ratio (entry 1). The reaction was also tried without solvent; substrate 4a was heated neat to 160 °C, unfortunately there were by-products formed most likely polymerized material (entry 2). The reaction temperature was decreased, and 4a was heated at 110 °C for 15 h, which resulted in 50% conversion and gave 32a and 33a in a 78:22 ratio (entry 3). Next the solvent effect was investigated; the reaction was performed in a few different solvents at 110 °C for 15 h (entries 4-9), and it was found that there is only a minor solvent effect, except for water, which slowed down the reaction drastically (entry 9). The ratio between 32a/33a does not appear to be affected considerably by different solvents. The use of DMF as solvent showed a slight improvement in the conversion of 4a (entry 6), it was thus selected as the solvent of choice. Next, 4a was heated for
24 h in DMF at 120 °C, which resulted in an improved ratio of 90:10 (entry 10) and complete conversion.

**Table 5: Thermal Stylization of 4a under different reaction conditions.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Ratio (32/33)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_3$CN</td>
<td>160</td>
<td>1</td>
<td>83:17</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>Neat</td>
<td>160</td>
<td>0.75</td>
<td>n.d.</td>
<td>100 (by-products)</td>
</tr>
<tr>
<td>3</td>
<td>CH$_3$CN</td>
<td>110</td>
<td>15</td>
<td>78:22</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>DCE</td>
<td>110</td>
<td>15</td>
<td>77:23</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>HOAc</td>
<td>110</td>
<td>15</td>
<td>n.d.</td>
<td>65 (by-products)</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>110</td>
<td>15</td>
<td>82:18</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>110</td>
<td>15</td>
<td>83:17</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>Ionic liquid$^c$</td>
<td>110</td>
<td>18</td>
<td>80:20</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>Water</td>
<td>110</td>
<td>15</td>
<td>n.d.</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>DMF</td>
<td>120</td>
<td>24</td>
<td>90:10</td>
<td>100</td>
</tr>
</tbody>
</table>

(a) Enallene 4a was dissolved in the specific solvent (10 mL/mmol) and heated to the indicated temperature. (b) Microwave heating (Smith Microwave Creator, Biotage AB). (c) Ionic liquid: 1-butyl-3-methylimidazolium ([BMIm]BF$_4$).

The optimized reaction conditions were employed on a series of enallenes, and the results are summarized in Table 6 and Figure 4. 32a+33a were obtained in 84% isolated yield after heating of 4a at 120 °C for 24 h (entry 1). The reaction time could be decreased by increasing the temperature; at 160 °C full conversion of 4a to 32a+33a was obtained after 1 h, without affecting the yield or ratio (entry 2). When altering the substituents on the allene to either methyl-ethyl (4b) or a cyclohexyl (4c) group, the corresponding products 32b+33b (in a ratio of 80:20) and 32c, was obtained in 87% and 88% yield, respectively (entries 3, 4). It is interesting to note that 32c was obtained as the sole product, none of the [2+2] cycloaddition product could be detected.

The effect of substituents in the allylic position of the olefin (enophile) was also investigated. Electron-donating substituents were found to slow down the reaction considerably; compound 4d required 4.5 days reaction time at 120 ºC to obtain full conversion to 32d+33d. Despite the long reaction time, 32d+33d could be isolated in a total yield of 86% in a 95:5 ratio (entry 5). The long reaction time of 4d compared to 4a-c is probably due to the increased electron density of the olefin in 4d. With a t-BuCO$_2$- or PhCO$_2$-group in the allylic position of the olefin (11 and 12), full conversion was obtained after 24 h. The substrate
**cis-11** gave 34+35 in a ratio of 90:10 and total yield of 82% (entry 6). The substrate **trans-12** gave 36+37 in a ratio of 81:19 and in a total yield of 72% (entry 7). There is a certain difference between the reactivity of the substrates having the substituent positioned **cis** or **trans** to the allene-substituent, as the product from the **cis** derivative is obtained with decreased chemoselectivity and yield.

The dependence of the substrate ring size was investigated next. In contrast to the cyclohexene derivatives 4a-d, 11 and 12 that all gave **cis**-fused ring systems with high stereoselectivity, the cycloheptene analogue 6 gave **trans-38** and **cis-38** in a ratio of 70:30, with small amounts of the [2+2] cycloaddition product 39 in a total yield of 81% (entry 8). The cyclopentene analogue 5 showed lower degree of chemoselectivity and gave 40+41 in a ratio of 65:35 and a total yield of 77% (entry 9).

**Table 6.** Thermal cyclization of allene-substituted olefins.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Ratio</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>32a+33a</td>
<td>24</td>
<td>90:10</td>
<td>84</td>
</tr>
<tr>
<td>2d</td>
<td>4a</td>
<td>32a+33a</td>
<td>1</td>
<td>90:10</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>4b</td>
<td>32b + 32b' + 33b</td>
<td>36</td>
<td>80:20</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>4c</td>
<td>32c</td>
<td>24</td>
<td>100:0</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>4d</td>
<td>32d+33d</td>
<td>4.5 days</td>
<td>95:5</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>34+35</td>
<td>24</td>
<td>90:10</td>
<td>82</td>
</tr>
</tbody>
</table>
When the acyclic substrate 7c was heated to 120 °C for 72 h, 22+42 were obtained in a ratio of 85:15 and a poor total yield, the residue being unidentified by-products (entry 10).\(^{103}\)

To investigate the possibility of creating a cyclohexene derivative instead of a cyclopentene derivative, substrate 43 was synthesized (entry 11). Unfortunately 43 gave no thermal ene-reaction and the starting material could be recovered after 24 h at 120 °C.

\(^{103}\)
It is interesting to notice that when compound 44 was subjected to the optimized reaction conditions (120 °C for 24 h in DMF) no reaction was detected, and the starting material was recovered (Scheme 39). This indicates that the allene moiety is crucial for the reaction to occur under these reaction conditions.

Scheme 39

The products obtained in the thermal ene-reaction contain a conjugated diene unit. These products could therefore be suitable substrates in a [4+2] Diels-Alder cycloaddition with an appropriate dienophile, providing a simple route to more complex polycyclic systems. The synthetic utility of the compounds synthesized were demonstrated by the reaction of 32a with maleic anhydride in refluxing toluene that gave 45 in excellent yield (Scheme 40). The stereochemistry of 45 was assigned by its X-ray crystal structure (Figure 5).

Scheme 40

Figure 5. ORTEP drawing of 5. Thermal ellipsoids are drawn at 50% probability level.
5.2 Conclusions

A mild, thermal ene-reaction of enallenes has been developed. The reaction forms stereodefined, functionalized bicyclic compounds with good regioselectivity and high yields. A synthetic application of the products has been demonstrated by reacting product \(32a\) with maleic anhydride, forming a stereodefined polycyclic product in high yield through a \([4+2]\) Diels-Alder cycloaddition.
Short Summary of Chapters 3-5

Chapters 3-5 can be summarized with a schematic overview, showing that enallenes can be cyclized in three different ways to form bicyclic products (Scheme 41).

Scheme 41
Palladium(II)-Catalyzed Carbocyclization of Allene-substituted Dienes

Pd(II)-catalyzed carbocyclization of 1,3-diene derivatives has been achieved with stabilized carbon nucleophiles, acetylenes and allylsilanes. Our group has recently reported that allene-substituted conjugated dienes also can undergo Pd(II)-catalyzed carbocyclizations. This reaction, which formally constitutes a carboacetoxylation of the 1,3-diene, is stereoselective and products are obtained in good yields (Scheme 42).

Scheme 42

As the solvent in the Pd(II)-catalyzed reaction of allene-substituted 1,3-dienes was limited to acetic acid, no other nucleophiles than acetate ions could be employed. To make this reaction more versatile in organic synthesis, we decided to investigate the possibility of using other nucleophiles.

6.1 Exploring Different Nucleophiles

As we want to use other nucleophiles than acetate, our first attempts were to make the Pd(II)-catalyzed reaction of allene-substituted 1,3-dienes work in a non-nucleophilic solvent. Thus, we used 14a with 20 equiv. of acetic acid in the presence of 10 mol% Pd(OAc)$_2$, lithium carbonate and benzoquinone in two different solvents, acetone and ethylacetate, as these reaction conditions had been shown to work on the diacyloxylation of cyclic 1,3-dienes. Other solvents as dichloromethane and THF were also tried, however, the reaction of 14a in acetone gave the best result, producing 46a in 79% yield (Table 7, entry 1), which is
a higher yield than that obtained in acetic acid. After demonstrating that acetone could be used as solvent in this reaction, the methodology was extended to other oxygen nucleophiles. Thus, a selection of carboxylic acids was employed in the reaction of 14a. Using benzoic acid, compound 46b was obtained in 50% yield (entry 2) and propanoic acid gave 46c in 42% yield (entry 3). Isobutanoic acid afforded 46e in only 15% yield (entry 5) and pivalic acid gave only traces of product 46f (entry 6). These results show that the bulkier the nucleophile, the poorer the yield. When alcohols were employed as nucleophiles, no reaction occurred in the case of phenol, benzyl alcohol, o-nitrophenol and thiophenol (entries 8-11). However, pentafluorophenol afforded 46g in high yield and with the same stereochemistry as 46a (entry 7).

Table 7. Pd(II)-catalyzed carbocyclization of 14a using different external nucleophiles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product 46</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOH</td>
<td>a</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>PhCOOH</td>
<td>b</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;COOH</td>
<td>c</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;C=CHCH&lt;sub&gt;2&lt;/sub&gt;COOH</td>
<td>d</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>i-PrCOOH</td>
<td>e</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>t-BuCOOH</td>
<td>f</td>
<td>traces</td>
</tr>
<tr>
<td>7</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;5&lt;/sub&gt;OH</td>
<td>g</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>PhOH</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>BnOH</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>o-NO&lt;sub&gt;2&lt;/sub&gt;PhOH</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>PhSH</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

(a) The starting material 14a was added to a solution of 10 mol% of Pd(OAc)<sub>2</sub>, 5 equiv. Li<sub>2</sub>CO<sub>3</sub>, 2 equiv. BQ, 20 equiv. of NuH in acetone at rt. over a 20 h period. (b) Isolated yield after flash chromatography.

The carbocyclization of cycloheptadiene derivative 14b with acetone as solvent and acetic acid as nucleophile afforded 47a/47a’ in high yield (Table 8, entry 1). Note that the stereochemistry of the ring-junction is trans for the products obtained from 14b. Furthermore, the yield was higher than that obtained from the analogous reaction in acetic acid. The regioselectivity in the cyclization of 14b was not affected by a change of solvent from acetic acid to acetone and a 1:1 mixture of 1,4- (47a) and 1,2-product (47a’) was obtained in both cases. Further investigation of the cyclization of 14b revealed that the regioselectivity could be controlled by altering the external nucleophile. With the use of pentafluoroprophene-
nol, only the 1,4-product 47b was obtained, while with pivalic acid only the 1,2-
product 47c’ was formed (entries 2, 3). The 1,4- and 1,2-product do not only
differ in regiochemistry, they also have different stereochemistry with respect to
the nucleophile.

Table 8. Pd(II)-catalyzed carbocyclization of 14b using different external nucleo-
philes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product 47 (%)</th>
<th>Product 47’ (%)</th>
<th>Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃COOH</td>
<td>a 50</td>
<td>a 50</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>C₆F₅OH</td>
<td>b 100</td>
<td>--</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>t-BuCOOH</td>
<td>--</td>
<td>c 100</td>
<td>65</td>
</tr>
</tbody>
</table>

(a) The starting material was added to a solution of 10 mol% of Pd(OAc)₂, 2 equiv. BQ, 10 equiv. of
NuH in acetone at rt. over a 20 h period. (b) Isolated yield after flash chromatography.

6.1.1 Stereochemical Assignment

The stereochemistry of 47a was assigned as follows: The trans ring junction was
established by NOE experiments. A small NOE enhancement (2%) was observed
for the bridgehead proton H-7 when irradiating the allylic bridgehead proton H-1
(Scheme 43). Irradiation of H-4 resulted in a 5% NOE enhancement for H-7, but
none for H-1, indicating that H-4 and H-7 are located on the same side of the
ring. To obtain further evidence for the stereochemistry of 47a, the epimer 47e
was synthesized from 47a via hydrolysis to the alcohol, followed by a Mitsunobu
reaction (Scheme 43). In the epimeric compound 47e, irradiation of H-1 gave 5%
NOE enhancement for H-4, which requires that these hydrogen atoms are on the
same side of the ring and hence the ring junction is trans.

Scheme 43

To establish the stereochemistry of 47a’ similar ¹H NMR experiments were per-
formed. The stereochemistry at the C-2 position was assigned based upon the
analysis of coupling constants between hydrogens (Figure 6). The large value of $^3J_{7,1}$ (9.8 Hz) indicates a diaxial coupling, and hence a trans relationship of the bridgehead protons. The small value of $^3J_{2,1}$ (2.5 Hz) implies that H-2 is equatorial and therefore that the acetate is located on the same side as the bridgehead proton H-7. Only a small NOE enhancement (2%) was observed between H-7 and H-1 in $47a'$ was observed, which indicates a trans ring-junction.

\[3J_{7a,1a} = 9.8 \text{ Hz}\]
\[3J_{7a,6a} = 11.0 \text{ Hz}\]

**Figure 6**

In order to confirm that the acetate stereochemistry in relation to the bridge is different in compounds $47a$ and $47a'$, both compounds were allowed to react with sodium malonate in a Pd(0)-catalyzed reaction (Scheme 44). Two different compounds were obtained from these reactions, which proves that the stereochemistry of the acetate in $47a$ and $47a'$ is different; if the acetate stereochemistry in relation to the bridge had been the same in $47a$ and $47a'$, oxidative addition of the allylic acetate to Pd(0), which is known to be an anti addition, would have led to the same ($\pi$-allyl)intermediate and consequently to the same product. An interesting observation is that both stereo- and regiochemistry is retained in the Pd(0)-catalyzed malonate substitution of $47a$ and $47a'$. These two reactions also demonstrate a synthetic application of the products.

\[3J_{2e,1a} = 2.5 \text{ Hz}\]

**Scheme 44**

The stereochemistry of compounds $46b$-$g$ was assigned by comparing the coupling constants with the previous NMR assignments for $46a$. H-4 shows small couplings to protons H-5, which indicates that H-4 is equatorial (Figure 7). Furthermore, the large value of $^3J_{5a,6}$ indicates that H-6 and H-5a are axial and thus trans to one another. As for $46a$, NMR-experiments implies that substrates with a
six-membered ring give a cis-fused [5,6]-ring system, as ~7 % NOEs between the bridge hydrogens were observed.

\[
\begin{array}{c}
\text{Figure 7}
\end{array}
\]

6.2 Conclusions

The Pd-catalyzed carbocyclization of allene-diene derivatives 14 has been found to proceed in a non-nucleophilic solvent, in the presence of a carboxylic acid or a phenol, allowing the use of other nucleophiles than acetate. The amount of nucleophile could be lowered to 10 equiv. and yields were improved compared to the previously reported reaction in acetic acid. The cyclization of cycloheptadiene derivative 14b turned out to generate the trans-bicyclo[5.3.0]dec-2-ene system, and the regioselectivity could be fully controlled to give either the 1,2-product 47’ or the 1,4-product 47 by altering the external nucleophile.
Several mechanisms were proposed for the Pd-catalyzed oxidative cyclization of allene-substituted conjugated dienes (Scheme 42).\textsuperscript{75} One suggestion involves a nucleophilic attack by the central atom of the allene on a \((\pi\text{-diene})\text{Pd(II)}\) complex (Scheme 46, path A). This attack would give a \textit{trans} carbopalladation of the diene. One of the reasons why this mechanism is considered, is because it has recently been reported by our group that allenes are able to act as a \(\pi\)-nucleophile on a \((\pi\text{-allyl})\text{palladium-complex}\) (Scheme 12, chapter 1.2.1). The only established example of \textit{trans}-attack by a \(\pi\)-nucleophile on a \((\pi\text{-diene})\text{Pd}\) complex, reported before, is where an allylsilane acts as a \(\pi\)-nucleophile (Scheme 45).\textsuperscript{54}

\begin{center}
\textbf{Scheme 45}
\end{center}

The possible mechanisms for the Pd(II)-catalyzed carbocyclization of 14\textit{a} to give 46 with benzoquinone as oxidant are shown in scheme 46. As already mentioned, one suggestion is attack by the allene on the \((\pi\text{-diene})\text{Pd}\) intermediate followed by nucleophile \textit{cis} migration (Path A).\textsuperscript{47-49} Another suggestion is nucleophilic attack by the allene on the Pd(II) center giving a vinylidene-Pd intermediate. Subsequent insertion of one of the diene double bonds gives a \((\pi\text{-allyl})\text{Pd}\) complex, followed by an external \textit{trans} attack of the nucleophile (Path B). A third suggestion is that a Pd-activated 1,3-diene is attacked by an external nucleophile to give a \((\pi\text{-allyl})\text{Pd}\) complex, followed by an insertion of the allene into the \(\text{C}_{\text{allyl}}\text{-Pd}\) bond, forming a new \((\pi\text{-allyl})\text{Pd}\) intermediate. The latter can undergo a \(\beta\)-hydride elimination to form product 46 (Path C).\textsuperscript{107}
7.1 Isolation of Reaction Intermediates

In order to get more insight into the mechanism of the Pd(II)-catalyzed carbo-cyclization of 14, reaction intermediates were sought to be isolated, with the use of stoichiometric amounts of palladium. In our first attempt to isolate an intermediate, 14a was treated with Pd(OAc)$_2$. Unfortunately this was unsuccessful; instead another product was obtained (see Chapter 8 for more information). In previous studies carried out in our laboratories, bicyclic ($\pi$-allyl)Pd complexes were isolated from intramolecular attack by a heteroatom or a carbon nucleophile on a 1,3-diene in the presence of stoichiometric amounts of Pd(II). The same reaction conditions were tested for the allene-substituted diene 14, and the best conditions were found to involve the use of PdCl$_2$(PhCN)$_2$ at low temperature (Scheme 47). When 14a and 14b were treated with PdCl$_2$(PhCN)$_2$, in THF at -20 ºC, 48a and 48b were isolated.

Scheme 47

To assign the stereochemistry of the complexes, a reporter ligand such as a 2,2'-bipyridine was used. The chloro dimer complex 48b was transformed into the bipyridyl complex 49 by treatment with silver triflate and 2,2'-bipyridine (Scheme 48). A NOE difference experiment was performed on 49 and the bridgehead proton H-1 was irradiated, which resulted in a 10% NOE enhance-
ment for bridgehead proton H-7, and a 5% NOE enhancement for the two reporter protons on the bipyridine moiety (H_a). The first NOE indicates that the ring junction is cis, and the second that the bridgehead proton H-1 is located on the same face of the ring as the palladium, and consequently that palladium is trans to the ring junction.

Scheme 48

Complexes 48a and 48b were subsequently transformed into their isoprenyl analogous 50a and 50b (Scheme 48).^111 To verify the stereochemistry, 50a and 50b were treated with silver triflate and 2,2’-bipyridine to give 51a and 51b, respectively. NOE difference experiments on these complexes were in agreement with the previous results, that the palladium center is trans to the carbon atoms in the fused five-membered ring, and that the ring junction is cis in both the cyclohexadiene and cycloheptadiene derivative complexes.

In order to compare with the results from the previously described catalytic reaction (Chapter 6) and to get further support for the stereochemistry of 50a and 50b, these Pd complexes were transformed to their allylic acetates 46a/53a and 52/53b, respectively (Scheme 49). This was made by treatment of 50a and 50b with AgOAc to give the (π-allyl)Pd acetate complex, followed by either addition of BQ to afford 46a/53a via acetate migration, or by addition of LiCl, LiOAc and BQ to afford 52/53b via external acetate attack. The stereochemistry assigned for 46a/53a and 52/53b, respectively, requires that the carbon atoms in the fused five-membered ring have to be trans to the palladium center, which confirms our earlier assignments of 49 and 50.
According to NMR-experiments we can also confirm that the stereochemistry of 52 is different compared to that of 47, the product formed in the catalytic reaction of 14b (Table 8). Thus, under the catalytic reaction conditions, 14b forms the trans-fused bicyclic system 47 and under the stoichiometric conditions used above, the cis-fused system 52 is obtained.

![Scheme 49]

**7.1.1 Conclusions**

The stereochemistry of complexes 48a, 48b, 50a and 50b has been established with the use of reporter ligand technique. Analysis of the (π-allyl)Pd complexes by NMR spectroscopy, shows that the formed C-C bond is trans to the palladium center. Furthermore, the bridgehead protons in both complexes are cis to one another. The stereochemistry of the (π-allyl)Pd complexes was confirmed by stereoselective transformations to their known allylic acetates.

**7.2 Mechanistic Discussion of the Palladium-Mediated Reaction of 1,3-Diene-Allene Derivatives**

As we were able to isolate the (π-allyl)Pd complexes 48a and 48b (Scheme 47), a mechanism analogous to path C seems unlikely (Scheme 46). Without knowing the stereochemistry of the π-allyl complexes, mechanisms analogous to pathways A and B are possible (Scheme 46). The complexes may either be formed by nucleophilic attack by the central carbon of the allene on the Pd(II)-activated 1,3-diene (trans carbopalladation), where the allylic carbocation intermediate would be trapped by a chloride ion (Scheme 50, path D), or they may be formed via chloropalladation of the allene followed by insertion of the 1,3-diene into the vinyl-Pd bond (cis carbopalladation, Scheme 50, path E). Considering that the former pathway proceeds via trans carbopalladation of the 1,3-diene while the latter involves a cis carbopalladation, the assigned trans stereochemistry of complexes 48a and 48b rules out pathway E. Thus, it can be concluded that the central carbon of the allene has attacked the Pd(II)-activated 1,3-diene on the oppo-
site face to the palladium center in the stoichiometric reaction. An interesting question, though, is whether the allene requires to be activated by an external nucleophile to act as a \( \pi \)-nucleophile. In the reaction of 14a and 14b with PdCl\(_2\)(PhCN)\(_2\), the chloride ion may activate the allene to a nucleophilic attack. The fact that no \textit{trans} carbopalladation occurs when PdCl\(_2\)(PhCN)\(_2\) is replaced by Pd(OAc)\(_2\) supports an activation by the chloride ion.\(^{113}\)

Scheme 50

7.3 Mechanistic Discussion of the Palladium-catalyzed Reaction of 1,3-Diene-Allene Derivatives

In the mechanistic study using stoichiometric amounts of Pd(II) the stereochemistry of product 48b from the cycloheptadiene-allene, is different from products 47 obtained in the catalytic reaction of the cycloheptadiene-allene. Furthermore, the stereodivergent acetate addition to (\( \pi \)-allyl)Pd complex 50b, obtained from 14b, gives 52 and 53b (Scheme 49), whereas the catalytic reaction with substrate 14b gives product 47 (Scheme 42). This strongly indicates that the mechanism for cyclization of 14b is different under catalytic and stoichiometric reaction conditions. The \textit{trans} carbopalladation mechanism, supported by the stoichiometric mechanistic study, cannot completely be ruled out for the Pd-catalyzed reaction of cyclohexadiene-allene derivative 14a. The mechanism could involve a \textit{trans} carbopalladation followed by \textit{cis} migration of the nucleophile from palladium to carbon; this would give the observed stereochemistry of the products 46 (Path A, Scheme 46). On the other hand, the results with pentafluorophenol (Table 7, entry 7) make this mechanism less likely, because pentafluorophenol is not known to undergo \textit{cis} migration.\(^{106,114}\) An external attack of pentafluorophenol on a \textit{trans}-carbopalladation intermediate would give the wrong stereochemistry of the product.

The mechanism that best accounts for the observed regio- and stereochemistry for the cyclization of 14a is shown in Scheme 51. The fact that allenes have nucleophilic properties\(^{34,35}\) supports a mechanism where the center carbon of the allene makes a nucleophilic attack on the electrophilic palladium, forming vinyl-Pd complex 54.\(^{115}\) Subsequent olefin insertion gives 55, which rearranges to the (\( \pi \)-allyl)Pd complex 56. Finally, \textit{trans} attack by the nucleophile would give product 46.
Cyclization of the cycloheptadiene derivative 14b to 47 is believed to proceed via the same mechanism as the cyclization of 14a. Thus, a vinyl-Pd complex 57 would be formed, followed by olefin insertion to give (π-allyl)Pd intermediate 59 (Scheme 52). The regioselectivity of the subsequent addition is believed to depend on the nature of the external nucleophile. π-Allyl intermediate 59 could be engaged in two competing routes, path F and G. In Path F, an external nucleophilic attack, trans to the palladium atom, gives rise to 47. In path G a cis migration of the nucleophile is believed to occur. The steric hindrance between the coordinated nucleophile and the isoprenyl moiety in 59, is believed to shift the equilibrium between (π-allyl)Pd and the (σ-allyl)Pd to the right, and give intermediate 60. Subsequent cis-migration of the nucleophile would give 47'. This pathway (G) would explain the formation of the 1,2-product 47'. Therefore a non-migrating nucleophile, such as pentafluorophenol, could only react through path F, which is observed. Nucleophiles such as acetate, that are known to migrate, could react via both pathways, giving a mixture of 47 and 47'. More bulky nucleophiles, such as pivalate, are believed to make the π-allyl intermediate 59 less favored compared to the σ-allyl intermediate 60, leading to product 47'.
7.4 Conclusions

In the mechanistic study of the Pd-mediated carbocyclization, the stereochemistry of the reaction intermediates was assigned, and this made it possible to suggest a mechanism for the reaction. Thus, the mechanism suggested is a trans carbopalladation of the 1,3-diene, where the allene acts as the carbon nucleophile. Due to the difference in the stereochemical outcome of the stoichiometric and catalytic reactions of 14, this mechanism can only explain the stoichiometric reaction. The catalytic reaction is believed to proceed via a cis carbopalladation, and the mechanism suggested above rationalizes both the regio- and stereochemistry of the products.
Palladium(0)-Catalyzed Carbocyclization of Allene-substituted Dienes$^{IV}$

In an attempt to detect a possible reaction intermediate in the Pd(II)-catalyzed reaction, 14a was treated with Pd(OAc)$_2$ without any benzoquinone. Instead of observing a reaction intermediate, another product 61a was obtained (Scheme 53). In contrast to the Pd(II)-catalyzed oxidative cyclization of 14a to give 46, the cyclization of 14a to give 61a is formally a telomerization reaction of the allene-substituted 1,3-diene, most likely catalyzed by Pd(0). This was confirmed by replacing Pd(OAc)$_2$ with a catalytic amount of Pd(dba)$_2$, affording 61a in 65% yield.

\[ \text{E E} \quad \text{Pd(dba)$_2$} \quad \text{LiOAc, HOAc} \quad \text{AcO$_2$} \quad \text{E E} \]

Scheme 53

This carbocyclization of 1,3-diene-allene derivatives requires the use of acetic acid as solvent, which limits the nucleophile to acetate. To make these reactions more versatile in organic synthesis, the aim is to develop a reaction that works with several other nucleophiles.

8.1 Exploring Different Nucleophiles

The reaction of 14a was tested with several different solvents, such as acetone, ethylacetate and dichloromethane, in the presence 10 mol% Pd(dba)$_2$, Li$_2$CO$_3$ (5 equiv.) and acetic acid as nucleophile (20 equiv.). The best result was obtained in anhydrous CH$_2$Cl$_2$. Next, the Pd and nucleophile loading was decreased and 14a was treated with 5 mol% Pd(dba)$_2$, Li$_2$CO$_3$ (5 equiv.) and 10 equiv. of acetic acid, which led to the formation of 61a in 73% yield (Table 9, entry 1). Under these conditions a variety of carboxylic acids were cyclized in moderate to good yields (entries 1-7). Also alcohols could be employed as nucleophiles. Pentafluorophenol reacted to give 61h in moderate yield, whereas phenol did not give any reaction at all. In contrast, thiophenol afforded 61i along with 61i’ (Figure 8) as a minor product in good total yield (entry 9). Benzyl alcohol was used neat in the reaction of 14a, to afford 61j in moderate yield (entry 10), whereas other aliphatic and chlorinated alcohols such as ethanol and trichloroethanol were unsuccessful nucleophiles. Despite the fact that they are commonly used in similar
reactions, nucleophiles such as piperidine, ammonium salts, nitromethane or dimethylmalonate were unreactive or gave a complex mixture of unidentified products.

**Table 9.** Pd(0)-catalyzed carbocyclization of 14a using various nucleophiles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product 61</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOH</td>
<td>a</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>t-BuCOOH</td>
<td>b</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>PhCOOH</td>
<td>c</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;COOH</td>
<td>d</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;COOH</td>
<td>e</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;=CHCH&lt;sub&gt;2&lt;/sub&gt;COOH</td>
<td>f</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td>Sorbic acid&lt;sup&gt;c&lt;/sup&gt;</td>
<td>g</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;5&lt;/sub&gt;OH</td>
<td>h</td>
<td>44</td>
</tr>
<tr>
<td>9</td>
<td>PhSH&lt;sup&gt;d&lt;/sup&gt;</td>
<td>i</td>
<td>78</td>
</tr>
<tr>
<td>10</td>
<td>BnOH&lt;sup&gt;e&lt;/sup&gt;</td>
<td>j</td>
<td>53</td>
</tr>
</tbody>
</table>

(a) A solution of 5 mol% of Pd(dba)<sub>2</sub>, 10 equiv. of nucleophile, and 5 equiv. of Li<sub>2</sub>CO<sub>3</sub> in dichloromethane was stirred for 24 h. (b) Isolated yield after flash chromatography. (c) 2,4-hexadienoic acid. (d) Gave a 3:2 ratio of 61i/61j. (e) 5 mol% of Pd(dba)<sub>2</sub> and 3.5 equiv. of Li<sub>2</sub>CO<sub>3</sub> in neat benzyl alcohol, was stirred for 24 h.

**Figure 8.** The minor product obtained in the reaction of 14a with thiophenol as nucleophile.

**8.1.1 Stereochemical Assignment of Products**

The stereochemistry of 61b-61j was assigned by comparing the coupling constants with previous NMR assignments of 61a (Figure 9). H-4 shows small coupling constants to protons H-5 and, as a consequence, H-4 must be equatorial. Furthermore the large value of<sup>3</sup>J<sub>5a,6</sub> indicates that H-6 and H-5a are axial and <em>trans</em> to one another. As for 61a, NOE-experiments imply that the ring-junction is <em>cis</em>. 

56
There are two possible mechanistic pathways for the formation of products 61. The amphiphilic behavior of bis-allyl-Pd complexes (see introduction, chapter 1.2) made us suggest a Pd(0)-catalyzed intramolecular telomerization mechanism (Scheme 54). Palladacycle 62 is formed by oxidative cycloaddition of 14a to Pd(0), this species rearranges to bis-(η^3,η^1-allyl)Pd complex 63. The latter will react with a proton in the γ-position on the σ-allyl ligand to give (π-allyl)Pd complex 64. An external nucleophilic attack on this (π-allyl)Pd complex would give products 61 and regenerate Pd(0).

The other possible mechanism involves a Pd-hydride species, generated from oxidative addition of NuH to Pd(0) (Scheme 55). An allenic double bond then inserts into the Pd(II)-H bond, forming a vinyl-Pd species 65. The latter intermediate would then insert a double bond into the C_vinyl-Pd bond to give (π-allyl)Pd complex 66, followed by external nucleophilic attack to yield products 61.
Both of these mechanisms account for the observed incorporation of deuterium in the 2-position of the isopropyl moiety of 61 (Nu = OAc) when DOAc was employed as the solvent (Scheme 56).

8.3 Conclusions

A Pd(0)-catalyzed carbocyclization of 14a was developed, which proceeds in a non-nucleophilic solvent with added nucleophiles (H-Nu). The use of alcohols, thiophenol and carboxylic acids as nucleophiles afforded products in moderate to good yields. Two possible mechanisms have been suggested.
Short Summary of Chapters 6-8

Chapter 6-8 can be summarized with a schematic overview, showing that allene-substituted dienes 14 can be cyclized in four different ways to form bicyclic products (Scheme 5).

![Scheme 57](image-url)
Acknowledgements

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Min Familj och mina Vänner.

Manne, tack för allt, du är världens bästa.
References and Footnotes

39. A single example of a cycloisomerization of a cyano-activated enallene catalyzed by palladium has been reported, see reference 38.


80. Traces of the regioisomer 17a was also detected, and the ratio was determined by GC. Traces of the corresponding regioisomers 17b-c were also detected, and the ratio was determined by $^1$H NMR. The ratio could not be determined by GC, because of the poor separation between the three products.

82. The ratio was determined by GC.

83. Attempts to improve regioselectivity, met with no success.

84. This was confirmed by performing the reaction of 7c, without Pd(0), in acetic acid and the same product (25) was obtained.


89. This is a similar result as in the non-aerobic version, see reference 73.

90. The steroselectivity is consistent with the non-aerobic version of this reaction, see reference 73.

91. The formation of vinyl-palladium complex A, could also be explained by an allylic C-H activation mechanism.


93. Compound 4a and 31 should be able to form the same (π-allyl)Pd complex C via allylic C-H activation, and should in this case both cyclize to give 26a.


98. See figure 4 for the structure of 35.

99. See figure 4 for the structure of 37.

100. See figure 4 for the structure of 39.

101. The stereochemistry of trans-38 and cis-38 was assigned by NOE measurements.

102. See figure 4 for the structure of 41.

103. See figure 4 for the structure of 42.


107. Other mechanisms involving formation of vinyl-palladium in the side chain followed by insertion of the 1,3-diene in the palladium-carbon bond and subsequent acetate attack would also account for the product, see reference 75.


110. The same procedure as in reference 109b was employed, except that methanol was replaced by acetonitrile as the solvent and Ag(CF₃SO₃) was used instead of Tl(CF₃SO₃).

111. Treatment of complexes 48a and 48b with silica gel at room temperature overnight afforded complexes 50a and 50b, respectively.

112. By ligand regulation, the nucleophilic acetate attack can be controlled to proceed either via migration from the palladium or by external attack, see Chapter 1.3.
113. A similar activation has been discussed in the Pd(0)-catalyzed cyclization of allenic allylic carboxylates (Scheme 12), where the mechanism is established to be a nucleophilic allene attack on a (π-allyl)Pd complex. Here either the allene is activated by the nucleophilic Pd(0) center to trigger the attack, or the carbonium ion that is formed after the nucleophilic attack by the allene is trapped by Pd(0), see reference 34.

114. To investigate the nucleophilic properties of pentafluorophenol, this was allowed to react with 1,3-cyclohexadiene and a catalytic amount of Pd(OAc)$_2$ in the presence of BQ at ambient temperature. It was shown that the stereochemistry of the product was cis, indicating that the nucleophile had added externally on the (π-allyl)Pd intermediate.

115. The formation of vinyl-palladium complex 54 could also be explained by an allylic C-H activation mechanism.