# C−C, C−O, C−N Bond Formation on sp$^2$ Carbon by Pd(II)-Catalyzed Reactions Involving Oxidant Agents

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## 1. Introduction

The transformation of unsaturated hydrocarbons through the action of metal complexes continues to constitute a very important field of organometallic chemistry, particularly when complexes act as catalysts. The past 20 years have witnessed a considerable effort to achieve selective C−H bond functionalization by means of transition metal complexes. The activation of an unsaturated carbon−carbon bond can be induced by its coordination to the metal, which makes the bond susceptible to addition reactions. Many of these are catalyzed by palladium, perhaps the most versatile and widely used transition metal, which can exist in three easily interconvertible oxidation states: Pd(0), Pd(II), and Pd(IV).

A wealth of reviews[1] and books[2] on organopalladium chemistry have been published. Literature reports on organopalladium-catalyzed reactions do not make a clear distinction between reactions catalyzed by Pd(0) and Pd(II), often treated together regardless of different mechanisms. Some confusion also arises from the use of Pd(II)-complexes to generate in situ Pd(0). Moreover, several reviews fail to clearly specify in the procedures they describe whether palladium is used in catalytic or stoichiometric amounts.

Within the field of palladium-catalyzed reactions, we are especially interested in those employing a Pd(II)/oxidant agent catalytic system. In these processes, the Pd(II)-catalyst is reduced to Pd(0) at the end of the reaction; in order to sustain the catalytic cycle, the presence of an oxidant agent is required to regenerate or to maintain Pd(II). The present review, focusing on this particular, increasingly expanding topic, shall limit its survey to all the literature concerning Pd(II)-complex-catalyzed reactions. The latter have been less extensively investigated than Pd(0)-catalyzed reactions (including Heck, Buchwald−Hartwig, and cross-coupling reactions), despite their advantage of starting from not-functionalized substrates that are easily accessible and also cheaper.

All types of bonds formed in Pd(II)-catalyzed processes shall be covered, particularly C−C, C−N, and C−O bonds. A section shall report on reactions involving the formation of more different bonds, and a separate section shall deal with processes involving the carbonylation reaction, i.e., the insertion of carbon monoxide under very mild conditions.

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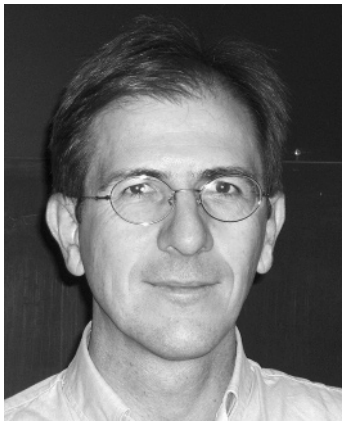
Egle Beccalli began her university training at the University of Milan, where she obtained her laurea degree in Pharmaceutical Chemistry and Technology in 1979. She spent some years as a researcher at the Department of Organic and Industrial Chemistry of the Milan University, and then she moved to the Faculty of Pharmacy of the same university, where she became Associate Professor in 1998. In 2003 she was appointed full Professor of Organic Chemistry at the Faculty of Pharmacy. Her research interests are focused on heterocyclic organic chemistry, in particular on reactivity and synthetic methodologies to obtain bioactives molecules. A great deal of studies have been directed to the chemistry of indoles, and palladium catalysis in the synthesis and functionalization of heterocycles has become the focus of the research area.



Gianluigi Broggini, born in 1961, received his Ph.D. degree from the University of Milan in 1993. He then worked at the same University as a postdoctoral fellow. After some years as an assistant lecturer at the University of Insubria, he is now Research Associate at the same university. His main research interest concerns the synthesis of heterocyclic compounds by way of inter- and intramolecular 1,3-dipolar cycloadditions and, more recently, of intramolecular organopalladium catalyzed processes.

Michela Martinelli, born in 1978, received her laurea degree in Chemistry at the University of Insubria in 2004. She is currently completing her Ph.D. program on the organopalladium-mediated synthesis of heterocycles at the University of Insubria in cooperation with the Istituto di Chimica Organica "A. Marchesini" of the University of Milan.

Silvia Sottocornola, born in 1980, obtained her laurea degree in Chemistry at the University of Insubria in 2004. She is currently carrying out her Ph.D. program on Pd-catalyzed domino reactions under the cosupervision of Dr. Gianluigi Broggini of the University of Insubria and Professor Giovanni Poli of the University Pierre et Marie Curie (Paris).

Palladium catalysis is so versatile because reaction conditions can be tuned by varying the ligand, base, solvent, temperature, and additives to optimize the desired process. A great tolerance of diverse functional groups is observed, and an excellent stereo- and regioselectivity is often achieved.

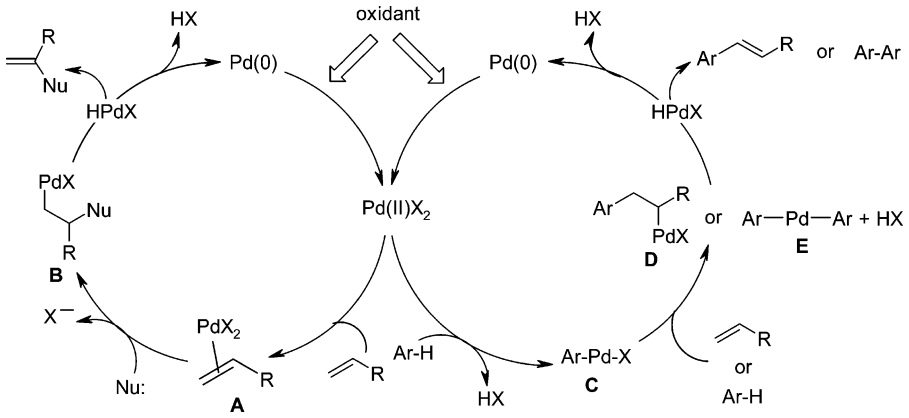
The transformation of olefins to carbonyls, usually referred to as the Wacker reaction, shall not be considered in the present review because it has been long-known and amply reviewed,[3] despite the fact that its efficiency has been improved in recent times.[4] With the aim to emphasize the Pd(II)-catalyzed processes, the reactions employing a stoichiometric amount of palladium will not be covered. Likewise, a group of reactions exploiting the Pd(II)/Pd(IV) catalytic system[5] shall not be included, although they are very efficient in the C−H bond activation and functionalization. The mechanistic study of these reactions employing $Pd(OAc)_2$ as catalyst and $PhI(OAc)_2$ as oxidizing agent showed that the alkyl−Pd(II) intermediate is oxidized in situ by the action of hypervalent iodine to an alkyl−Pd(IV) intermediate. At the end of the catalytic cycle, reductive elimination yields the product and regenerates the Pd(II) catalyst.

## 1.1. Mechanistic Details

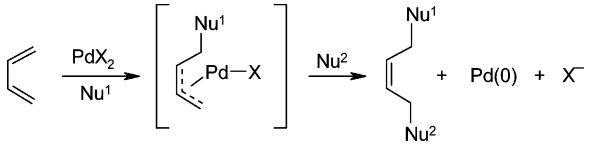
Being electrophilic species, palladium(II) salts tend to react with $\pi$-nucleophiles such as olefins, alkynes, and arenes. The mechanisms of these processes have been extensively studied. A typical reaction with alkenes starts with the complexation of the olefin by the Pd(II) salt, as shown in Scheme 1, left-hand side. The resulting $\pi$-olefin complex **A** can undergo an intermolecular or intramolecular nucleophilic attack, usually at the more substituted vinylic carbon, to give a $\sigma$-alkylpalladium(II) complex **B**. The final product normally results from $\beta$-hydride elimination as HPdX, but different processes may also be observed.

For aromatic substrates, a different mechanism has been proposed that involves the electrophilic substitution of an aryl hydrogen by palladium to give **C**, and the subsequent formation of a $\sigma$-bonded aryl−Pd(II) complex **D** or **E** (Scheme 1, right-hand side). This palladation intermediate can undergo a homocoupling reaction or, in the presence of

**Scheme 1**




**Scheme 2**




alkenes, a vinylic substitution reaction. Also in this case, elimination of HPdX is the final step.

Reactions exploiting conjugated dienes as substrates generally lead to double functionalization. They run via nucleophilic addition to the terminal position of the 1,3-diene to form a $\pi$-allylpalladium intermediate. A second nucleophilic attack on the $\pi$-allyl complex gives the 1,4-addition product (Scheme 2).

In all these processes, the key event is the production of Pd(0) in the final elimination step; the presence of an oxidant in stoichiometric amount is then required to reconvert Pd(0) to Pd(II). An efficient oxidation of the catalyst is critical for a successful performance. Many oxidants such as Ag(I), Cu(II), TBHP, $PhCO_3Bu$, BQ, and $O_2$ itself have been tried. Obviously $O_2$ is the most environmentally friendly; however, in the absence of a cocatalyst, it often fails to achieve a complete oxidation of palladium, as the formation of inactive bulk metal is a competing process. The most frequently used oxidant is BQ. Several mechanistic pathways are involved in regenerating the Pd(II) species during catalytic turnover. Scheme 3 shows the relationship between oxygen and BQ as stoichiometric oxidants of the Pd(0) species.[6]

In the opinion of some authors, the generation of the active Pd(II) catalyst can arise from the insertion of $O_2$ in a pathway where the formal oxidation state of palladium is preserved throughout the reaction. Scheme 4 shows the insertion of $O_2$ on the intermediate Pd(II) hydride **F** to produce a Pd(II) hydroperoxide species **G**, which, upon protonation, releases $H_2O_2$ and reforms the Pd(II) catalyst. Only very recently has it been proved that it is possible to insert $O_2$ directly into a Pd(II) hydride.[7]

In a different pathway, BQ acts as an electron-transfer mediator, which in turn is reoxidized by oxygen (acting as the terminal oxidant) via activation by $MnO_2$ or metal macrocycles (Scheme 5).[8]

In general, palladium oxidation chemistry is dominated by ligand-free reaction conditions, perhaps because many common ligands for late-transition metals, such as phosphines, are susceptible to oxidative decomposition. In contrast, the use of $O_2$ generally requires a ligand for efficient catalysis, which introduces the possibility of making the reactions chemo- or stereoselective. Great efforts are under way to follow this lead.

## 2. C–C Bond Formation

Carbon−carbon bond formation taking place when C−H units are functionalized through the action of palladium complexes is one of the most important subjects of contemporary chemistry; its use appears particularly striking when the metal complex is active in a catalytic amount. The aim of this section is to document reactions known to date by which C−C bonds are formed, starting from unactivated olefinic and aromatic hydrocarbons.

We shall cover reactions in which two alkenes or arenes are homocoupled as well as reactions between arenes and alkenes leading to arylated olefins. Heterocyclic compounds have also been used both in homocoupling reactions and to prepare heteroaromatic-substituted olefins.

In general, Pd(II) acts as a Lewis acid activating the olefin for a subsequent nucleophilic attack. In the case of direct arylation of olefins via aromatic C−H bond activation, $\sigma$-aryl−Pd complexes are formed by electrophilic substitution of aromatic C−H bonds. These complexes have been proved to be the intermediates in the catalytic cycle.[9] The addition to olefins of a variety of carbon nucleophiles could be very interesting in a synthetic perspective.

### 2.1. Alkene–Alkene Couplings

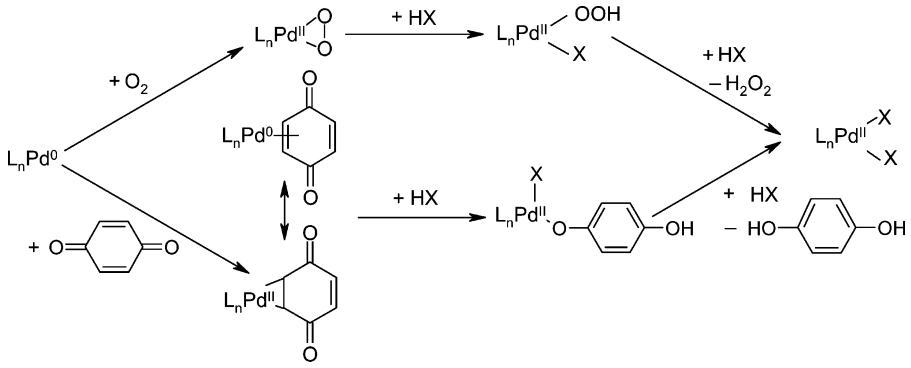
Olefins are one of the most important carbon sources in the synthesis of fine chemicals. Nevertheless, relatively few examples are reported of direct utilization of simple olefins.

Several examples of coupling of alkenes are reported, most of which concern intramolecular processes. They are often exploited in the synthesis of natural products. In all cases, useful catalyst systems are very similar or identical to those described for alkene−arene couplings.

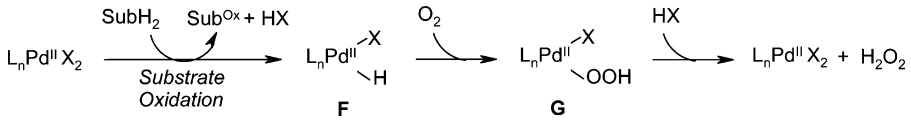
#### 2.1.1. Intramolecular Reactions

After the work on the intramolecular addition of silyl enol ethers to alkenes carried out by Saegusa and co-workers, who employed 0.5 equiv of palladium and BQ to prepare cyclic $\alpha,\beta$-unsaturated ketones,[10] recently a similar cycloalkenylation of silyl enol ethers **1**, using catalytic amounts of palladium, was applied to the construction of 6/5 and 5/5 fused-ring ketones **2**, in particular bicyclo[4.3.0]nonanes and bicyclo[3.3.0]octanes (Scheme 6).[11] All these reactions were carried out in DMSO in the presence of a catalytic amount of $Pd(OAc)_2$ under 1 atm of oxygen. Additionally, benzo-

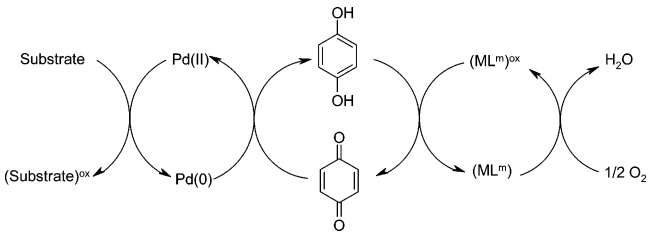
**Scheme 3**



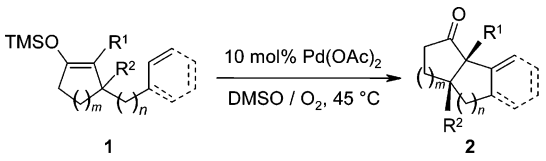
**Scheme 4**



**Scheme 5**



**Scheme 6**

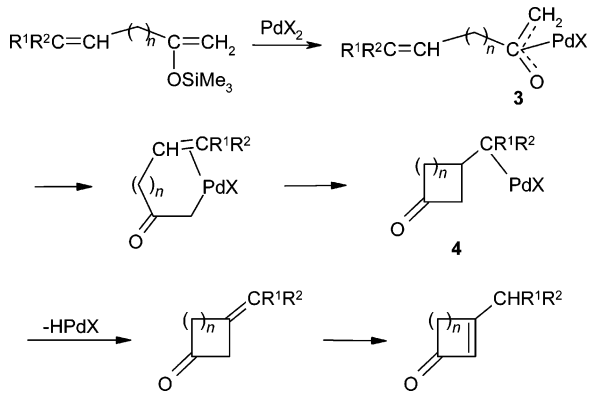


| substrate | $R^1$ | $R^2$ | *m* | *n* | product | yield % |
|---|---|---|---|---|---|---|
| allyl derivatives | H | Me | 1 | 1 | **2a** | 30 |
| | Me | Me | 1 | 1 | **2b** | 41 |
| | H | Me | 1 | 2 | **2c** | 7 |
| | Me | Me | 1 | 2 | **2d** | 24 |
| | H | Me | 2 | 1 | **2e** | 11 |
| | Me | Me | 2 | 1 | **2f** | 37 |
| phenyl derivatives | H | Me | 1 | 1 | **2g** | 40 |

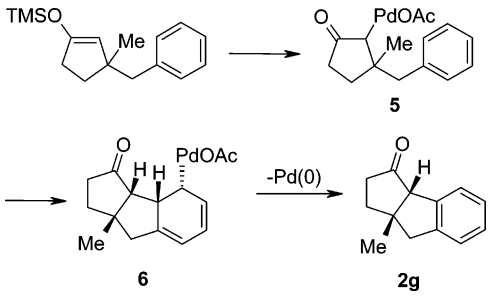
fused bicyclo[3.3.0]octanes were prepared starting from silyl enol ethers and aromatic rings. In this case, to improve the unsatisfactory yields, the reactions were performed with 1 equiv of $Pd(OAc)_2$. The effect of substituents on silyl enol ethers was studied.

Two plausible pathways for the cyclization reaction were described. For acyclic unsaturated silyl enol ethers, Saegusa and co-workers assumed the formation of the oxa-($\pi$-allyl)-palladium(II) complex (**3**), which would undergo an intramolecular insertion of the olefin, resulting in the $\sigma$-alkylpalladium complex (**4**) also if an alternative process via enolate addition to Pd(II)-activated alkenes cannot be ruled out. $\beta$-Elimination of the palladium hydride species followed by

**Scheme 7**



**Scheme 8**



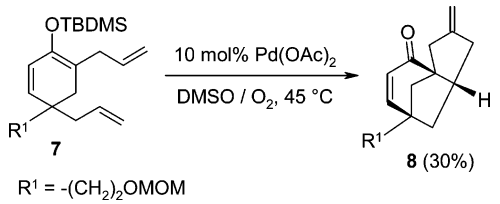
double bond isomerization would originate the final product (Scheme 7).

For aromatic substrates, the authors proposed a mechanism involving the insertion of palladium to give $\sigma$-alkylpalladium complex **5**, followed by coupling with the double bond of the aromatic ring. The $\beta$-elimination of the intermediate **6** would yield the tricyclic compound **2g** (Scheme 8).[11] However, a more plausible electrophilic palladation of the aryl group can be envisioned.

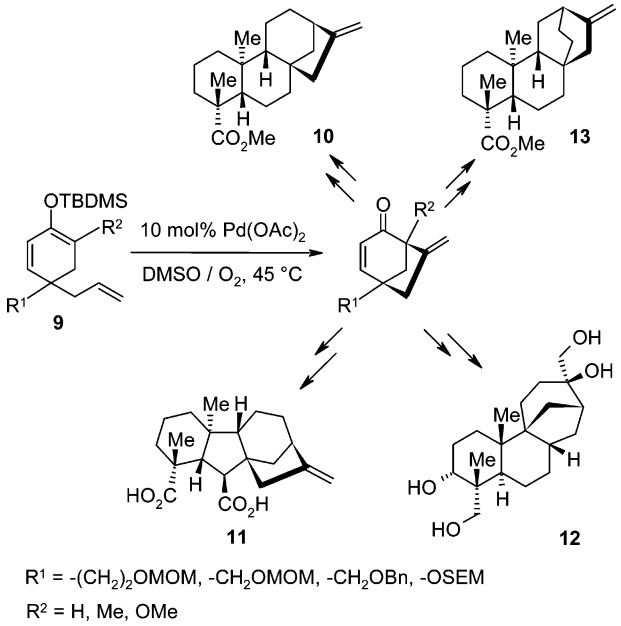
Compound **7**, bearing two allyl groups, underwent a tandem cycloalkenylation that was exploited for the construction of the sesquiterpene cedrane skeleton **8** (Scheme 9).[12]

Cycloalkenylation of 2-silyloxy-5-allyl-1,3-cyclohexadienes **9** was examined.[13] Several reaction parameters, such as palladium catalysts, substituent groups, and solvents, were evaluated. The best results were obtained with the bulky

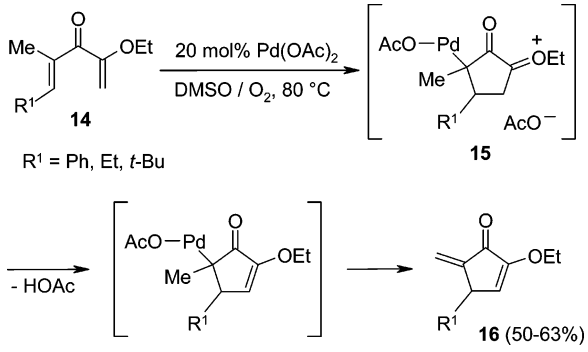
**Scheme 9**




**Scheme 10**



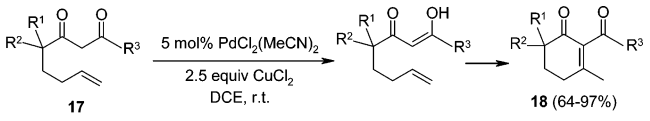

**Scheme 11**




protecting group TBDMS. The catalytic reaction proceeded smoothly even in aqueous media. This approach was exploited for the total synthesis of several tetracyclic diterpenoids possessing a bicyclo[3.2.1]octane ring system, such as kaurene **10**, $C_{20}$ gibberellin **11**, aphidicolin **12**, and of diterpenoid possessing a bicyclo[2.2.2]octane system, such as atisirene **13** (Scheme 10).[14]

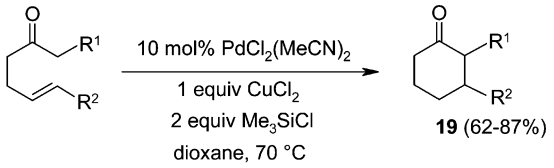
Cross-conjugated cyclopentenones **16** were formed from α-alkoxydienones **14** through an oxidative process that was carried out with 20 mol % $Pd(OAc)_2$ in DMSO under oxygen atmosphere at 80 °C (Scheme 11).[15] According to the authors' suggestion, the electron-poor olefin was activated by complexation to palladium, and subsequent intramolecular attack afforded the intermediate **15**. Final $\beta$-elimination yielded the observed product. A different cyclopentenone product was achieved by using $PdCl_2(MeCN)_2$; in this case, the intermediate **15** underwent hydrolysis with loss of HCl giving directly the Pd(II) species.

**Scheme 12**



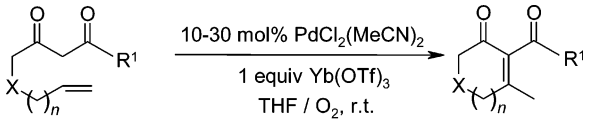

R1, R2 = H, Me, -(CH2)5-
R3 = Me, Et, *i*-Pr, *t*-Bu, Cy, Ph

**Scheme 13**




R1 = $CO_2$Me, Ph, naphthyl, hexyl, Cy, Bu
R2 = Me, Ph, Et, H

**Scheme 14**




R1 = OMe, $NMe_2$
X = O, N-Ts, N-Boc, $CH_2$
*n* = 1, 2, 3

A more direct approach to C−C bond formation involves the nucleophilic addition of a carbon nucleophile to an ethylenic double bond; alkenyl-substituted $\beta$-dicarbonyls such as **17** are suitable substrates (Scheme 12). Substantial work by Widenhoefer on this line exploited the intramolecular addition of the enolic carbon atom of **17** across the unactivated ethylenic bond.[16] After the preliminary palladium complexation of the latter, a cyclohexyl palladium intermediate was formed. Subsequent isomerization and $\beta$-hydride elimination resulted in product **18**.

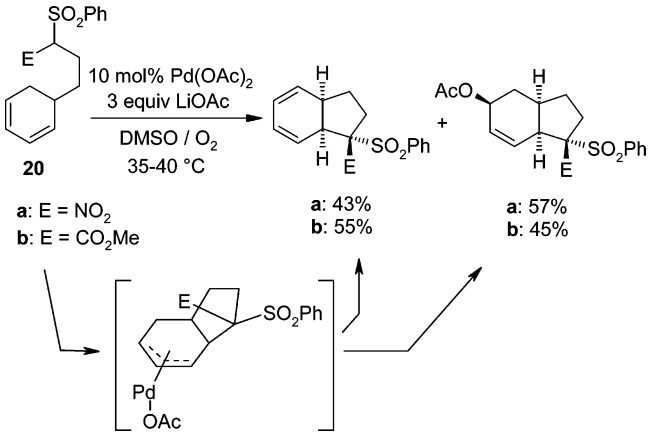
In the presence of stoichiometric amounts of $Me_3SiCl$ and $CuCl_2$, a competing hydroalkylation reaction was observed, also in the case of benzylic ketones, to form 2-substituted cyclohexanones **19** (Scheme 13).[17] No evidence emerged regarding the formation of the silyl enol ether. Subsequent studies revealed that $Me_3SiCl$ was not directly involved in the hydroalkylation but served as a source of HCl that actually promoted it.

Likewise, the association of PEG-400 and $CuCl_2$ catalyzed a hydroalkylation cyclization reaction of alkenyl $\beta$-ketoesters. The role of PEG-400, forming a nonvolatile, separated liquid phase, was to immobilize the catalyst. The catalytic system could be recycled five times without any loss of activity.[18]

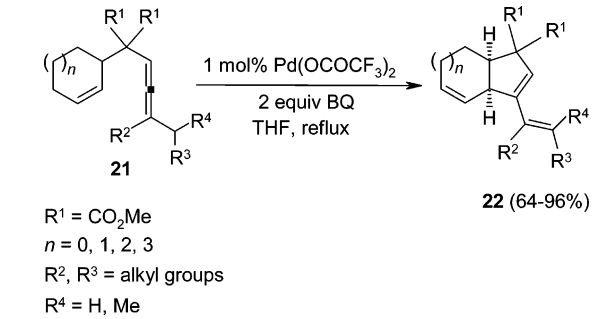
The intramolecular oxidative cyclization of unsaturated $\beta$-ketoamides and $\beta$-ketoesters has been developed under aerobic condition by way of a palladium-catalyzed reaction in the presence of $Yb(OTf)_3$.[19] Specifically, the latter served as a Lewis acid to promote the enolization of the substrate and to enhance its nucleophilicity toward the Pd(II)-activated olefin (Scheme 14). A variety of six-, seven-, and eight-membered *N*- and *O*-heterocycles obtained regioselectively in good yields under very mild conditions.

Cyclic 1,3-dienes bearing side chains with electron-withdrawing substituents (such as **20**) acted as carbon nucleophiles in coupling reactions (Scheme 15).[20] Yields were optimized by the use of $DMSO/O_2$ as oxidant. The 1,4-addition to the diene occurred with an overall *syn*-stereo-

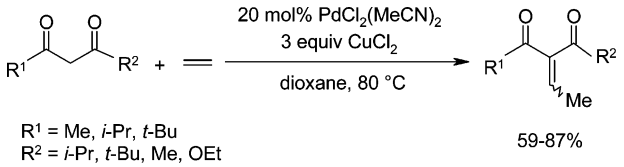
**Scheme 15**




**Scheme 16**




**Scheme 17**




chemistry via $\pi$-(allyl)palladium intermediate. Diene formation via $\beta$-hydride elimination competed with nucleophilic attack by acetate. The relative stereochemistry of the four stereogenic centers, dictated by the exo/endo selectivity, was dependent on the different bulk of the electron-withdrawing groups.

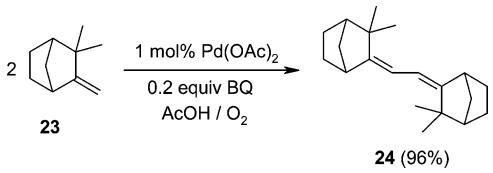
Bäckvall and co-workers were the first to report an example of oxidative cyclization of cyclic olefins bearing a 1,2-diene pendant (**21**) (Scheme 16).[21] A catalytic amount of $Pd(OCOCF_3)_2$ and BQ used as oxidant led to the fused-ring system **22**. The probable mechanism runs via a ($\pi$-cyclohexene)palladium complex and nucleophilic attack on palladium to the central atom of the allenic group. The same result was achieved in a more recent study by using only 4 mol % of BQ and 1 mol % of FePc in an $O_2$ atmosphere following the mechanism described in Scheme 5.[22]

### 2.1.2. Intermolecular Reactions

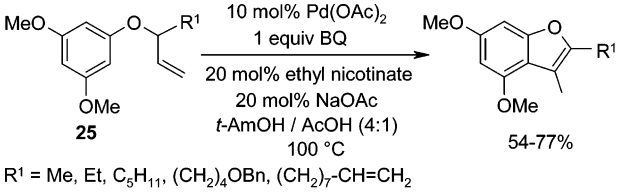
The intermolecular version of the alkenylation of carbon nucleophiles consists of the addition of $\beta$-dicarbonyl compounds to ethylene or propylene. In the latter case, the $\beta$-diketone was activated with $EuCl_3$ (Scheme 17).[23]

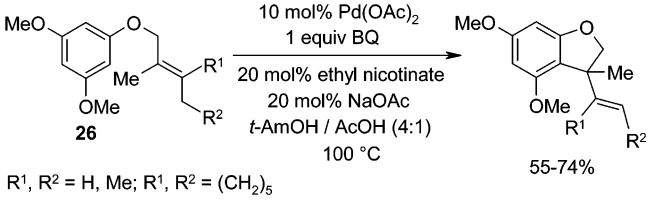
A rare example of intermolecular coupling was applied to the synthesis of some natural products. Terpene derivative **23**, when subjected to the Pd-catalyzed oxidative coupling reaction in the presence of $Pd(OAc)_2$ and BQ as oxidant, gave homocoupling product **24** (Scheme 18).[24]

**Scheme 18**

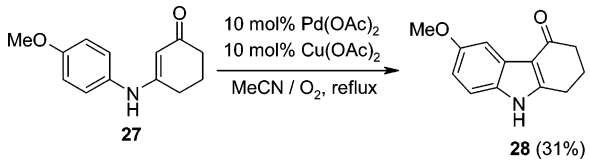



**Scheme 19**




**Scheme 20**




## 2.2. Alkene–Arene Couplings

Compared with alkene−alkene coupling, a much greater wealth of data is available on reactions involving alkenes and arenes as substrates. A large variety of arylated olefins have been prepared in a single step. Intramolecular applications have given polycyclic aromatic and nonaromatic systems.

### 2.2.1. Intramolecular Reactions

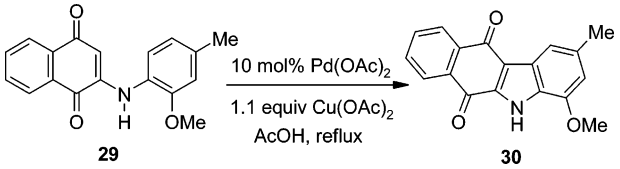
Starting from allylaryl ethers **25** and **26**, the construction of electron-rich heterocycles as highly substituted benzofurans and dihydrobenzofurans was developed by employing $Pd(OAc)_2$, a particular type of pyridine ligand, and BQ as oxidant, under acidic conditions (*t*-AmOH−AcOH 4:1) with or without added base (AcONa 0.00−1.0 equiv) (Scheme 19).[25] An elegant stereochemical mechanistic study demonstrated that *o*-aryl-palladation precedes olefin insertion and $\beta$-hydride elimination. The reaction sequence was classified as Fujiwara−Moritani/oxidative Heck cyclization.

The same strategy was applied to the synthesis of carbazole derivatives. By employing a catalytic amount of $Pd(OAc)_2$ and $Cu(OAc)_2$ under $O_2$, 3-(4-methoxyanilino)cyclohex-2-en-1-one **27** was cyclized to 1,2-dihydrocarbazol-4(3*H*)one **28** (Scheme 20).[26]

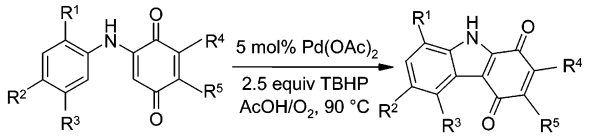
Carbazoloquinone **30** was produced by a facile one-step oxidative coupling reaction from 2-arylamino-1,4-benzoquinone **29** with $Pd(OAc)_2$ in a catalytic amount and $Cu(OAc)_2$ as oxidant in refluxing AcOH (Scheme 21).[27]

Different reaction conditions were tested by Åkermark: $Pd(OAc)_2$ and $Cu(OAc)_2$ in AcOH, $Pd(OAc)_2$ and TBHP in AcOH, and 5 mol % $Pd(OAc)_2$ or $Pd(OCOCF_3)_2$ and 10 mol % $Sn(OAc)_2$ in AcOH under oxygen atmosphere as the only

**Scheme 21**

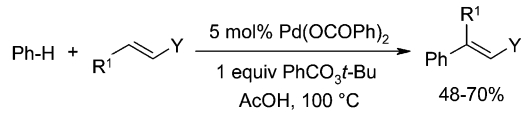



**Scheme 22**




| $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | yield % |
|---|---|---|---|---|---|
| OMe | H | H | -(CH=CH)$_2$- | | 74 |
| H | OMe | H | -(CH=CH)$_2$- | | 66 |
| OMe | H | Me | -(CH=CH)$_2$- | | 65 |
| OMe | Me | H | -(CH=CH)$_2$- | | 59 |
| H | H | H | H | Me | 67 |
| H | H | H | Me | H | 68 |

**Scheme 23**




R$^1$ = H, Me, Ph
Y = COMe, CHO, $CO_2Me$

oxidant (Scheme 22).[28] Knolker took advantage of this synthetic path to achieve the total synthesis of antibiotic carbazole alkaloids carbazomycin G, H, and carbazoquinocin C.[29]

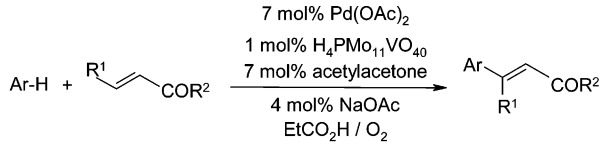
### 2.2.2. Intermolecular Reactions

The arylation of alkenes, promoted by catalytic $Pd(OAc)_2$ using $Cu(OAc)_2$ or AgOAc and air as oxidants, was first reported in 1967 by Fujiwara and Moritani.[30] The reaction provides a convenient method for the synthesis of a wide variety of arylated olefins. Its mechanism, as proposed in the introduction, proceeds via electrophilic attack of palladium on the aromatic moiety to form the ArPdX complex, which then reacts with the olefin. The formation of the $\sigma$-bonded aryl−Pd(II) complex is the rate-determining step. $\beta$-Elimination of palladium hydride gives the arylated alkenes. Reactions exploiting *t*-butyl perbenzoate as hydrogen acceptor were also reported (Scheme 23).[31]

Yields were increased by the presence of electron-withdrawing groups on the olefins and electron-donating groups on the arene. The reaction is highly regio- and stereoselective, chiefly giving $\beta$-aryl-*trans*-olefins. The use of catalytic amounts of $Pd(OAc)_2$ (1% mol) and BQ (10% mol) with *t*-butyl hydroperoxide as oxidant improved yields with high turnover numbers (up to 280, several times higher than previously reported for this reaction).[32]

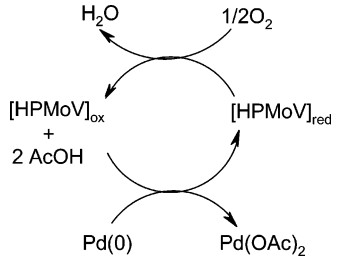
In 1971, Shue reported the first coupling reaction of benzene and olefins using a mild oxygen pressure in conjunction with $Pd(OAc)_2$ and no reoxidation catalyst or cosolvent.[33] The absence of organic oxidants or electron-transfer mediators ensured that water was the only byproduct.

**Scheme 24**




| arene | $R^1$ | $R^2$ | product | yield % |
|---|---|---|---|---|
| | H | OEt | tolyl-CH=CH-$CO_2Et$ | 70 |
| MeO- | H | OEt | MeO- -CH=CH-$CO_2Et$ | 73 |
| Cl- | H | OEt | Cl- -CH=CH-$CO_2Et$ | 74 |
| S | H | OEt | S -CH=CH-$CO_2Et$ | 86 |
| | Ph | H | Ph-CH=C(Ph)-CHO | 93 |
| | H | OMe | Ph-CH=CH-$CO_2Me$ | 68 |
| | H | OBu | Ph-CH=CH-$CO_2Bu$ | 70 |
| | H | O*i*-Bu | Ph-CH=CH-$CO_2i$-Bu | 73 |

**Scheme 25**

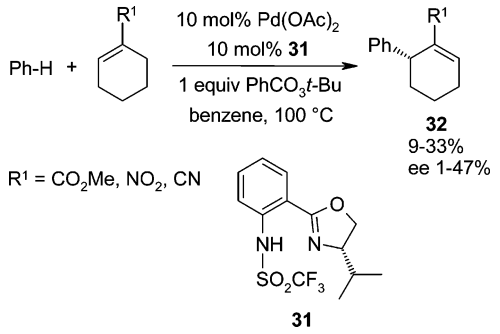



Several regioisomers were formed under these solvent-free conditions. The accelerating effect observed when benzoic acid was present as additive suggests that the reaction may occur through an electrophilic attack on the aromatic compound.[34]

Very recently, a catalytic mixture of $Pd(OAc)_2$ and the molybdovanadophosphoric heteropolyacid system as a palladium reoxidant was employed in the reaction of benzene with olefins bearing an electron-withdrawing group (Scheme 24).[35] The method was extended to the coupling of various arenes with $\alpha,\beta$-unsaturated esters and aldehydes. Propionic acid at 90 °C was the best solvent tested. [HPMoV]red is oxidized to [HPMoV]ox with $O_2$ as shown in Scheme 25.

The first asymmetric example of the so-called "Fujiwara−Moritani" reaction catalyzed by a chiral Pd(II) complex was reported by Mikami et al.[36] Optically active phenyl-substituted cyclohexenes **32** were formed in the coupling reaction of benzene with cycloalkenes through *syn*-$\beta$-*H*-elimination from the opposite side to the phenyl group

**Scheme 26**




(Scheme 26). Enantiopure sulfonylaminooxazoline ligand **31** was mixed with $Pd(OAc)_2$ in dry benzene, and the mixture was heated in the presence of *t*-butyl perbenzoate as a reoxidant.

Arenes and benzoquinones or naphthoquinones also underwent the oxidative coupling reaction in the presence of $Pd(OAc)_2$ and several oxidants, among which peroxodisulfate salts were found to be particularly effective (Scheme 27).[37]

The benzene nucleus of anilides **33** was particularly reactive toward electron-poor alkenes. In its coupling with butyl acrylate in the presence of $Pd(OAc)_2$ and BQ in AcOH at room temperature, alkenylation took place in the *ortho*-position (Scheme 28).[38] No other isomer was formed because of the strong *ortho*-directing effect of the amide group. Simple anilines and *N*-methylacetanilides were not reactive under the tested conditions.

Decarboxylative olefination of benzoic acid **34** with styrene, *t*-butyl acrylate, and acrylonitrile was reported in the presence of $Pd(OCOCF_3)_2$ and $Ag_2CO_3$ in DMSO/DMF at 80 °C (Scheme 29).[39] The mechanism proposed by the authors assumes the cleavage of the C−C bond of the arylcarboxylic acid as the rate-determining step to form the arylpalladium(II) trifluoroacetate **36** intermediate and carbon dioxide. Intermediate **36** was isolated and crystallographically characterized. An electron-deficient palladium center was essential for the decarboxylative step to occur. In fact, other palladium derivatives such as $Pd(OAc)_2$ and $PdCl_2$ were ineffective. Olefin insertion and $\beta$-hydride elimination gave product **35** with complete *syn*-stereospecificity.

## 2.3. Alkene–Heteroarene Couplings

Several Pd-promoted coupling reactions have been reported involving alkenes and electron-rich heteroarenes, mainly indoles and pyrroles, but also furans and thiophenes, as well as their benzoderivatives. Both intermolecular and intramolecular versions are known.

### 2.3.1. Intramolecular Reactions

A mixture of two isomeric pyrrolopyridines was obtained in the coupling cyclization reaction of *N*-allylpyrrole-2-carboxamide derivatives, using the catalytic system $PdCl_2(MeCN)_2$/BQ in DMF/THF at 100 °C (Scheme 30).[40] A transient cationic spiro-palladium complex was hypothesized as intermediate, from which two different skeleton types are formed through an anionotropic shift and subsequent loss of a proton.

Indole derivatives offer an attractive field for the development of synthetic strategies leading to polycyclic systems. In 1978, Trost et al. reported the first intramolecular application by using the $PdCl_2(MeCN)_2$/silver ion system for the total synthesis of alkaloid ibogamine.[41]

3-(Alken-4-yl)indoles **37** underwent an annulation reaction through a Pd(II)-promoted coupling when 10 mol % $Pd(OAc)_2$ and $O_2$ as the sole oxidant were used (Scheme 31).[42] When comparing different pyridine ligands and different solvents, the best results were reported with 3-carbethoxypyridine as the electron-poor ligand and a 4:1 mixture of *t*-amyl alcohol−AcOH as the polar solvent. Annulation can also proceed from the C-2 to the C-3 position as well as from N-1 to C-2. Ring sizes of 5 and 6 atoms can be obtained by the oxidative cyclization. The same substrate bearing different substituents was tested in the presence of the $Pd(OAc)_2$/BQ catalytic system (Scheme 32).[43] The *endo*-mode oxidative cyclization was observed, giving first dihydrocarbazoles, which under the chosen conditions aromatized to the corresponding carbazoles **38**. When the indole moiety carried electron-donating groups, better yields were obtained. Excellent results from the oxidative coupling step were obtained in the synthesis of $\beta$-carbolinones **40** from *N*-allylindole-2-carboxamide derivatives **39** by using $PdCl_2(MeCN)_2$ and BQ in DMF/THF as solvent (Scheme 33).[44]

Extending the unsaturated chain to a homoallyl group led to azepinoindoles. Moreover, when $CuCl_2$ was used instead of BQ, one H atom of the methyl group was replaced with a Cl atom.[45]

### 2.3.2. Intermolecular Reactions

Numerous applications of intermolecular alkene−arene coupling reactions involving indole derivatives were reported. 1-Acylindoles and 1-benzenesulfonylindoles have been exploited for alkenylation with olefins bearing electron-withdrawing substituents to yield 3-substituted derivatives **41** (Scheme 34).[46] Different oxidation agents were tested.

An application of this strategy, starting from a pyrido-[2′,3′-*d*]pyrazino[2,3-*a*]indole derivative and ethyl acrylate, was aimed at the synthesis of pentacyclic *E*-azaeburnane.[47] Likewise, a total synthesis of ergot alkaloid clavicipitic acid **43** was achieved by exploiting the coupling reaction of 4-bromoindole with dehydroalanine methyl ester as the key step to give intermediate **42** (Scheme 35).[48] The presence of chloranil as oxidant avoided the use of a stoichiometric amount of palladium. Also, 2-substituted indoles readily coupled with electron-poor alkenes, forming 3-alkenyl derivatives when the catalytic system $Pd(OAc)_2$/AgOAc was used in AcOH at reflux.[49]

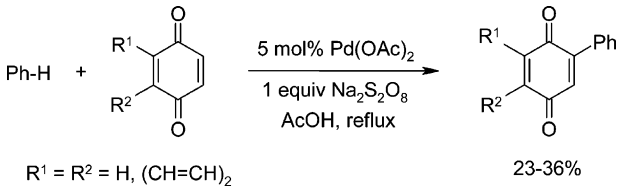
A very recent achievement is the regioselective alkenylation of indoles using appropriate solvents and additives (Scheme 36).[50] In polar solvent like DMSO and DMF, alkenylation at C-3 was observed, resulting from palladium attack on C-3. In a weakly coordinating solvent such as dioxane, alkenylation at C-2 was prevalently observed, for which the migration of the intermediate **44** was hypothesized.

Moreover, in the case of *N*-(2-pyridylmethyl)indole, the 2-pyridylmethyl substituent played the role of metal-directing group, so that 2-alkenylated indoles **45** were formed exclusively (Scheme 37).[51]

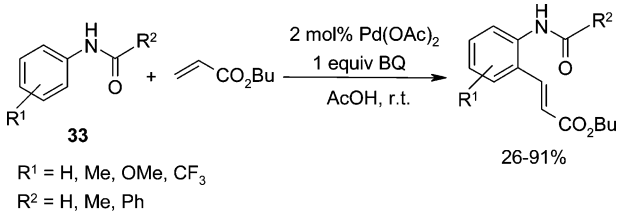
The reaction of 1-aroylpyrroles **46** with ethyl acrylate was found to give both mono- and dialkenylated products (Scheme 38).[52] Under the same conditions, 1-aroylpyrazoles **47** yielded 4-alkenylated products.

Very recently, regioselective pyrrole alkenylation and annulation at either the C-2 or C-3 position were obtained, with the preferred one depending on the nature of the

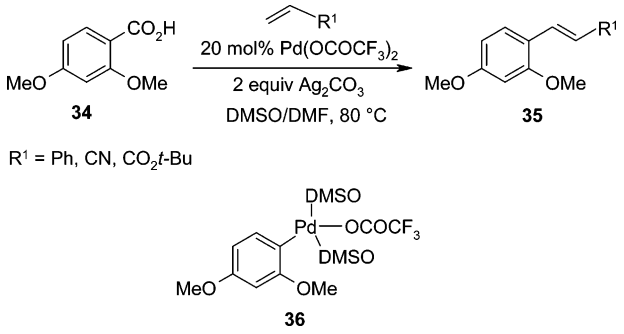
**Scheme 27**



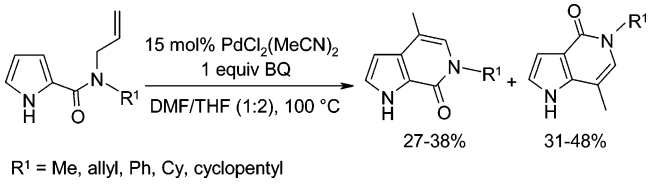

**Scheme 28**



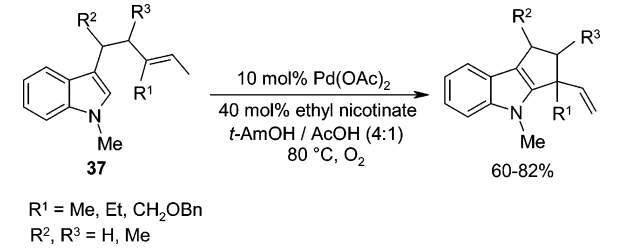

**Scheme 29**




**Scheme 30**



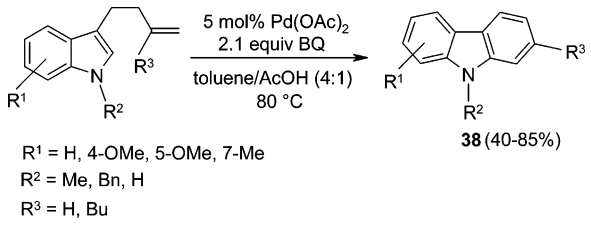

**Scheme 31**



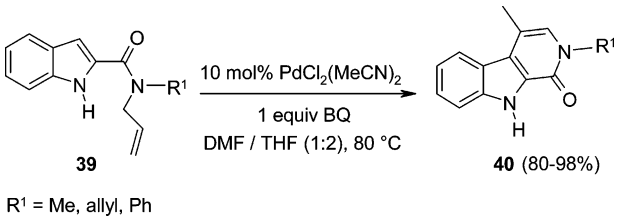

*N*-protecting group (Scheme 39).[53] Electron-withdrawing substituents reduced the reactivity of the pyrrole and afforded only the C-2 product **48** in good yield. In contrast, *N*-TIPS pyrrole only gave the C-3 product **49**; this result was attributed to the sterically demanding nature of the TIPS group that shielded the C-2 position from reaction with the palladium catalyst.

Five-membered aromatic heterocycles like furan and thiophene reacted with various olefins to yield mono- (**50**) and dialkylated (**51**) derivatives at positions 2 and 5 (Scheme 40).[54] The corresponding reactions of benzofuran and benzothiophene with acrylonitrile gave a mixture of products alkenylated at positions 2 and 3 as *Z*/*E* isomeric mixtures (Scheme 41).[55]

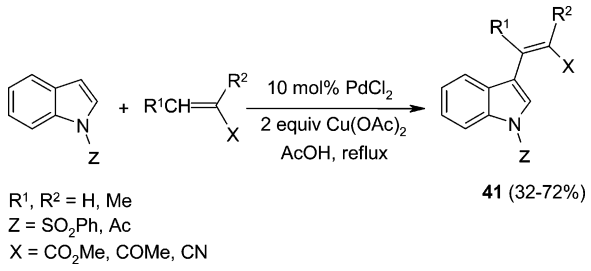
**Scheme 32**




**Scheme 33**




**Scheme 34**




The catalytic system $Pd(OAc)_2$/BQ with TBHP as oxidant especially promotes highly regio- and stereoselective coupling of furan and benzofuran with activated alkenes, leading predominantly to *trans*-isomers **52** (Scheme 42).[32] Finally, it must be mentioned that, by using $Pd(OAc)_2$ and *t*-butyl perbenzoate in acetonitrile, uracils reacted with olefins to give the corresponding 5-(1-alkenyl)uracil derivatives **53** (Scheme 43).[56]

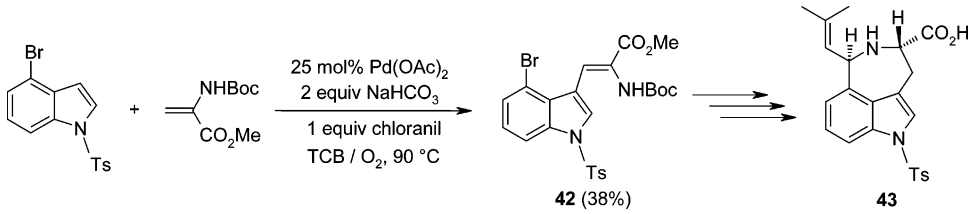
## 2.4. Arene–Arene Couplings

Since biphenyl compounds carry a strong industrial interest as key building blocks in various agrochemical and pharmaceutical processes, several synthetic procedures have been developed for them. The direct coupling of two arenes or heteroarenes to form a biaryl or biheteroaryl is economically more advantageous than other methods.

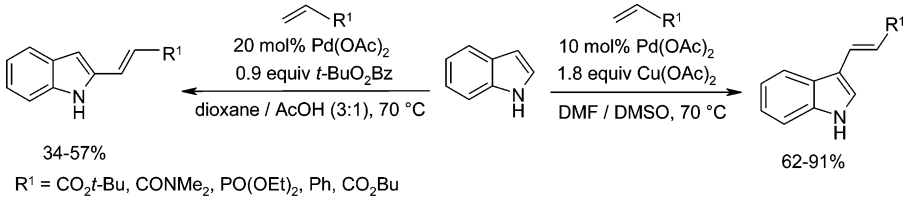
The homocoupling of arenes in the presence of $PdCl_2$ and sodium acetate in acetic acid as solvent was first reported in the middle 1960s to yield biaryls **54** (Scheme 44).[57] The rate-determining step is the formation of a complex between benzene and $PdCl_2$, followed by a fast reaction of the complex with the acetate anion to yield biphenyl. No reaction occurred in the absence of sodium acetate because the breakdown of the intermediate complex was initiated by this salt.

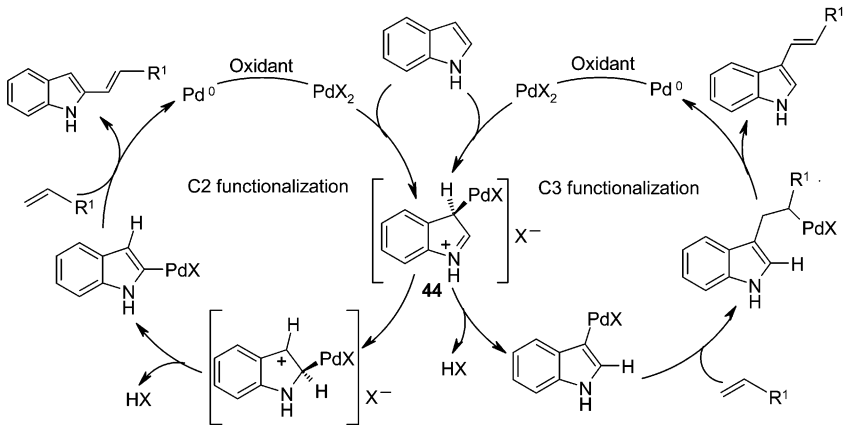
A catalytic amount of palladium sufficed when a stoichiometric amount of molecular oxygen or $Cu(OAc)_2$ was employed to regenerate Pd(II) from Pd(0). The addition to the system of acetylacetone or EDTA remarkably im-

**Scheme 35**

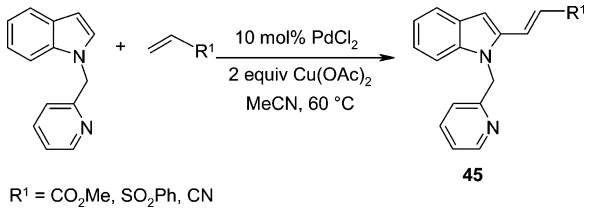



**Scheme 36**




**Scheme 37**



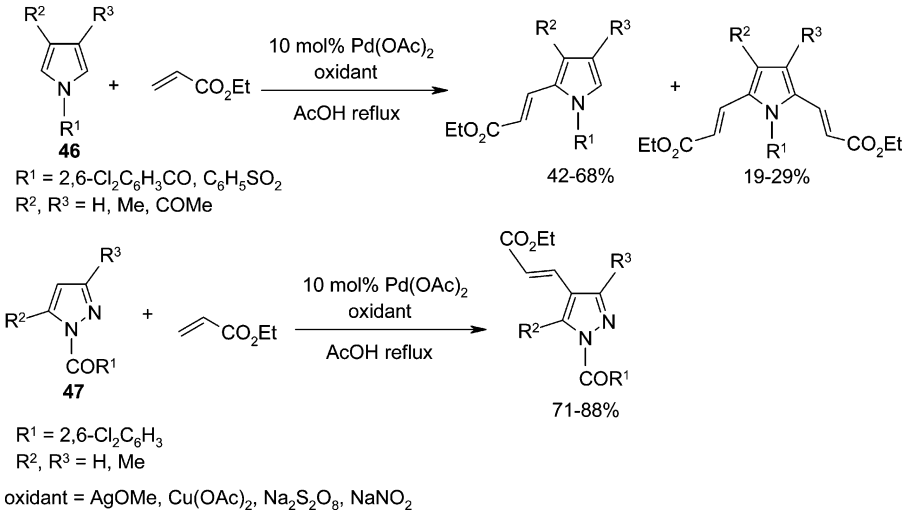

proved yields of coupling products.[58] The mechanism, as reported in the Introduction (Scheme 1, right-hand side), involves substitution of an aryl hydrogen by palladium; the subsequent formation of a $\sigma$-bonded aryl−Pd(II) complex is considered the rate-determining step.

The coupling of substituted benzenes follows the orientation pattern usually expected for an electrophilic attack. Substituents exert a weak polar effect: electron-donating groups increase the rate, while the opposite holds for electron-attracting groups. Steric effects play an important role. The isomeric distribution may vary depending on such reaction variables as temperature, additives, and the nature of substituents on a benzene ring.[59] When the coupling reaction of benzene was carried out in acetic acid in the presence of $O_2$ and $MoO_2(acac)_2$ as a cocatalyst, a high yield of biphenyl was attained compared to phenol and phenyl acetate byproducts.[60] The reactivity was enhanced by trifluoromethanesulphonic acid, arguably because protonation of the aromatic ring activated the C−H bond.[61] The homocoupling reaction of arylsulfonyl chlorides upon treatment with titanium(IV)isopropoxide in the presence of a catalytic amount of $PdCl_2(MeCN)_2$ gives biaryls.[62] The reaction presumably proceeds with expulsion of sulfur dioxide from arene sulfinic acids and formation of an arylpalladium complex (see Scheme 44). Biaryls were the decomposition products of the intermediate. Whenever $Pd(OAc)_2$ proved inactive for oxidative coupling, the $Pd(OAc)_2$−dialkyl sulfide was tried instead. The effects of the sulfide alkyl group, the molar ratio of sulfide/$Pd(OAc)_2$, and the oxygen atmosphere have been investigated.[63] More recently, a fast regeneration of the active Pd(II) species was accomplished by combining several oxygen-binding catalysts such as the acetates of Zr(IV), Mn(II), and Co(II).[64]

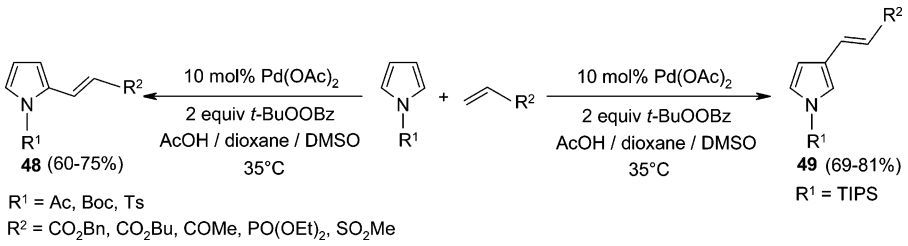
The homocoupling reaction of arenes was also observed with the protocol based on $Pd(OAc)_2$ and the HPMoV system exploited as a palladium reoxidant (Scheme 45).[65] The same catalytic system was employed in DMF to transform thiophene and 2-methylfuran into the corresponding dihetaryls.[66]

The homocoupling of heterocycles such as thiophene, furan, and their derivatives in the presence of $Pd(OAc)_2$ and Fe(III) or Cu(II) as oxidants mainly afforded the corresponding 2,2′-bifuryls and 2,2′-bithienyls.[67] Electron-withdrawing substituents made the reaction proceed also in the presence of $Pd(OAc)_2$ and air.[68] Coupling of 1-benzoylpyrroles with $Pd(OAc)_2$ was also reported.[69] Recently, 4,4′-dimethyl-2,2′-bipyridine was prepared by homocoupling of 4-methylpyridine using Pd/C and $O_2$ as oxidant under reflux of 4-methylpyridine (Scheme 46).[70]

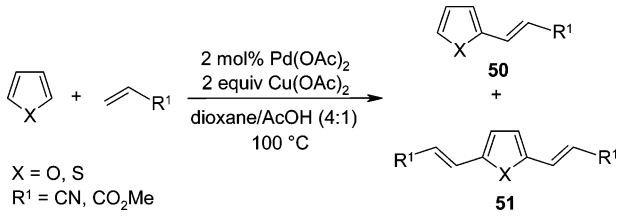
**Scheme 38**




**Scheme 39**




**Scheme 40**




## 2.5. Coupling Involving Organometallics

In this paragraph, we report C−C bond formation in which metals other than palladium are used in separate steps. Normally the metal binds to the substrate to form an organometallic derivative. A similarity can be seen with Pd(0)-catalyzed cross-coupling reactions in the absence of reoxidant agents. A bit of confusion has arisen because some authors have used the term "cross-coupling reaction" also for the processes presented here, in which Pd(II) was employed. To our knowledge, only intermolecular examples of this type of reactions have been reported.

The addition of metal aryls to olefins was first reported by Heck in 1968.[71] He described in particular the arylation of alkenes with mercury aryls using palladium salts in the presence of air at room temperature. The catalytic cycle involves transmetallation followed by olefin addition to form a $\sigma$-aryl−Pd complex. Final $\beta$-hydride elimination gives the coupling product (Scheme 47).

Besides organomercuries, lead and tin alkyls/aryls were also reported as arylating agents. Methanol, ethanol, acetic acid, or acetonitrile were the common solvents. Cupric chloride, ferric or mercuric salts, and oxygen were used to reoxidize the palladium (Scheme 48).[71]

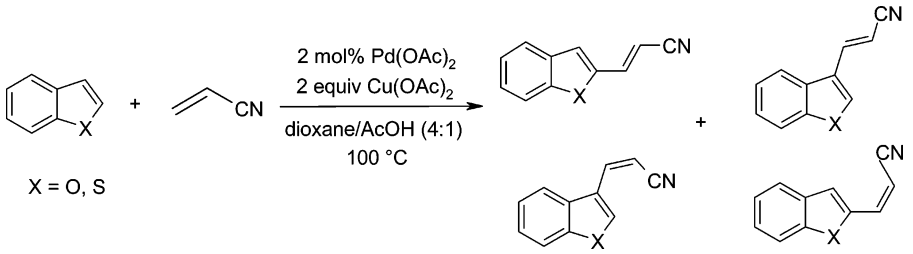
With unsymmetric olefins, the aryl or alkyl group generally bound to the less-substituted carbon atom of the double bond. In the case of 1,6-diene derivative **55**, cyclization was observed to yield cyclopentene derivative **56** (Scheme 49).[72]

Oxidative homocouplings as well as aryl−alkenyl couplings by means of alkenyl- and arylstannanes,[73] areneboronic acids, boronates and sodium tetraphenylborate,[74] triarylbismuthines,[75] and triarylstibines[76] were reported, using palladium acetate as catalyst and oxygen, cupric chloride, or TBHP as oxidants (Scheme 50). Novel oxidants, i.e., ethyl 2,3-dibromo-3-phenylpropanoate and ethyl 2,3-dibromo-3-methylbutanoate (Ph-ACDB and $Me_2$-ACDB), appeared in this context.[77] These compounds work by oxidative addition of their $\alpha$-C−Br bond to Pd(0), followed by $\beta$-elimination to form a Pd(II)$Br_2$ species together with the $\alpha,\beta$-unsaturated ester.

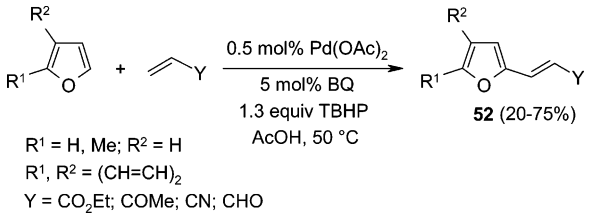
A regio- and stereoselective route to substituted allylic (**57**) and homoallylic (**58**) alcohols was found by reacting vinylepoxides and vinyloxetanes with aryl or vinylic mercurials by using $Li_2PdCl_4$ as catalyst and $CuCl_2$ as oxidant under oxygen atmosphere (Scheme 51).[78] The reactions of aryl and vinylic mercurials with 4-alkenyl-2-azetidinones involved a ring opening with the formation of acyclic unsaturated amides. The reaction was catalytic using $Li_2PdCl_4$ and 1 equiv of $CuCl_2$ in $O_2$ atm.[79]

Biaryls were obtained by oxidative coupling of benzenes bearing electron-donating or electron-withdrawing substituents with the use of thallium trifluoroacetate in the presence of catalytic amounts of $Pd(OAc)_2$ (Scheme 52).[80] The first step was the formation of an aryl thallium intermediate; transmetallation was then the rate-determining step. Among the possible isomers, 4,4′-biaryls were the major products.

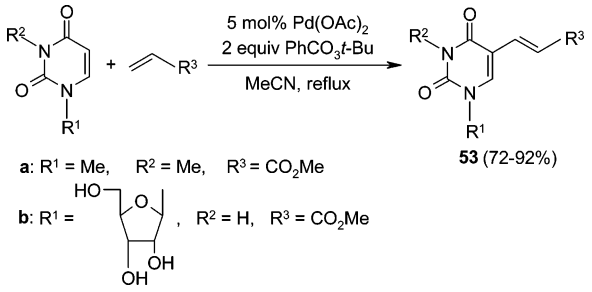
**Scheme 41**



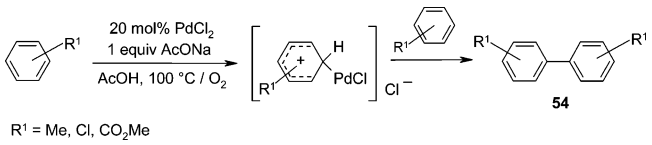

**Scheme 42**



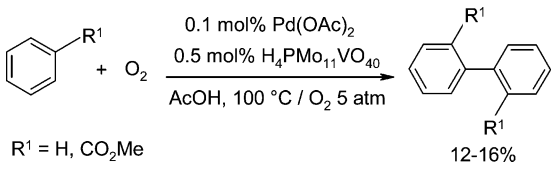

**Scheme 43**



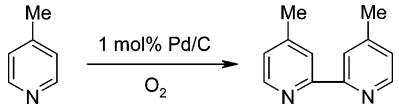

**Scheme 44**




**Scheme 45**




**Scheme 46**

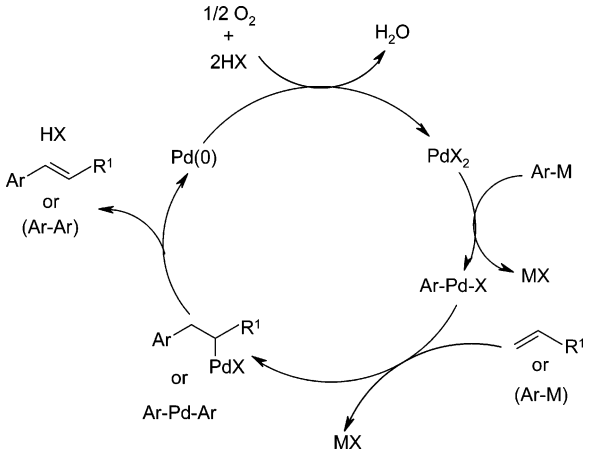



A variety of important oxygen and nitrogen heterocycles (isocumarins, 3,4-dihydrocumarins, indoles, and isoquinolines) were prepared by the thallation and subsequent Pd-catalyzed olefination of *p*-tolyl acetic acid, benzamide, *N*-methylbenzamide, and acetanilide.[81] An explicative example is presented in Scheme 53.

## 2.6. C–C Bond Rearrangements

Pd(II)-catalyzed reactions also include transformations of small-ring compounds by way of a C−C bond transposition. The unique reactivity of the ring-strained cyclobutanols and cyclopropanols stems from the facile cleavage of a C−C bond after Pd-complexation. The alkylpalladium intermediate formed at first may then follow different pathways depending on the ring substituents; ring expansion or rearrangement may take place.

**Scheme 47**




The reaction of 1-vinyl-1-cyclobutanol **59** with bis-(benzonitrile)palladium dichloride and BQ in THF led to 2-cyclopenten-1-one **61** (Scheme 54).[82] An analogous result was obtained by starting from α-alkoxy-1-vinyl-1-cyclobutanols using $Pd(OAc)_2$ catalyst and DDQ as oxidant agent.[83] According to a plausible mechanistic pathway, palladium addition gives an intermediate carbocation **60**, which rearranges through ring expansion. This procedure was also exploited for the synthesis of pentalenolactone antibiotics, for a novel and efficient synthesis of benzo- and naphthohydrindanes, intermediates for the synthesis of steroids, as a key step in the total synthesis of scirpene, and for a synthetic approach to triquinane skeleton.[84]

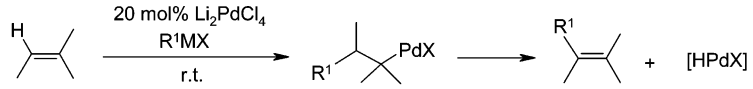
A different C−C bond cleavage occurred by treating the bicyclic cyclobutanols **62** with $Pd(OAc)_2$/pyridine/MS3 Å in toluene under oxygen atmosphere, thus affording $\beta,\gamma$-unsaturated ketones **63** via a selective $\beta$-carbon elimination (Scheme 55).[85] The authors suppose that the reaction proceeds via the formation of Pd(II)−alcoholate **64** followed by $\beta$-carbon elimination. The alkyl palladium species **65** so-formed is prone to eliminate palladium with $\beta$-hydride to give the final products **63** (Scheme 56).

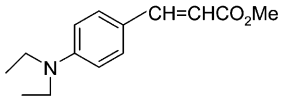
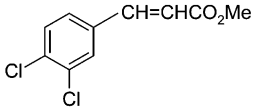
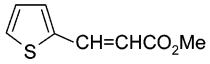
A similar rearrangement involving ring opening of cyclopropanols **66**, observed under oxidative conditions, provided a convenient method for functionalizing monosubstituted olefins (Scheme 57).[86]

## *3. C–O Bond Formation*

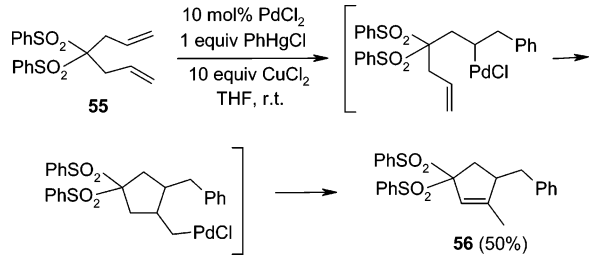
Studies and applications of palladium(II) catalysis aimed to form C−O bonds have marked an epoch-making turn in

**Scheme 48**




| olefin | $R^1MX$ | product | yield % |
|---|---|---|---|
| ethylene | diphenylmercury | styrene | 63 |
| methyl acrylate | diphenylmercury | methyl cinnamate | 88 |
| methyl acrylate | tetraphenyltin | methyl cinnamate | 100 |
| methyl acrylate | tetraphenyllead | methyl cinnamate | 82 |
| methyl acrylate | phenyltin trichloride | methyl cinnamate | 77 |
| methyl acrylate | *p*-chloromercuridiethylaniline |  | 22 |
| methyl acrylate | 1-chloromercuri-3,4-dichlorobenzene |  | 45 |
| methyl acrylate | 2-chloromercurithiophene |  | 36 |
| styrene | pentamethylphenylmercuric chloride | 2,3,4,5,6-pentamethylstilbene | 42 |
| 4-vinylbiphenyl | 4-chloromercuri-2-nitroanisole | 4-methoxy-3-nitro-4'-phenylstilbene | 17 |
| methyl acrylate | bis(acetoxymercuri)mesitylene | dimethyl (1,3,5-trimethylbenzene)-2,4-bis(3-acrylate) | 17 |
| methyl acrylate | 3,5-bis(chloromercuri)nitrobenzene | dimethyl 3-nitrobenzene-1,5-bis-(3-acrylate) | 18 |

**Scheme 49**




metal-catalyzed functionalization of organic compounds. In particular, a prominent role has been played by the addition of oxygen nucleophiles to an olefin. In this context, we must quote the impressive contributions of Bäckvall and co-workers[87] as well as the pioneering investigations of Hosokawa and Murahashi.[88]

Different types of C−O bonds may be formed depending on the nature of the nucleophilic reagent and of the solvent, which may also behave as nucleophile on its own account.

## 3.1. Alkoxylations

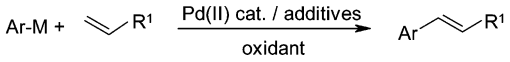
Nucleophilic attack on a carbon−carbon double bond by the OH group of alcohols or phenols results in an alkoxylation reaction. When the double bond bears an alkyl substituent, the oxypalladation intermediate may lead, through $\beta$-PdH elimination, to the formation of vinyl or allyl ether derivatives. Some authors called this functionalization a "Wacker-type" reaction or oxidation. Both intramolecular and intermolecular processes are reported in the present section.

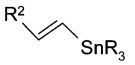
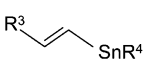
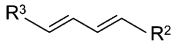
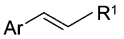
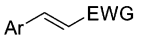
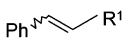
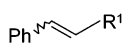
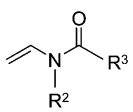
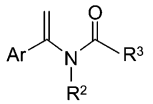
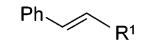
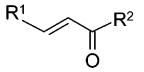
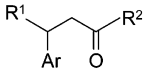
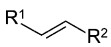
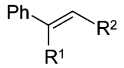
### 3.1.1. Intramolecular Reactions Involving Phenols

Pioneering work on C−O bond formation in Pd(II)-catalyzed intramolecular processes is due to Hosokawa and co-workers, who reported the cyclization of 2-allylphenols to yield oxygen-containing heterocycles. However, the regioselectivity of the process to generate five- or six-membered rings was largely dependent on the nature of the Pd(II) salt (Scheme 58).[89] The presence of sodium salts of carboxylic acids bearing electron-withdrawing substituents resulted in predominant formation of the six-membered products.

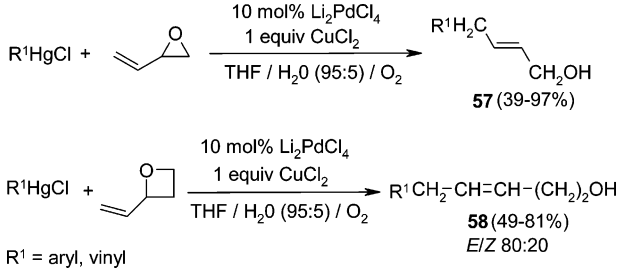
3,4-Dihydro-2-vinyl-2*H*-1-benzopyran was readily obtained by Pd(II)-catalyzed cyclization of 2-(*trans*-3-pentenyl)-phenol with $Cu(OAc)_2/O_2$ as oxidant.[90] The intramolecular oxypalladation of 2-allylphenols to yield benzofurans and their 2,3-dihydro-derivatives was achieved with catalytic amounts of $Pd(OAc)_2$ or $PdCl_2$ in the presence of $O_2$.[91] Products could be obtained in optically active form when working in the presence of $\beta$-pinene or (1*R*,5*R*)-2(10),3-pinadiene, generating in situ $\eta^3$-pinanylpalladium complexes **68** (Scheme 59). The 2-(*trans*-2-butenyl)phenols **67** led to

**Scheme 50**

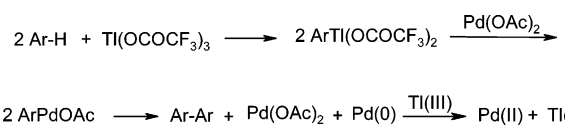



| Ar-M | substrate | Pd(II) cat /additives | oxidant | product | ref. |
|---|---|---|---|---|---|
| $Ph_3Bi$ | - | $Pd(OAc)_2$ | air | Ph-Ph | 75 |
| $R^1SnBu_3$ | - | $Pd(OAc)_2$ | $CuCl_2$ | $R^1$-$R^1$ | 73b |
| $ArSnBu_3$ | - | $Pd(OAc)_2$ | $CuCl_2$ | Ar-Ar | 73b |
| $ArSnBu_3$ | - | $PdCl_2(CH_3CN)_2$ | Ph-ACDB | Ar-Ar | 77 |
| $ArB(OH)_2$ | - | $PdCl_2$(dppb) | Ph-ACDB | Ar-Ar | 77 |
| $ArSiF_2$ | - | $PdCl_2(PEt_3)_2$ | $Me_2$ACDB | Ar-Ar | 77 |
|  |  | $Pd(OAc)_2$ | $t$-$BuO_2H$ |  | 73a |
| $ArB(OH)_2$ |  | $Pd(OAc)_2$ | $Cu(OAc)_2$ |  | 74b |
| $ArB(OH)_2$ |  | $Pd(OAc)_2$ | $O_2$ |  | 74a |
| $PhSnBu_3$ |  | $Pd(OAc)_2$ | $O_2$ |  | 73d |
| $PhSnBu_3$ |  | $Pd(OAc)_2$/LiOAc | $Cu(OAc)_2$ |  | 73c |
| $ArB(OR)_2$ |  | $Pd(OAc)_2$ | $O_2$ |  | 74d 74g |
| $ArB(OR)_2$ |  | $Pd(OAc)_2$ | $O_2$ |  | 74c |
| $PhB(OH)_2$ |  | $Pd(OAc)_2$/LiOAc | $Cu(OAc)_2$ |  | 74e |
| $Ar_3Sb$ |  | $Pd(OAc)_2$ | AgOAc |  | 76a |
| $Ph_2SbCl$ |  | $Pd(OAc)_2$ | air |  | 76b |

**Scheme 51**

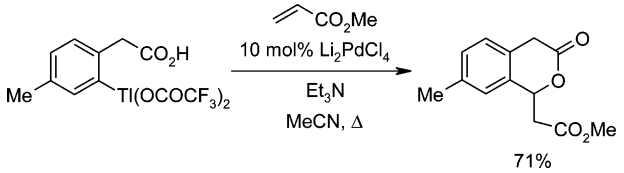



**Scheme 52**




the predominant formation of *S*-(+)-2,3-dihydro-2-vinylbenzofurans (*S*)-**69**, while the *cis* isomer **70** gave (*R*)-**69** as the prevailing enantiomer, although the heterocyclization took place with a low degree of enantioselectivity (up to 29% ee). A catalysis of not forming Pd(0) from Pd(II) with TBHP or the $O_2$−$Cu(OAc)_2$ system was mentioned.[92] Substituted 2-methylbenzofurans were prepared from 2-allylphenols in the presence of $Pd(OAc)_2$ as catalyst and $Cu(OAc)_2$/LiCl as oxidant system in DMF as solvent.[93]

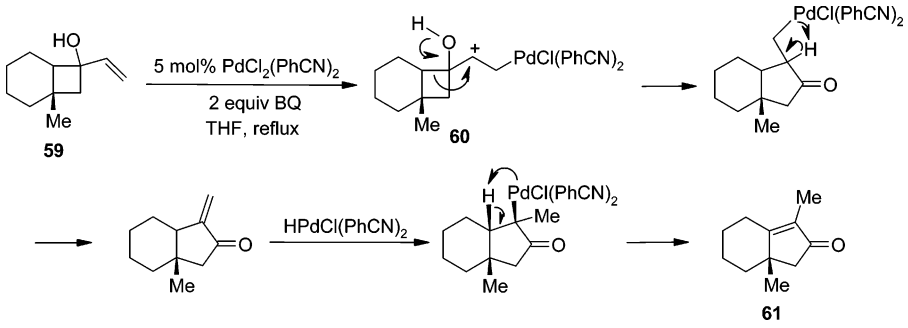
**Scheme 53**



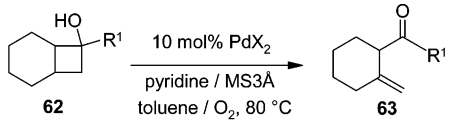

In a related study on the synthesis of optically active benzofurans **73**, Uozumi and co-workers improved the enantioselectivity of the cyclization of 2-allylphenols **71** up to 90−97% ee by the use of $Pd(OCOCF_3)_2$ as catalyst, coordinated with chiral BOXAX **72** based on the 1,1′-binaphthyl backbone (Scheme 60).[94] In 2004, the authors published deuterium-labeling studies aimed to unambiguously clarify the stereochemistry of the oxypalladation step. The cyclization key step takes place with a predominantly *syn*-stereochemistry with regard to palladium and oxygen in the absence of chloride ion, while the outcome is mainly anti in the presence of chloride.[95]

The same products were formed in excellent yields in the presence of 10 mol % $Pd(OCOCF_3)_2$, $Ca(OH)_2$, and MS3 Å in toluene at 80 °C under $O_2$ atmosphere (Scheme 61).[96] In particular, a high degree of enantioselectivity (90% ee) was obtained in the presence of (−)-sparteine **74**.

**Scheme 54**

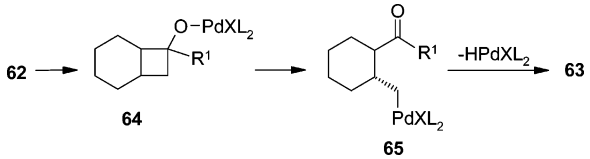



**Scheme 55**

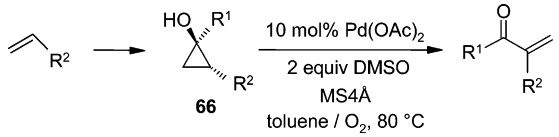



| $R^1$ | time (h) | Pd(II)-catalyst | yield % |
|---|---|---|---|
| vinyl | 20 | $Pd(OAc)_2$ | 56 |
| Ph | 48 | $Pd(OAc)_2$ | 60 |
| Ph | 16 | $PdCl_2(MeCN)_2$ | 97 |
| Bu | 38 | $PdCl_2$(dppb) | 71 |

**Scheme 56**

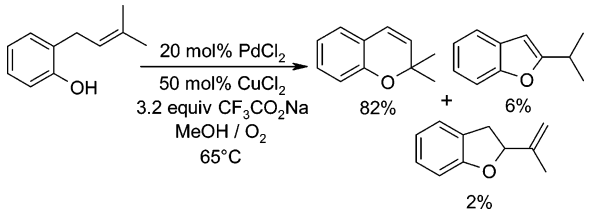



**Scheme 57**



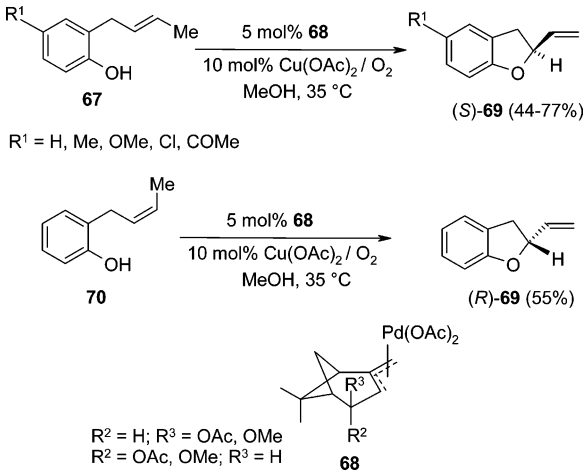

| $R^1$ | $R^2$ | yield % |
|---|---|---|
| Me | $-(CH_2)_2OTIPS$ | 75 |
| $c$-$C_6H_{11}$ | $-(CH_2)_2OTIPS$ | 11 |
| 1-cyclohexenyl | $-(CH_2)_2OTIPS$ | 7 |

**Scheme 58**

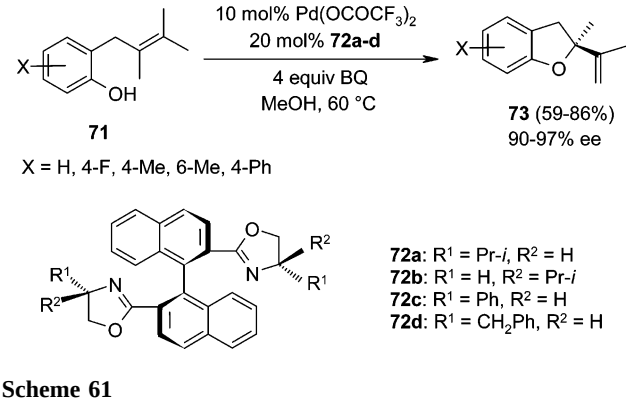



Recently an alternative intramolecular cyclization of 2-allylphenols was reported by Muñiz (Scheme 62).[97] 2,3-Dihydrobenzofurans can be obtained in high yields by Pd(II)−carbene catalysts **75** derived from in situ complexation of NHC **76** to $Pd(OCOCF_3)_2$. In all cases, the following requirements hold: (i) a basic reaction medium to maintain catalyst activity and (ii) an $O_2$ atmosphere to ensure catalyst reoxidation.

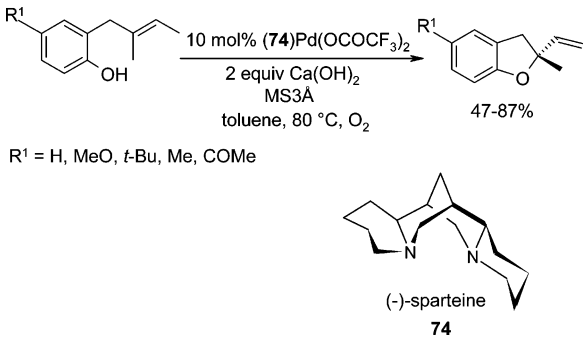
**Scheme 59**




**Scheme 60**

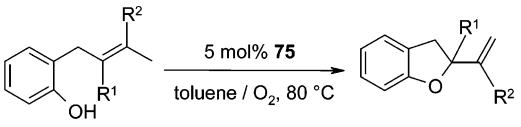



**Scheme 61**

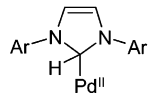



Larock and co-workers described a highly regioselective procedure by which 2-allylphenols **77** were heterocyclized to 2*H*-1-benzopyrans **78** (Scheme 63).[98] The use of $Pd(dba)_2$ as catalyst, in addition to $KHCO_3$ in DMSO/water, determined the attack on the terminal olefinic carbon: air sufficed to reoxidize the catalyst to Pd(II). When electron-deficient

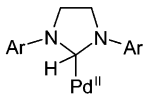
**Scheme 62**



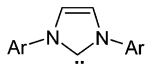

| R¹ | R² | catalyst | yield % |
|---|---|---|---|
| H | Me | **75a** | 91 |
| H | Me | **75b** | 92 |
| Me | H | **75a** | 92 |
| Me | Me | **75a** | 96 |
| H | H | **75a** | 89 |
| Me | H | **75c** | 87 |
| Me | Me | **75c** | 88 |



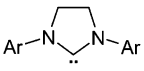
**75a**: Ar = mesityl
**75b**: Ar = 2,6-diisopropylphenyl



**75c**: Ar = 2,6-diisopropylphenyl



**76a**: Ar = mesityl
**76b**: Ar = 2,6-diisopropylphenyl



**76c**: Ar = 2,6-diisopropylphenyl

**Scheme 63**


**77** **78**

| R¹ | R² | R³ | R⁴ | R⁵ | R⁶ | R⁷ | yield % |
|---|---|---|---|---|---|---|---|
| H | H | H | H | H | H | H | 80 |
| Me | H | H | H | H | H | H | 74 |
| H | H | Me | H | H | H | H | 80 |
| H | Me | Me | H | H | H | H | 72 |
| H | H | Ph | H | H | H | H | 65 |
| Ph | H | H | H | H | H | H | 59 |
| H | H | H | Me | H | H | H | 65 |
| H | H | H | H | OMe | H | H | 71 |
| H | H | H | H | Ac | H | H | 23[a] |
| H | Me | Me | H | CN | H | H | 41[a] |
| H | Me | Me | H | OMe | OMe | H | 42 |
| H | H | H | H | H | —(CH=CH)— | | 77 |
| H | Me | Me | H | H | —(CH=CH)— | | 28 |

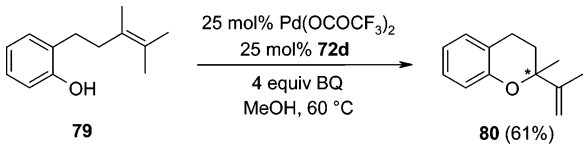
[a] 5 mol% $Pd(OAc)_2$ is used in place of $Pd(dba)_2$

phenols were employed as starting materials, $Pd(OAc)_2$ proved a more suitable catalyst.

Under appropriate conditions, enantioselective cyclization of 2-homoallylphenol **79** gave 3,4-dihydro-2*H*-1-benzopyran **80** with a 97% ee, with its absolute stereochemistry being still undetermined (Scheme 64).[94a]

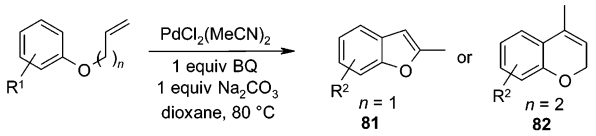
With $PdCl_2(MeCN)_2$ and BQ in dioxane, aryl allyl ethers cyclized to benzofuran derivatives **81** (Scheme 65).[99] According to the authors' hypothesis, a Claisen rearrangement of the Pd-complexed olefin occurred first to form an *o*-allylphenol, and then the Pd-coordinated olefin underwent

**Scheme 64**




**79** **80** (61%)
97% ee

**Scheme 65**




| *n* | R¹ | R² | $Pd(MeCN)_2Cl_2$ mol% | yield % |
|---|---|---|---|---|
| 1 | 3-hydroxy- | 6-hydroxy- | 5 | 45 |
| | | 4-hydroxy- | | 9 |
| 1 | 3-methoxy- | 6-methoxy- | 20 | 45 |
| | | 4-methoxy- | | 6 |
| 1 | 3,5-dimethoxy- | 4,6-dimethoxy- | 5 | 60 |
| 1 | 3,5-dimethyl- | 4,6-dimethyl | 25 | 49 |
| 1 | 3-hydroxy-2-methyl- | 6-hydroxy-7-methyl- | 10 | 49 |
| 1 | 3,4,5-trimethoxy- | 4,5,6-trimethoxy- | 5 | 66 |
| 2 | 3,5-dimethoxy- | 5,7-dimethoxy- | 5 | 72 |
| 2 | 3-methoxy- | 7-methoxy- | 25 | 61 |
| | | 5-dimethoxy- | | 1 |
| 2 | 3-hydroxy- | 7-hydroxy- | 20 | 54 |
| 2 | 3-hydroxy- | 5-hydroxy- | | 3 |
| 2 | 3-hydroxy-2-methyl- | 7-hydroxy-8-methyl | 20 | 39 |

a nucleophilic attack by the phenoxide anion; finally, $\beta$-hydride elimination from the $\sigma$-alkylpalladium complex completed the catalytic cycle. Under the same conditions, aryl homoallyl ethers gave substituted chromenes **82**.

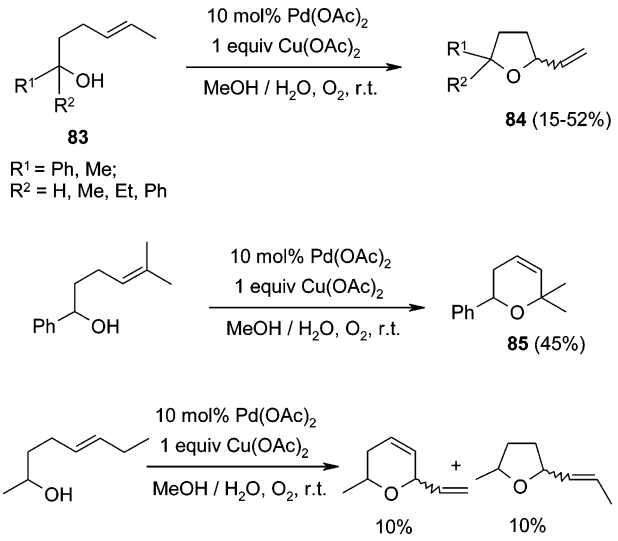
### *3.1.2. Intramolecular Reactions Involving Alcohols*

Ethylenic alcohols, eventually endowed with additional functionalities, are typically susceptible to Pd(II)-catalyzed intramolecular alkoxylation. In the case of alkadienols, because of the presence of the second ethylenic bond, the Pd(II)-catalyzed oxidative cyclization usually determines a double intramolecular/intermolecular functionalization. However, the second functionalization involves an external nucleophile so that it belongs to alkoxylations or acyloxylations depending on the use of an alcohol or a carboxylic acid, respectively, as the reaction solvent.

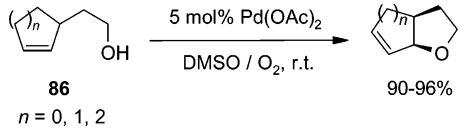
**3.1.2.1. Involving Alkenols.** In 1976, $\gamma,\delta$-unsaturated alcohols **83** were cyclized to a diastereoisomeric mixture of 2-vinyltetrahydrofurans **84** by the action of $Pd(OAc)_2$−$Cu(OAc)_2$ catalyst under $O_2$ atmosphere in $MeOH/H_2O$ at room temperature (Scheme 66).[100] However, the presence of two methyl groups in the $\delta$-position determined the formation of the six-membered ring product **85**. With one ethyl group in the same position, two regioisomeric products were obtained.

The Pd(II)-catalyzed intramolecular cyclization of cyclic alkenols **86** using molecular oxygen as oxidant provides a useful route to bicyclic unsaturated ethers (Scheme 67).[101] The most promising results were obtained when the substrate was allowed to react under $Pd(OAc)_2$ catalysis in $O_2$/DMSO at room temperature. The addition of LiCl or $K_2CO_3$ was found to inhibit the reaction.

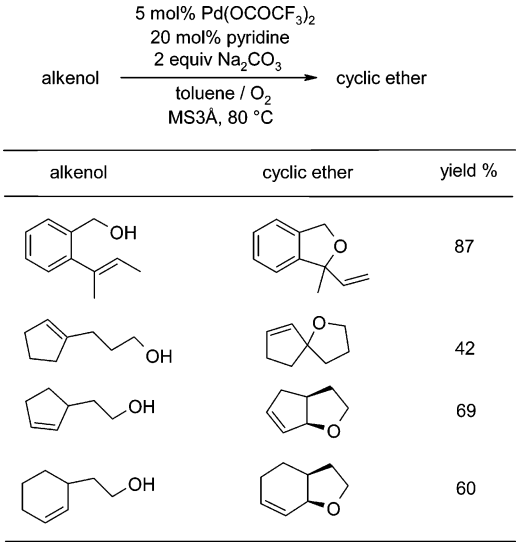
**Scheme 66**




**Scheme 67**




**Scheme 68**

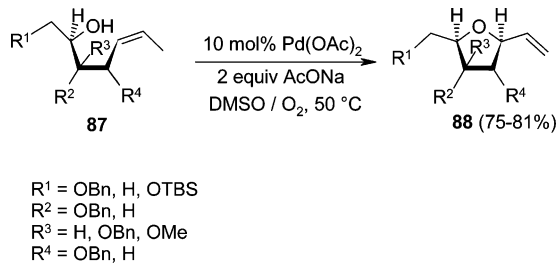



Besides phenols, Stoltz and co-workers investigated the oxidative cyclization of primary alkenols. Various substrates afforded cyclic ethers in moderate to excellent yields. Starting from cyclic alkenols, the final bicyclic products may be fused-ring or spiranic depending on the disposition of the ethylenic bond with respect to the hydroxyl (Scheme 68).[96] In agreement with reports from Hayashi et al. on related systems,[95] deuterium labeling studies confirmed a *syn*-oxypalladation mechanism.[96b]

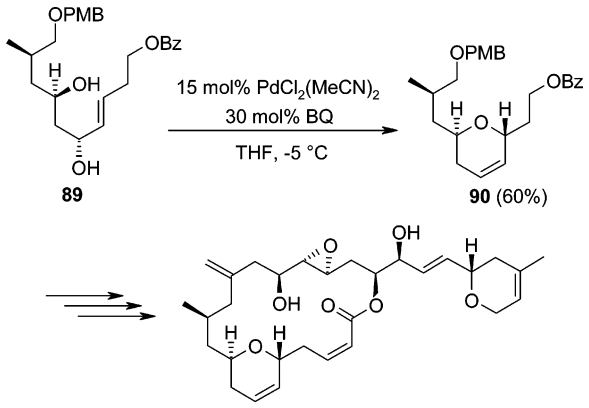
An intramolecular oxidative cyclization protocol, using the $Pd(OAc)_2/NaOAc/O_2$ system in DMSO, has been developed for the efficient conversion of sugar-derived $\gamma,\delta$-unsaturated alcohols **87** to *C*-vinyl furanosides **88** (Scheme 69).[102]

A similar strategy was applied to the stereospecific construction of the 3,6-dihydro[2*H*]pyran unit of (−)-laulimalide (Scheme 70).[103] In the presence of 15 mol % $PdCl_2(MeCN)_2$ and BQ in THF, the enantiopure unsaturated

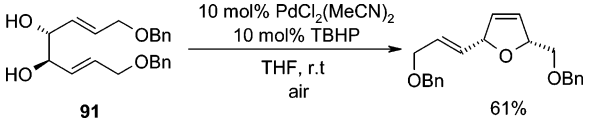
**Scheme 69**




**Scheme 70**




**Scheme 71**




diol **89** underwent ring formation in a 6-*endo*-trig fashion to give the desired *trans*-2,6-disubstituted pyran **90**. The cyclization of **89** occurred through a *syn* $S_N2'$ process where the hydroxy group attacks the *re* face of the olefinic carbon atom to form the *trans*-(*R*)-dihydropyran ring. Likely, a $\pi$-allyl intermediate should be involved in the reaction mechanism, as suggested in related papers.[104]

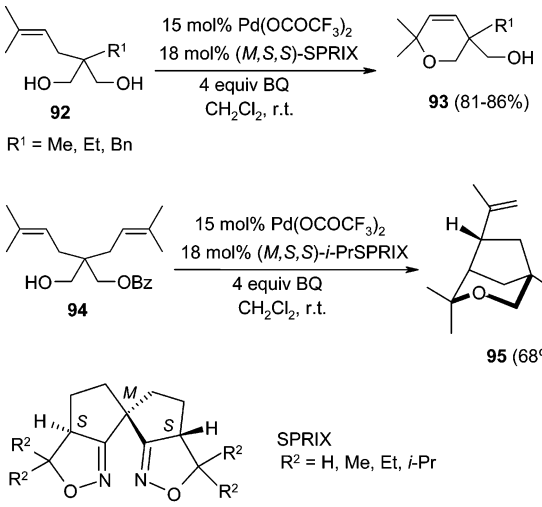
A Pd(II)-catalyzed dehydroxylative heterocyclization process to yield optically active 2,5-dihydro-furans was also observed in the case of substrate **91** and similar compounds (Scheme 71).[105]

A catalytic system based on SPRIXs and $Pd(OCOCF_3)_2$ promoted the asymmetric Wacker-type cyclization of alkene-diol **92** in the presence of BQ in $CH_2Cl_2$ to give 6-endo-cyclized product **93** in good yield and moderate ee (Scheme 72).[106] Under the same conditions, tandem cyclization via oxypalladation of substrate **94** resulted in bridged product **95** in 95% ee. MeOH as a solvent increased the yield of **95**, although its ee was slightly decreased.

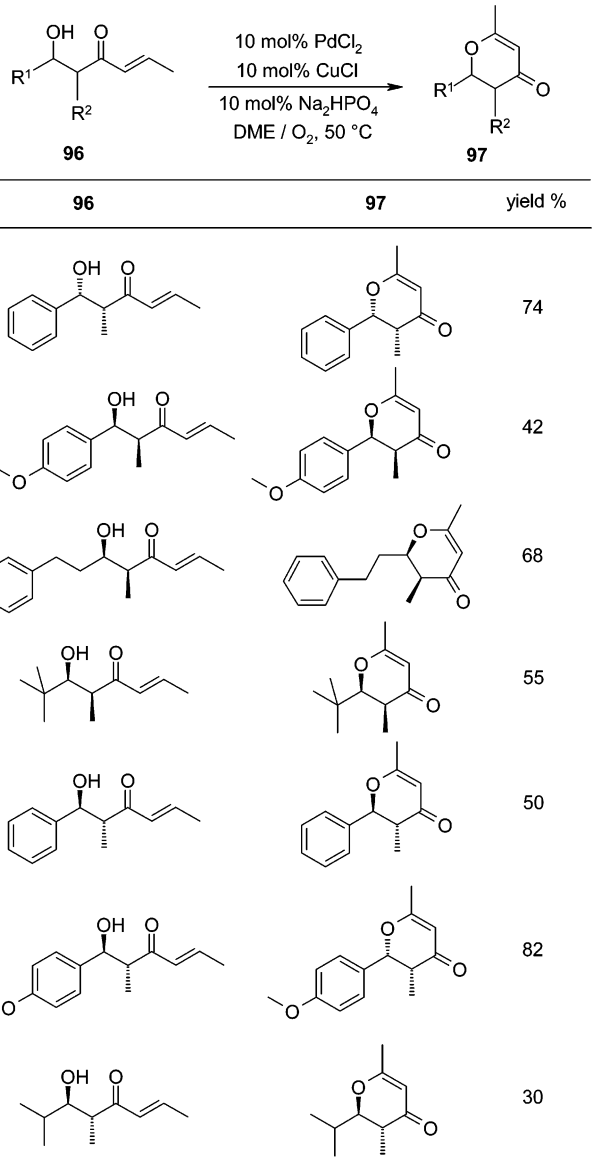
The cyclization of $\beta'$-hydroxy $\alpha,\beta$-unsaturated ketones by the combined use of 10 mol % $PdCl_2$, $O_2$, CuCl, and $Na_2HPO_4$ was reported. By this procedure, enantiopure enones **96** were transformed into 2,3-dihydro-4*H*-pyran-4-ones **97** without loss of optical purity (Scheme 73).[107] In analogous conditions, achiral $\alpha'$-hydroxy-$\alpha,\beta$-unsaturated ketones cyclized to furan-3(2*H*)ones. The peculiar behavior of dihydroxyenone **98**, which yielded regioselectively compound **99**, must be noted (Scheme 74).[107b]

Treatment of $\alpha$-alkenyl $\beta$-diketones **100** with a catalytic amount of $PdCl_2(MeCN)_2$ and a stoichiometric amount of $CuCl_2$ in dioxane at 60 °C afforded 2,3,5-trisubstituted furans **101** in moderate to good yields (Scheme 75).[108] The oxidative

**Scheme 72**



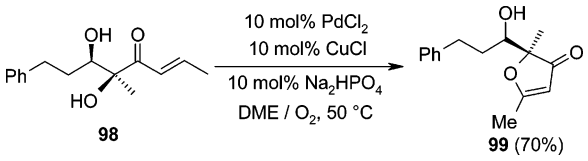

**Scheme 73**



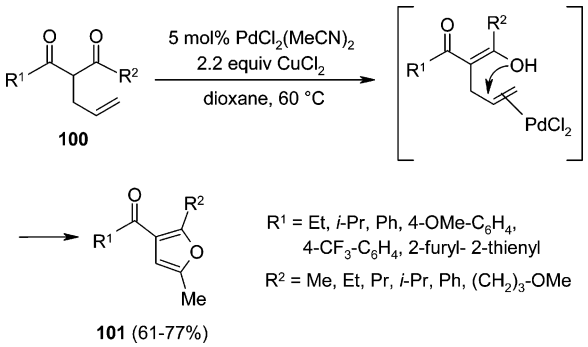

alkoxylation is possible through the enolic form of the substrate that behaves as an alkenol.

An application of the classical Wacker-type oxidation conditions (i.e., $PdCl_2$, $CuCl_2$, and $O_2$ in DMF−water)

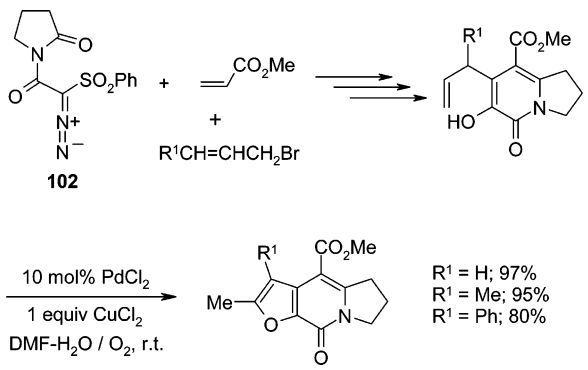
**Scheme 74**



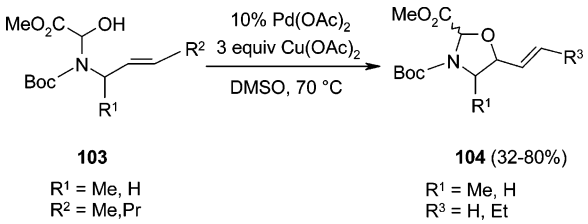

**Scheme 75**




**Scheme 76**




**Scheme 77**

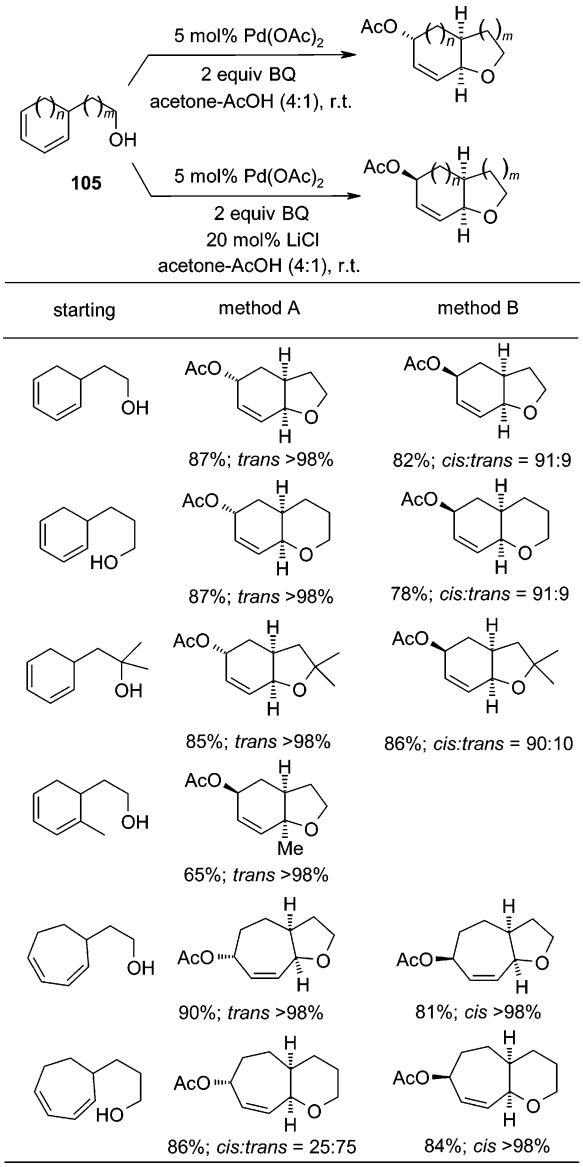



provided an efficient access to a furan ring assembled to an indolizinone core (Scheme 76). The starting bicyclic system was built from methyl acrylate and 2-pyrrolidinone **102** through a Rh(II)-catalyzed 1,3-dipolar cycloaddition.[109]

Finally, oxazolidines **104** were synthesized through oxypalladation and subsequent $\beta$-hydride elimination of 2-aza-4-alkenols **103** (Scheme 77).[110] With $Pd(OAc)_2$ as catalyst and an excess of $Cu(OAc)_2$ as oxidant in DMSO, only 5-*exo*-cyclization took place in good yield. In order to improve the oxidation step, the authors investigated the use of molecular oxygen as a clean alternative to $Cu(OAc)_2$.[111] DMSO plays an essential role in the process as stabilizing ligand of the giant palladium clusters.[112]

**3.1.2.2. Involving Alkadienols.** A number of fused tetrahydrofurans were readily obtained by stereocontrolled Pd(II)-catalyzed 1,4-additions from 1,3-cyclodienes **105** bearing a 2-hydroxyalkyl chain in the presence of 5 mol % $Pd(OAc)_2$, BQ, acetone, and AcOH as solvent (Scheme 78).[113] The overall stereoselective outcome is determined by

**Scheme 78**



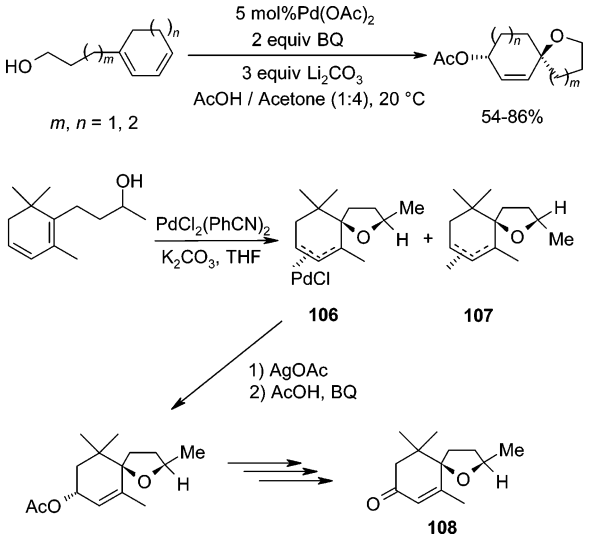

the presence or absence of LiCl. In its absence, a *trans*-acetoxylation product is formed, while its presence in a 20% ratio promotes the formation of a *cis*-acetoxylation product. The addition of 2 equiv of LiCl resulted in the incorporation of chloride as nucleophile instead of the acetoxy group. A similar behavior was found when 3-hydroxyalkyl-1,3-cycloalkadienes were used for the stereoselective synthesis of fused tetrahydropyrans.[114]

Cyclic dienes bearing the hydroxyalkyl substituent in position 1 yield oxaspirocyclic systems with high regio- and stereoselectivity, as illustrated in Scheme 79.[115] Spirocyclization was applied to the total synthesis of theaspirone (**108**); in this instance, two diastereoisomeric $\pi$-allyl complexes (**106** and **107**) were isolated.

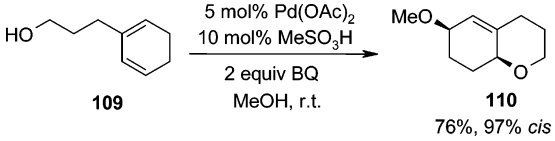
Intramolecular/intermolecular 1,4-dialkoxylation of 2-(hydroxyalkyl)-1,3-cyclohexadienes was described by Bäckvall and co-workers[116] working in methanesulfonic acid and the appropriate alcohol, as shown in Scheme 80 for the conversion of dienol **109** to compound **110**.

Bäckvall's protocol, carried out in the presence of a $RCO_2X$ species, determined the oxypalladation/cyclization of 5-(2-hydroxyethyl)-1,3-cyclohexadiene to bicyclic products **111** (Scheme 81).[117] Their *cis/trans* ratio depended on

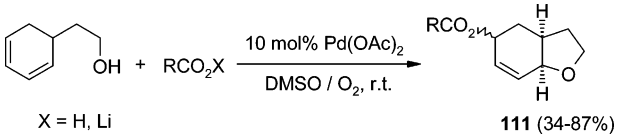
**Scheme 79**




**Scheme 80**




**Scheme 81**




the $RCO_2X$ species. Carboxylic acids generally favored a *cis* product, while their salts favored the *trans* isomers.

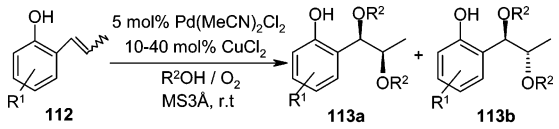
### *3.1.3. Intermolecular Reactions*

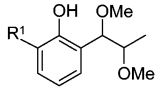
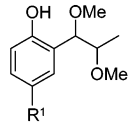
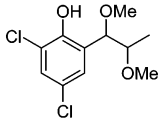
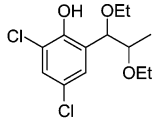
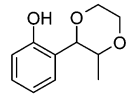
Intermolecular Pd(II)-catalyzed dialkoxylation of *o*-hydroxystyrenes was reported by Schultz and Sigman in 2006. A procedure based on the use of 5 mol % $PdCl_2(MeCN)_2$, 40 mol % $CuCl_2$, and MS3 Å in alcohol under $O_2$ atmosphere converted **112** to the diastereoisomeric products **113a** and **b** with an *anti/syn* ratio ranging from 1 up to 7.5 (Scheme 82).[118] Because the presence of the phenol moiety was found to be essential for the dialkoxylation to occur, the observed outcome was attributed to nucleopalladation at the styrene $\beta$-carbon, after which a second equivalent of MeOH attacks a quinone methide species, as shown in Scheme 83.

The same authors disclosed a mild aerobic hydroalkoxylation of *o*-hydroxystyrenes, performed with 5 mol % $PdCl_2$(sparteine), 20 mol % $CuCl_2$, and MS3 Å at 35 °C under $O_2$ atmosphere in ethanol. When the same process was carried out on *o*-vinylphenols, these substrates proved to be more reactive, allowing the use of lower catalyst loadings.[119]

The reaction of 1,3-dienes with 5 mol % $Pd(OAc)_2$ and excess BQ, carried out in an alcoholic solvent, afforded 1,4-dialkoxy-2-alkenes (Scheme 84).[120] The reaction was highly regio- and stereoselective for both cyclic and acyclic systems. Internal acyclic dienes gave 1,4-dialkoxylations with the (*E*)-double bond formation. Trifluoroacetate in combination with acetate or alcohols was utilized to obtain 1,4-acetoxytrifluoroacetoxylation and 1,4-alkoxytrifluoroacetoxylation.

**Scheme 82**




| product | R¹ | yield % | a:b |
|---|---|---|---|
|  | H | 70 | 4.5 : 1 |
| | Me | 70 | 6 : 1 |
|  | Me | 62 | 4.5 : 1 |
| | Cl | 63 | 3.8 : 1 |
|  | | 72 | 3.8 : 1 |
|  | | 50 | 2.9 : 1 |
|  | | 43 | 7.5 : 1 |

This reaction can be made enantioselectively by the use of a chiral benzoquinone catalyst (Scheme 85).[8a,121]

## 3.2. Acyloxylations

The use of carboxylic acids as nucleophiles on the double carbon−carbon bond results in acyloxylation (acetoxylation when acetic acid is used). Subsequent, fast palladium hydride elimination at room temperature leads not to vinyl esters but typically to allylic esters or lactones. These products may arise via acyloxypalladation on the double bond or a $\pi$-allylpalladium intermediate, depending on the reaction conditions and the substrate structure.

### *3.2.1. Intramolecular Reactions*

Intramolecular cyclization to unsaturated lactones of a wide range of acyclic and cyclic, aliphatic, and aromatic alkenoic acids using $Pd(OAc)_2$ in DMSO in the presence of molecular oxygen has been reported by Larock and Hightower.[122] Generally, the protocol, when applied to 4- or 5-alkenoic acid, leads to $\gamma$- or $\delta$-lactones, respectively, because the hydroxyl group has a preference for linking to the internal olefinic carbon. A great variety of monocyclic, fused or bridged bicyclic, and spiroannulated lactones were obtained by this method. Representative examples are collected in Scheme 86. It is important to note that oxygen alone is a remarkably efficient oxidant under these reaction conditions.

Stoltz and co-workers subjected a series of carboxylic acids bearing an alkenyl moiety to the conditions used for phenols and alcohols (Scheme 87).[96] They obtained spirocyclic and fused-ring lactones in moderate to high yields. For some substrates (**114** and **115**), the addition of an inorganic base was found to be unnecessary. Only *cis* adduct was observed in the case of fused bicyclic lactones.

*Exo*-methylene butyrolactones can be synthesized in good yields from the appropriate 2-cycloalkenylacrylic acids using a catalytic amount of $Pd(OAc)_2$ with NaOAc in THF in the presence of molecular oxygen (Scheme 88).[123]

An effective application of the Pd-promoted lactonization of alkenoic acids is the key step in the synthesis of precursors of the vitamin $B_{12}$ C-ring.[124] Enolic lactone structures **117** were prepared in three steps by carrying out the intramolecular acetoxylation of **116** with $PdCl_2$ and $CuCl_2$ under $O_2$ atmosphere (Scheme 89).

This strategy was essential for building the $\gamma$-lactone ring of the interleukin-1$\beta$ inhibitors, EI-1941-1, -2, and -3.[125] The intramolecular carboxypalladation took place in the presence of a catalytic amount of $PdCl_2(PhCN)_2$ with BQ in THF at room temperature (Scheme 90). Under the same conditions, *o*-alkenylbenzoic acids cyclized to isocumarins in high yields (Scheme 91).[126]

The regioconvergent Pd(II)-catalyzed intramolecular acetoxylation of cyclopentenylacetic acids bearing a hydroxymethyl group afforded the versatile racemic lactone **121**, a building block for the synthesis of biologically active compounds such as iridoids and $F_2$-isoprostanes (Scheme 92).[127] Because of the easy availability of alkenoic acids **119** and **120** from $\delta$-lactone **118**, this synthetic sequence is a useful example of conversion from $\gamma$- to $\delta$-lactones. Under improved conditions (i.e., a combination of $Pd(OAc)_2$/$Cu(OAc)_2$ and 1.1 equiv of AcOH as a proton source under a stream of $O_2$ in MeOH/MeCN as solvent), the reaction ran smoothly at room temperature to give **121** in 60% yield, along with isomeric lactone **122** in 30% yield. The authors provided some evidence for the intervention of two mechanisms depicted in Scheme 93, involving an intramolecular 1,2-acyloxypalladation (path *1*, leading to **121**) and the formation of two $\pi$-allyl complexes (path *2*, leading to **121** through *2a* and **122** through *2b*). Very recently, the compound **121** was obtained in enantiopure form and exploited for the synthesis of (−)-preclavulone A.[128]

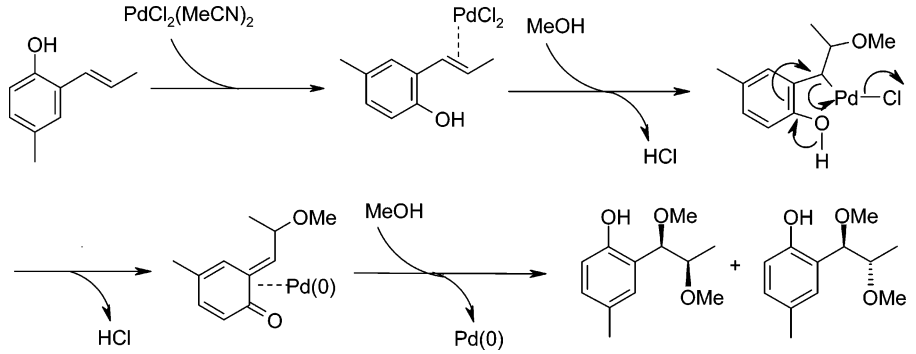
Intramolecular versions of the 1,4-oxidative functionalization of conjugated dienes bearing a carboxylic group have been developed. Bäckvall and co-workers demonstrated an intramolecular cyclization of cyclohexadienylacetic acid **123** to the corresponding acetoxylated *cis*-fused $\gamma$-lactone (Scheme 94).[129] This reaction, which is highly regio- and stereoselective, takes place by successive intramolecular and intermolecular nucleophilic attacks. First, the carboxylate attacks intramolecularly the palladium-complexed diene in *anti* fashion. This cyclization then generates a $\pi$-allylpalladium complex, which is attacked intermolecularly by acetic acid, leading to the observed stereochemistry. Manipulating the reaction conditions, to end up with either a *syn*- or *anti*-lactone, has elegantly controlled the intermolecular attack by acetic acid. This reaction has also been applied to the synthesis of natural products, i.e., paeonilactone A and B.[130]

In a more recent paper, the same research group reported the synthesis of acetoxylated $\delta$-lactones using an analogous protocol on 2-substituted 1,3-cycloalkadienes bearing a carboxylic group in the side chain. In this case, too, Pd complexation of the allylic substrates dictates the access to *cis*- or *trans*-substituted bicyclic systems (Scheme 95).[131] A benzoxylated $\gamma$-lactone was also synthesized.

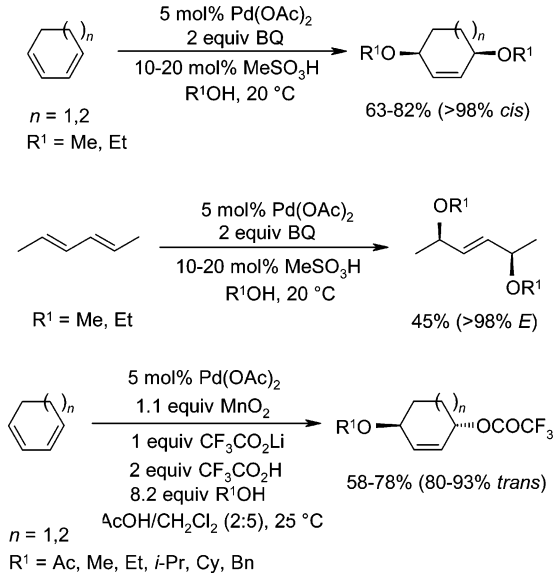
### *3.2.2. Intermolecular Reactions*

**3.2.2.1. Acyloxylation of Alkenes.** The $Pd(OAc)_2$ (5 mol %)/BQ (20 mol %)/$MnO_2$ (1.2 equiv) system is a synthetically useful tool for the allylic acetoxylation of olefins. In particular, five-, six-, seven-, and eight-membered cycloole-

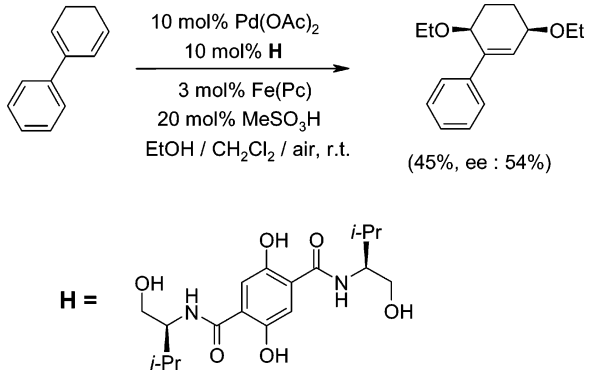
**Scheme 83**




**Scheme 84**




**Scheme 85**



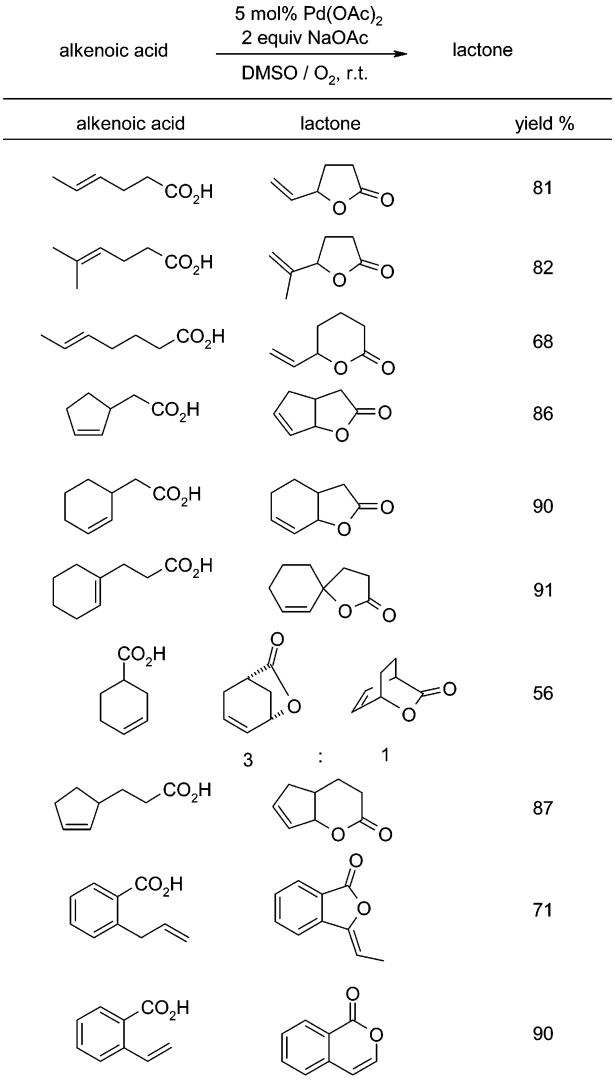

fins are oxidized to the corresponding allylic carboxylates (Scheme 96).[132] This catalytic system is also effective for the acyloxylation of alkenes and cycloalkenes.[133]

Working in AcOH and employing an aerobic three-component catalytic system with Co(salophen) as oxygen-activating catalyst, cyclohexene is quantitatively oxidized to 3-acetoxycyclohexene (Scheme 97).[8a]

Other metal−macrocycle oxygen-activating catalysts[134] or a heteropolyacid[135] can also be employed. Substituents and ring size strongly influence the reaction outcome. Larger rings often require longer reaction times, whereas substituents, with some exceptions, do not affect the reaction rate.[132a]

Allylic acetoxylation is normally carried out in acetic acid at moderate temperatures (50−60 °C), although reactions at

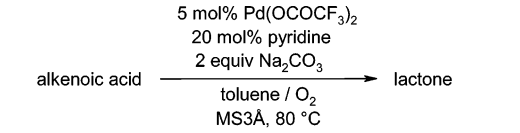
**Scheme 86**

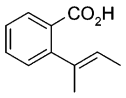
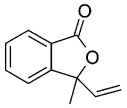
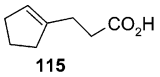
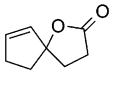
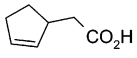
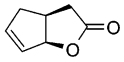
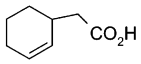
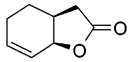



room temperature have been reported.[132a,b,136] By changing the solvent to $CH_2Cl_2$ and employing the desired carboxylic acid as a reagent, an allylic acyloxylation was achieved with $Pd(OAc)_2$ as catalyst and BQ as cocatalyst in the presence of hydrogen peroxide or TBHP as oxidant (Scheme 98).[137] Some years ago, other catalytic systems such as $Pd(OAc)_2$−BQ−$H_2O_2$ and $PdCl_2$−AgOAc−$TeO_2$−TBHP were reported for allylic acetoxylation of olefins.[138] Nitro-complexes of palladium(II) have also been used.[139]

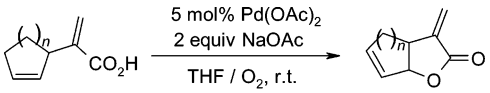
A very interesting development is an asymmetric reaction with chiral bimetallic palladium(II) complexes **124** by which

**Scheme 87**

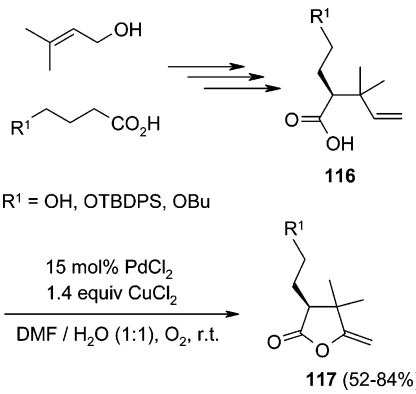



| alkenol | lactone | yield % |
|---|---|---|
|  **114** |  | 90 |
|  **115** |  | 62 |
|  |  | 77 |
|  |  | 86 |

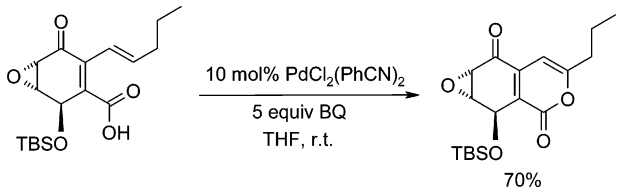
**Scheme 88**




**Scheme 89**




**Scheme 90**

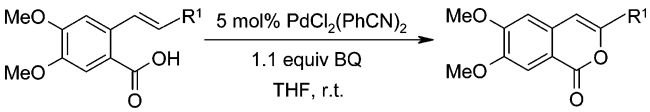


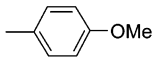
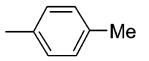
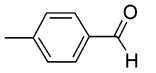

cyclohexene is oxidized to the corresponding allylic acetate with 52−55% ee (Scheme 99).[136]

The mechanism of quinone-based allylic acetoxylation has been studied using 1,2-dideuterated cyclohexene (Scheme 100).[140] After activation of the olefin by coordination to the metal (step i), removal of an allylic hydrogen leads to a ($\pi$-allyl)palladium intermediate (step ii).[141] The latter coordinates a BQ molecule and undergoes nucleophilic attack by the acetate at either allyl terminus to give the allylic acetate and Pd(0) (step iii).

In 2004, White reported an allylic acetoxylation of terminal alkenes using $Pd(OAc)_2$ as catalyst and BQ as reoxidant, where the novel bisulfoxide ligand **125** controls the regio-

**Scheme 91**




| $R^1$ | yield % |
|---|---|
| Ph | 97 |
|  | 84 |
|  | 63 |
|  | 61 |
| Bu | 83 |

and chemoselectivity of the process (Scheme 101).[142] Without **125** added, linear products were obtained, while the employment of **125** in $CH_2Cl_2$/AcOH switched the regioselectivity, to yield the branched product **126**.

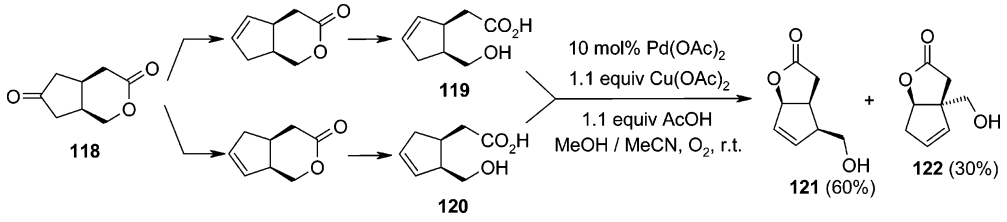
In a recent paper, Kaneda and co-workers described the regioselective acetoxylation of terminal alkenes to linear allylic acetates using molecular oxygen as oxidant in cocatalyst-free conditions (Scheme 102).[143] Olefinic substrates bearing two substituents at the allylic position undergo Pd(II)-catalyzed acetoxylation at the terminal sp² carbon.[144] Pd(II)-catalyzed allylic oxidation, using different catalytic systems, has been reported also on naturally occurring terpenes.[145]

**3.2.2.2. Acyloxylation of 1,3-Dienes.** Palladium-catalyzed 1,4-oxidative functionalizations of conjugated dienes make up a group of synthetically useful regio- and stereoselective transformations in which a wide range of nucleophiles can be employed. The reaction proceeds smoothly at room temperature in conditions that are much milder than those required for the related allylic acetoxylation of monoalkenes discussed in the previous section.

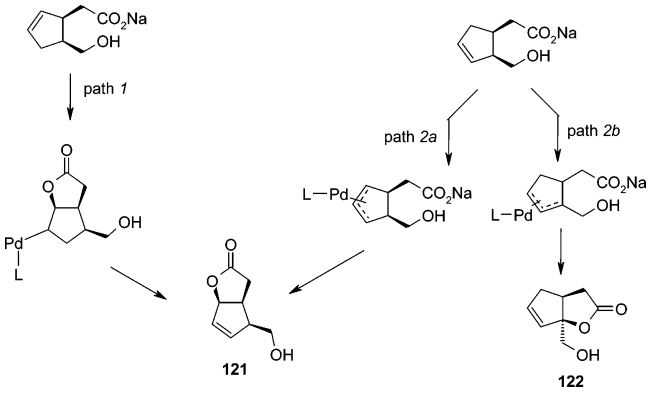
A catalytic reaction that gives high yields of 1,4-diacetoxy-2-alkenes was observed in acetic acid in the presence of lithium acetate and BQ.[8b,146] The reaction was highly regio- and stereoselective with both cyclic and acyclic dienes. The mechanism involves a *trans*-acetoxypalladation of the conjugated diene to give an intermediate ($\pi$-allyl)palladium complex followed by either *cis* or *trans* attack by acetate on the allyl group. Treatment of the complex with BQ in AcOH in the presence of LiCl and LiOAc afforded the *cis* product via an external trans attack by acetate. When the complex was pretreated with AgOAc (to remove chloride), the acetate attack occurred exclusively from the same face via internal *cis* migration (Scheme 103). LiCl seems to work by blocking the coordination of acetate and so inhibiting a *cis* migration pathway. The selectivity for the trans product in chloride-free conditions is further enhanced if the reaction is carried out in the presence of a sulfoxide cocatalyst.[147] When a chiral sulfoxide-substituted quinone catalyst was used, 2-phenyl-1,3-cyclohexadiene gave the corresponding *trans*-diacetate with an ee of 45%.[148]

BQ seems to act not only as an oxidant but also as a ligand. In fact, the attempt to replace it by other oxidants was ineffective. Best results were obtained with catalytic amounts of BQ in combination with equimolecular $MnO_2$ as external oxidant[8b] or molecular oxygen in association with Co-

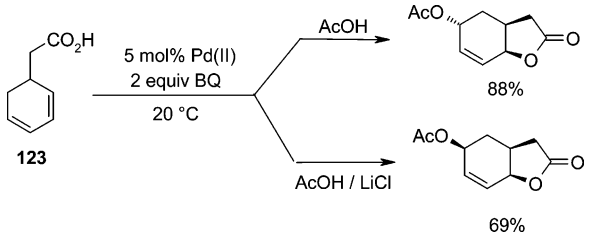
**Scheme 92**




**Scheme 93**




**Scheme 94**




(salophen), metalloporphyrins,[8c−e] or heteropolyacids as oxygen-activating catalysts.[8a,f,g] The BQ catalyst can also be reoxidized electrochemically.[149]

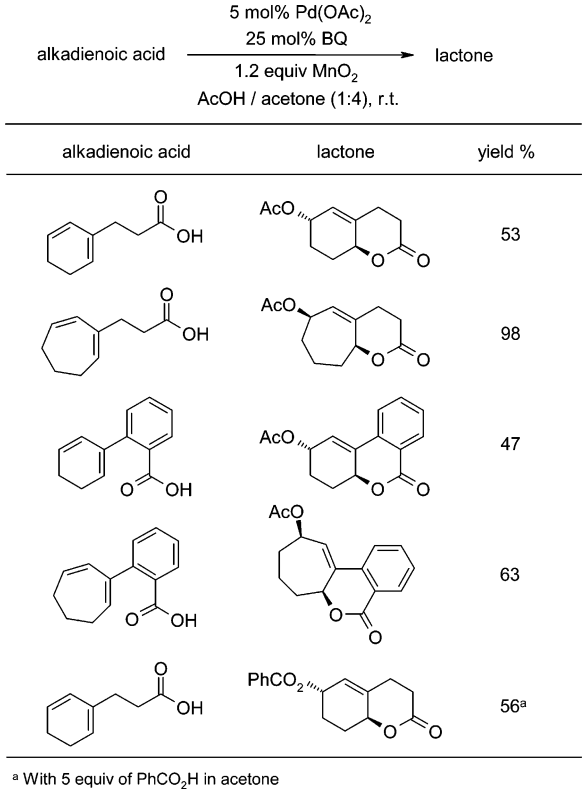
Several substituted cyclic 1,3-dienes have been studied to determine the scope of the reaction and the role of substituents on its stereoselectivity.[8b] With this method, 3,6-diacetoxy-4-cycloheptenol, an enantiopure intermediate for the synthesis of both enantiomers of the tropane alkaloids calystegines, was prepared.[150]

In 2003, Bäckvall and co-workers performed the Pd(II)-catalyzed 1,4-diacetoxylation of 1,3-dienes in the presence of a series of chiral ligands having a 9,10-dihydro-9,10-ethanoanthracene structure. Application of ligand **127** to 2-phenyl-1,3-cyclohexadiene afforded the diacetoxylation product with high regio- and diastereoselectivity and 42% ee (Scheme 104).[151]

## 3.3. Acetalizations

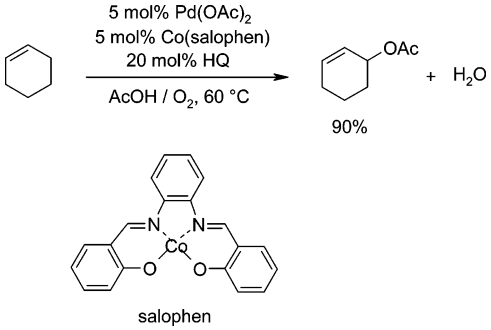
When the vinylic ether intermediate arising from the oxypalladation of an alkene undergoes a nucleophilic attack by an alcoholic function, acetals are formed. This is typically the case whenever oxypalladation is carried out with a diol, but alkenols can also yield acetals if a second alcohol is present in the reaction medium. Of course, both intramolecular and intermolecular processes are conceivable. Such chemistry strictly resembles the Wacker reaction, but more peculiar systems are formed in this protocol, particularly in intramolecular reactions potentially leading to ring-closed products.

**Scheme 95**




**Scheme 96**

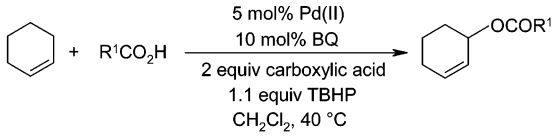

**Scheme 97**




### 3.3.1. Intramolecular Reactions

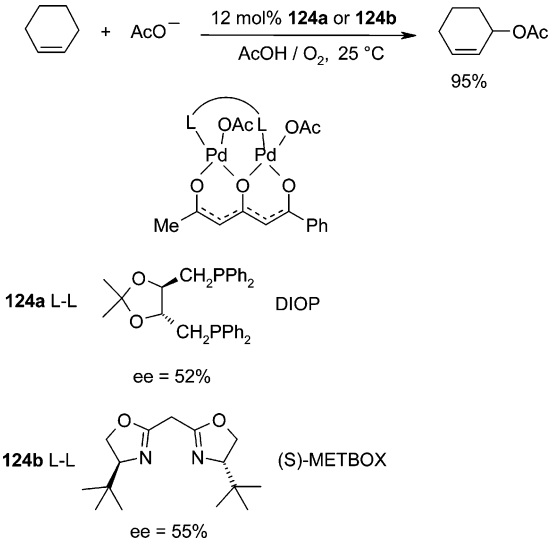
It seems advisable to state preliminarily that the oxypalladation of alkenols in the presence of an alcohol leads to cyclic acetals, while the oxypalladation of alkenediols

**Scheme 98**




| carboxylic acid | time (h) | yield % | catalyst |
|---|---|---|---|
| AcOH | 24 | 76 | $Pd(OAc)_2$ |
| $PhCO_2H$ | 13 | 77 | $Pd(OCOCF_3)_2$ |
| $p$-$NO_2$-$C_6H_4CO_2H$ | 12 | 82 | $Pd(OCOCF_3)_2$ |
| $p$-MeO-$C_6H_4CO_2H$ | 48 | 85 | $Pd(OAc)_2$ |
| cinnamic acid | 14 | 89 | $Pd(OCOCF_3)_2$ |
| $t$-$BuCO_2H$ | 64 | 65 | $Pd(OAc)_2$ |
| $PhCH(OAc)CO_2H$ | 14 | 82 | $Pd(OAc)_2$ |

**Scheme 99**




originates bridged-ring bicyclic acetals. The Pd(II)-catalyzed intramolecular cyclization of 2-(*p*-toluenesulfonyl)-3-alkenols **128** in methanol served to prepare several 2-methoxytetrahydrofurans **129** (Scheme 105).[152] A coordinating group in the allylic position was necessary to make oxidation selective. The best results were obtained when the cyclization was carried out using TMU to quench the HCl produced, together with EOA, anhydrous $CuCl_2$, and $PdCl_2$.

The diastereoselective cyclization of enantiomerically pure (2*S*,3*S*)-alkenols **130** in the presence of methanol with catalytic amounts of $PdCl_2(MeCN)_2$ and $CuCl/CuCl_2$ under $O_2$ afforded 2-methoxytetrahydrofurans **131** in 71−80% yields and 81−88% de (Scheme 106). The cyclization of (2*S*,3*S*)-dihydroxyalkene **132** gave diastereoselectively the bridged compound **133**.[153]

The oxidative cyclization of 1-alken-4-ols **134** to 2-*t*-butoxytetrahydrofurans by $PdClNO_2(MeCN)_2$ in the presence of $CuCl_2/O_2$ in *t*-butyl alcohol was described by Feringa and co-workers (Scheme 107).[154] The reaction also proceeded in the absence of a substituent in the allylic position.

Sturgess and co-workers reported the conversion of hydroxysubstituted α,β-unsaturated esters **135** to tetrahydrofuran derivatives **136**, which behave as protected β-ketoesters (Scheme 108).[155] The best results were obtained using a catalytic amount of $PdCl_2$ and a mixture of CuCl (3 equiv) and $CuCl_2$ (3 equiv) as reoxidant in the presence of LiCl and in methanol. It was found that either the use of less reoxidant or the omission of LiCl lowered the yield of **136**.

Alkoxysubstituted alkenols **137** and **138** underwent cyclization to hemiacetals **139** and **140**, which can be converted to *C*-glycosides (Scheme 109).[156] The optimized protocol, using $PdCl_2/CuCl/O_2$ in aqueous MeCN at room temperature, yielded five-membered heterocycles in good yields exclusively via 5-*exo*-mode cyclization.

Under the action of palladium(II) salts, alkenols also undergo Wacker-type oxidations to form hemiacetals. Nokami and co-workers showed that γ-butyrolactols could be obtained by the oxypalladation of 1-alken-4-ols using $PdCl_2$/BQ or $PdCl_2/CuCl_2/O_2$ in DMF at room temperature (Scheme 110).[157] The unsaturated alcohol requires a substituent in the allylic position; γ-butyrolactols are formed in 43−87% yields along with smaller amounts of hydroxyketone side-products.

Optically active morpholine-type acetals **142** and **143** were obtained in high yields from enantiopure *N*-allyl aminoalcohols **141** by making slight changes in the $Li_2PdCl_4/CuCl_2$ reagent system, as depicted in Scheme 111.[158]

An efficient synthetic sequence leading to (+)-buergerinin F (**146**) (a potential antiphlogistic agent) from α-hydroxy-γ-butyrolactone **144** involved an intramolecular Wacker-type acetalization of the intermediate alkenediol **145** as one of the key steps (Scheme 112).[159]

Unsaturated vicinal diols gave the corresponding cyclic bridged acetals by palladium(II)-catalyzed intramolecular cyclization.[160] *Threo*- and *erythro*-3,4-dihydroxy-8-nonene cyclized to *exo*- and *endo*-brevicomin in the presence of $PdCl_2$ and $CuCl_2$ (Scheme 113).[161] Likewise, the same catalytic system was used in the synthesis of frontalin in racemic[162] or enantiopure form[163] and promoted the key step in the synthesis of the macrolide antibiotic rosaramicin.[164]

### 3.3.2. Intermolecular Reactions

Palladium-catalyzed acetalization reactions were first achieved by treatment of olefins with diols by using $PdCl_2$ as catalyst in the presence of $CuCl_2$ as reoxidant.[165] The same catalytic system, with the addition of molecular oxygen, was used by Hosokawa et al. for the regioselective acetalization of terminal olefins bearing electron-withdrawing substituents (Scheme 114).[166] $Na_2HPO_4$ was used as an additive to prevent the formation of Michael-type adducts. A combination of $BiCl_3$ and LiCl can replace CuCl as efficient cocatalyst.[167]

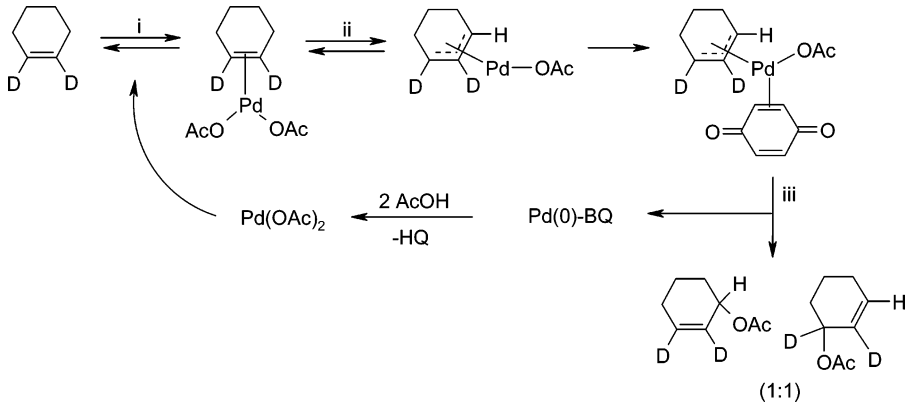
The process was also employed with optically active diols (Scheme 115).[166,168] When (*R*,*R*)-2,4-pentanediol **147** was used, homochiral cyclic acetals **148** were obtained in good yields.

The treatment of styrenes with 4 mol % Pd[(−)sparteine]-$Cl_2$, 5 mol % $CuCl_2$, and MS3 Å in alcoholic solvents at room temperature under $O_2$ atmosphere afforded Markovnikov acetals in high yields (Scheme 116).[169]

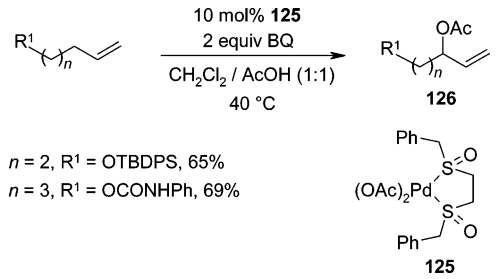
α-Cyanoallyl acetates were acetalized with $PdCl_2(MeCN)_2$, CuCl, and HMPA in oxygen atmosphere and DME as solvent to give useful intermediates for the synthesis of 2-cyanovinyl ketones (Scheme 117).[170]

The same catalyst/cocatalyst system promoted the oxidation of methyl acrylate to methyl 3,3-dimethoxypropanoate. This ran with high selectivity and conversion rate at lower temperature when supercritical carbon dioxide was used instead of DME as the reaction medium, with HMPA being omitted.[171]

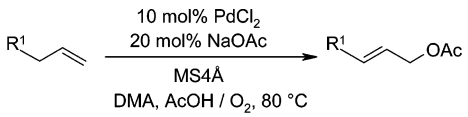
**Scheme 100**




**Scheme 101**




**Scheme 102**

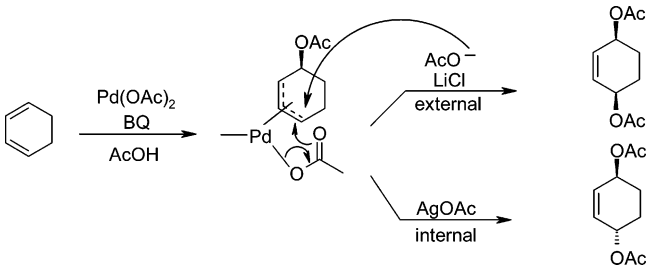



| $R^1$ | conv. % | *E* / *Z* | yield % |
|---|---|---|---|
| $C_7H_{15}$ | 86 | 1:1 | 86 |
| $C_{17}H_{35}$ | 93 | 2:1 | 90 |
| | 65 | 6:1 | 43 |
| $MeO_2C(CH_2)_4$ | 95 | 9:1 | 90 |
| NC | 85 | 8:1 | 80 |
| | 85 | >99:1 | 79 |
| | 85 | >99:1 | 85 |

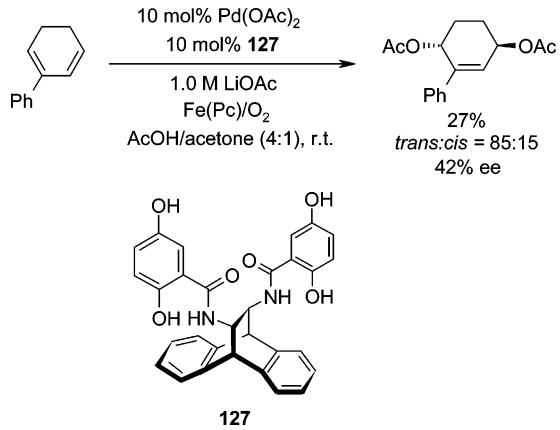
Asymmetric acetalization of methacryloyl derivatives **149**, bearing a 4-substituted oxazolidin-2-one unity as chiral auxiliary, opened a route to the enantiomers of 3-hydroxy-2-methylpropanal acetals (Scheme 118).[172] The best stereochemical result was achieved with $PdCl_2$ as catalyst in the presence of CuCl and oxygen atmosphere when $R^1$ = *t*-butyl, to give the corresponding acetal **150** in 95% de.

With 10 mol % $Li_2PdCl_4$, excess $CuCl_2$, and alcohol as solvent, oxypalladation of allylamines took place at the external terminal carbon of the double bond to give the corresponding acetals in good yields. The regioselectivity of the nucleophile attack is due to the directing influence of the heteroatom (Scheme 119).[173]

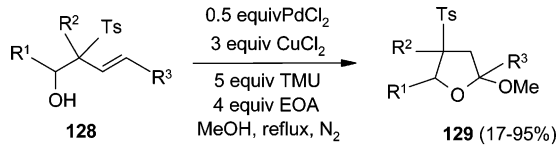
**Scheme 103**




**Scheme 104**




**Scheme 105**



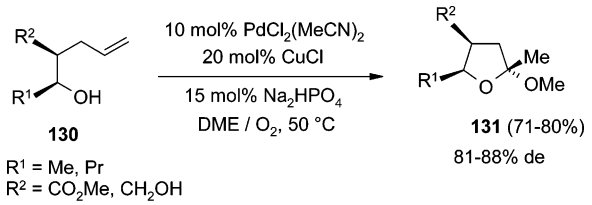

$R^1$ = H, Me, Ph, $Ph(CH_2)_2$-, Me-$(CH_2)_8$-, $Me_2CHCH_2$-
$R^2$ = H, Bn
$R^3$ = H, Me

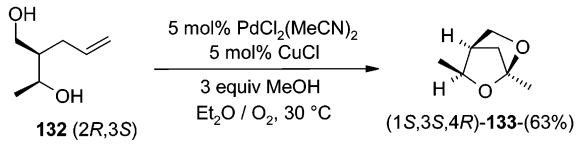
Palladium-catalyzed acetalization of 2-nitrostyrenes took place with alkyl nitrites in methanol under oxygen atmosphere and gave 2-nitrophenylacetaldehyde dialkyl acetals, whose reductive cyclization was exploited to synthesize indole derivatives in good yields (Scheme 120).[174]

## 4. C–N Bond Formation

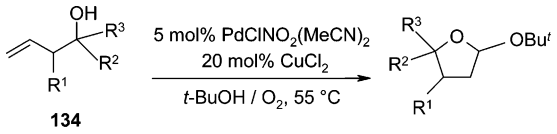
Palladium(II)-promoted nucleophilic addition of amino nitrogen to the carbon−carbon double bond results in oxidative amination. Activation of the substrate by coordina-

**Scheme 106**



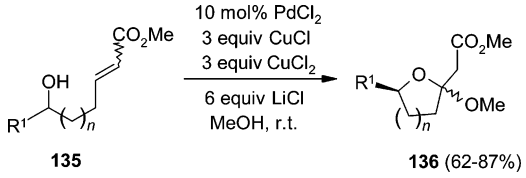




**Scheme 107**

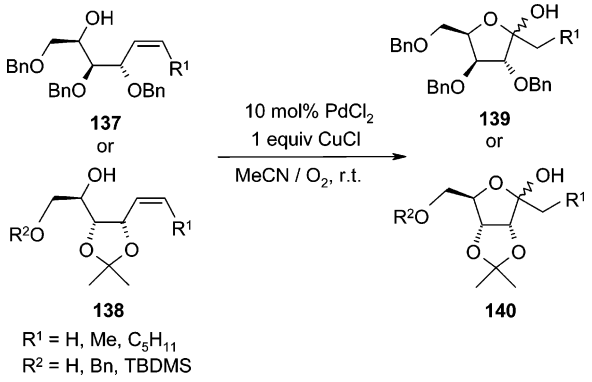



| R¹ | R² | R³ | yield % |
|---|---|---|---|
| H | H | H | 30 |
| H | Me | Me | 80 |
| H | Me | Et | 70 |
| H | Ph | Ph | 32 |
| Me | Me | Me | 70 |
| H | Me | $CO_2Et$ | 63 |
| H | Ph | $CO_2Et$ | >90 |

**Scheme 108**

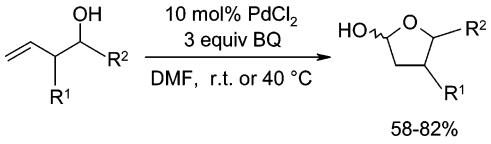



**Scheme 109**

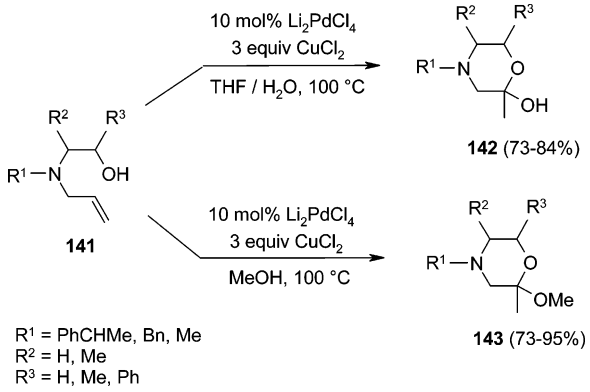



tion to palladium helps to overcome the repulsion between the $\pi$ bond and the lone electron pair on the nitrogen atom. As illustrated in Scheme 1, olefin coordination to electrophilic palladium(II) makes the carbon−carbon double bond susceptible to nucleophilic attack by the amino atom. The key intermediate in the overall process is the $\beta$-aminoalkylpalladium complex from which $\beta$-hydride elimination leads to the oxidative amination product, i.e., the unsaturated amine. Of course, the final step generates Pd(0), which must be reoxidized to Pd(II) if the catalytic cycle is to resume.

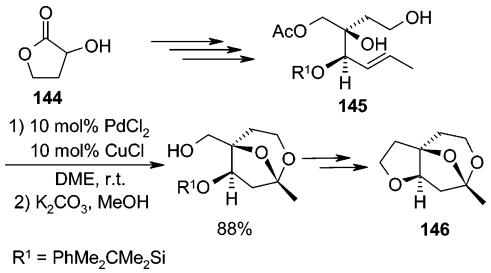
**Scheme 110**



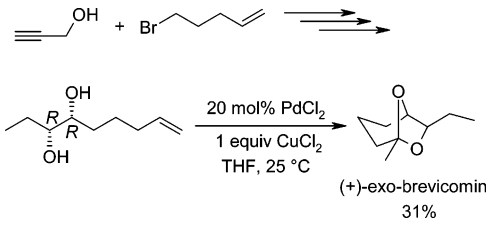

**Scheme 111**



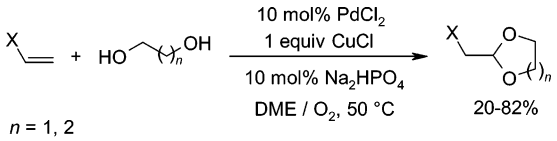

**Scheme 112**




**Scheme 113**




**Scheme 114**

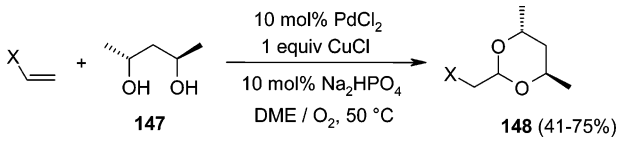



Although the term "amidation" is employed when the nitrogen atom of an amide acts as a nucleophile toward the Pd(II)-coordinated alkene to give vinyl amides, the term "amination" is also commonly used in these instances, so that the use of these terms may create some confusion. Consequently, in this section, we make no distinction between amination and amidation reactions.

The main features of these reactions are as follows:

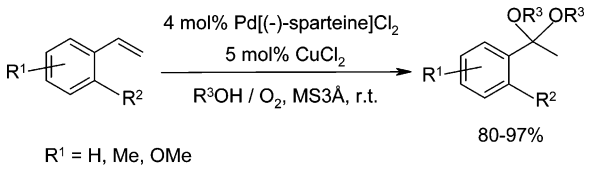
(a) Higher yields are obtained with less basic nitrogen atoms, namely, those of acylated or tosylated amines.

**Scheme 115**



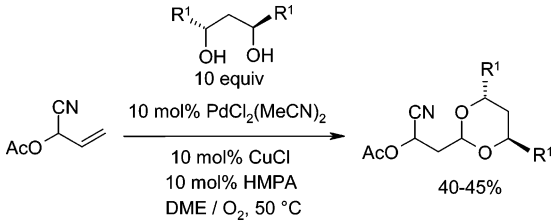

X = electron-withdrawing group

**Scheme 116**




R1 = H, Me, OMe
R2 = H, Me
R3 = Me, Et

**Scheme 117**




R1 = H, Me

(b) Electron-deficient $\pi$-systems are more prone to the nucleophilic addition of amines.

(c) Generally, between the two regioisomeric Markovnikov and anti-Markovnikov products, the latter is favored.

(d) Intramolecular oxidative amination is much easier than the corresponding intermolecular reaction.

(e) The catalytic system often requires the presence of a ligand, whose nature and concentration are crucial for the outcome.

(f) Recent studies show that the use of nitrogenated ligands has a significant effect on both catalytic efficiency and regioselectivity of reaction.

## 4.1. Intramolecular Reactions

A landmark in the field of aminopalladation reactions was laid by Hegedus and co-workers, who initially used stoichiometric amounts of Pd(II) and later turned to the use of catalytic amounts. Starting from 2-allylaniline derivatives **151**, he obtained indoles **152** using $PdCl_2(MeCN)_2$ or $PdCl_2$ in catalytic amounts and BQ in a stoichiometric amount as reoxidant (Scheme 121).[175] The degree of substitution determined several changes in the cyclization reaction. When $R^2$ was other than H, amination yielded preferably quinoline derivatives **153**. Cyclization of 2-crotylaniline under the standard conditions resulted in the exclusive formation of 2-methylquinoline, whereas 2-ethylindole was the sole product in the presence of excess LiCl. Very soon, Harrington and Hegedus noted that the electron-poor nitrogen of amides or sulfonamides gave better results in coupling reactions.[176]

A similar approach was afterward utilized by other authors for the preparation of indoles and isoquinolinones starting from *o*-vinylacetanilides and *o*-vinylbenzamides, respectively (Scheme 122).[177] In these cases, the cyclizations are formally amidation reactions. The same methodology served for the construction of an alkaloid skeleton such as that of bukittinggine, a *Daphniphyllum* alkaloid.[178]

Analogously, *N*-tosylated *o*-allylanilines **154** gave the different cyclization products **155**−**157**, depending on the reaction conditions (Scheme 123).[179] Catalyst stability and product yields were recently improved by the use of compounds in which Pd(II) was coordinated to NHC ligands such as IMes, IPr, or the seven-membered heterocyclic ring **158**. The reactions proceeded also with air rather than oxygen, provided that carboxylic acid cocatalysts such as AcOH or $PhCO_2H$ were employed.

A divergent synthesis of quinazolin-4-ones **160** and 1,4-benzodiazepin-5-ones **161** by Pd(II)-catalyzed intramolecular amidation of tosylated *N*-allylanthranilamides **159** was described (Scheme 124).[180]

As illustrated in part B of the Scheme 125, the intramolecular nucleophilic attack by the tosylated nitrogen to the $\pi$-olefin-Pd complex **163** led to compounds **161**. Conversely, the formation of **160** can be justified only by invoking the intermediacy of a $\eta^3$-allylpalladium complex **162**, in which the internal allylic carbon would undergo selectively the nitrogen attack, as depicted in part A of Scheme 125.

Carbazoles **165** were obtained from *o*-arylacetanilides **164** by combined C−H functionalization and C−N bond formation (Scheme 126).[181] A plausible reaction pathway shows the formation of a six-membered palladacycle from which reductive elimination leads to product and Pd(0). The latter was reoxidized to Pd(II) by $Cu(OAc)_2$, and the reduced Cu species was in turn reoxidized to Cu(II) by oxygen.

The intramolecular cyclization of 2-(1-silyloxyallyl)-anilines **166** gave 3-silyloxyindoles **167** (Scheme 127). Removal of the protecting group followed by trapping of the hydroxyl anion with alkyl halides afforded 3-alkoxyindoles.[182]

The same method was applied to the synthesis of 1*H*-pyrrolo[3,2-*b*]pyridines **168** starting from 2-(1-hydroxyallyl)-3-aminopyridines (Scheme 128).[183] Protection of the hydroxyl group with TBDMS group followed by treatment with Pd(II)/BQ gave the final products.

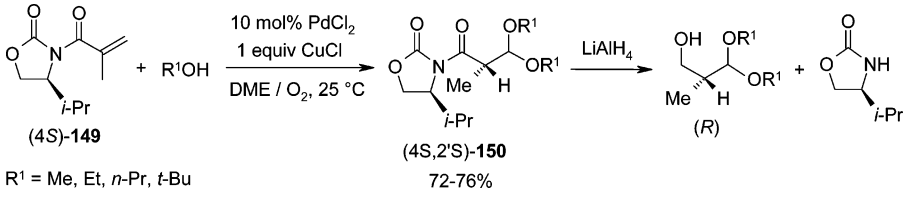
The peculiar allyl-substituted aminobenzoquinone **169** underwent a similar cyclization to give indoloquinone **170** (Scheme 129).[184]

Pyrazino[1,2-*a*]indole derivatives **172** were obtained in high yields through intramolecular amidation of 1-allyl-2-indolecarboxamides **171** (Scheme 130),[185] which plausibly proceeds by cyclization of a palladium-complex intermediate and subsequent double-bond isomerization.

Intramolecular amidation reactions of aminoalkenes have been reported. The starting aminoalkenes were first converted to the corresponding *p*-toluenesulfonamides **173**, which cyclized to *N*-tosylated cyclic enamines **174** (Scheme 131).[186] In general, six-membered rings were formed with more difficulty than five-membered ones.

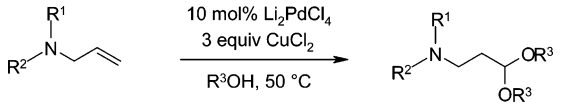
Other authors reported the cyclization of acyclic and cyclic olefinic *N*-tosylamines to give heterocycles containing an allylic nitrogen (Scheme 132).[101,187] The reaction was carried out in DMSO under an oxygen atmosphere, avoiding the use of other reoxidants. Mechanistic studies on the $Pd(OAc)_2$/$O_2$/DMSO catalytic oxidation system revealed that reoxidation of palladium by molecular oxygen was the turnover-limiting step of the catalytic cycle. Stahl and co-workers suggested that the presence of pyridine or other imine donor ligands would increase catalytic efficiency in oxidative amination reactions.[188] The catalytic system $Pd(OAc)_2$/pyridine (1:2) works well in a variety of solvents ranging

**Scheme 118**



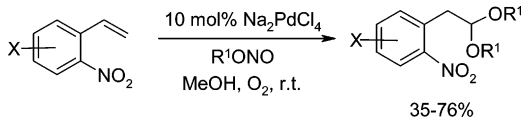

R¹ = Me, Et, *n*-Pr, *t*-Bu

**Scheme 119**



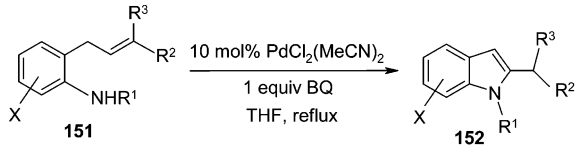

R¹ = Bn, Me, Et
R² = Bn, PhCHMe, Et
R³ = Me, Et, $(CH_2OH)_2$

**Scheme 120**




X = H, 4-OMe, 5-OMe, 4-Me, 4-$CO_2$Me, 4-Cl, 6-Me
R¹ = Me, Et, Bu, *t*-Bu

**Scheme 121**




| X | R¹ | R² | R³ | indole yield % | quinoline yield % |
|---|---|---|---|---|---|
| H | MeCO | H | H | 71 | - |
| 5,6-diOMe | H | H | H | 48 | - |
| 5-OMe | H | H | H | 32 | - |
| H | H | Me | H | - | **153a** (58) |
| H | H | Me | Me | | **153b** (54) |
| H | H | Me | H | 79[a] | - |

[a] In the presence of LiCl (10 equiv)

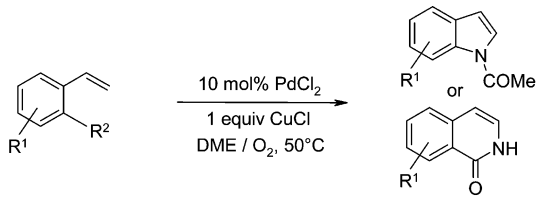

from nonpolar to polar, and the need for a cocatalyst is obviated to achieve efficient dioxygen-coupled turnover.

Nitrogenated heterocycles **175** and **176** were the cyclization products of hex-5-enylamine under Wacker-type conditions (Scheme 133).[189] Other alkenes bearing a primary or secondary amino group yielded the corresponding cyclic imines, while tertiary aminoalkenes led to aminoketones **177**.

Pyrrole derivatives were also formed from tosylated 2-hydroxy-3-butenylamines **178** (Scheme 134).[190] The hydroxyl group was essential for the cyclization reaction. No addition took place when $Pd(OAc)_2$ was used instead of $PdCl_2(MeCN)_2$. Actually, the chloride ion plays a crucial role in this cyclization by allowing the addition of $PdCl_2$ at C3−C4 followed by nucleophilic substitution of chlorine by nitrogen.

Tandem 1,4-additions involving the formation of two C−N bonds occurred with amides of alkadienoic acids. By varying

**Scheme 122**




| R¹ | R² | indole yield % | isoquinoline yield % |
|---|---|---|---|
| H | NHCOMe | 61 | - |
| 3-$CO_2$Me | NHCOMe | 67 | - |
| 5-Cl | NHCOMe | 64 | - |
| 5-Cl | $CONH_2$ | - | 85 |
| 3-Me | $CONH_2$ | - | 84 |
| 4-Me | $CONH_2$ | - | 90 |

the length of the tether between the conjugated unsaturations and the amide group, pyrrolizidine **179** or indolizidine **180** skeletons were formed (Scheme 135).[191]

Imidazolidine derivatives **182** were resulted from the cyclization of formaldehyde aminals **181** prepared from *N*-Boc-protected allylic amines, formaldehyde, and a nitrogen source (Scheme 136).[192] Standard oxidative cyclization conditions converted these substrates to the corresponding imidazolidines that may be easily transformed into vicinal diamines.

The first example of Pd-catalyzed cyclization of *O*-alkenyl-substituted hydroxylamines resulted in the formation of isoxazolidines (Scheme 137).[193] An electron-withdrawing group on the nitrogen was essential for the successful of the reaction.

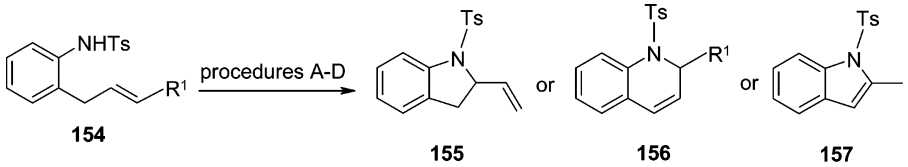
The peculiar rearrangement of isoxazolidine-5-spirocyclopropanes **183** to dihydro- **184** or tetrahydropyridones **185** was affected by reductive opening of the isoxazolidine ring to γ-aminocyclopropanol and subsequent domino Pd(II)-catalyzed ring opening/cyclization/oxidation (Scheme 138).[194] Moreover, the oxidation level of the products can be controlled by a mere change of catalyst.

## 4.2. Intermolecular Reaction

The intramolecular amination strategy described by Bozell and Hegedus was extended to the intermolecular reactions of substituted anilines **186** with electron-deficient olefins to yield β-arylamino α,β-insaturated ketones, esters, and nitriles (Scheme 139).[195] Interaction of conjugated enones with palladium was particularly sensitive to substitution, since the insertion reaction failed completely if the enone was substituted in either α or β position.

An efficient procedure for the preparation of enamides has been developed involving the reaction of primary amides with conjugate olefins (Scheme 140).[196] The preference for the formation of *Z*-enamides is presumably due to the

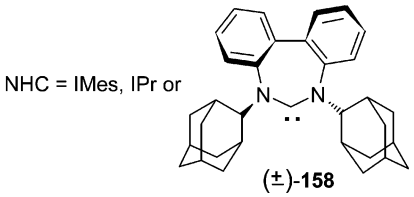
**Scheme 123**




**154** **155** **156** **157**

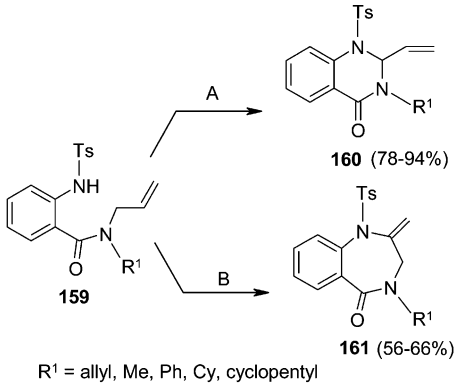
| $R^1$ | procedure | yield % **155** | yield % **156** | yield % **157** |
|---|---|---|---|---|
| H | A | - | 86 | - |
| H | B | - | - | 60 |
| Ph | A | - | 62 | - |
| Me (Z/E = 83:17) | A | 84 | 4 | |
| Me (Z/E = 83:17) | C | 86 | - | - |
| Me (E) | B | 91 | - | - |
| Me (Z) | D | 94 | - | - |

procedure A = 5 mol% $Pd(OAc)_2$ / 2 equiv NaOAc / DMSO / $O_2$
procedure B = 5 mol% $Pd(OAc)_2$ / 10 mol% Py / xylene / $O_2$
procedure C = 5 mol% $Pd(OAc)_2$ / DMSO / $O_2$
procedure D = 5 mol% $Pd(TFA)_2$ / 20% AcOH-toluene/ $O_2$ / 5 mol% ligand NHC




(±)-**158**

**Scheme 124**




Procedure A = 10 mol% $Pd(OAc)_2$ / 1 equiv AcONa / DMSO / air / 100 °C
Procedure B = 10 mol% $Pd(OAc)_2$ / 0.2 equiv Py / xylene / air / 100 °C

presence of an intramolecular hydrogen bond between the amido proton and the carbonyl oxygen.

The addition of urethane to alkenes such as methyl acrylate by means of the catalytic system $PdCl_2(MeCN)_2/CuCl/O_2$ yielded olefinic carbamates **187** (Scheme 141).[197] With conjugated dienes like isoprene and 2,3-dimethylbutadiene, better results were obtained with the catalytic system $Pd(acac)_2$/phosphorus ligand/Lewis acid.

*N*-Sulfonyl-2-aminodiphenyls **188** in the presence of $Pd(OAc)_2$ and $Cu(OAc)_2$ under air gave a coupling reaction with electron-deficient alkenes to form phenanthridine derivatives **189** (Scheme 142).[198]

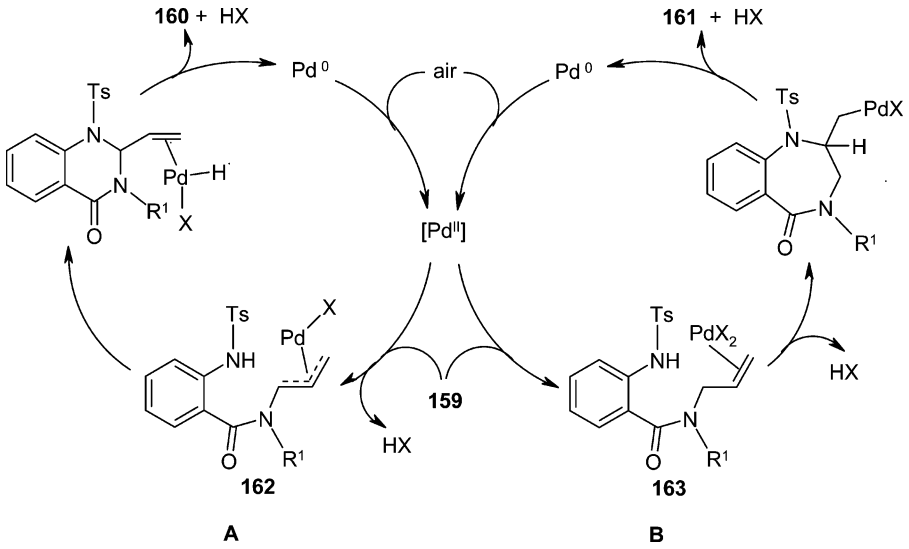
According to Hosokawa and co-workers, the amidation of electron-deficient alkenes with cyclic carbamates or lactams as nucleophiles gave the corresponding *N*-substituted compounds **190**. $PdCl_2(MeCN)_2$ and CuCl were used as catalyst under 1 atm of $O_2$ (Scheme 143).[199] Carbamates were more reactive than lactams. The copper cocatalyst was not essential for the reaction to take place.

More recently, oxazolidinone was used to achieve direct amidation of *p*-substituted styrenes with $PdCl_2(MeCN)_2$ and $CuCl_2$ under 1 atm of $O_2$ (Scheme 144).[200] The concomitant presence of TEA ensured complete regioselectivity with the exclusive formation of the Markovnikov product **191**. Some experiments confirmed that this regioselectivity arises from a Brönsted-base effect. In fact, the use of previously deprotonated oxazolidinone resulted in the formation of the Markovnikov product even in the absence of an external base.

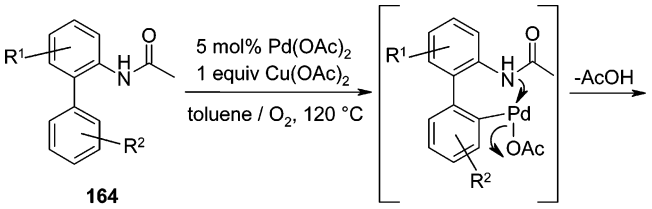
The same author reported that vinyl ethers underwent a cross-coupling reaction with nitrogen nucleophiles such as amides, carbamates, and sulfonamides to give enamide derivatives **192** (Scheme 145).[201] A thorough screening of catalysts found optimal performance with $Pd(OCOCF_3)_2$ and DPP in open air. Nitrogen nucleophiles like primary and secondary amines did not react even under the optimal conditions.

The reaction was also applied to unactivated alkenes. Phthalimide, when treated with cycloalkenes (cyclooctene, cyclopentene) or acyclic alkenes (1-hexene, 1-octene), gave nitrogenated compounds **193** arising from *cis*-aminopalladation of the double bond (Scheme 146).[202] Optimal conditions, identified after a thorough screening of catalysts, were

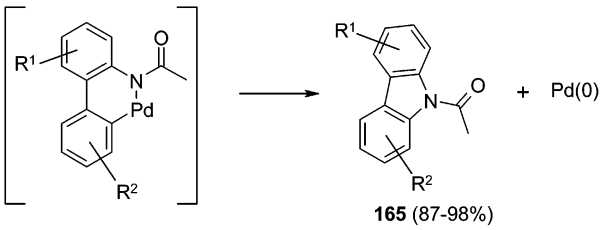
**Scheme 125**



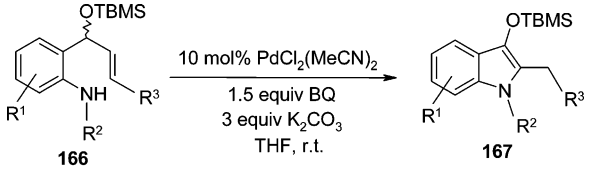

**Scheme 126**




$R^1$ = 4-Me, 4-F, 4-$CF_3$; $R^2$ = H, 4-OMe
$R^1$ = H; $R^2$ = 4-Me, 4-*t*-Bu, 4-OMe, 4-$CF_3$, 4-F, 2-OMe, 2-$CF_3$, 2-F, 3-Me




**Scheme 127**

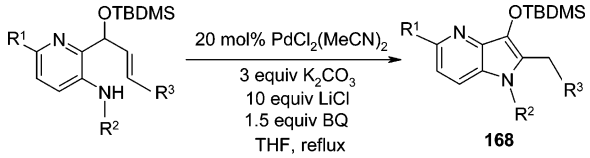



| $R^1$ | $R^2$ | $R^3$ | yield % |
|---|---|---|---|
| H | Me | H | 77 |
| 4-OMe | (4-Br-$C_6H_4$)$CH_2$ | H | 84 |
| H | Me | Ph | 47 |

$Pd(OAc)_2$ in benzonitrile under oxygen atmosphere, a finding that highlights the value of cocatalyst-free oxidation. Non-acidic NH groups including morpholine, piperidine, and anilines were unreactive under the same conditions.

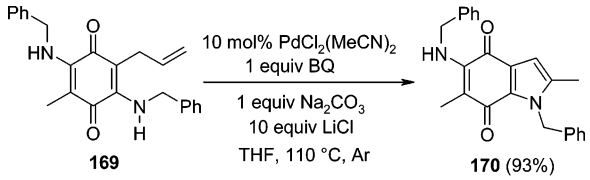
The first, recently observed instance of diamination of conjugated dienes involved dienes and *N*,*N*′-dialkylureas. With isoprene in the presence of BQ or molecular oxygen, a mixture of isomeric products **194** and **195** was obtained (Scheme 147).[203] With other 1,3-dienes, the amination process gave products **196** with high regioselectivity (Scheme 148). BQ proved far superior to $O_2$ as reoxidant, avoiding

**Scheme 128**

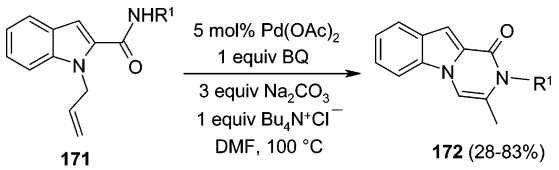



| $R^1$ | $R^2$ | $R^3$ | yield % |
|---|---|---|---|
| OMe | Me | H | 100 |
| OMe | Me | Me | 51 |
| OMe |  | Me | 63 |
| Cl | Me | Ph | 54 |

**Scheme 129**




**Scheme 130**



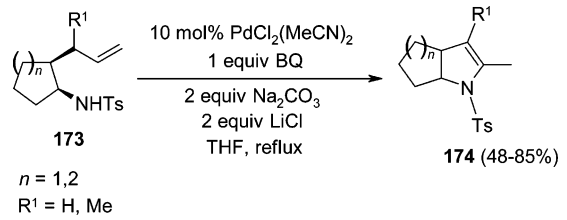

$R^1$ = Ph, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-$NO_2$-$C_6H_4$, Cy, $CH_2CO_2Et$, Bz, (2-furyl)methyl

the unwanted Wacker-type side reaction. Current work shows that both a chloride-bearing Pd(II) catalyst and a weakly coordinating solvent are essential for the reaction to succeed.

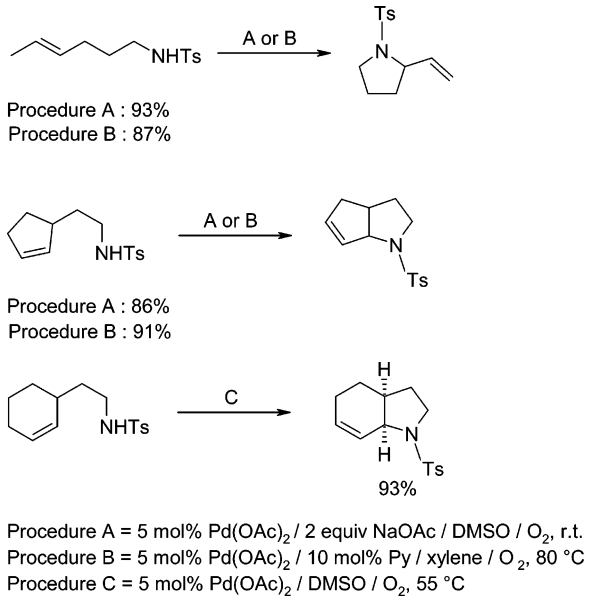
## 5. Formation of More Than One Type of Bond

The concomitant addition of two nucleophilic atoms, whether one carbon and one heteroatom or two heteroatoms, across an olefinic C═C bond provides a valuable tool for the synthesis of complex organic molecules. Effective palladium-based catalytic systems have been developed for alkoxylation/carboannulation and amination/carboannulation reactions of unactivated olefins. Less frequently, acyloxyl-

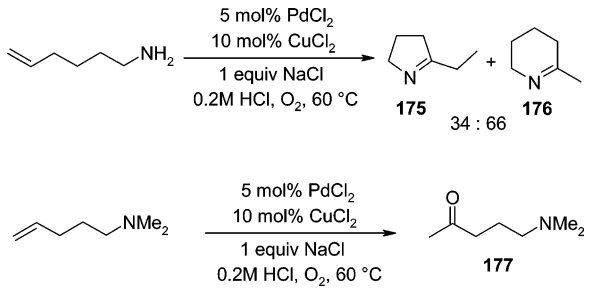
**Scheme 131**




**Scheme 132**




**Scheme 133**




ation/halogenation, amination/halogenation, and acyloxylation/amination reactions have also been described. In some cases, palladium complexes mediate the formation of all new bonds; in other cases, only one of them is formed by their intervention. While alkoxylation, amination, and addition of a carbon nucleophile may occur both inter- and intramolecularly, halogenation always takes place by the attack of an external nucleophile.

## 5.1. Formation of C–C and C–O Bonds

The oxidative ring closure of hexa-1,5-dienes leads to the formation of unsaturated cyclopentyl derivatives. The choice of oxidation system is crucial. The classical Wacker catalyst $PdCl_2/CuCl_2$ is not useful in a general way. With the three-component system $Pd(OAc)_2/BQ/MnO_2$, selective processes generally occurred, while cyclization in acetic acid resulted in a mixture of unsaturated acetates (Scheme 149).[204] Mechanistic investigation revealed involvement of acetoxypalladation of the olefinic bond of the palladium complex, followed by migratory insertion of the remaining unsaturated bond into the palladium−carbon $\sigma$ bond. Dienes with two nonequivalent double bonds preferentially underwent attack by acetate at the less sterically hindered site, but products were usually mixtures of *cis* and *trans* diastereoisomers.[204c,205]

In contrast to the above reaction, a remarkably high degree of diastereoselectivity was observed in the cyclization of 1,2-divinylcyclohexane. The *cis*-isomer yielded (1*R**,6*S**,7*S**)-7-acetoxy-9-methylenebicyclo[4.3.0]nonane as the sole product, while *trans*-1,2-divinylcyclohexane cyclized to the (1*S**,6*S**,7*S**)-diastereoisomer.[204c] When acetic acid was replaced with other organic solvents such as acetone and chiral acids were used as nucleophiles, stereoselectivity was enhanced by the addition of water-containing molecular sieves.[206] This procedure was exploited to construct 4-acetoxy-1-(5-hydroxy-3-pentenyl)-2-methylenecyclopentane, a crucial step for the synthesis of sativene (**197**) and of functionalized bicyclo[3.3.0]octane system **198** (Scheme 150).[207]

The total synthesis of mycalamide A, a powerful antitumoral and antiviral natural product, was achieved via the construction of the intermediate pederic acid framework **199** (Scheme 151).[208] The tetrahydropyran ring was obtained as a 5.7:1 mixture of diastereoisomers.

Alkenols having a terminal double bond with a substituent on the inside $sp^2$ carbon undergo intramolecular oxypalladation to originate an organopalladium intermediate that is not susceptible to $\beta$-hydride elimination and, hence, can be trapped by external olefins. Thus, the reactions of alkenols **200** or **201** in the presence of catalytic amounts of $Pd(OAc)_2$ and $CuCl/O_2$ as reoxidant gave tetrahydrofurans **202** or pyrans **203**, respectively (Scheme 152).[209] They were inhibited when BQ or $CuCl_2/O_2$ were employed as reoxidants.

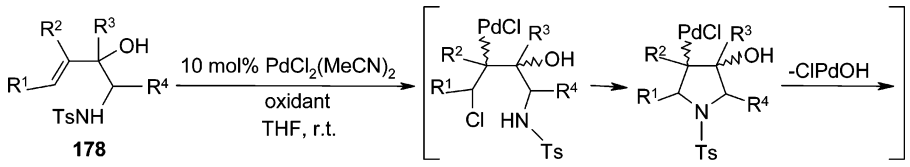
In 2005, Tietze and co-workers reported an elegant synthesis of vitamin E analogues based on a Pd(II)-catalyzed enantioselective domino process with formation of one intramolecular C−O bond and one intermolecular C−C bond (Scheme 153).[210] The first key step consists of the heterocyclization of the *o*-homoallylphenol **204** with capture of the $\sigma$-alkylpalladium complex intermediate by an electron-poor alkene and subsequent $\beta$-hydride elimination. The best result (96% ee in 84% yield) was achieved when using 10 mol % of $Pd(OCOCF_3)_2$, **204**, methyl acrylate, and BQ in the presence of (*S*,*S*)-BOXAX (**72a**)[94] as chiral ligand.

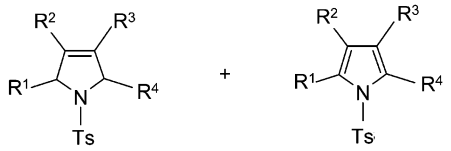
Butyl vinyl ether and allylic alcohols underwent oxidative transformation through the intermediates shown in Scheme 154 to afford 4-vinyl-2-butoxytetrahydrofurans. The reaction was carried out using 10 mol % $Pd(OAc)_2$ and $Cu(OAc)_2$ as oxidant in MeCN.[211]

An analogous cyclization to 2-alkoxytetrahydrofurans was promoted by catalytic amounts of $Pd(OAc)_2$ and $Cu(OAc)_2$ in the presence of 2 mol % catechol and molecular oxygen as stoichiometric oxidant. The use of catechol as activator of a Pd(II)−Cu(II) catalyst was unprecedented. The reaction proceeded via oxypalladation of allylic alcohols to give vinyl ethers followed by cyclization of the intermediate and subsequent $\beta$-elimination of PdH.[212]

A general picture of the $\pi$-nucleophilicity of allenes is emerging. According to Bäckvall and co-workers, 5-allenyl-substituted cyclic 1,3-dienes cyclized through the formation of a carbon−carbon bond between the allene middle carbon and the terminal carbon of the 1,3-diene system (Scheme 155).[213] Bicyclo[4.3.0] or bicyclo[5.3.0] skeletons (**205** and **206**, respectively) were formed. The reaction was highly regio- and stereoselective. According to mechanistic studies, it proceeds through the formation of a ($\pi$-1,3-diene)palladium

**Scheme 134**



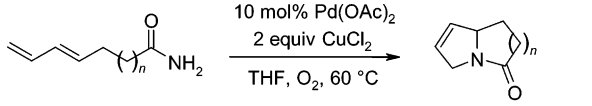



A B

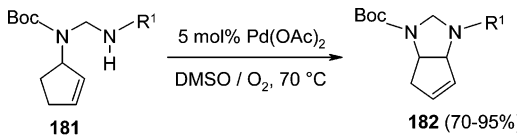
| R¹ | R² | R³ | R⁴ | oxidant (equiv) | A | B |
|---|---|---|---|---|---|---|
| Me | H | H | H | $CuCl_2$(2.0) | 72 | 24 |
| H | Me | H | H | $CuCl_2$(2.0) | - | 41 |
| H | Me | H | H | BQ(1.0) | 18 | 40 |
| H | H | Me | H | - | - | 78 |
| H | H | H | $CH{=}CH_2$[a] | - | 83 | 7 |
| H | H | H | $CH{=}CH_2$[b] | $CuCl_2$(2.0) | 18 | 47 |
| H | H | H | $CH{=}CH_2$[b] | $O_2$ | 19 | 41 |

[a] erythro diastereoisomer
[b] threo diastereoisomer

**Scheme 135**

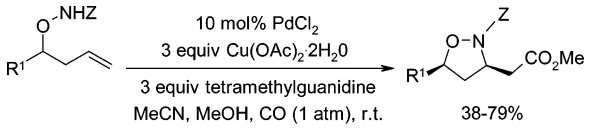



**Scheme 136**



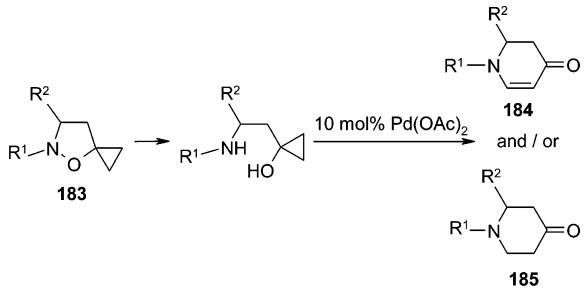

R¹ = Ts, CHO, COMe, $CONH_2$, $CO_2Me$, $CO_2Bn$, H

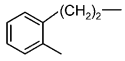
**Scheme 137**




Z = $CO_2Me$, Ns, Cbz, *t*-Boc
R¹ = Ph, *i*-Pr, $TBSOCH_2$

**Scheme 138**




| R¹ | R² | **184** yield % (procedure) | **185** yield % (procedure) |
|---|---|---|---|
| Me | Ph | 65 (A)<br>85 (B)<br>- | -<br>-<br>70 (C) |
| —$(CH_2)_2$CHO*t*-Bu— | | 40 (A)<br>70 (B)<br>- | -<br>-<br>45 (C) |
|  | | 35 (A)<br>75 (B)<br>13 (C) | 52 (A)<br>15 (B)<br>62 (C) |

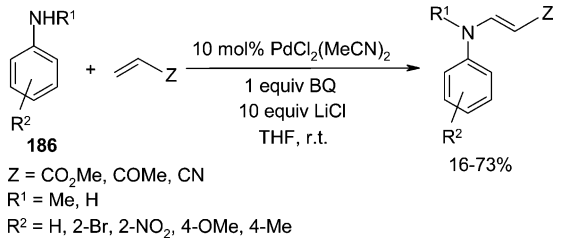
procedure A = 2 equiv pyridine, air, toluene 80 °C
procedure B = 2 equiv pyridine, $O_2$ 5 atm, toluene, 80 °C
procedure C = 3 equiv LiOAc, 2 equiv $Cu(OAc)_2$, DMF, 100 °C

complex that can be attacked by the central atom of the allene pendant. As this nucleophile attacks the face lying opposite to that of the palladium atom, the result is a *trans*-carbopalladation of the diene, hence, a *cis*-ring junction. The use of different reaction conditions can control the stereochemical outcome of the second nucleophilic attack, brought about by AcOH.[214]

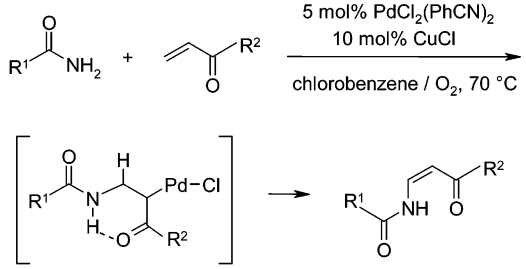
Numerous external nucleophiles such as carboxylic acids, alcohols, phenols, and thiophenols were used to introduce a variety of substituents at the C-4 position of the **205**-type bicyclic system. These reactions were run in non-nucleophilic solvents such as dichloromethane or acetone. Their regioselectivities varied, depending on the nature of the nucleophile.[215]

In 2002, Ma and Gao developed an efficient Pd(II)-catalyzed cyclization of 2,3- and 3,4-dienols involving allyl halides with formation of one intramolecular C−O bond and one intermolecular C−C bond (Scheme 156).[216] This reaction, which provides a mild route to variously substituted

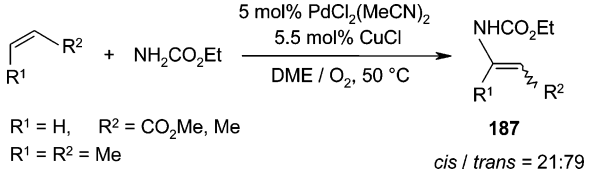
**Scheme 139**



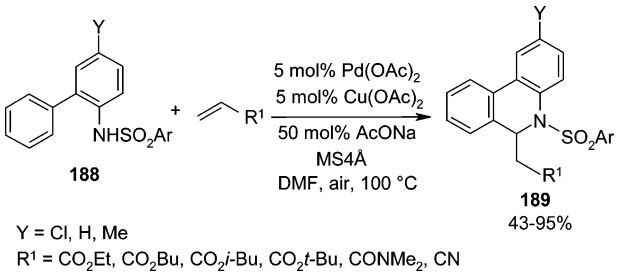

**Scheme 140**




**Scheme 141**




**Scheme 142**




2,5-dihydrofurans and 5,6-dihydro-2*H*-pyrans, proceeds through the intermediates shown in Scheme 157.

A couple of differently functionalized allenes can undergo a sequential cyclization−dimerization reaction under mild conditions and in good yields (Scheme 158).[217] Such heterodimerization took place with amides of 2,3-butadienoic acids **207** and allenyl ketones **209**, yielding 4-(3-furanyl)-2(5*H*)-furanimines **210**, in the presence of 5 mol % $PdCl_2(MeCN)_2$ in acetonitrile at room temperature.[218]

Under the same conditions, 2,3-butadienoic acids **208** and allenyl ketones **209** yielded 4-(3-furanyl)-2(5*H*)-furanones **211**. Excess of **209** ensures regeneration of the catalyst. The allenyl ketone reacts with the Pd(0) species to give cyclic Pd complex **212**, which undergoes protonolysis due to in situ generated HCl to form **213** and the Pd(II) species (Scheme 159).[217]

Catalytic amounts of $PdCl_2$ promoted the oxidative dimeric cyclization of a variety of substituted 2,3-dienoic acids **214** to give the corresponding butenolides **215** (Scheme 160).[219] The reaction runs through a double oxypalladation and reductive elimination to form **215** and a Pd(0) species. The latter is reoxidized to the catalytically active Pd(II) species by the in situ formed $I_2$, which may be produced by the reaction of alkyl iodide with air.

## 5.2. Formation of C–C and C–N Bonds

Tosylated allylamines **216** reacted under mild conditions with butylvinyl ether or styrenes to produce 2,4-substituted pyrrolidines **217** (Scheme 161).[220] Several nontraditional cocatalysts (including catechol, cyclooctadiene, and methyl acrylate) had a beneficial effect on these reactions. Acetonitrile at room temperature was the best solvent. The authors proposed a catalytic mechanism initiated by the aminopalladation of the ethylenic substrate. Insertion of the double bond of the allyl tosylamide into the Pd−C bond would form the pyrrolidine ring, and subsequent $\beta$-hydride elimination would give the observed product (Scheme 162).

Very recently, tandem cyclization of acrylanilides **218** was achieved with molecular oxygen as the sole oxidant (Scheme 163).[221] In this case, 10 mol % palladium acetate was used as catalyst with 40 mol % of pyridine in toluene at 50 °C. A thorough screening of different reaction parameters (temperature, chiral ligands, and additives) showed improvements in both catalytic activity and enantioselectivity (75−91% ee) when employing sparteine as the chiral ligand in the presence of molecular sieves and the bulky tertiary amine DIPEA.

The catalytic system $PdCl_2(MeCN)_2$/BQ worked well in a tandem oxidative cyclization/olefin insertion reaction of bis(allylamino)benzoquinone **219** to give mitosenes (a large class of antibiotic, antineoplastic pyrroloindoloquinones) (Scheme 164).[184] The reaction may be accounted for by a primary alkylpalladium intermediate via sequential elimination/addition of a hydridopalladium species.

Regiospecific arylation−amination of *N*-tosylated alkenyl amines in the presence of $ArSnBu_3$ provided either 2-arylpiperidines **220** or the open-chain products **221** depending on the nature of the arylating agent (Scheme 165).[222]

## 5.3. Formation of C–C and C–Halogen Bonds

An allylsilane pendant on 1,3-cyclohexadiene behaved as carbon nucleophile, attacking as "masked carbanion" the Pd(II)-coordinated diene and resulting in cyclization. When the $Li_2PdCl_4$/BQ catalytic system was used, the intermediate $\pi$-allyl-Pd complex underwent an external *anti* attack by chloride (Scheme 166).[223] The addition of both the carbon nucleophile and the $Cl^-$ across the diene was completely stereoselective, with 1,4-*syn*-addition products being observed exclusively.

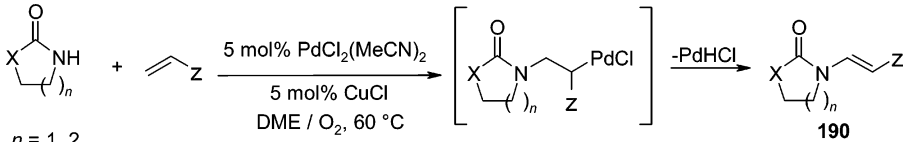
## 5.4. Formation of C–C and More Types of C–Heteroatom Bonds

5-Methylenecyclooctene was exploited as a diene system to obtain compounds **222**−**225** by the cyclization reaction; chlorine and acetoxy groups were inserted at the same time by the use of $PdCl_2/CuCl_2$/buffered AcOH (Scheme 167).[224] Addition of chloride and acetate to *endo*-5-vinyl-2-norbornene also occurred with the same catalytic system yielding 2-acetoxy-5-chlorobrendane.[225]

## 5.5. Reactions without C–C Bond Formation

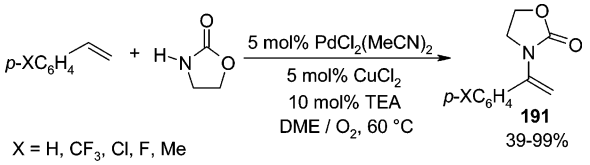
Palladium-catalyzed reactions of 1,3-dienes in the presence of heteroatom nucleophiles can also proceed without C−C bond formation. Bäckvall and co-workers reported the

**Scheme 143**



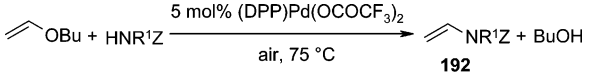

*n* = 1, 2
X = $CH_2$, O
Z = $CO_2Me$, COMe, CHO, $CONEt_2$

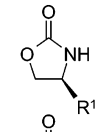
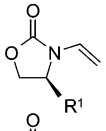
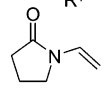
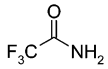
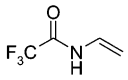
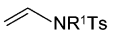
**Scheme 144**



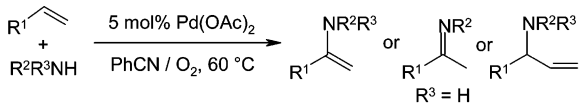

X = H, $CF_3$, Cl, F, Me

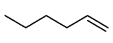
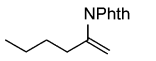
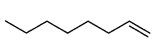
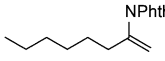
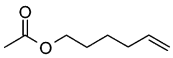
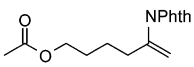
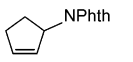
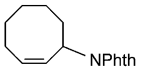
**Scheme 145**




| $HNR^1Z$ | product | yield % |
|---|---|---|
|  |  | 91 |
| $R^1$ = H | | |
| $R^1$ = *i*-Pr | | 95 |
| $R^1$ = Bn | | 92 |
|  |  | 89 |
|  |  | 76 |
| NHR¹Ts $R^1$ = Me |  | 64 |
| $R^1$ = $(CH_2)_2CO_2Me$ | | 87 |

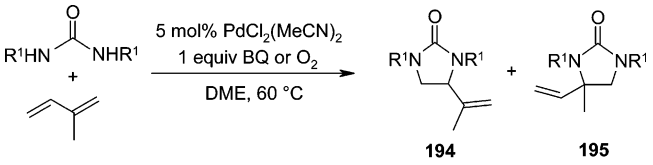
**Scheme 146**




| alkene | $R^2R^3NH$ | product | yield % |
|---|---|---|---|
|  | PhthNH |  | 90 |
|  | PhthNH |  | 87 |
|  | PhthNH |  | 86 |
|  | PhthNH |  | 80 |
|  | PhthNH |  | 60 |
|  | $TsNH_2$ |  | 63 |

acetoxychlorination of 1,3-dienes, performed in AcOH in the presence of LiCl and LiOAc, to yield 1-acetoxy-4-chloro-2-alkenes **226** with high regioselectivity (Scheme 168).[226]

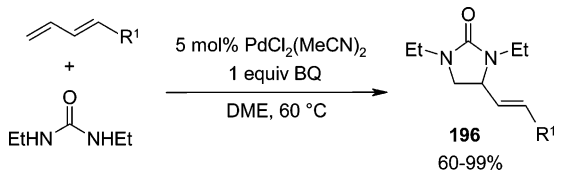
**Scheme 147**




| $R^1$ | yield % | **194** yield % / **195** yield % (procedure)[a] |
|---|---|---|
| Me | 45 | 78 / 22 (A) |
| Et | 81 | 77 / 23 (B) |
| Bu | 82 | 90 / 10 (B) |

[a] procedure A: $O_2$ as oxidant; B: BQ as oxidant

**Scheme 148**



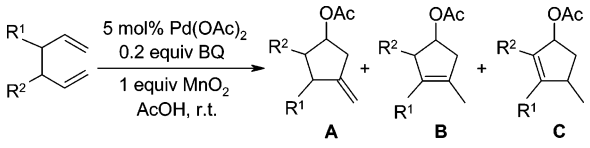

$R^1$ = Et, Ph, 4-$OMeC_6H_4$, 4-$CF_3C_6H_4$, 2-naphthyl

Cyclic 1,3-dienes gave an overall *cis*-1,4-addition. In fact, the mechanism involved a *trans*-acetoxypalladation of one double bond followed by an external *trans*-attack by the chloride ion, thus resulting in the formation of a *cis*-product. BQ, uniquely active as oxidant, also acted as a ligand to palladium.

The method was improved by working in acetone or ethyl acetate in the presence of the appropriate carboxylic acid and LiCl. In the presence of LiBr, 1,4-bromoacetoxylation was observed; however, in the absence of lithium halide, 1,4-diacetoxylation occurred.[227]

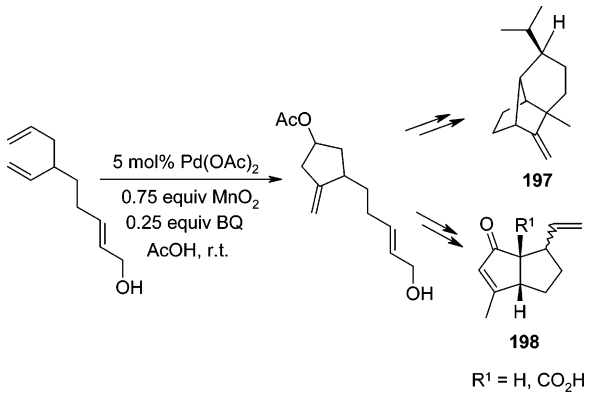
Tosylamides, carbamates, and alcohols behave as nucleophiles in an intramolecular 1,4-addition of 1,3-cyclohexadienes and 1,3-cycloheptadienes, leading to 5,6 and 5,7 fused-ring systems, respectively.[113,228] In the presence of an external nucleophile like acetate or halide, both nucleophiles were added across the diene in a regio- and stereospecific manner, giving **227** and **228** (Scheme 169). The stereochemical outcome was dependent on the reaction conditions. As shown for the intermediate **229**, the intramolecular reaction resulted in a *cis*-1,4-oxyamidation to give **228** in the presence of catalytic LiCl, while *trans*-1,4-oxyamidation product **231** was obtained in the absence of LiCl. This is explicable because the chloride blocks the coordination of acetate to palladium in the catalytic intermediate, thus suppressing the *cis* migration of acetate. The intermediate **229** would react only with external acetate to give product **228**, whereas *cis* migration converts **230** into the trans product **231** (Scheme 170).

**Scheme 149**

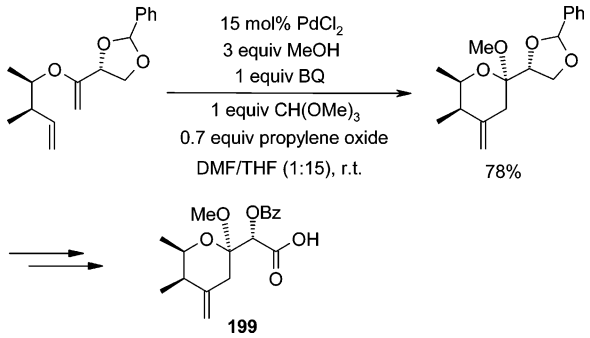



| $R^1$ | $R^2$ | yield % A | yield % B | yield % C |
|---|---|---|---|---|
| H | H | 47 | 18 | 7 |
| Me | H | 34 | 6 | 9 |
| Ph | H | 52 | 2 | 6 |
| $(CH_2)_2CH=CHCH_2OAc$ | H | 54 | | |
| | $-(CH_2)_4-$ | 67 | | |

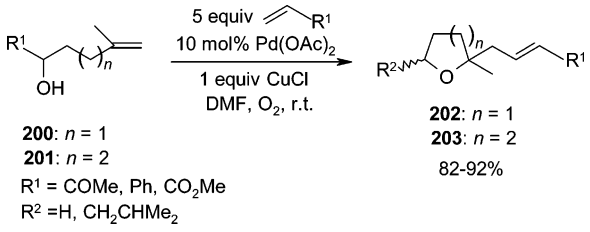
**Scheme 150**




**Scheme 151**



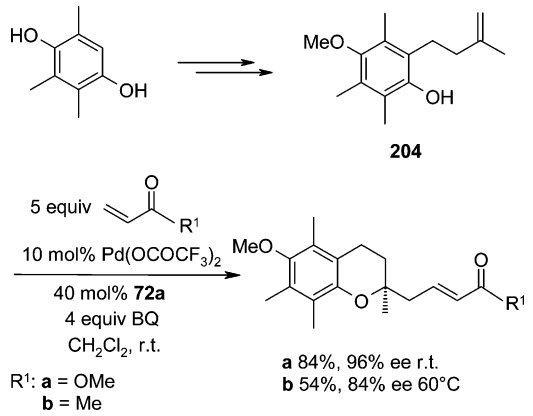

**Scheme 152**




1,3-Cycloalkadienes bearing a hydroxyalkyl substituent at the 1-position underwent Pd(II)-catalyzed oxaspirocyclization owing to the 1,4-addition of the hydroxy function and of an external nucleophile like chloride or acetate anion. The reaction proceeds via a spirocyclic $\pi$-(allyl)palladium intermediate that is attacked by the external nucleophile. The stereochemistry can be directed to give either *cis*- or *trans*-1,4-addition across the double bond. When LiCl was added as external nucleophile, only *cis*-addition was observed with formation of compounds **232** (Scheme 171).[115]

The bridged-ring skeleton **234** was formed by Pd(II)-catalyzed double cyclization of 6-(benzyloxycarbonylamino)-hex-1-en-3-ol **233** (Scheme 172).[229] A significant solvent effect on the chemoselectivity was recently observed. Using DMF or THF as solvent, epimeric C-1 chlorinated azasugars **235** were obtained besides the bicylic derivative **234**.

**Scheme 153**




The already mentioned aminoalcohols **141** gave the cyclic chloromethyl derivatives **236** in high yields when reacted in the presence of $Li_2PdCl_4$ as catalyst, $CuCl_2$ as oxidant, and THF as solvent (Scheme 173).[158]

The intramolecular 1,4-chloroamidation reaction on benzyl *N*-[2-(2,4-cyclohexadienyl)ethyl]carbamate was exploited as an important step toward the total synthesis of lycorane alkaloid **237** (Scheme 174).[230]

Halomethyl-substituted oxazolidinones and imidazolinones **238** were the haloamination products of allylic alcohol and allylic amines, respectively, with *p*-toluenesulfonyl isocyanate in the presence of $Pd(OAc)_2/CuCl_2$/LiCl. The reaction proceeded with high chemo-, regio-, and diastereoselectivity (Scheme 175).[231]

Regioselective chlorohydroxylation of allylic amines and sulfides to yield compounds **239** and **240**, respectively, was achieved under mild conditions (Scheme 176).[232] In the case of allylamines, the hydroxyl group is added to the double bond in an *anti*-Markovnikov fashion through a nucleophilic attack of water on the Pd(II)-activated alkene. With allyl sulfides, the regiochemistry differs from that observed with allylamines and seems to be governed by the coordination of the heteroatom to the metal complex.

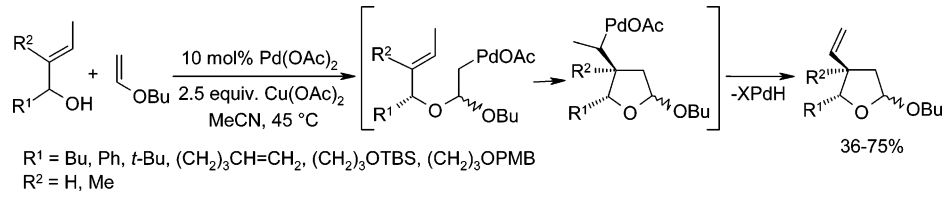
Asymmetric chlorohydrins **241** were formed by oxidation of alkenes using $PdCl_2/CuCl_2$ in the presence of (*R*)-Tol-BINAP ligand (Scheme 177), which ensured stereoselective *anti* addition to the initially formed $\pi$-complex, followed by cleavage of a Pd(II)−carbon bond and chloride substitution.[233]

Intramolecular cyclization of allenic acids **242** in the presence of a catalytic amount of $Pd(OAc)_2$ and $Cu(OAc)_2$, $K_2CO_3$, and LiBr afforded $\gamma$- or $\delta$-lactones **243** (Scheme 178).[234] The external attack by the bromide ion usually gave the *Z*-isomer as the main product.

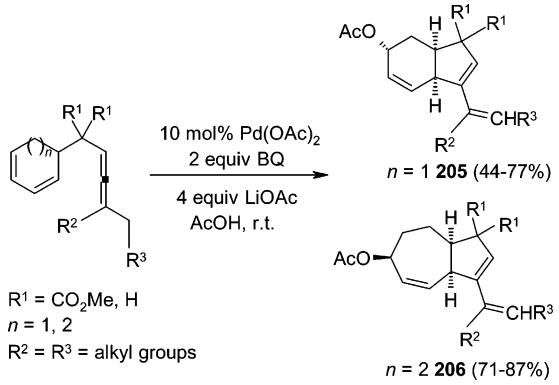
Under the same conditions, $\gamma$-allenic alcohols **244** or tosylamides (or ureas) **245** were converted to tetrahydrofurans **246** or pyrrolidines **247**, respectively (Scheme 179).[234b,c]

Spiroderivatives **249** were the oxybromination products of 3-allenyl-3-hydroxyoxindoles **248**. The reaction should involve the initial formation of an allene palladium complex, then a nucleophilic attack by the bromide, and finally an intramolecular alkoxylation of the $\pi$-allylpalladium complex (Scheme 180).[235]

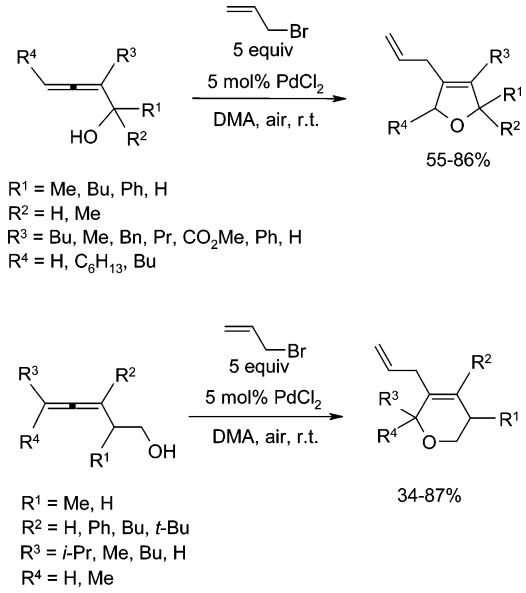
**Scheme 154**



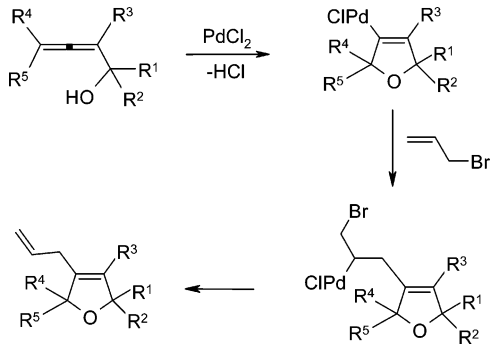

**Scheme 155**




**Scheme 156**




**Scheme 157**



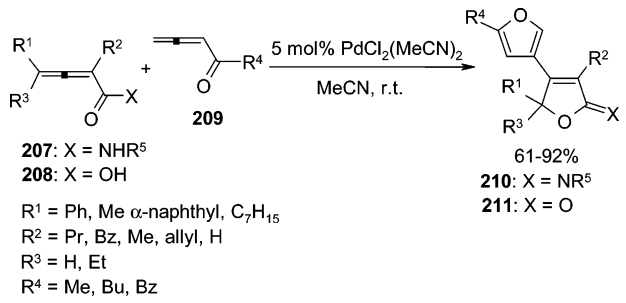

## 6. Reactions Involving Carbonylations

Oxidative carbonylations constitute an important class of Pd(II)-mediated reactions.[1g] CO is a very valuable and inexpensive carbon source, as well as being thermally stable and chemically reactive. Industry has been very keen on developing a direct catalytic route to the synthesis of a wide variety of oxygenated compounds such as carboxylic acids and their derivatives, ketones, aldehydes, alcohols, and nitrogenated compounds such as heterocyclic systems.

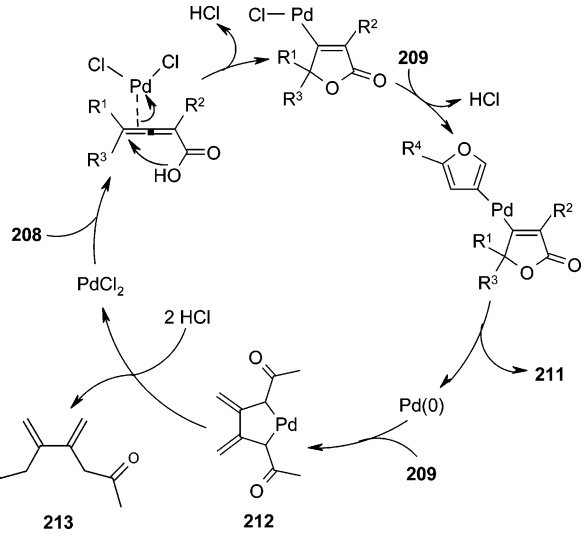
The catalytic process starts with an alkene−Pd−CO complexation followed by the formation of an acylpalladium complex. The latter is finally converted to the products by reaction with a variety of nucleophiles (Scheme 181, part A).

Carbonylation is often effected on unsaturated substrates having a nucleophilic function in a suitable position. In such cases, an intramolecular nucleophilic attack on the alkene−Pd(II) complex may occur prior to the true carbonylation, as shown in Scheme 181, part B, thus forming derivatives

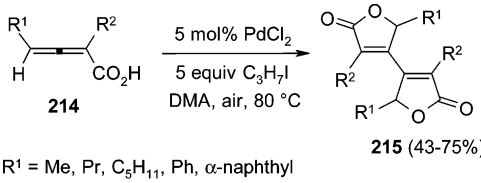
**Scheme 158**



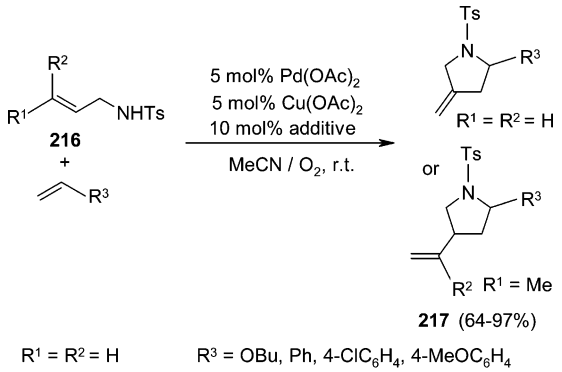

**Scheme 159**



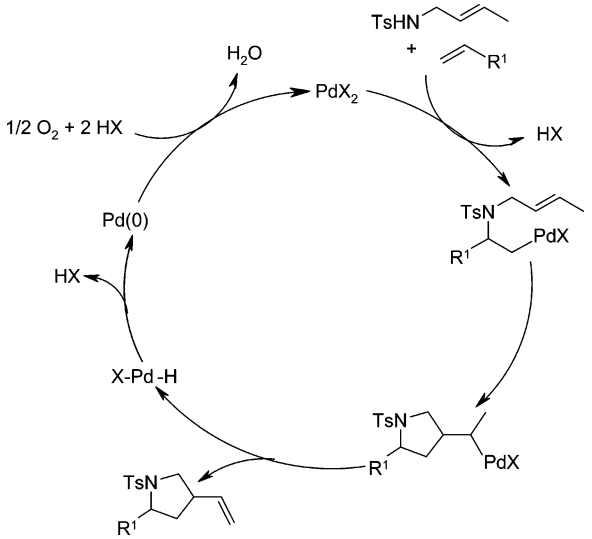

**Scheme 160**



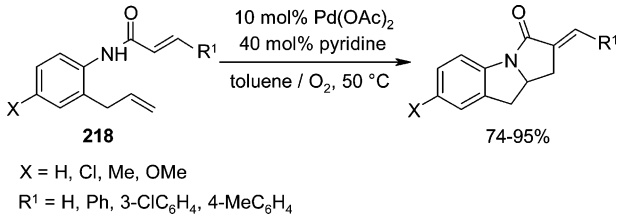
**Scheme 161**



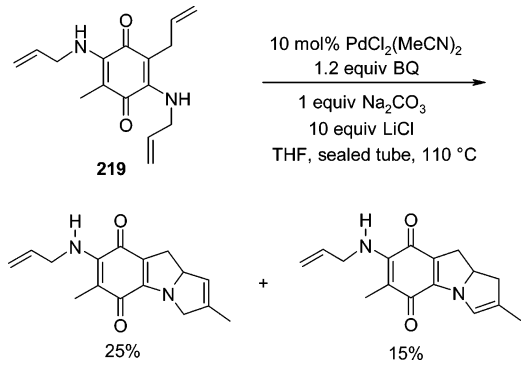

**Scheme 162**




**Scheme 163**

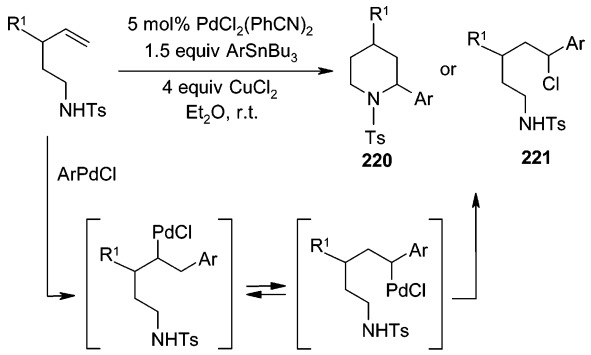



**Scheme 164**




of heterocyclic carboxylic acids. In some cases, cyclocarbonylations were reported, when an intramolecular nucleophilic attack resulted in ring formation with CO incorporation into the ring.

**Scheme 165**




| R1 | Ar | yield % 220 | yield % 221 |
|---|---|---|---|
| H | 3,4-$(MeO)_2C_6H_3$ | 78 | - |
| Me | Ph | - | 65 |
| Ph | Ph | - | 77 |
| OAc | 4-MeO-$C_6H_4$ | 77 | - |

## 6.1. Alkoxycarbonylations

At the end of 1970, Stille and co-workers began to study the carbonylation reactions of olefins. Carbonylation of *cis*- and *trans*-2-butene in methanol under Wacker-type catalysis ($Pd(OAc)_2/CuCl_2/CO$) resulted in *threo*- and *erythro*-3-methoxy-2-methylbutanoic esters, respectively (Scheme 182).[236] This result showed that the methoxypalladation reaction was *trans*-stereospecific. Addition of sodium acetate completely changed its outcome, as 2,3-dimethyl succinic esters were the exclusive products. In this case, the dicarbonylation took place with a *cis* stereospecificity; in fact, while *trans*-2-butene gave exclusively the *dl*-diastereoisomer, *cis*-2-butene afforded only dimethyl *meso*-2,3-dimethylsuccinate.

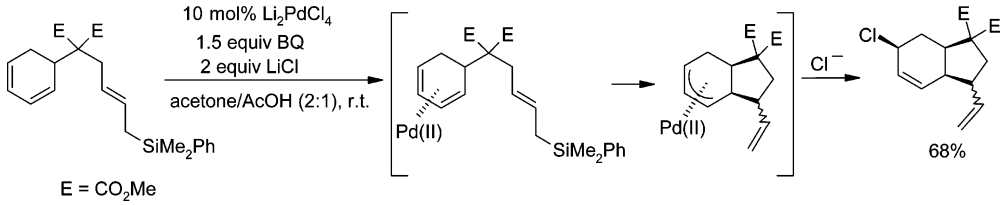
Enantioselective bis(alkoxycarbonylation) of styrene in MeOH under carbon monoxide pressure was reported using the in situ generated catalytic system $Pd(acac)_2$/chiral diphosphane ligand/*p*-$MeC_6H_4SO_3H$. Dimethyl phenylsuccinate and oligomeric products were formed in modest yields.[237] Thiourea-based ligands were evaluated for the Pd-catalyzed bis(methoxycarbonylation) of terminal olefins. The usefulness of these ligands was endowed with their stability to oxidizing agent and their superiority in preventing palladium precipitation and double-bond isomerization.[238]

Alkenes can be converted regioselectively to carboxylic acids with 10 mol % $PdCl_2$, $CuCl_2$, HCl, and $THF/H_2O$ in an atmosphere of CO and $O_2$ (Scheme 183).[239] The omission of molecular oxygen lowered the reaction rate and product yields. Using MeOH as solvent instead of water, the same reaction conditions promoted the alkoxy/alkoxycarbonylation of allenes through the formation of one C−C bond and two C−O bonds.

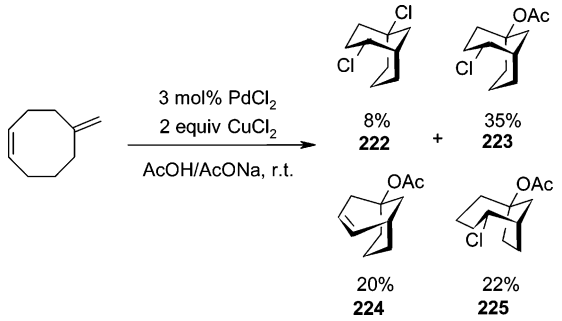
Aromatic carboxylic acids can be prepared directly from arenes and CO with $Pd(OAc)_2$ as catalyst and $K_2S_2O_8$ (or TBHP) as oxidant agent (Scheme 184).[240]

Carbonylation of cyclic olefins **250** in methanol, with or without added base, predominantly afforded isomeric diester products (Scheme 185).[241] Both 1,2- and 1,3-cycloalkanedicarboxylic esters were obtained as *cis* diastereoisomers. Product stereochemistry and isomer distribution were consistent with a mechanism requiring initial $\pi$-complexation of the olefin followed by a *cis* addition of a carbomethoxypalladium species to form $\sigma$-bonded complex **251**. The latter

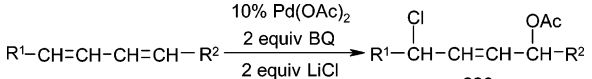
**Scheme 166**




**Scheme 167**

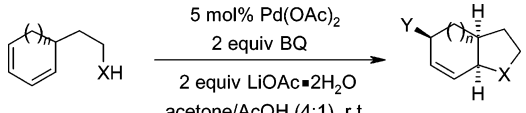



**Scheme 168**



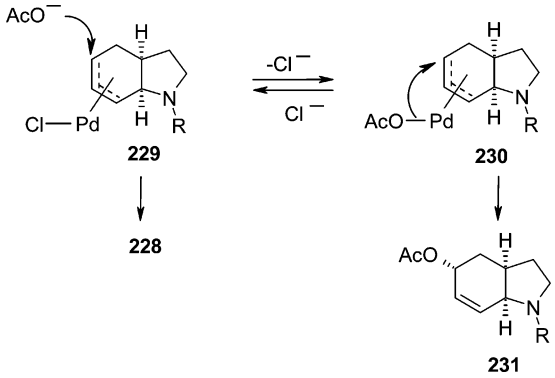

| $R^1$ | $R^2$ | yield % |
|---|---|---|
| H | H | 78 (*E*/*Z* = 9:1) |
| H | Me | 51 (*E*) |
| Me | Me | 54 (*E*) |
| — $(CH_2)_2$— | | 87 |
| — $(CH_2)_3$— | | 72 |
| — $(CH_2)_4$— | | 46 |

**Scheme 169**

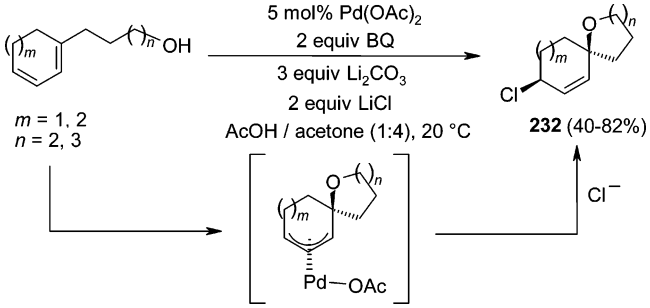



*n* = 1, 2
**227** Y = Cl with 2 equiv LiCl
**228** Y = OAc with 0.2 equiv LiCl
X = Ts, $CO_2t$-Bu, O

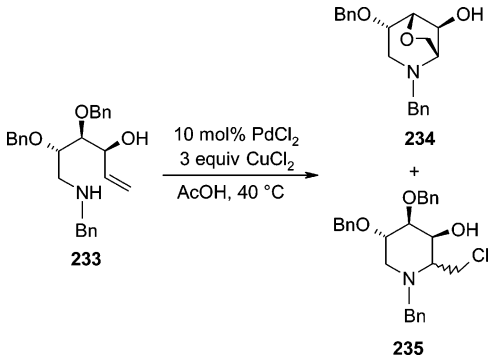
**Scheme 170**




**Scheme 171**




**Scheme 172**




can afford 1,2-diester **252** directly or rearrange via palladium hydride *cis* elimination and readdition, to give ultimately 1,3-diester **253**.

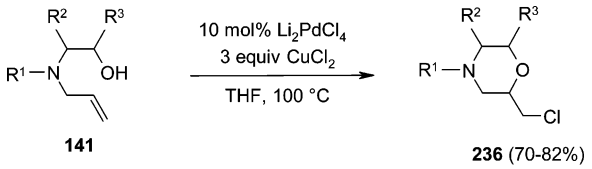
The outcomes of the carboxylation reaction with conjugated and nonconjugated diolefins were investigated a long time ago. While cyclic diolefins gave a mixture of *cis*- and *trans*-1,3-dicarboxylates alkenes, 1,5-hexadiene afforded different products depending on carbon monoxide pressure, and so did 1,3-butadiene depending on the ligands employed and the reaction conditions.[242]

The oxypalladation and subsequent carbonylation of hydroxyalkenes can provide a very useful route to a wide variety of cyclic ethers. The effect of alkene geometry on the selectivity between five- or six-membered rings formation was studied by Semmelhack and co-workers (Scheme 186). While *E*-isomer **254** mainly gave pyran **255**, *Z*-isomer **256** afforded furan **257** as the predominant products when catalytic $PdCl_2$ and a stoichiometric amount of $CuCl_2$ were used in methanol as solvent at room temperature under 1.1 atm of CO.[243]

An application of the same protocol served for the construction of the third ring of frenolicin,[244] a naphthoquinone antibiotic based on the isochroman skeleton, as well as a portion of tetronomycin antibiotics.[245] This procedure also led to the selective synthesis of the tetrahydropyran subunit of the polyether antibiotic nigericin[246] and, more recently, of the plakortone B.[247]

In a similar manner, alkenols with a terminal double bond **258** are cyclized to lactones **259** by a dicarbonylative reaction. As an additive, propylene oxide gave the best results

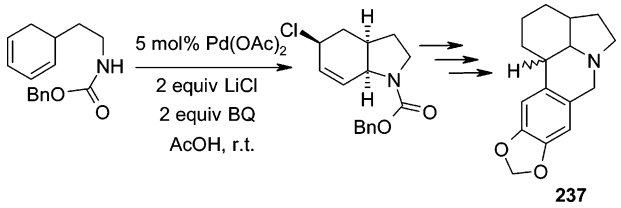
**Scheme 173**




**141** **236** (70-82%)

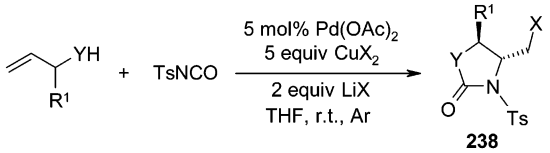
$R^1$ = PhCHMe, Bn, Me
$R^2$ = H, Me
$R^3$ = H, Me, Ph

**Scheme 174**




**237**

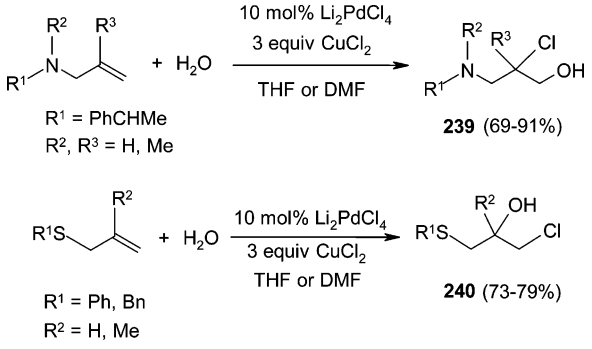
**Scheme 175**




**238**

| $R^1$ | Y | X | yield % **238** |
|---|---|---|---|
| Me | O | Cl | 66 |
| Me | O | Br | 65 |
| $C_5H_{11}$ | O | Cl | 64 |
| $C_5H_{11}$ | O | Br | 70 |
| H | NH | Cl | 86 |
| H | NH | Br | 78 |
| H | NBn | Cl | 97 |
| H | NBn | Br | 93 |

**Scheme 176**

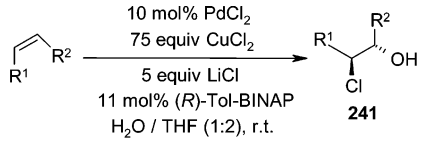



(Scheme 187).[248] Small amounts of EOA as a second additive improved cyclization yields for a series of 3-buten-1-ols **260** (Scheme 188). The most plausible mechanism involves first lactonization, followed by methoxycarbonylation, rather than vice versa.

In oxypalladation/carbonylation processes, unsaturated 1,3-diols **261** behave as precursors of bicyclic lactones **262** (Scheme 189).[249] Generally the cyclization, using $PdCl_2$/$CuCl_2$ in the presence of NaOAc and AcOH under CO atmosphere, affords a *cis*-lactone as the sole product. The reaction yield is highly dependent on the nature of the olefin substituents.

Intramolecular alkoxycarbonylation was applied as a key step to the construction of functionalized polycyclic portion

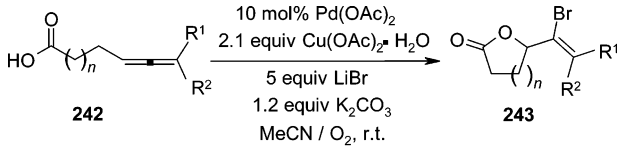
**Scheme 177**




**241**

| $R^1$ | $R^2$ | yield % | ee(%) |
|---|---|---|---|
| $CH_2OPh$ | H | 35 | 80 |
| COMe | H | 78 | 82 |
| —$O(CH_2)_2$— | | 56 | 56 |

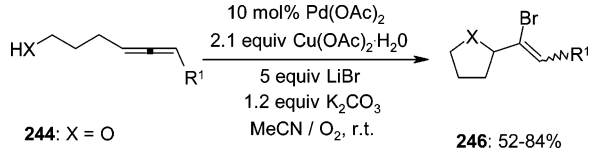
**Scheme 178**




**242** **243**

| *n* | $R^1$ | $R^2$ | *Z*/*E* | yield % |
|---|---|---|---|---|
| 1 | $C_5H_{11}$ | H | 54 / 46 | 89 |
| 1 | *i*-Pr | H | 37 / 63 | 90 |
| 1 | Me | Me | | 74 |
| 2 | $C_5H_{11}$ | H | 90 / 10 | 83 |
| 2 | *i*-Pr | H | 88 / 12 | 82 |

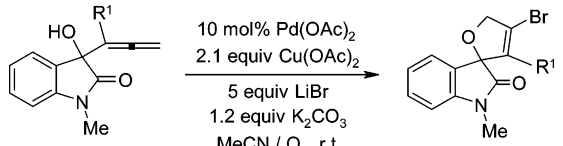
**Scheme 179**




**244**: X = O
**245**: X = NTs, NCONHBn
$R^1$ = Me, Et, $C_5H_{11}$

**246**: 52-84%
**247**: 28-80%

**Scheme 180**




**248**
$R^1$ = Me, Ph

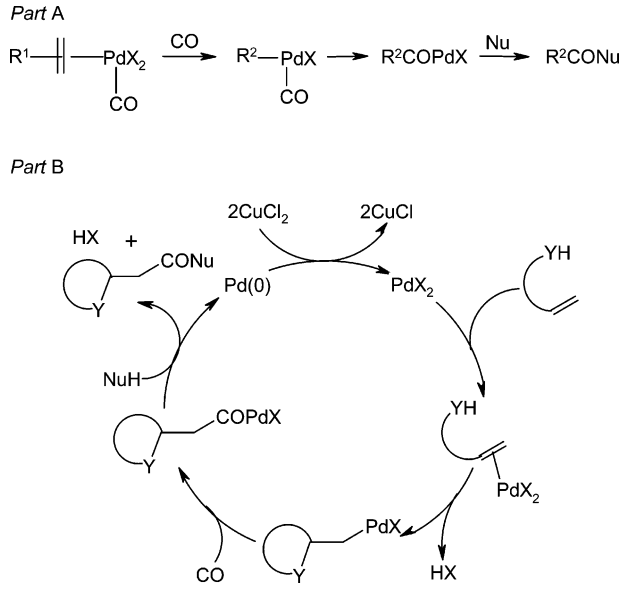
**249** (38-52%)

of micrandilactone A. The use of thiourea **263** as ligand ensures the stereoselectivity of the reaction (Scheme 190).[250]

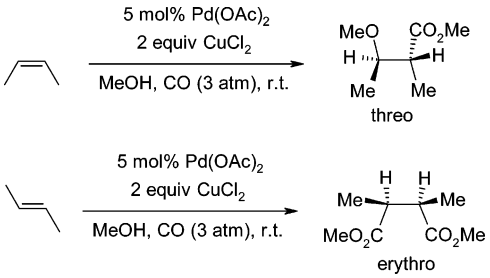
The Pd(II)-catalyzed oxycarbonylation of unsaturated polyols constitutes the key step of the synthesis of several diastereoisomeric 3,6-anhydro-2-deoxy-7-phenylglyconolactones such as the natural (+)-goniofufurone, a cytotoxic bicyclic lactone.[251] The tetrahydrofuran core of kumausynes (the red algal metabolites) was stereoselectively obtained by a strategy based on a tandem intramolecular alkoxycarbonylation−lactonization.[252]

Under similar conditions, the double lactonization of 3-hydroxy-4-pentenoic acids **264** was observed. (Scheme 191).[253] The reaction is characterized by the following features: (i) substitution at C-2 increases the reactivity; (ii) substituents on the double bond do not significantly affect yields; (iii) diastereoisomers show similar reactivities when the terminal double bond is unsubstituted, but large differ-

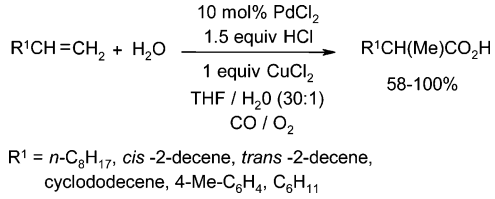
**Scheme 181**



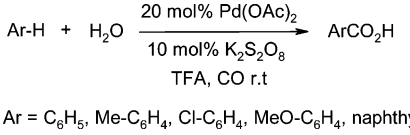

**Scheme 182**




**Scheme 183**




**Scheme 184**



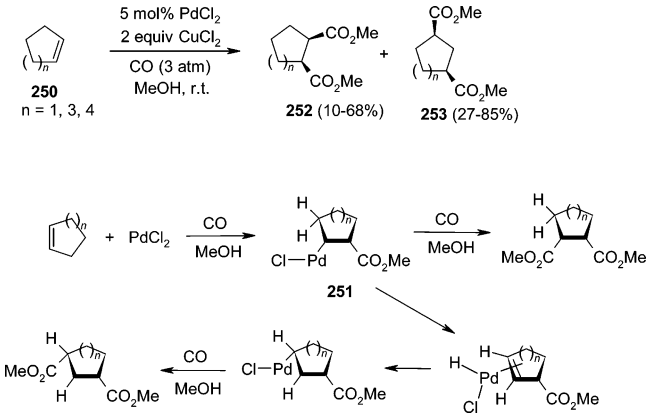

ences of reactivity when it is substituted; and (iv) the reaction is totally stereoselective.

A Pd(II)-catalyzed intramolecular double cyclization of dienones to spirobis cyclic acetals has been described.[254] It was carried out in the presence of a catalytic amount of $PdCl_2$, $CuCl_2$, and trimethyl orthoformate in methanol as solvent under CO atmosphere (Scheme 192). The formation of the products **265** also involves the insertion of two carbomethoxy groups on the side chains.

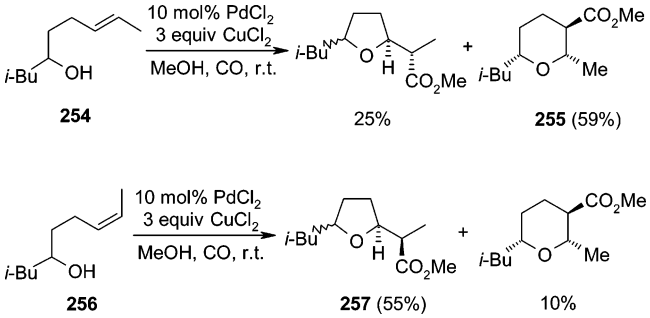
Analogously, an intramolecular process for the formation of lactones has been described on alkenols in THF as solvent.[255] Under the same conditions, in the presence of poly L-leucine as chiral ligand, 2-buten-1-ol yielded (*R*)-α-methyl-γ-lactone in 61% ee.[256]

Liu and Widenhoefer were the first to report the Pd-promoted addition of a carbon nucleophile carbon monoxide

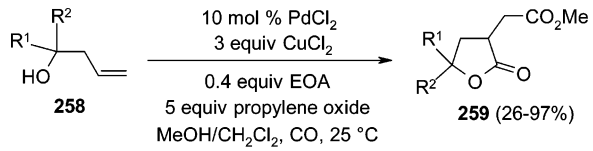
**Scheme 185**




**Scheme 186**




**Scheme 187**



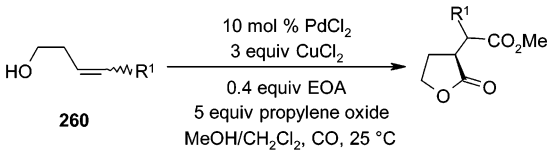

R¹; R² = H, Me, $CH_2CH_2Ph$, Cy

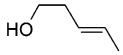
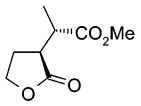
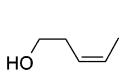
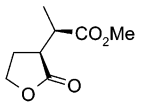
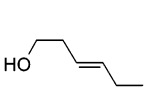
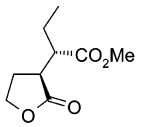
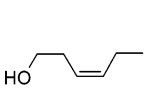
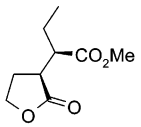
across the C═C bond.[257] On treatment with 5 mol % of $PdCl_2(MeCN)_2$ and $CuCl_2$ (3 equiv) in methanol at room temperature, 2-(4-alkenyl)indole derivatives **266** underwent cyclization/carboalkoxylation to form the corresponding tricyclic systems **267** with excellent regioselectivity (Scheme 193). Substitution on the various positions of the alkenyl chain was tolerated.

Cyclic ketones react with $PdCl_2$ in methanol under CO atmosphere to give mainly acyclic diesters along with some Cl-substituted monoesters (Scheme 194).[258] The major product is formed by a mechanism involving Pd(II)−$CO_2$-Me insertion across the double bond of the enol form of the ketone.

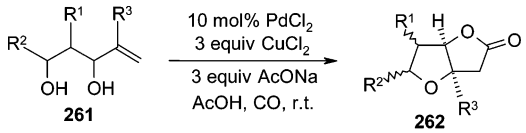
In 1987, the synthesis of tetrahydrofuran derivatives **269** by the Pd-carbonylative cyclization of allenes tethered to a hydroxy or silyloxy group (**268**) was reported. A mixture of *cis* and *trans* isomers was formed by a 5-*exo*-trig cyclization using 10 mol % $PdCl_2$, $CuCl_2$, and CO in methanol at room temperature (Scheme 195).[259] Under similar conditions 4,5-hexadienal **270** and 4,5-hexadienoic acid **272** underwent intramolecular carbonylative oxypalladation involving the formation of three C−O bonds and one C−C bond, to give tetrahydrofuran **271** and tetrahydrofuranone **273**. Propylene oxide was used as an acid trap, and EOA was used as a water scavenger.[260]

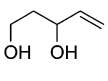
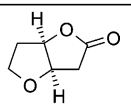
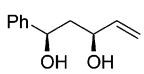
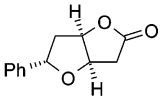
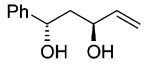
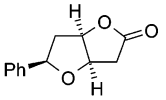
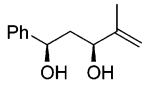
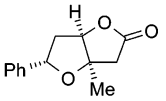
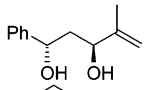
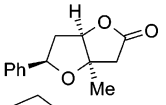
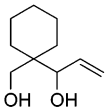
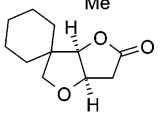
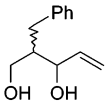
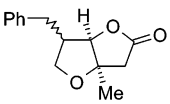
**Scheme 188**




| starting material | product | yield % |
|---|---|---|
|  |  | 55 |
|  |  | 56 |
|  |  | 63 |
|  |  | 42 |

**Scheme 189**



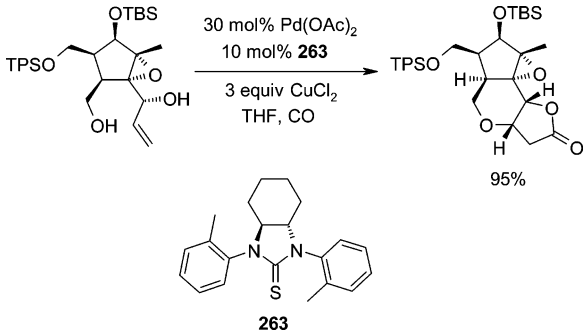

| starting diol | product | yield % |
|---|---|---|
|  |  | 60 |
|  |  | 80 |
|  |  | 70 |
|  |  | 80 |
|  |  | 29 |
|  |  | 86 |
|  |  | 79 |

## 6.2. Aminocarbonylations

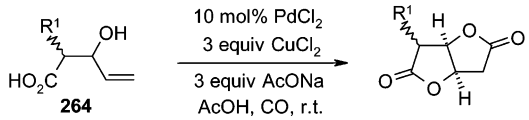
CO insertion into intermediate aminopalladium adducts provided an intriguing entry to functionalized nitrogen heterocycles. Interesting experiments by Tamaru and co-workers under Wacker-type conditions, exploiting a variety of unsaturated ureas and carbamates as nitrogen nucleophiles, led to imidazolidinones, pyrimidinones, and related nitrogen heterocycles (Scheme 196).[261] In particular, when urea derivatives were utilized as substrates, both the nitrogen atoms acted as nucleophiles. Among nitrogen nucleophiles, *endo*-carbamates displayed a distinctive reactivity, requiring addition of sodium acetate as buffered conditions to react.

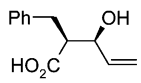
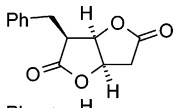
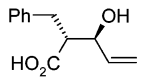
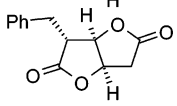
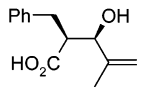
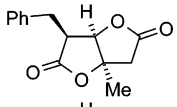
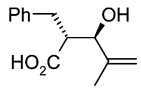
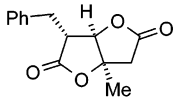
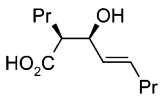
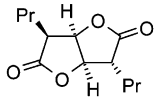
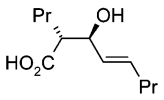
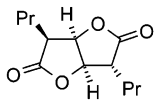
Intermolecular carbonylation of different substituted amines with CO in $Pd(OAc)_2-Cu(OAc)_2-O_2$ as the catalytic system provided ureas, carbamates, 1,3-oxazolidinones, and benzolactams.[262] For example, carbonylation of primary amines in the presence of secondary amines produced *N*,*N*,*N*′-trisubstituted ureas (Scheme 197).

**Scheme 190**

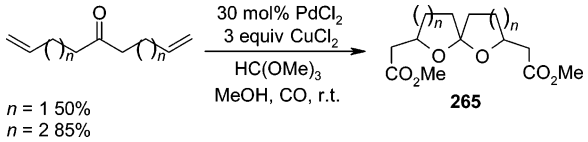



**Scheme 191**

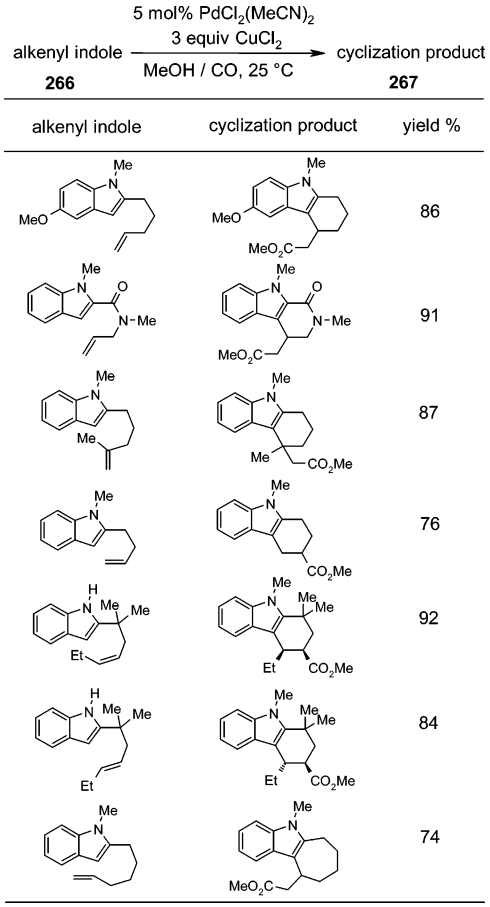



| starting material | product | yield % |
|---|---|---|
|  |  | 60 |
|  |  | 60 |
|  |  | 84 |
|  |  | 39 |
|  |  | 83 |
|  |  | 88 |

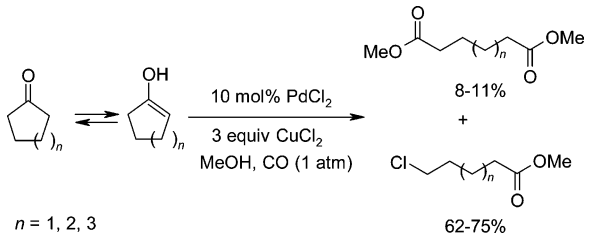
**Scheme 192**



**Scheme 193**




**Scheme 194**

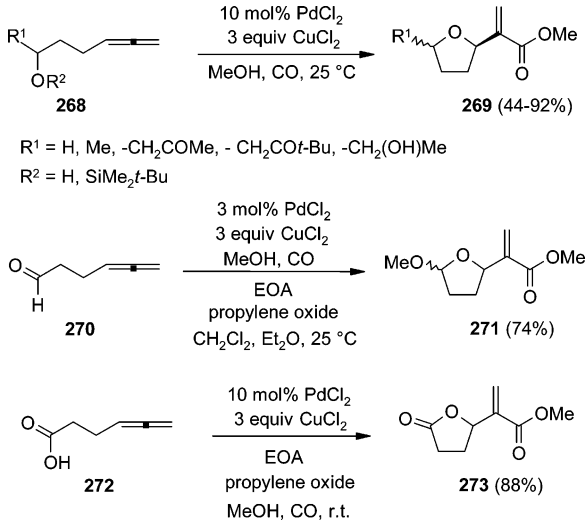



Aminocarbonylation of carbamates **274** gives selectively products **275** or **276** depending on the reaction conditions. The presence of MOA (under buffered conditions) plays an important role, both as an additive and as a solvent, to enhance the reactivity of the *endo*-nitrogen, leading to **275** (Scheme 198).[263] Under the above conditions, but using methanol as a solvent (acidic conditions), only the *exo*-nitrogen of **274** reacts to give products **276**.

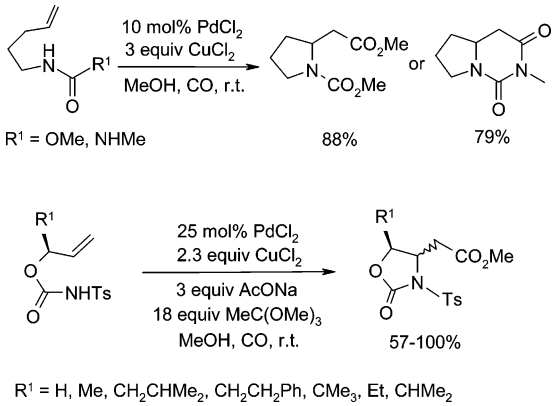
Aminocarbonylation of *N*-(3-hydroxy-4-pentenyl)-substituted tosylamides, carbamates, and ureas **277**, in the presence of $PdCl_2/CuCl_2$ and AcOH as solvent, afforded lactones **278** (Scheme 199).[264] A similar cyclization was observed in the case of ureas **279**. Substituted benzylamine **280** gave a different stereoselective outcome depending on different catalytic conditions (Scheme 200).[265]

Compound **278**, named Geissman−Waiss lactone when $R^1 = H$, an important intermediate in the synthesis of a number of pyrrolizidine alkaloids, was formed in an optically active form by Pd(II)-catalyzed intramolecular aminocarbonylation starting from (*R*)-*N*-benzyloxycarbonyl-3-hydroxy-4-pentenylamine.[266] This procedure was also applied to synthesize 1,4-iminoglycitols[267] and to build the 9-azabicyclico-

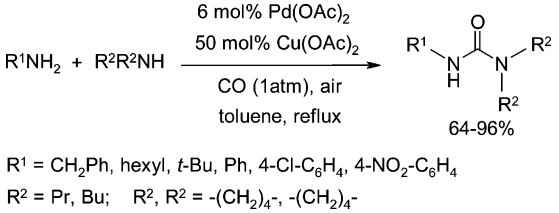
**Scheme 195**



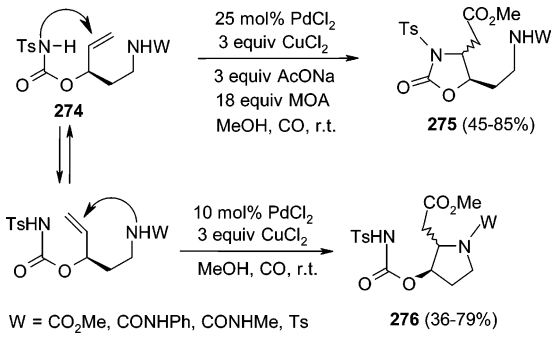

**Scheme 196**




**Scheme 197**



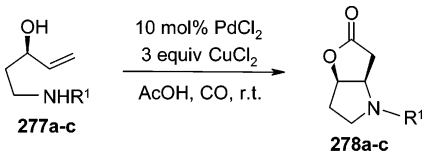

**Scheme 198**



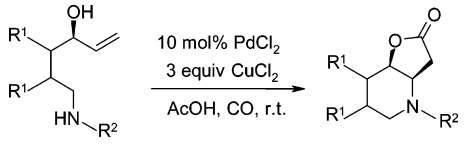

[4.2.1]nonane skeleton, which could be converted to tropane alkaloids ferruginine[268] and anatoxin.[269]

Gallagher and co-workers reported the methoxycarbonylative cyclization of allenic sulfonamides **281** to afford pyrrolidines **282** (Scheme 201).[270] It took place with 10 mol % of $PdCl_2$, 3 equiv of $CuCl_2$, and CO in methanol. Yields were significantly improved by adding $Et_3N$. The same

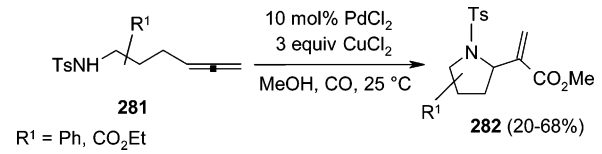
**Scheme 199**



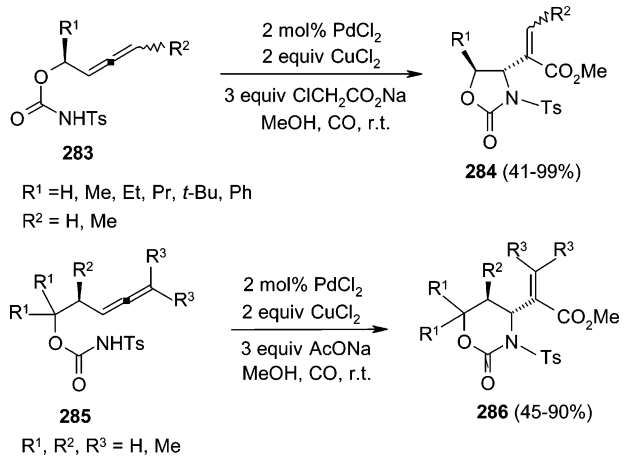

**Scheme 200**




**Scheme 201**




**Scheme 202**




reaction conditions promoted the cyclization of allenic amines bearing a chiral benzylic residue on the nitrogen atom. The pyrrolidine products were formed with a degree of diastereoselectivity that could reach 43%.[271] This procedure was exploited to prepare pyrrolidine derivatives, chief intermediates in the synthesis of alkaloids based on the indolizidine nucleus, e.g., pumiliotoxins.[272]

The same catalytic system, but under buffered conditions, was also exploited for the aminocarbonylation of allenic *N*-tosylcarbamates **283** and **285** to afford 1,3-oxazolidin-2-ones **284** and 1,3-oxazin-2-ones **286**, all bearing an acrylate side chain. The reaction occurred with high stereoselectivity, giving only *trans*-4,5-disubstituted heterocycles (Scheme 202).[273]

## 7. Conclusion

This review clearly demonstrates that palladium(II)-catalyzed processes constitute an efficient strategy for functionalization of alkenes and arenes with C−C, C−O, and C−N bond formation and continue to offer new applications to synthesize an increasingly wide range of polyfunctionalized compounds. Inside this typology of reactions, olefins arylation or heteroarylation, alkoxylation, and amination are some of the most enlightening results.

The possibility to use unsaturated substrates without prefunctionalized C−X bonds (X = halogens, OTf, etc.) for the construction of complex structures, often polyheterocyclic systems, as well as to attain the target in a few steps, is of considerable importance. Such a goal may not be easily obtainable by other methods. Moreover, these reactions proceed under relatively mild reaction conditions and tolerate a wide variety of functional groups, thus avoiding protection-group chemistry. One practical advantage of these reactions is the ease of handling palladium, which is stable and can be handled without rigorous exclusion of air. Another important aspect to be considered is that solvents can coordinate and stabilize palladium catalysts in different degrees, thus modulating the reaction rate.

The results reviewed also demonstrate that, in the Pd-catalyzed reactions, the role of the catalytic species is critically important. Profound changes of the reaction course and product yields are obtained by changing the catalyst. For example, the reactivity of palladium acetate and halides are quite different. Careful selection of the reaction conditions in term of catalyst and solvent happens to be determinant.

One key component of the Pd(II) oxidation catalysis is the demand of an oxidant agent. The majority of palladium-mediated oxidation reactions still require a terminal oxidant other than molecular oxygen, and the factors underlying these limitations are not fully understood. The ongoing elucidation of mechanistic principles will play an important role in guiding the development of new catalysts, especially when operating in very mild conditions. On the other hand, the use of an efficient oxidation system for the palladium is of great importance to favor a major impact on industry.

The good regio- and stereoselectivity, which are essential for practical organic syntheses, of Pd(II)-mediated olefins functionalization must be underlined. However, some challenges remain regarding the use of new chiral ligands to improve asymmetric catalysis. Finally, palladium-catalyzed reactions in general minimize waste byproducts, thus belonging to the environmentally friendly chemical processes.

## 8. List of Abbreviations

| | |
|---|---|
| Acac | acetylacetonate |
| BINAP | 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl |
| Boc | *t*-butoxycarbonyl |
| BOXAX | 2,2′-bis(4-alkyloxazolyl)-1,1′-binaphthyl |
| BQ | 1,4-benzoquinone |
| Cbz | benzyloxycarbonyl |
| Cy | cyclohexyl |
| Dba | dibenzylideneacetone |
| DCE | 1,2-dichloroethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| Dppb | bis(diphenylphosphino)butane |
| DME | 1,2-dimethoxyethane |
| DIOP | (−)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane |
| DPP | 4,7-diphenyl-1,10-phenanthroline |
| DIPEA | diisopropylethylamine |
| EDTA | ethylenediaminetetraacetic acid |
| EOA | ethyl orthoacetate |
| FePc | iron phthalocyanine |
| HPMoV | molybdovanadophosphoric heteropolyacid |

| | |
|---|---|
| HQ | 1,4-hydroquinone |
| IMes | *N*,*N*′-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene |
| IPr | *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene |
| $Me_2$-ACDB | ethyl 2,3-dibromo-3-methylbutanoate |
| METBOX | 2,2′-methylbis[(4*S*)-4-*tert*-butyl-2-oxazoline] |
| MOA | methyl orthoacetate |
| MOM | methoxymethyl |
| MS | molecular sieves |
| NHC | *N*-heterocyclic carbene |
| Ns | *p*-nitrobenzenesulphonyl |
| PEG | polyethylene glycol |
| Ph-ACDB | ethyl 2,3-dibromo-3-phenylpropanoate |
| PMB | *p*-methoxybenzyl |
| SEM | 2-(trimethylsilyl)ethoxymethyl |
| SPRIX | spiro bis(isoxazoline) ligand |
| TBDMS | *t*-butyldimethylsilyl |
| TBDPS | *t*-butyldiphenylsilyl |
| TBHP | *t*-butyl hydroperoxide |
| TCB | 1,2,4-trichlorobenzene |
| TEA | triethylamine |
| TIPS | triisopropylsilyl |
| TMS | trimethylsilyl |
| TMU | tetramethylurea |
| Ts | tosyl |

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## 10. References

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