Synthesis of Heterocycles via Palladium π-Olefin and π-Alkyne Chemistry

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Received September 30, 2003

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1. Introduction

Palladium is probably the most versatile and widely used metal for the synthesis of heterocycles today. Palladium has found such wide utility because it effects an extraordinary number of very different reactions, including many carbon−carbon bond-forming reactions, under relatively mild reaction conditions. Furthermore, palladium can usually be used in only catalytic amounts and tolerates a wide variety of functional groups, thus avoiding protection group chemistry. Most palladium-based methodology proceeds stereo- and regioselectively in excellent yields. Thus, a number of books[1] and major review articles[2] have been published on various aspects of organopalladium chemistry, including one book devoted exclusively to heterocyclic synthesis.[1g]

In this review, we will cover the many processes involving palladium π-olefin and π-alkyne chemistry which have been developed to prepare heterocycles, with the emphasis on fundamental processes used to generate the ring systems themselves. Methodology for the simple functionalization of heterocycles will not be discussed. The synthesis of heterocycles via π-allylpalladium chemistry will be discussed in a neighboring review by Professor Yoshinori Yamamoto. We anticipate reviewing the many, very important approaches to heterocycles via palladium oxidative addition/reductive elimination chemistry soon.

2. Palladium Chemistry—General Comments

Palladium is a member of the nickel triad in the periodic table. Palladium complexes exist in three oxidation states: Pd(0), Pd(II), and Pd(IV). The facile interconversion between these oxidation states is responsible for the broad utility of palladium in organic chemistry, since each oxidation state exhibits different chemistry. Palladium(0) complexes are fairly nucleophilic, rather labile, and also easily oxidized, usually to the Pd(II) state. The most synthetically useful Pd(0) chemistry is based on the oxidative addition of aryl, vinylic, or allylic halides or triflates to Pd(0). This chemistry can be very useful for the synthesis of heterocycles and will be reviewed separately.

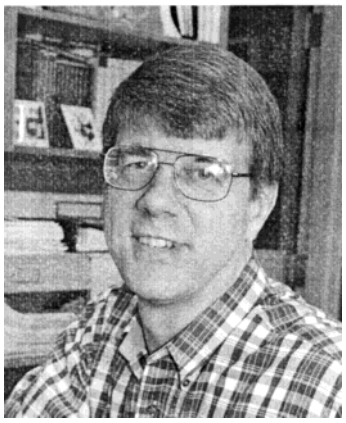
Palladium(II) complexes are extremely important in organopalladium chemistry. They are typically electrophilic, soluble in most common organic solvents, and stable to air. Thus, they are easily stored and handled. The most common organic substrates for Pd(II) are electron-rich species, such as olefins, alkynes, and arenes. Some of the most useful Pd(II) chemistry is based on the fast and reversible formation of Pd(II) complexes with olefins and alkynes, which undergo subsequent attack by nucleophiles. That chemistry will be the focus of this review. Numerous Pd(II) complexes of the type L_2PdCl_2 are easily formed from $PdCl_2$ and the appropriate ligand L. The most useful Pd(II) complexes are $PdCl_2(PPh_3)_2$,[3] $Pd(OAc)_2$,[4] and $PdCl_2(RCN)_2$.[5]

Pd(IV) complexes are quite rare, although a few complexes are known.[6] These complexes have been little explored, but transient Pd(IV) species have been increasingly implicated as intermediates in palladium reactions. They appear to play little role in palladium π-olefin and π-alkyne chemistry directed toward heterocyclic synthesis.

There are a large number of organic reactions, which palladium catalyzes, that generate heterocycles. This review will focus on the more recent developments in palladium-catalyzed cyclization pro-

10.1021/cr020085h CCC: $48.50
Published on Web 02/20/2004

Gilson Zeni was born in 1970 in Irai, Brazil. He received his M.S. degree from the Federal University of Santa Maria-RS (south Brazil) in 1996, working under the direction of Professor A. L. Braga, and his Ph.D. degree (1999) under the direction of Professor J. V. Comasseto (the University of São Paulo). He then moved to the Federal University of Santa Maria, where he is now an associate professor. His current research interests center around the synthesis and reactivity of organochalcogen compounds, the development of new synthetic methods, and novel catalysts for cross-coupling reactions of vinylic tellurides. He is currently a visiting faculty member in the research group of Professor Larock.



Richard C. Larock was born in Berkeley, CA, in 1944 and raised in the San Francisco Bay Area. He received his B.S. degree summa cum laude in Chemistry at the University of California at Davis in 1967. Dr. Larock received an NSF Graduate Fellowship to pursue his graduate training at Purdue University, working with Nobel Laureate Herbert C. Brown on the mercuration of organoboranes. After obtaining his Ph.D. degree in 1971, he received an NSF Postdoctoral Fellowship to work with Nobel Laureate E. J. Corey at Harvard University. In 1972 he joined the organic faculty at Iowa State University, where he is presently University Professor of Chemistry. He has received a DuPont Young Investigator Award, an Alfred P. Sloan Foundation Award, two Merck Academic Development Awards, the 2003 ACS Edward Leete Award, and most recently the 2004 Paul Rylander Award of the Organic Reactions Catalysis Society and a 2004 ACS Arthur C. Cope Senior Scholar Award. His current research interests include new synthetic methods involving organopalladium migration, cyclization, and annulation chemistry and the electrophilic cyclization of alkynes, plus the synthesis of industrially useful oils and polymers from natural oils, such as soybean oil.

cesses involving Pd π-olefin and π-alkyne complexes. Heterocycles prepared via π-allylpalladium intermediates or palladium oxidative addition/reductive elimination chemistry will not be considered in this review.

3. Cyclization of π-Olefin and π-Alkyne Palladium Complexes

3.1. General Comments

The intramolecular cyclization of palladium π-olefin and π-alkyne complexes is a powerful method for the construction of heterocycles. This process normally involves the fast and reversible complexation of the olefin or alkyne by a Pd(II) salt. The resulting π-olefin or π-alkyne complexes are stable but reactive in the presence of a nucleophile. Nucleophilic attack on the π-olefin species usually occurs anti to the metal at the more substituted vinylic carbon to give a σ-alkylpalladium(II) complex, which may then undergo a wide variety of processes resulting in the final heterocycle. Depending on the reaction conditions, these subsequent processes may involve palladium β-hydride elimination, reduction, nucleophilic substitution of the metal, transmetalation, or various insertion processes as outlined in Scheme 1. Pd(0) is usually produced in the final step, which means that a reoxidant is required to transform Pd(0) to Pd(II) to affect a process catalytic in palladium. Reoxidants commonly used are $O_2/CuCl_2$, benzoquinone, O_2/DMSO, $FeCl_3$, and $K_2S_2O_8$. The mechanistic details of these processes have been reviewed a number of times[1] and will not be covered here. The Pd(II)-catalyzed reactions of simple alkenes and dienes, olefins bearing internal nucleophiles, and alkynes thus provides a very valuable approach to a wide range of heterocycles, which will be discussed in the following sections.

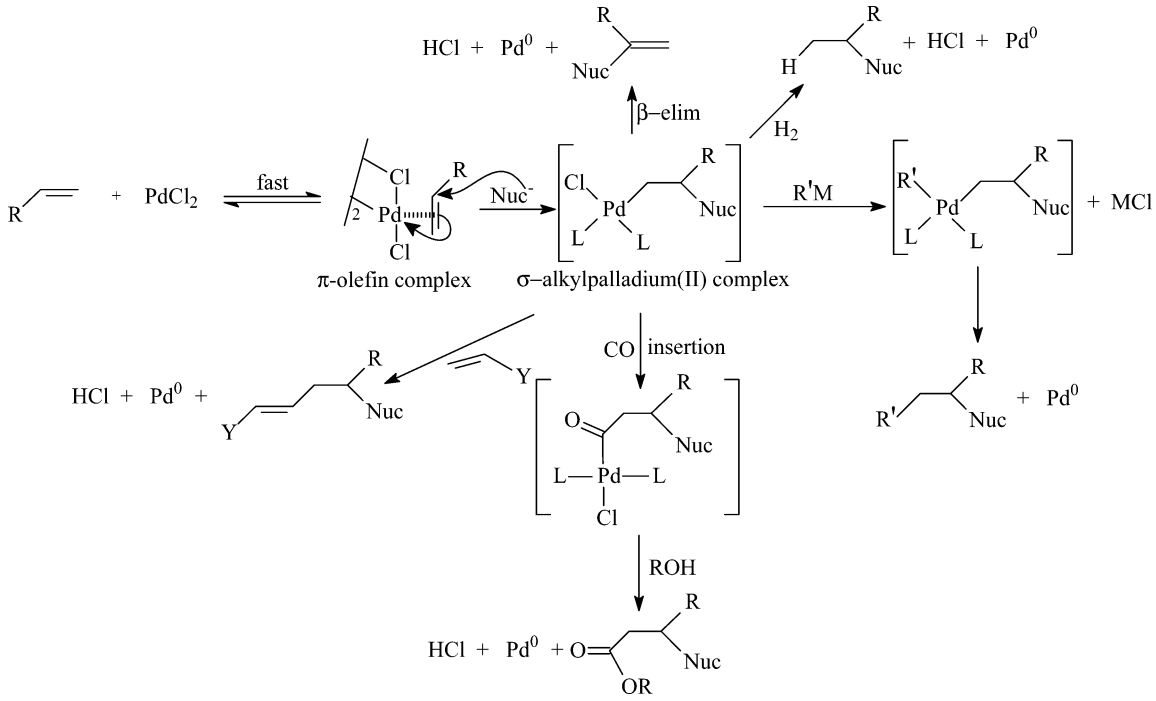
3.2. Cyclization of Alkenes

3.2.1. Cyclization of Olefinic Phenols

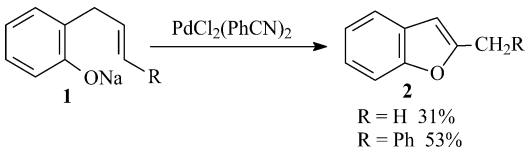
Alkenes bearing a phenol at an appropriate distance from the carbon−carbon double bond can readily undergo palladium(II)-catalyzed intramolecular cyclization to generate a wide variety of oxygen heterocycles under mild reaction conditions.[7] The first report of the synthesis of a benzofuran by such a cyclization appeared in 1973 when the sodium salts of phenols **1** were cyclized to 2-substituted benzofurans **2** using stoichiometric amounts of $PdCl_2(PhCN)_2$ (Scheme 2).[8]

Subsequently, the Hosokawa group studied the intramolecular oxypalladation of a variety of allylic phenols. 2-Allylic phenols undergo either 5-exo-trig or 6-endo-trig cyclizations depending on the catalyst system used. Phenols **3** bearing relatively simple allylic groups react with NaOMe and stoichiometric amounts of $PdCl_2(PhCN)_2$ or $Pd(OAc)_2$ or catalytic amounts of $Pd(OAc)_2$ plus $Cu(OAc)_2 \cdot H_2O$ to afford exclusively five-membered ring products **4** in moderate yields (Scheme 3).[9] Analogous reactions using $PdCl_2$ on 2-(3-methyl-2-butenyl)phenol (**5**) afford predominantly the six-membered ring ether **6** (Scheme 4). However, a mixture of the six-membered ring ethers **6** and **7** was obtained using $PdCl_2$ plus NaOAc or $Pd(OAc)_2$.[10] A mixture of five-membered ring double-bond isomers **9** and **10** has been observed in the reaction of 2-(2-cycloalkenyl)phenols such as **8**

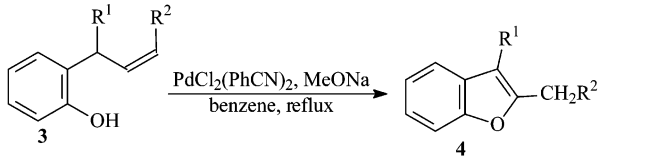
Scheme 1. Reaction Pathways Available to π-Olefin Palladium(II) Complexes



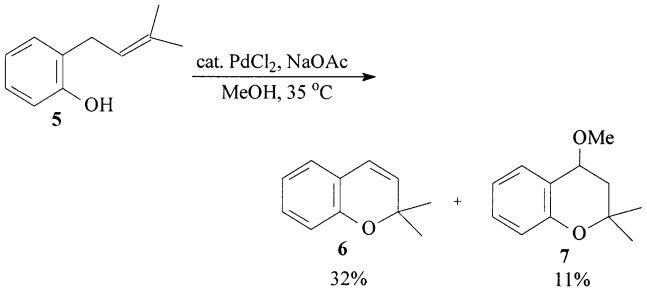
Scheme 2



Scheme 3

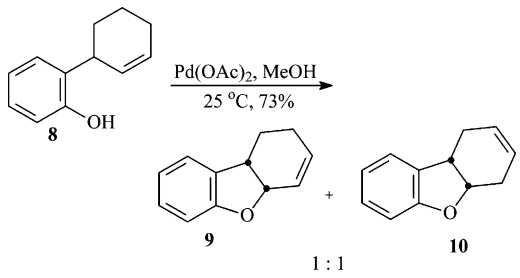


Scheme 4

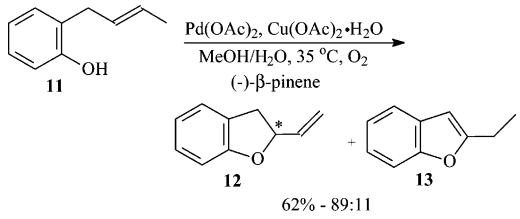


when using a stoichiometric amount of $Pd(OAc)_2$ (Scheme 5). Early attempts to effect the enantioselective cyclization of 2-(2-butenyl)phenol (**11**) using a stoichiometric amount of a chiral Pd catalyst plus (−)-*β*-pinene as the source of chirality, in the presence of O_2 and $Cu(OAc)_2$, afforded a mixture of five-membered ring ethers **12** and **13** with only moderate enantioselectivities (Scheme 6).[11]

Scheme 5



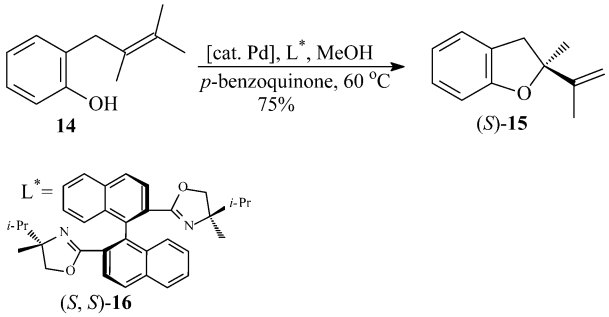
Scheme 6



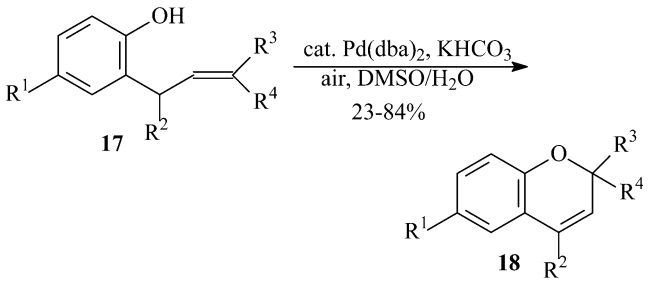
Recently, Uozumi and co-workers demonstrated that 2-(2,3-dimethyl-2-butenyl)phenol (**14**) can be cyclized to the corresponding five-membered ring ether **15** with high enantioselectivity using 10 mol % $Pd(O_2CCF_3)_2$, a chiral ligand **16,** and benzoquinone as a reoxidant (Scheme 7).[12] The yields and enantioselectivities in this system are strongly dependent on the anionic ligands present in the Pd catalyst and the ratio of ligand to Pd salt. Best results are obtained using 10 mol % $Pd(O_2CCF_3)_2$[13] and 5 mol % $[Pd(MeCN)_4](BF_4)_2$.[14]

We have reported that a catalytic amount of $Pd(dba)_2$ in the presence of oxygen and DMSO provides

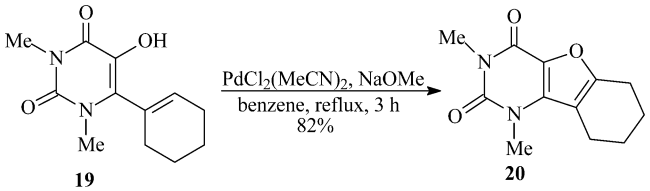
Scheme 7



Scheme 8



Scheme 9



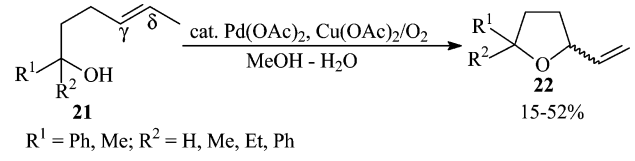
an excellent catalyst for the cyclization of *o*-allylic phenols **17** to benzopyrans **18** (Scheme 8).[15] Optimal conditions for this cyclization utilize the *o*-allylic phenol **17** (0.5 mmol) and $KHCO_3$ (0.55 mmol) in 9:1 DMSO/water (10 mL) at 60 °C in the presence of air. The process is highly regioselective, accommodates a variety of substitution patterns in the aryl ring and allylic moiety, proceeds in good to excellent yields, and utilizes air as the sole reoxidant for Pd.

3.2.2. Cyclization of Olefinic Alcohols

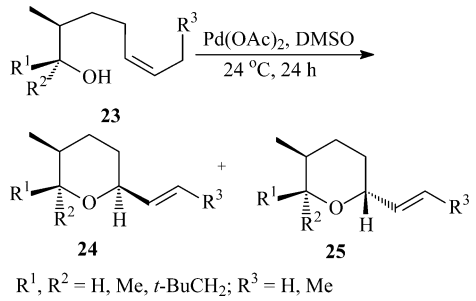
The palladium(II)-catalyzed intramolecular cyclization of alkenes bearing an alcohol group at an appropriate distance from the carbon−carbon double bond is a versatile way to generate a wide variety of oxygen heterocycles under mild reaction conditions. Thus, 5-hydroxyuracil **19** is cyclized to pyrimidine-2,4-dione **20** in an 82% yield by refluxing with a stoichiometric amount of $PdCl_2(PhCN)_2$ in benzene in the presence of NaOMe for 3 h (Scheme 9).[16]

In 1976, the γ,δ-unsaturated alcohols **21** were cyclized to 2-vinyltetrahydrofurans **22** using only a catalytic amount of $Pd(OAc)_2$ plus catalytic amounts of $Cu(OAc)_2$ and O_2 as a reoxidant in $MeOH/H_2O$ at room temperature for 24 h (Scheme 10).[17] Under these reaction conditions, the tetrahydrofurans **22** were obtained in only moderate yields as a mixture of diastereoisomers. Whether the process proceeds by

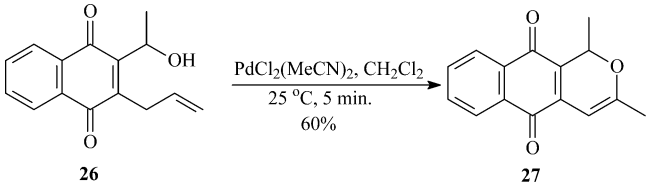
Scheme 10



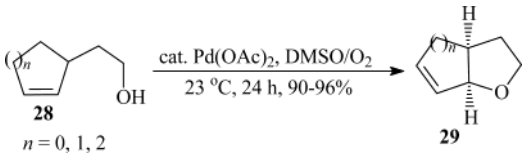
Scheme 11



Scheme 12



Scheme 13



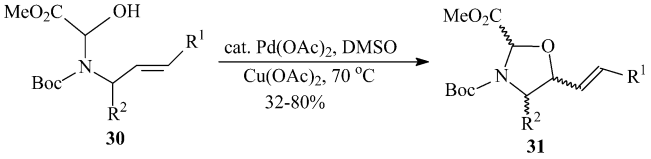
an *exo* or *endo* cyclization depends on the substituent in the δ-position of the alcohol **21**. The presence of two methyl groups in the δ-position affords the six-membered ring *endo* product. When the substituent is a simple ethyl group, the five-membered ring *exo* product is obtained.

The intramolecular alkoxypalladation of alkenols using DMSO as the solvent allows one to control the subsequent β-hydride elimination. This has been used to introduce a trans double bond into the side chain of 2,6-disubstituted tetrahydropyrans (Scheme 11).[18] Thus, the hydroxyalkenes **23** have been allowed to react with a stoichiometric amount of $Pd(OAc)_2$ in the presence of DMSO to produce a mixture of the tetrahydropyrans **24** and **25**. When other solvents, such as DMF, acetic acid, CH_3CN, or THF, were used, low yields and selectivities were obtained.

The cyclization of *o*-alkenylbenzylic alcohols to the corresponding isochromenes has been described by Giles and co-workers (Scheme 12).[19] For example, the treatment of 2-allyl-3-(1-hydroxyethyl)-1,4-naphthoquinone (**26**) with stoichiometric amounts of $PdCl_2(MeCN)_2$ in dry dichloromethane afforded 1,3-dimethylbenzoisochromenequinone **27** in a 60% yield, together with 28% of the starting material.

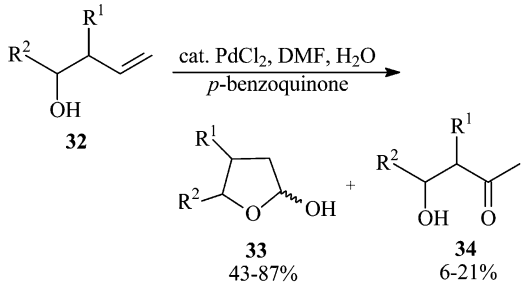
The Pd(II)-catalyzed intramolecular cyclization of cyclic alkenols using molecular oxygen as the reoxidant provides a useful route to bicyclic olefinic ethers (Scheme 13).[20] The most promising results were

Scheme 14



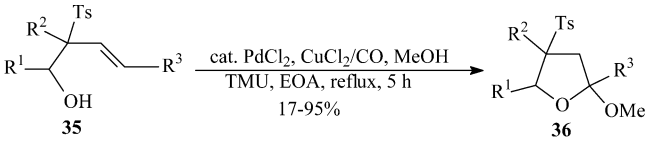
R^1 = Me, Pr, H; R^2 = Me, H; R^3 = H, Me

Scheme 15



R^1 = CH_3, $(CH_2)_7CO_2CH_3$, CO_2CH_3, SO_2-*p*-Tol, OCH_2Ph
R^2 = H, *n*-C_6H_{13}, *n*-C_5H_{11}, CH_2OCO_2H, CH=$CHCH_3$

Scheme 16



R^1 = $PhCH_2CH_2$, $CH_3(CH_2)_8$, $(CH_3)_2CHCH_2$, Ph, CH_3, H
R^2 = H, $PhCH_2$
R^3 = H, CH_3

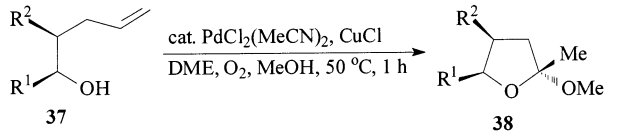
obtained when the alkenol **28** was allowed to react with $Pd(OAc)_2$ in O_2/DMSO at room temperature. The addition of LiCl or K_2CO_3 was found to inhibit the reaction, and the use of DMSO/1,4-benzoquinone as solvent/reoxidant was found to give the cyclized product **29** together with a larger amount of the homoallylic isomer.

In a related study, Hiemstra showed that the oxazolidines **31** are formed through oxypalladation and subsequent β-hydride elimination of the *N*-Boc-protected allylic amines **30** (Scheme 14).[21] The cyclization took place in good yield using $Pd(OAc)_2$ as the catalyst and an excess of $Cu(OAc)_2$ as the reoxidant. The only product observed was that of 5-*exo* cyclization.

Alkenols also undergo Wacker-type oxidations when subjected to palladium(II) salts. For example, Nokami has shown that γ-butyrolactols can be obtained by the oxypalladation of 1-alken-4-ols **32** using $PdCl_2$/*p*-benzoquinone or $PdCl_2/CuCl_2/O_2$ in DMF at room temperature (Scheme 15).[22] The γ-butyrolactols **33** are formed in 43−87% yields alongside smaller amounts of hydroxyketone side-products **34**.

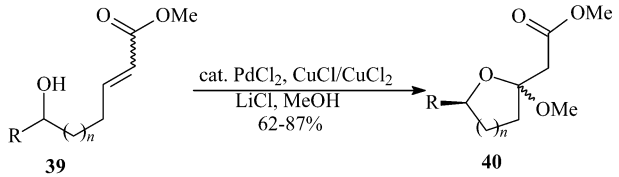
Several furan derivatives **36** have been prepared through the Pd(II)-catalyzed intramolecular cyclization of 2-(*p*-toluenesulfonyl)-3-alkenols **35** (Scheme 16).[23] The best results have been obtained when the cyclization is carried out using *N*,*N*,*N*,*N*-tetramethylurea (TMU) to quench the HCl produced, together with ethyl orthoacetate (EOA), anhydrous $CuCl_2$, and $PdCl_2$.

Scheme 17



R^1 = CH_3, *n*-Pr; R^2 = CO_2Me, CH_2OH 71-80% yields 81-88% de's

Scheme 18



R = CH_2Ph, *n*-C_7H_{15}, *n*-C_5H_{11}; *n* = 1, 2

The Pd(II)-catalyzed diastereoselective cyclization of hydroxyalkenes **37** to methoxytetrahydrofurans **38** has been described by Hosokawa and co-workers (Scheme 17).[24] Thus, the cyclization of enantiomerically pure (*2S*,*3S*)-hydroxyalkenes **37** in methanol in the presence of catalytic amounts of $PdCl_2(MeCN)_2$ and $CuCl/CuCl_2$ under O_2 gives tetrahydrofurans **38** in 71−80% yields and 81−88% de's. Under the same reaction conditions, the 1,1-dimethyl-substituted olefin gives only a low yield and de.

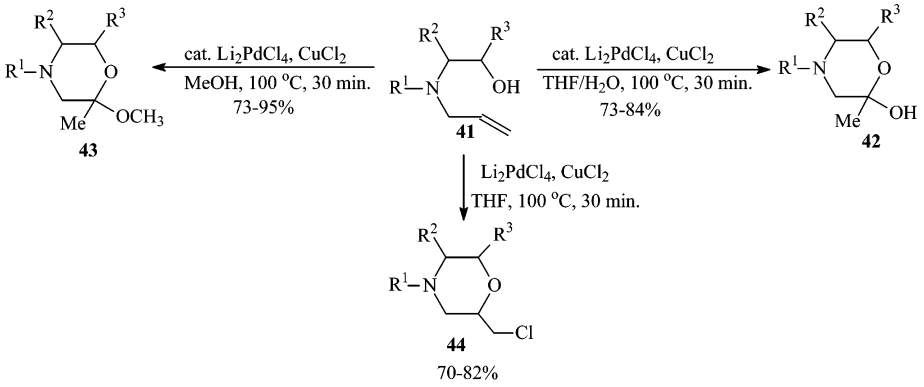
In 1992 Sturgess and co-workers reported the conversion of hydroxy-substituted α,β-unsaturated esters to furan-containing, protected β-ketoesters under essentially neutral reaction conditions (Scheme 18).[25] Thus, the oxidation of alkenols **39** gives protected β-ketoesters **40** by intramolecular nucleophilic addition of the alcohol group to the carbon−carbon double bond in the presence of Pd(II) as a catalyst. The best results were obtained using a mixture of CuCl (3 equiv) and $CuCl_2$ (3 equiv) as the reoxidant in the presence of LiCl and a catalytic amount of $PdCl_2$ in methanol. It was found that either the use of less reoxidant or the absence of LiCl was detrimental to the yield of **40**.

Three types of morpholine products **42**−**44** have been obtained from the same hydroxyalkene **41** by slight variations in the $Li_2PdCl_4/CuCl_2$ reagent system employed (Scheme 19).[26] In each of the three procedures, both Pd(II) and Cu(II) are necessary to affect the reaction. No cyclization occurs when only the Pd(II) salt is used. In the formation of product **44**, a stoichiometric amount of the Pd salt is necessary.

The oxidations of 1-alken-4-ols **45** to 2-alkoxytetrahydrofurans by $PdClNO_2(MeCN)_2$ in the presence of $CuCl_2/O_2$ in *tert*-butyl alcohol has been described by Feringa and co-workers (Scheme 20).[27] When the carbon chain of the hydroxyalkene is lengthened by one carbon, both five- and six-membered ring ethers are formed. Formation of the six-membered ring is less favorable than formation of the five-membered ring **46**. The reaction proceeds in high selectivity either with or without a substituent in the allylic position.

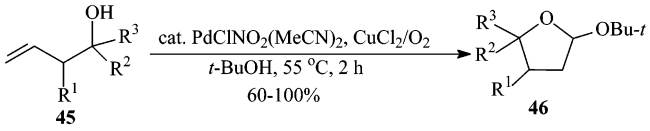
The olefinic alcohols **47** and **48**, having alkoxy and 1,3-dioxolane susbstituents, have been subjected to

Scheme 19



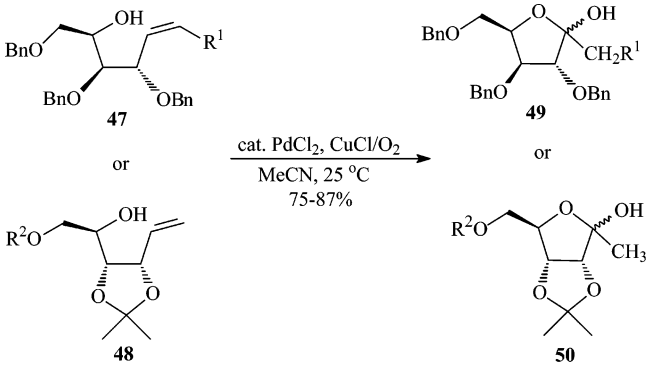
R^1 = $PhCHCH_3$, Bn, CH_3; R^2 = H, CH_3; R^3 = H, CH_3, Ph

Scheme 20



R^1 = H, CH_3; R^2 = H, CH_3, C_6H_5; R^3 = H, CH_3, CH_3CH_2, C_6H_5

Scheme 21



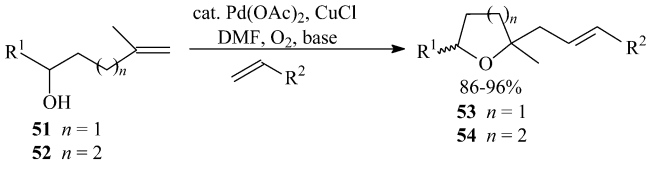
R^1 = H, CH_3, n-C_5H_{11}; R^2 = H, Bn, TBS

oxidative cyclization using $PdCl_2-CuCl_2-O_2$ in aqueous MeCN at room temperature (Scheme 21).[28] The hemiketals **49** and **50** were found to be the exclusive products formed in good yields. This intramolecular oxidative cyclization proceeds by a 5-*exo* mode cyclization leading to the corresponding five-membered ring ethers.

When alkenols possessing a terminal double bond and a substituent in the 2-position of the alkene are subjected to intramolecular oxypalladation, palladium β-hydride elimination is impossible in the resulting organopalladium intermediate, which can be trapped by external olefins in a Heck-type olefination (Scheme 22).[29] Thus, the reactions of 5-hydroxy-1-alkenes **51** and 6-hydroxy-1-alkenes **52** with catalytic amounts of $Pd(OAc)_2$ and $CuCl/O_2$ as a reoxidant form the furans **53** or pyrans **54,** respectively. The olefin products are not formed when benzoquinone or $CuCl_2-O_2$ are employed as reoxidants, instead of CuCl.

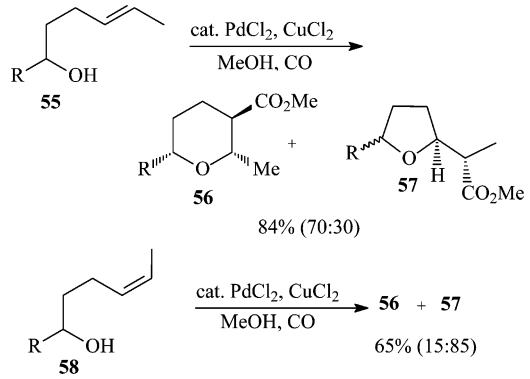
The oxypalladation of hydroxyalkenes and subsequent carbonylation can provide a very useful route

Scheme 22

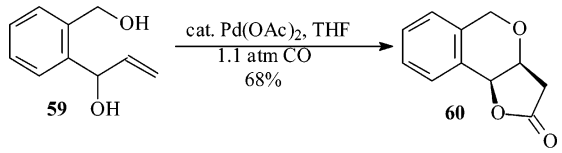


R^1 = H, Me_2CHCH_2; R^2 = COMe, CO_2Me, Ph; base = NaOAc or $NaHCO_3$

Scheme 23



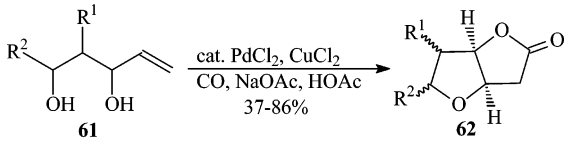
Scheme 24



to a wide variety of cyclic ethers. Semmelhack and co-workers studied the effect of the alkene geometry on the selectivity for pyran or furan formation (Scheme 23).[30] Using catalytic amounts of $PdCl_2$ plus stoichiometric amounts of $CuCl_2$ in methanol as the solvent at room temperature under 1.1 atm of CO, the *E* isomers **55** give mainly the six-membered ring pyrans **56** and the *Z* isomers **58** afford mainly the five-membered ring furans **57**.[31]

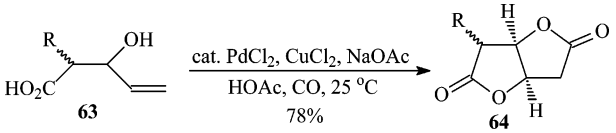
The palladium-promoted carbonylative cyclization of olefinic diols **59** provides a very useful route to lactone-containing ethers **60** (Scheme 24).[32] The use of $Pd(OAc)_2$ in THF under 1.1 atm of CO produces better results than the standard conditions usually used for oxypalladation ($PdCl_2/CuCl_2/CO$). The reac-

Scheme 25

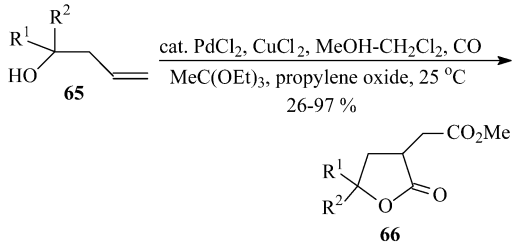


R^1 = H, CH_2Ph, CH_2CH_2OH; R^2 = H, Ph

Scheme 26



Scheme 27



R^1; R^2 = H, Me, CH_2CH_2Ph, *c*-C_6H_{10}

tion generally produces good yields with moderate stereoselectivities, and formation of the *cis*-lactone is favored over formation of the *trans*-lactone.

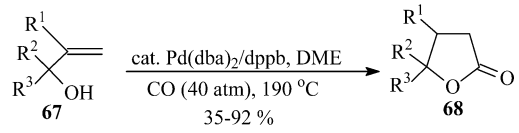
In a closely related investigation, Yoshida and Tamaru reported the use of 1,3-diols **61** as precursors to *cis*-lactones **62** via oxypalladation/carbonylation catalyzed by Pd(II) (Scheme 25).[33] These reactions were conducted in acetic acid plus NaOAc, using $PdCl_2/CuCl_2$ as the catalyst system under a CO atmosphere. The cyclization proceeds at room temperature with high stereoselectivity (only the *cis*-lactone was obtained), and the products are formed in moderate to good yields. The yields of the reaction are dependent on the substitution pattern of the diol **61**. The presence of a methyl group at either C_4 or C_5 lowers the yield.

In a similar manner, the double cyclization of 3-hydroxy-4-pentenoic acids **63** provides bis-lactones **64** (Scheme 26).[34] The effect of substitution at C_2 and on the double bond of the 3-hydroxy-4-pentenoic acids was studied. It was found that substituents at C_2 increase the reactivity of the substrate and terminal double bonds are more reactive than more substituted double bonds. The reaction exhibits high stereoselectivity with only *cis*-products being formed.

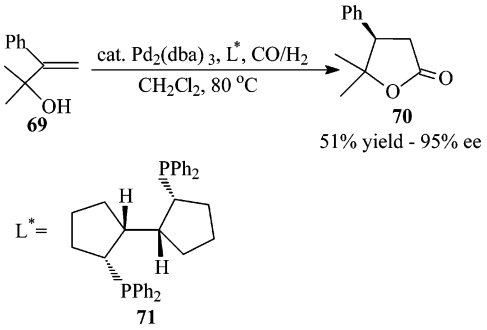
Using similar reaction conditions, simple 1-alken-4-ols **65** can be cyclized to butyrolactones **66** (Scheme 27).[35] The choice of additives is crucial for the success of this process. The best results are obtained when propylene oxide is used as an additive.

Alper and co-workers reported the Pd-catalyzed cyclization of allylic alcohols **67** to butyrolactones **68** in good yields using catalytic amounts of $Pd(dba)_2$/dppb in DME under 40 atm pressure of CO at 190 °C (Scheme 28).[36] The use of other bidentate phosphines, such as dppe or dppp, or other Pd complexes gave lower yields. Mechanistically, this process is

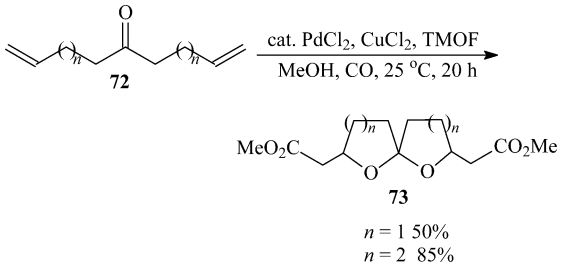
Scheme 28



Scheme 29



Scheme 30



probably quite different from the other palladium π-olefin chemistry described herein.

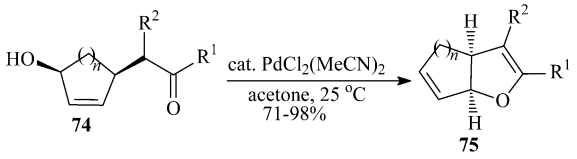
Using somewhat different reaction conditions, the asymmetric Pd-catalyzed cyclization of allylic alcohols, such as **69**, to lactones, such as **70**, has been described by Zhang and Cao (Scheme 29).[37] Their process has been carried out using either $Pd_2(dba)_3$ or $Pd(OAc)_2$ as the catalyst and a chiral 1,4-bisphosphine **71** to afford γ-butyrolactones in good yields and high enantioselectivities.

3.2.3. Cyclization of Olefinic Ketones

The use of an oxygen atom from the carbonyl group of an alkenone as a nucleophile in Pd(II)-catalyzed intramolecular C−O bond formation has been described (Scheme 30).[38] Thus, spiroacetals **73** can be prepared by the Pd-catalyzed double cyclization of dienones **72** with simultaneous introduction of two carbomethoxy groups in the side chains. The use of a catalytic amount of $PdCl_2$ in the presence of $CuCl_2$, CO, methanol, and trimethylorthoformate (TMOF) in a single operation afforded spiroacetals **73** in moderate to good yields.

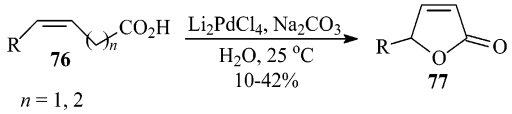
The bicyclic dihydrofurans **75** are obtained from *cis*-1,4-disubstituted cyclopentenones **74** in 71−98% yields using $PdCl_2(MeCN)_2$ as a catalyst (Scheme 31).[39] The reaction is most efficient with a hydroxyl group as a leaving group. The corresponding acetate derivatives afforded the cyclization products in lower yields and required a longer reaction time. This process apparently involves cyclic oxypalladation followed by palladium hydroxide elimination.

Scheme 31



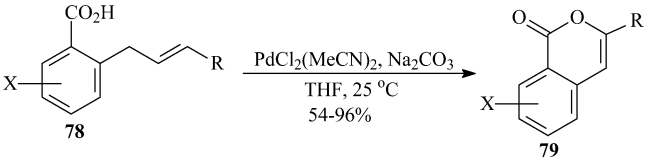
R^1 = Me, Ph, *n*-Bu, CH_2CO_2Me, OEt, OMe; R^2 = COMe, COPh, CO_2Me, NO_2
n = 1, 2

Scheme 32



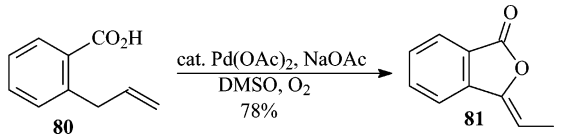
n = 1, 2

Scheme 33



R = Me, Et, *i*-Pr; X = H, 6-Cl, 7-OMe

Scheme 34



3.2.4. Cyclization of Alkenoic Acids

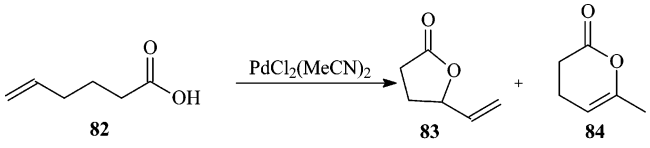
The cyclization of alkenoic acids to unsaturated lactones is a very valuable synthetic transformation most commonly effected by a two-step process involving electrophilic cyclization and subsequent elimination.[40] However, this process can be achieved in one synthetic step employing Pd. This transformation, employing stoichiometric or catalytic amounts of Pd, produces lactones via acyloxypalladation and subsequent, immediate, room-temperature palladium hydride elimination.

An early investigation by Kasahara and co-workers reported the Pd-catalyzed cyclization of 3- and 4-alkenoic acids **76** to butenolides **77** in low yields using stoichiometric amounts of Li_2PdCl_4 (Scheme 32).[41]

Hegedus and co-workers simultaneously showed that isocoumarins **79** can be obtained from 2-allylbenzoic acids **78** using a Pd-promoted cyclization involving nucleophilic attack of a carboxylate group on a olefin−Pd complex (Scheme 33).[42] This process affords good yields using a stoichiometric amount of $PdCl_2(MeCN)_2$ and Na_2CO_3 in THF at room temperature. It proceeds by a 6-*endo*-trig pathway and subsequent double bond isomerization.

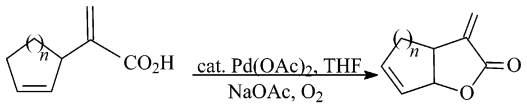
We described similar palladium-catalyzed cyclizations using an experimentally simple, very mild, and versatile procedure employing only catalytic amounts of $Pd(OAc)_2$ and O_2/DMSO as the reoxidant.[43] When employed on 2-allylbenzoic acid (**80**), we obtained the 5-*exo*-trig cyclization product **81** (Scheme 34). This unusual example apparently proceeds by subsequent double-bond isomerization into conjugation. In virtually all other examples reported by us, no double-bond isomerization was observed, presumably because the DMSO strongly coordinates the intermediate palladium hydride, preventing readdition of the palladium hydride to the double bond and subsequent elimination to the isomerized product. Monocyclic, fused and bridged bicyclic, and spirocyclic lactones bearing five- or six-membered rings are formed readily by this process. We found that the relative reactivity of alkenoic acids follows the order disubstituted > trisubstituted > monosubstituted. There appears to be a fine balance between the effects produced by electron density and steric hindrance. In general, five-membered rings are more easily closed than six-membered rings.

Scheme 35



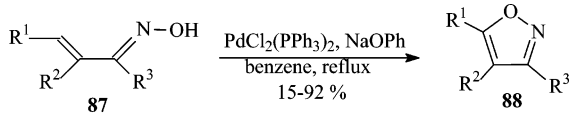
DMSO/Na_2CO_3 70 : 30
MeCN/NaOAc 10 : 90

Scheme 36



n = 1, 2, 3
75-80%

Scheme 37



R^1 = Ph, *i*-Pr; R^2 = H, CH_3; R^3 = Ph, *t*-Bu

Annby and co-workers have shown that the acyclic unsaturated carboxylic acid **82** reacts in the presence of a stoichiometric amount of $PdCl_2(MeCN)_2$ and Na_2CO_3/DMSO to afford a 70:30 ratio of lactones **83** and **84** in a good yield (Scheme 35).[44] The selectivity for formation of either the five- or six-membered ring unsaturated lactone is governed by the choice of solvent and base. Thus, MeCN and NaOAc give a very different ratio of lactones.

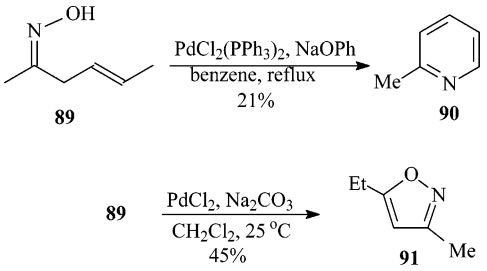
Finally, exo-methylene-γ-butyrolactones **86** can be similarly synthesized from the corresponding 3-cycloalkenyl-3-butenoic acids **85** in good yields using only catalytic amounts of $Pd(OAc)_2$ with NaOAc as the base in THF in the presence of oxygen (Scheme 36).[45]

3.2.5. Cyclization of Olefinic Oximes

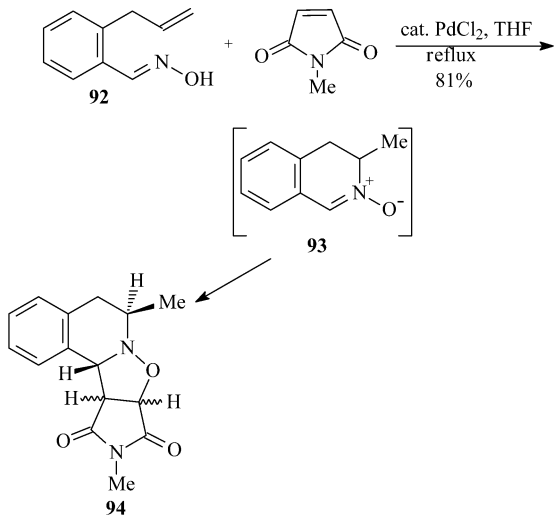
The Pd-promoted cyclization of the oxygen atom of an oxime onto a carbon−carbon double bond was first reported by Murahashi and co-workers (Scheme 37).[46] They observed the formation of isoxazoles **88** from α,β-unsaturated ketoximes **87** using stoichiometric amounts of Pd.

The same group later reported the preparation of pyridine **90** upon reaction of a stoichiometric amount of a Pd(II) complex and oxime **89** (Scheme 38).[47]

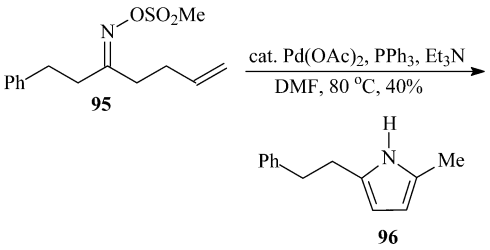
Scheme 38



Scheme 39



Scheme 40

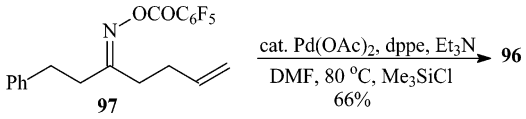


Interestingly, by simply changing the reaction conditions, one can obtain instead isoxazole **91** from the same starting material **89**.

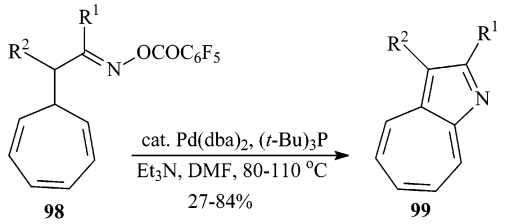
In 1994 Grigg and co-workers described the preparation of a six-membered ring cyclic nitrone **93** by a $PdCl_2$-catalyzed cyclization of alkenyloxime **92** and subsequent trapping to afford heterocycle **94** in an 81% yield (Scheme 39).[48]

Recently, a series of studies on the use of oxime derivatives in Pd-catalyzed cyclizations has been carried out by Narasaka and co-workers.[49] They report that the α,β-unsaturated *O*-sulfoxime **95** readily affords pyrrole **96** after heating with triethylamine and a catalytic amount of $Pd(OAc)_2/Ph_3P$ in DMF (Scheme 40).[50] However, they obtained better results using the *O*-pentafluorobenzoyl oxime **97** as the substrate (Scheme 41). Thus, the Pd-catalyzed cyclization of the *o*-pentafluorobenzoyl oxime, followed by isomerization with trimethylsilyl chloride, afforded the desired pyrrole in a good yield. This process has recently been developed into a general synthesis of azaazulenes (Scheme 42).[51] Thus, substituted 1-azaazulenes **99** have been synthesized

Scheme 41

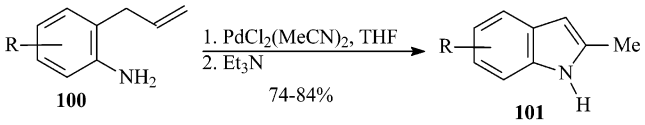


Scheme 42



R^1 = Ph, *t*-Bu, *i*-Pr, Me, Et, HC=CHPh; R^2 = H, Me, Ph

Scheme 43



R = H, 5-Me, 5-CO_2Et, 6-OMe

from cycloheptatrienyl methyl ketone *O*-pentafluorobenzoyloximes **98** in good yields using $Pd(dba)_2/(t\text{-}Bu)_3P$ as the catalyst.

3.2.6. Cyclization of Olefinic Amines

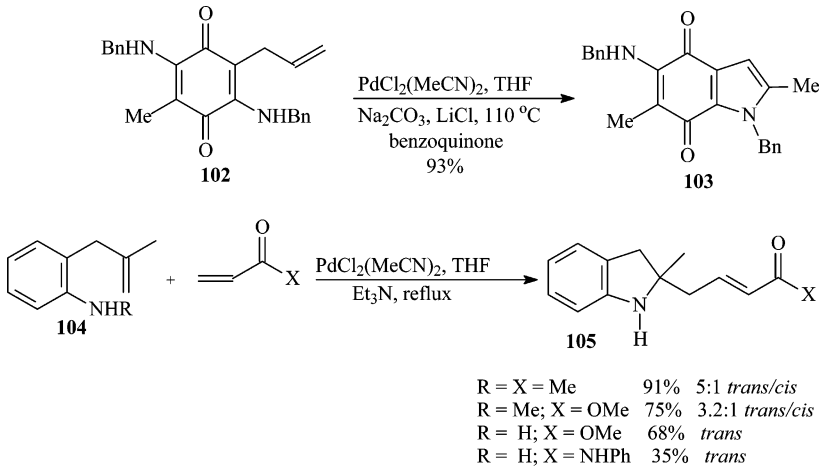
A large number of nitrogen heterocycles can be synthesized by Pd-catalyzed intramolecular cyclization of aminoalkenes.[52] Intramolecular C−N bond formation mediated by Pd compounds was first investigated by Hegedus and co-workers.[53,54] They found that *o*-allylic anilines **100** can be cyclized to 2-methylindoles **101** in high yields under mild reaction conditions using a stoichiometric amount of Pd (Scheme 43). This reaction tolerates not only functional groups on the benzene ring but also alkyl substitution at the 2 or 3 position of the allyl side chain.

This chemistry was subsequently employed for the synthesis of indoloquinones **103** from aminoquinones **102** (Scheme 44).[55] When a methallyl side chain is employed in the anilines **104**, palladium hydride elimination is prevented and the cyclized organopalladium intermediate can be trapped by olefins in a Heck-type process (Scheme 44).

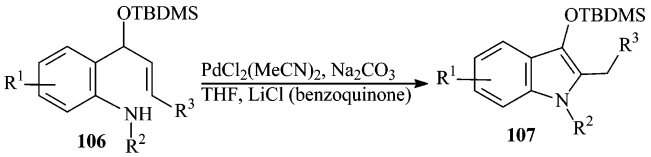
Lau prepared *N*-alkyl-3-(silyloxy)indoles **107** by the intramolecular Pd-promoted cyclization of *N*-alkyl-2-(silyloxyallyl)anilines **106** (Scheme 45).[56] Both catalytic and stoichiometric procedures have been developed using THF as the solvent and $PdCl_2(MeCN)_2$ as the catalyst. Benzoquinone is used in the catalytic process as the reoxidant. The 3-(silyloxy)indoles **107** were obtained in 54−93% (stoichiometric process) and 47−84% (catalytic process) yields.

Using similar reaction conditions, Lau also described the synthesis of 4-azaindoles **109** in very good yields by the Pd-catalyzed intramolecular cyclization of 2-(1-hydroxyallyl)-3-aminopyridines **108** (Scheme 46).[57] The best results were obtained by using 20 mol % $PdCl_2(MeCN)_2$, 1.5 equiv of benzoquinone as reoxidant, 3 equiv of K_2CO_3, and 10 equiv of LiCl in THF.

Scheme 44



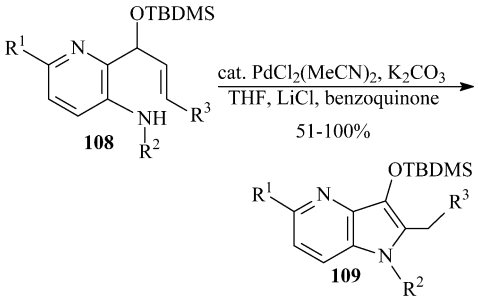
Scheme 45



	yield (%) a	b
R^1 = H; R^2 = Me; R^3 = H	93	77
R^1 = H; R^2 = Me; R^3 = Me	55	50
R^1 = H; R^2 = Me; R^3 = Ph	76	47
R^1 = 4-OMe; R^2 = C_6H_4Br-*p*; R^3 = H	-	84
R^1 = H; R^2 = $CH_2CH{=}CH_2$; R^3 = H	54	54

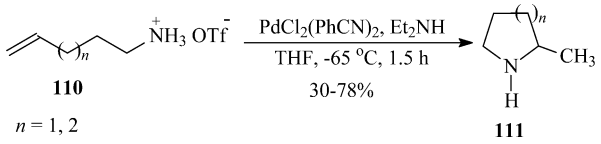
a - stoichiometric; b - catalytic

Scheme 46



R^1 = OMe, Cl; R^2 = Me, *n*-C_3H_7; R^3 = H, Me, Ph

Scheme 47

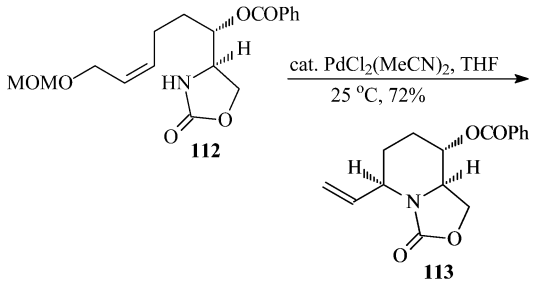


Finally, Venanzi and Pugin[58] cyclized the trifluoromethanesulfonate salts of the aminoalkenes **110** in the presence of stoichiometric amounts of $PdCl_2(PhCN)_2$ and a nitrogen base to produce the corresponding saturated cyclic amines **111** in moderate to good yields (Scheme 47).

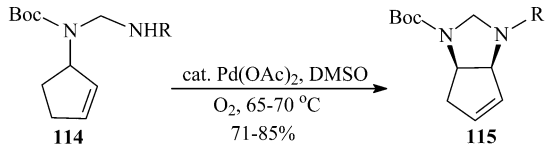
3.2.7. Cyclization of Olefinic Amides

Nitrogen heterocycles can also be readily synthesized from alkenamides by Pd-catalyzed intramolecular C−N bond formation. Optically active bicyclic oxazolidinone **113** has been prepared by the stereocontrolled cyclization of urethane **112** (Scheme 48).[59] The Pd catalyst used was $PdCl_2(MeCN)_2$, and the product was obtained in a 72% yield as a single diastereoisomer.

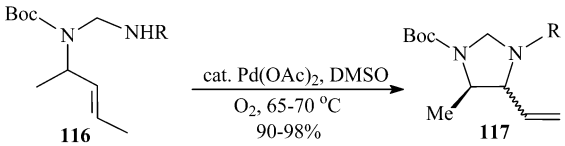
Scheme 48



Scheme 49



R = Ts, CHO, $COCH_3$, $CONH_2$, CO_2Me, CO_2Bn

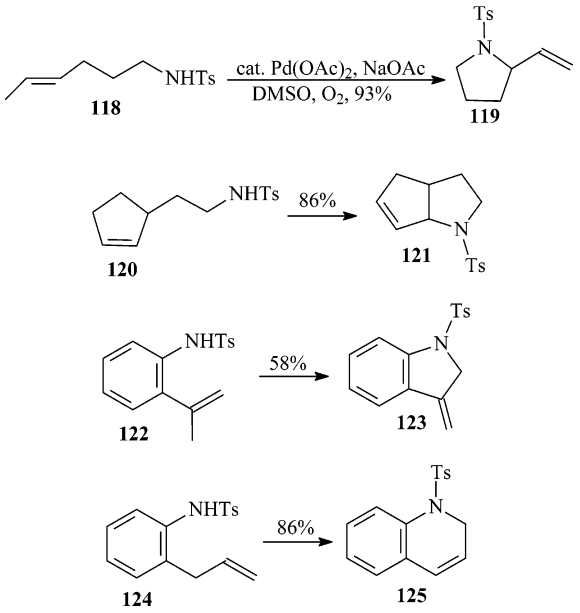


R = Ts, CHO, CO_2Me

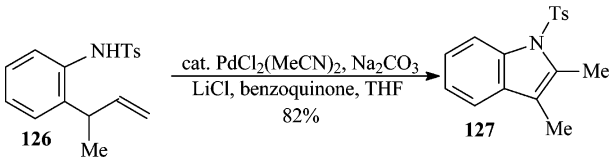
The relative reactivity of the nitrogen atom as a nucleophile in the Pd-catalyzed cyclization of various nitrogen derivatives has been reported (Scheme 49).[60] Thus, urea, acetamide, carbamates, *p*-toluenesulfonamides, and formamides **114** and **116** have been cyclized in excellent yields to five-membered ring imidazolidines **115** and **117**. The reactivity of the amides tested was found to be urea > formamide > *p*-toluenesulfonamide > carbamates > acetamide.

Tosylamides have been widely employed to synthesize nitrogen heterocycles via Pd oxidative cyclization. Various tosylamides will react under standard catalytic Pd cyclization conditions to produce

Scheme 50



Scheme 51



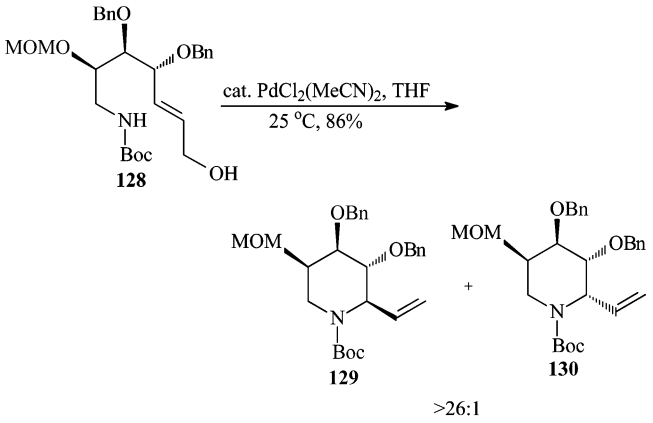
nitrogen heterocycles. Five-membered ring pyrrolidines and pyrroles are obtained as the principal products in most of these cyclizations.[61]

We[62] and others[20] have described the use of Pd(OAc)$_2$ plus DMSO and molecular oxygen as a reoxidant in the cyclization of olefinic tosylamides (Scheme 50). In general, acyclic (**118**), cyclic (**120**), and arene-containing (**122**) tosylamides can be cyclized to five-membered ring products (**119**, **121,** and **123**) containing an allylic nitrogen moiety. Six-membered rings can also be formed by this process. Particularly interesting is the clean cyclization of tosylamide **124** to the six-membered ring derivative **125**. This process appears to be proceeding by way of a π-allylpalladium intermediate rather than Pd π-olefin chemistry. These examples contrast with previous work on the cyclization of olefinic tosylamides **126** using $PdCl_2$, where *N*-vinylic tosylamides and indoles, such as **127**, were formed exclusively (Scheme 51).[63]

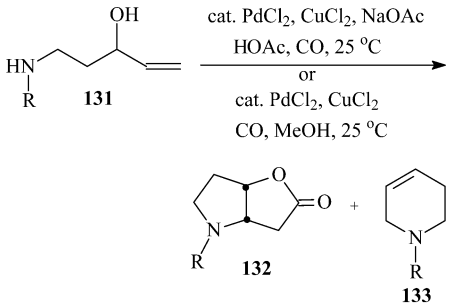
Hirai and co-workers reported the preparation of chiral piperidine derivatives **129** and **130** from the optically active urethane **128** with high intramolecular chirality transfer by Pd-catalyzed cyclization and subsequent palladium hydroxide elimination. They observed that the Pd(II) salts are not reduced and the catalytic system works well without any reoxidant (Scheme 52).[64]

Tamaru and Yoshida developed a very interesting Pd(II)-catalyzed carbonylative cyclization using 3-hydroxypent-4-enylamides **131** as substrates (Scheme 53).[65] Reaction with $PdCl_2/CuCl_2$ in acetic acid under a CO atmosphere affects cyclization and subsequent carbonylation to afford selectively lactones **132** in good yields. This reaction is highly solvent dependent.

Scheme 52

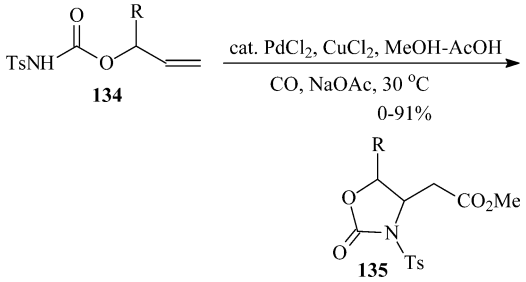


Scheme 53



R = CO_2Me, SO_2Tol

Scheme 54



R = H, CH_3, CH_2CH_2Ph, $CH_2CH(CH_3)_2$, $C(CH_3)_3$

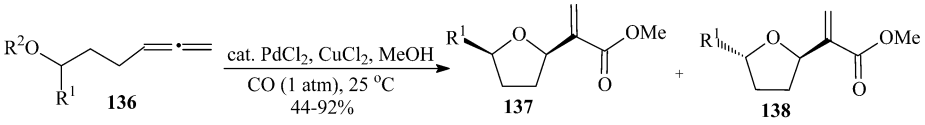
When the reaction is carried out using acetic acid, only the pyrrolidine **132** is observed. However, when using dry methanol as the solvent, a mixture of pyrrolidine **132** and tetrahydropyridine **133** is obtained.

Similar reaction conditions were used to prepare oxazolidinones **135** from carbamates **134** (Scheme 54).[66] The reaction utilizes $PdCl_2$ as the catalyst and $CuCl_2$ as an oxidant for Pd in a mixture of methanol−acetic acid as solvent under 1 atm of CO. Oxazolidinones **135** are obtained in good yields. The cyclization is sensitive to the substituents on the nitrogen and the allylic moiety (R). Only carbamates with a tosyl group on the nitrogen produced the desired product. *N*-Tosyl carbamates with R = *t*-butyl or $PhCH_2CH_2$ afforded the desired products in only low yields.

3.2.8. Cyclization of Dienes

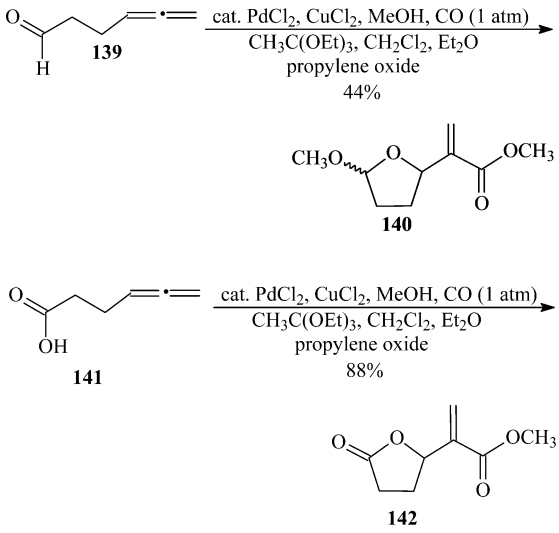
The Pd-catalyzed cyclization of dienes has been extensively studied, and it has emerged as an ef-

Scheme 55



R^1 = H, CH_3, $CH_2COC(CH_3)_3$, CH_2COCH_3, $CH_2CH(OH)CH_3$; R^2 = H, $SiMe_2t$-Bu

Scheme 56



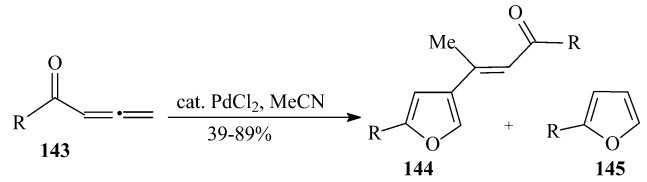
ficient method for the stereoselective synthesis of various heterocycles.[67] A variety of mechanisms have been proposed for the cyclization of dienes by Pd salts. One common cyclization mode involves initial double-bond complexation with the Pd salt to form a π-olefin complex. Subsequent intramolecular nucleophilic attack on this complex affords a π-allylpalladium species, which eventually affords the cyclized product.[68]

Cyclization of 1,2-Dienes. In 1987, Walkup and Park described the synthesis of tetrahydrofuran derivatives **137** and **138** by the Pd-catalyzed carbonylative cyclization of allenes **136** bearing a hydroxyl or silyl group (Scheme 55).[69] A mixture of cis and trans isomers was formed by a 5-*exo*-trig cyclization using $PdCl_2$, $CuCl_2$, and CO at room temperature. Subsequently, the intramolecular carbonylative oxypalladation of 4,5-hexadienal **139** and 4,5-hexadienoic acid **141** under similar reaction conditions was reported (Scheme 56).[70] Furan derivative **140** and furanone **142** are formed in good yields. In these reactions, propylene oxide is used as an acid trap and triethyl orthoacetate as a water scavenger.

In 1997, Hashmi reported the formation of furan derivatives **144** as the major product, along with a small amount of furan **145**, by a sequence involving the Pd(II)-catalyzed cyclization/dimerization of allenic ketones **143** (Scheme 57).[71] The yield is dependent on the solvent, and best results were obtained using acetonitrile. When benzene, acetone, or $CDCl_3$ was used, a complex mixture of products was obtained. This reaction exhibits high selectivity for the allene moiety over other functional groups, such as aryl halides, terminal alkynes, and enynes.

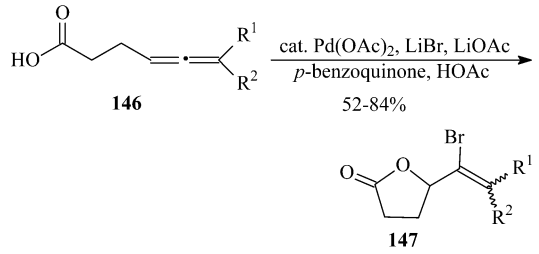
A variety of functionally substituted allenes have been cyclized by Bäckvall and co-workers to a number

Scheme 57



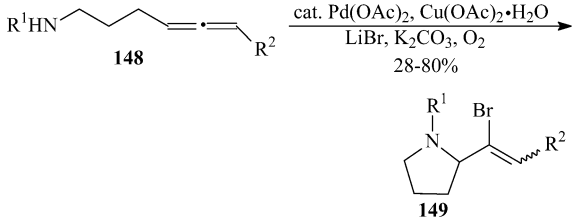
R = $(CH_2)_2CH_3$, $CH(CH_2)_4$, CH_2Ph, $CH(OMOM)CH_3$, $(CH_2)_3OH$, 4-ClC_6H_4, 1-naphthyl, 9-anthryl, C_6H_4CHO-*p*

Scheme 58

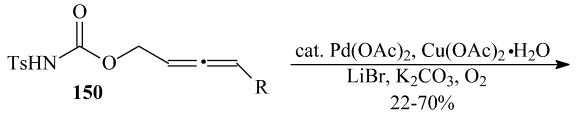


R^1 = Me, Et, n-C_4H_9, n-C_5H_{11}; R^2 = H, Me, Et

Scheme 59



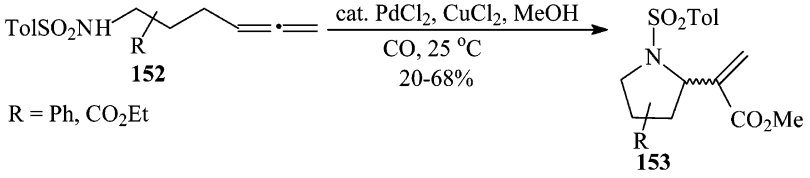
R^1 = CONHBn, CO_2Bn, Bn; R^2 = n-C_5H_{11}, *i*-Pr



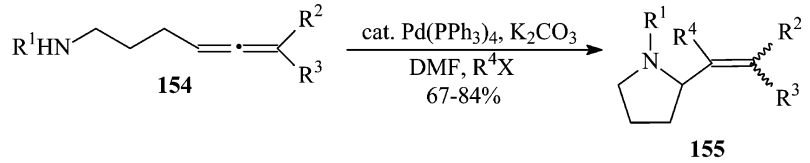
R = n-C_5H_{11}, *i*-Pr

of useful products using Pd catalysis. The Pd(II)-catalyzed oxidation of allenic acids **146** in the presence of a catalytic amount of $Pd(OAc)_2$, *p*-benzoquinone, LiOAc, and LiBr affords lactones **147** in moderate to good yields (Scheme 58).[72] The carbon−carbon double bond is obtained with mainly *Z*-stereochemistry. Recently, Bäckvall described extensions of this methodology to the cyclization of 1,2-dienes bearing nitrogen functionality as an internal nucleophile (Scheme 59).[73] Thus, allenic amines and amides **148** and **150** are cyclized by catalytic amounts of $Pd(OAc)_2$, LiBr, and K_2CO_3 in acetonitrile using Cu-

Scheme 60

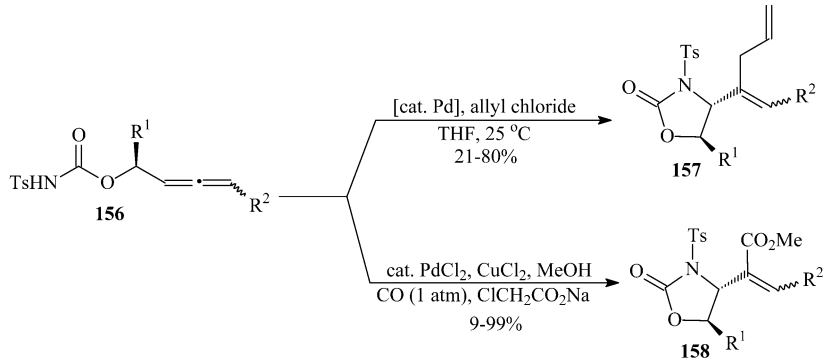


Scheme 61



R^1 = Bn, Ts, Boc; R^2 = R^3 = Me, H; R^4 = aryl, alkyl, alkenyl; X = Br, I

Scheme 62



R^1 = H, Me, Et, *n*-Pr, *i*-Pr, *t*-Bu, Ph, Me_2; R^2 = H, Me; [cat. Pd] = $PdCl_2(PhCN)_2$, $Pd_2(dba)_3$•$CHCl_3$ or $Pd(PPh_3)_4$

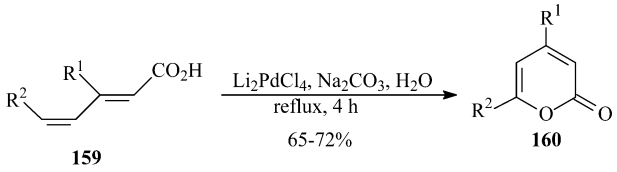
$(OAc)_2$•H_2O/O_2 as the reoxidant for Pd(0). *N*-Tosyl allenic amides, carbamates, and ureas as well as *N*-benzyl allenic amines have all been successfully cyclized. The heterocyclic products **149** and **151** were obtained in moderate to good yields, and the stereoselectivity for the ureas is higher than that of the other *N*-substituted allenic amides employed.

The Pd(II)-catalyzed carbonylative cyclization of allenic sulfonamides **152** produces *cis*- and *trans*-disubstituted pyrrolidenes **153** (Scheme 60).[74] The cyclization is best carried out using $PdCl_2$, $CuCl_2$, MeOH, and CO at room temperature. In case of low yields, the addition of Et_3N improves significantly the yields of cyclization products.

Gallagher extended this process by reacting *N*-substituted allenic amines and tosylamides **154** with organic halides and a Pd(0) catalyst to produce pyrrolidenes **155** in good yields (Scheme 61).[75] The process no doubt involves initial oxidative addition of the organic halide to the Pd(0) catalyst and subsequent electrophilic attack of the resulting organopalladium compound on the allene. Cyclization and reductive elimination produces the observed products.

Tosylcarbamates **156** undergo stereoselective cyclization/allylation and carbonylative cyclization to give oxazolidinones **157** and **158,** respectively, in good yields and excellent trans selectivity (Scheme 62).[76] The best results in the carbonylation reaction were obtained using $PdCl_2(PhCN_2)$ or $Pd_2(dba)_3$ as catalyst in the presence of Et_3N or K_2CO_3. These processes probably involve attack of an organopalladium(II) species on the allene followed by cyclization and reductive elimination.

Scheme 63

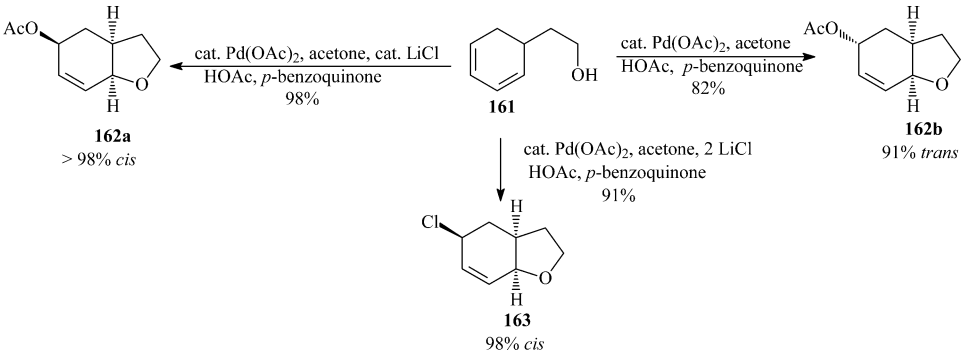


R^1; R^2 = H, CH_3, Ph

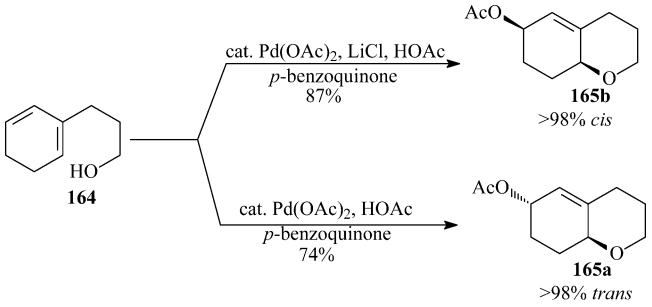
Cyclization of 1,3-Dienes. The first report of the Pd(II)-promoted cyclization of 1,3-dienes came from Izumi and Kasahara in 1975.[77] They reported that the intramolecular cyclization of alka-2,4-dienoic acids **159** with a stoichiometric amount of Li_2PdCl_4 in 1:1 water/dioxane affords exclusively six-membered ring pyrones **160** (Scheme 63).

More recently, Bäckvall and Andersson prepared a number of oxygen- and nitrogen-containing heterocycles by the Pd(II)-catalyzed oxidative cyclization of a wide variety of 1,3-dienes bearing various functional groups in the side chain. For example, the reaction of dienol **161** with $Pd(OAc)_2$ under appropriate reaction conditions produces quite stereoselectively chloro- or acetoxy-substituted five-membered

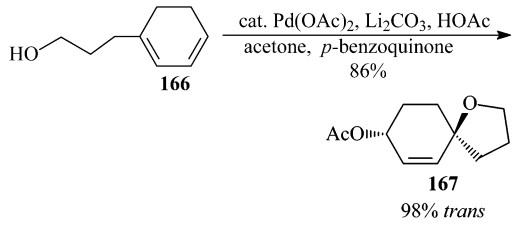
Scheme 64



Scheme 65

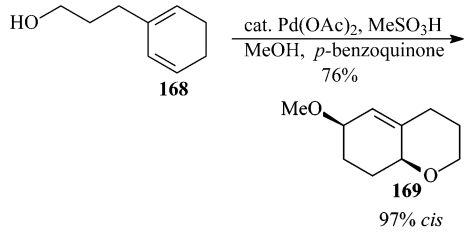


Scheme 66



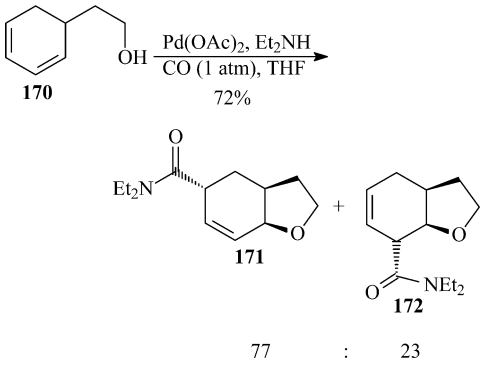
9 examples prepared in 40-86% yields

Scheme 67



7 examples prepared in 76-96% yields

Scheme 68



ring ethers **162** or **163** (Scheme 64).[78] These processes involve electrophilic addition of the alcohol functionality and the palladium(II) salt to the diene to produce a π-allylpalladium intermediate, which subsequently undergoes stereoselective substitution with either retention or inversion of stereochemistry. The key is the presence or absence of LiCl, which induces substitution of the π-allylpalladium moiety with inversion. In a similar fashion, one can prepare the corresponding six-membered ring acetoxy ethers **165** stereoselectively from dienol **164** (Scheme 65).[79] The stereochemistry is once again determined by the presence or absence of LiCl in the reaction.

This type of cyclization can also be carried out to form spirocyclic ether products, such as **167**, from dienols such as **166** (Scheme 66).[80]

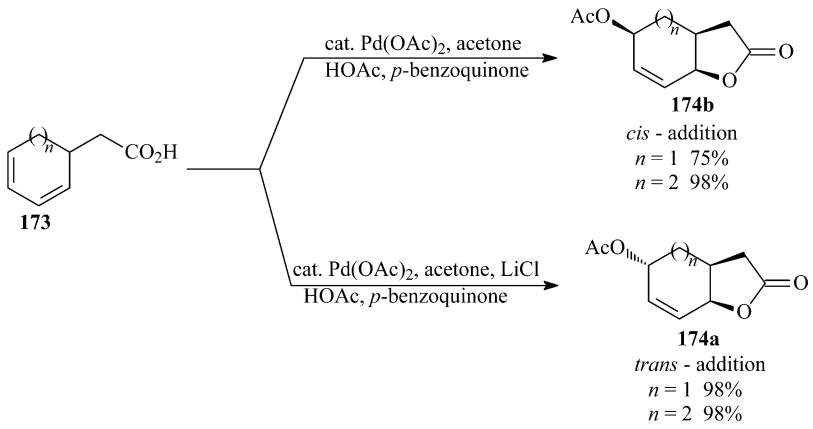
One can also substitute the palladium moiety of the π-allylpalladium intermediate by a methoxy group by simply running the reaction in methanesulfonic acid and methanol as illustrated by the conversion of dienol **168** to diether **169** (Scheme 67).[80]

If the cyclization is carried out in the presence of CO and an amine using a stoichiometric amount of $Pd(OAc)_2$, one can prepare amide-containing ethers, but the process is not very regioselective (Scheme 68).[81] The choice of solvent and CO pressure significantly affects the regiochemistry of substitution.

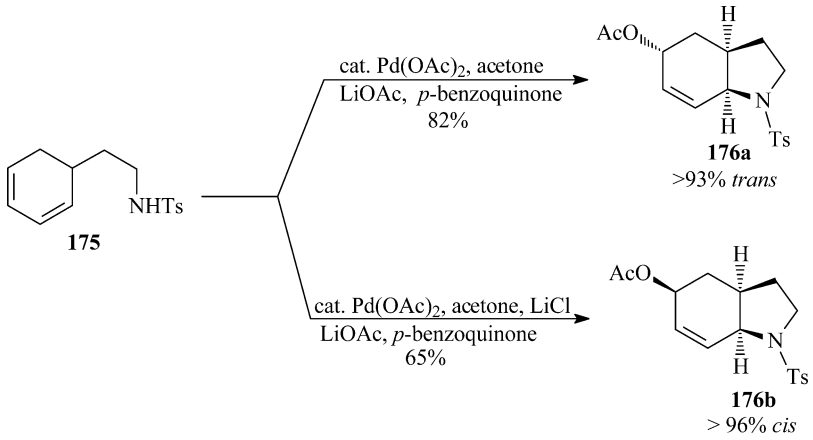
The stereocontrolled Pd(II)-catalyzed cyclization of cyclic 1,3-dienecarboxylic acids **173** to γ-lactones **174** produces lactones, where the acetoxy substitutent is either trans or cis to the lactone ring (Scheme 69).[82,83] In the absence of LiCl, the cis lactone is formed almost exclusively. The presence of LiCl is once again observed to affect complete inversion of the stereochemistry.

The Bäckvall group has also shown that 1,3-dienes bearing nitrogen functionality readily undergo Pd(II)-catalyzed intramolecular 1,4-addition. Thus, the reaction of aminodiene **175** with a catalytic amount of $Pd(OAc)_2$ in the presence of LiCl and acetic acid, using benzoquinone as a reoxidant, affords 1,4-acetoxyamination products **176** in good yields (Scheme 70).[84] The stereochemistry of this reaction is controlled by the presence or absence of LiCl. An analogous reaction reported by the same authors uses diene amides **177** as substrates to produce pyrrolizidine **178a** and indolizidine **178b** in high yields (Scheme 71).[85] The reaction is best affected using $Pd(OAc)_2$ in THF at 60 °C with $CuCl_2/O_2$ as the reoxidant. Other reoxidant systems, such as benzoquinone, $LiNO_3$, and $CuCl_2$ alone, gave lower yields.

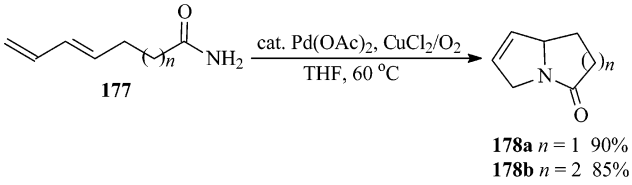
Scheme 69



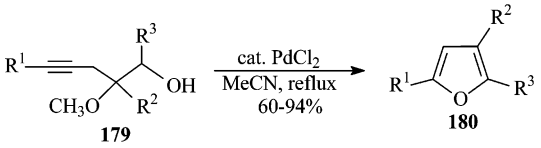
Scheme 70



Scheme 71



Scheme 72



$R^1 = CH_3CH_2, CH_3(CH_2)_5; R^2; R^3 = -(CH_2)_4-, H, CH_3$

3.3. Cyclization of Alkynes

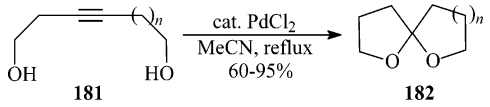
3.3.1. Cyclization of Alkynols

The Pd(II)-catalyzed cyclization of alkynes bearing an oxygen nucleophile is a powerful method for the construction of various oxygen-containing heterocycles. For example, Utimoto first reported the Pd(II)-catalyzed cyclization of 2-methoxy-3-alkyn-1-ols **179** to furans **180** in good yields (Scheme 72).[86]

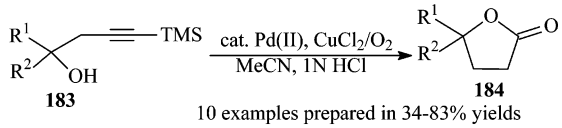
The successive intramolecular addition of two hydroxyl groups to the internal triple bond of alkynediols such as **181** gives the spirocyclic acetal **182** (Scheme 73).[86]

Compain and co-workers reported that γ-butyrolactones **184** can be obtained in good yields by the

Scheme 73



Scheme 74



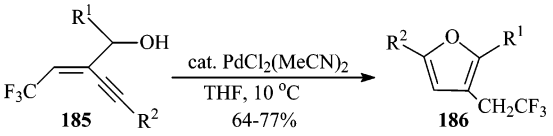
$R^1 = R^2 = H$, Ph, alkyl, cycloalkyl
cat. Pd(II) = $Pd(OAc)_2$, $PdCl_2(PhCN)_2$ or $PdClNO_2(MeCN)_2$

Pd(II)-catalyzed cyclization of 4-trimethylsilyl-3-alkyn-1-ols **183** using different Pd(II) salts, such as $Pd(OAc)_2$, $PdCl_2(PhCN)_2$, and $PdClNO_2(MeCN)_2$, in the presence of $CuCl_2/O_2$ as a reoxidant (Scheme 74).[87]

Recently, a series of studies on the Pd(II)-catalyzed cyclization of alkenynols **185**, **187,** and **189** has been described. Using various Pd reaction conditions, 3-(trifluoroethyl)furans **186** (Scheme 75),[88] 4-trifluoromethyl-*2H*-pyrans **188** (Scheme 76),[89] and a variety of substituted furans **190** (Scheme 77)[90] have been obtained in good yields under mild reaction conditions.

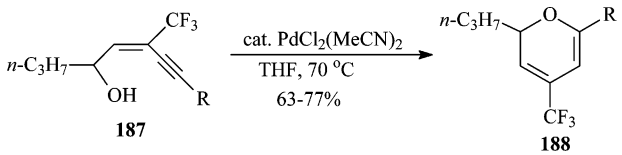
The Pd(II)-catalyzed cyclization of cyclic (**191**) and acyclic (**193**) 3-alkynols in the presence of CO provides a very useful synthetic route to α-methylene-γ-butyrolactones such as **192** and **194** (Scheme 78).[91]

Scheme 75



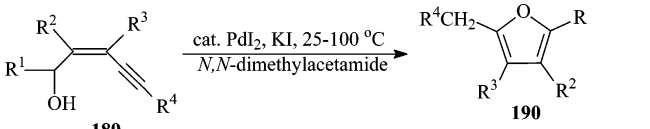
R^1 = Ph, *n*-C_3H_7, H; R^2 = Ph, *n*-C_6H_{13}, *p*-$CH_3OC_6H_4$

Scheme 76



R = Ph, *n*-C_6H_{13}, *p*-$CH_3OC_6H_4$

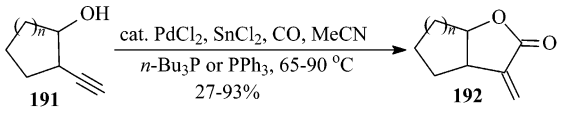
Scheme 77



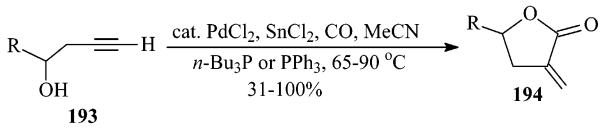
19 examples prepared in 30-95% yields

R^1, R^2, R^3, R^4 = H, Ph, alkyl

Scheme 78

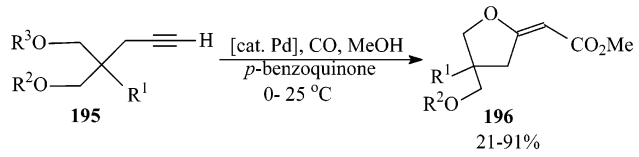


n = 0, 1, 2



R = H, CH_2CH_2Br, $CH_2CH_2CH{=}CH_2$

Scheme 79



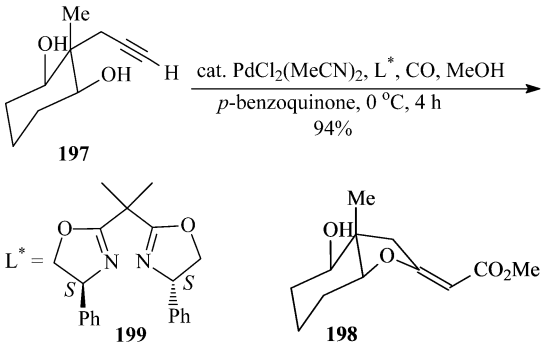
R^1 = Bn, propargyl; R^2 = H, Ac, TBDMS, MOM, THP; R^3 = H, Ac
[cat. Pd] = $Pd_2(dba)_3$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $PdCl_2$ or $PdCl_2(MeCN)_2$

Best results are obtained using a catalyst system consisting of $PdCl_2$, $SnCl_2$, and a tertiary phosphine in dry acetonitrile under a pressure of CO. The addition of $SnCl_2$ seems to increase the catalyst turnover rate and the yields of the reaction.

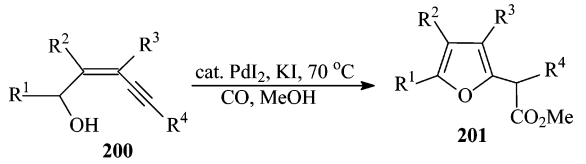
Employing different reaction conditions for carbonylation, Kato and co-workers described the preparation of cyclic β-alkoxyacrylates **196** in good yields from simple alkynols such as **195** (Scheme 79).[92] The best results were obtained using the catalyst system $PdCl_2(MeCN)_2$/*p*-benzoquinone in methanol at 0 °C under a CO atmosphere.

An asymmetric variant of this type of cyclization has recently been described by the same group (Scheme 80).[93] The reaction of cyclic alkynediol **197** with a Pd(II) catalyst and chiral bisoxazoline **199** in

Scheme 80



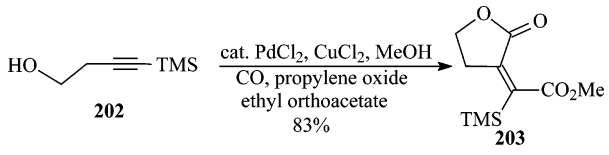
Scheme 81



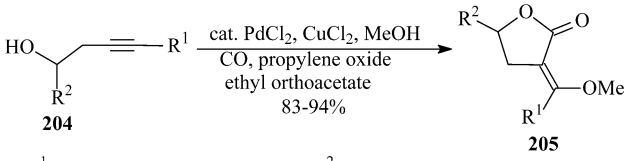
16 examples prepared in 51-82% yields

R^1, R^2, R^3 = H, Ph, alkyl; R^4 = H, Ph, *n*-Bu, TMS

Scheme 82



Scheme 83



R^1 = Ph, CH_3, $C(CH_3)_3$, CH_2CH_3; R^2 = H, Me

methanol under a CO atmosphere affords bicyclic alkoxyacrylate **198** in good yield with moderate enantioselectivity. Other substrates and chiral ligands were also studied.

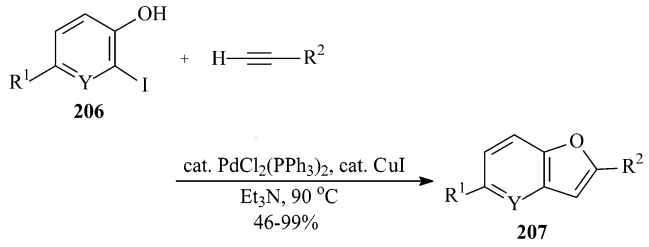
Enynols **200** bearing a terminal or internal triple bond can also be readily cyclized using a catalytic amount of PdI_2 plus KI under CO in methanol to afford furan-2-acetic acid esters **201** in good yields (Scheme 81).[94]

The Pd(II)-catalyzed cyclization/carbonylation of 3-butyn-1-ols produces α-methylidene-γ-butyrolactones with various substituents in the side chain.[95] Thus, the reaction of 4-trimethylsilyl-3-butyn-1-ol (**202**) with $PdCl_2$ and $CuCl_2$ under a CO atmosphere in the presence of propylene oxide affords the butyrolactone **203** (Scheme 82). Under similar conditions, 4-alkyl- and 4-aryl-3-butyn-1-ols **204** afford the methoxy butyrolactones **205** (Scheme 83).

3.3.2. Cyclization of Alkynyl Phenols

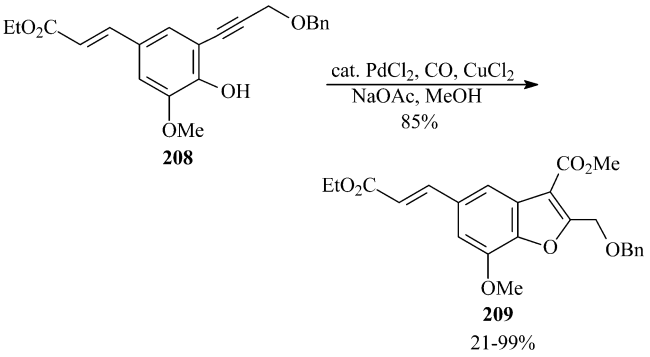
The Pd(II)-catalyzed cyclization of 2-(1-alkynyl)-phenols provides a very convenient synthetic route to benzofurans. Thus, the reaction of terminal alkynes and *o*-halophenols **206** in the presence of catalytic amounts of Pd and Cu salts provides a direct route

Scheme 84

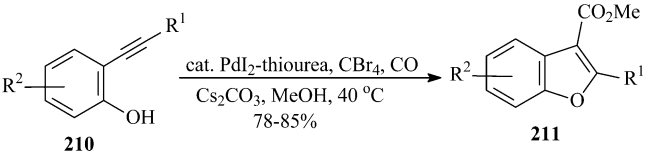


Y = CH, N; R^1 = H, Me, Cl; R^2 = Ph, C(OH)$(CH_3)_2$, *n*-C_6H_{13}, CH_2OTHP

Scheme 85



Scheme 86

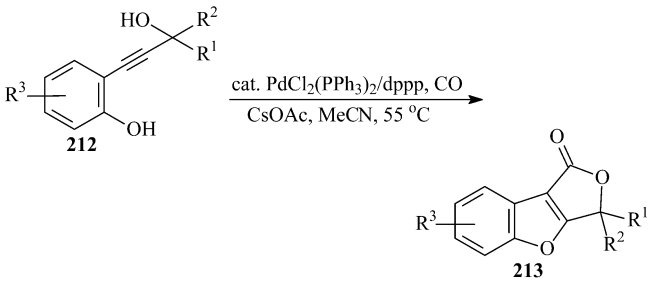


to benzofurans **207** in good yields (Scheme 84).[96] Various halogens and alkyl, aryl, and cyclic substrates are tolerated in this reaction, which most likely proceeds by initial substitution of the halide by the alkyne to produce a 2-(1-alkynyl)phenol followed by Pd- or Cu-catalyzed cyclization to the benzofuran.

The palladium-catalyzed reaction of 2-(1-alkynyl)-phenols and CO provides 3-benzofurancarboxylic acid esters (Scheme 85).[97] This process may proceed by palladium-promoted cyclization to the benzofuran and subsequent carbonylation or by cyclization induced by an alkoxycarbonylpalladium species followed by reductive elimination. This chemistry has been used to prepare a series of potential adenosine antagonists **209** in good yields by the reaction of alkynylphenols **208** with $PdCl_2/CuCl_2$ as the catalyst/reoxidant system plus NaOAc in methanol under CO pressure.

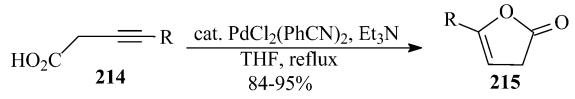
Another variant of this basic process has recently been reported by Yang and co-workers (Scheme 86).[98] Thus, 2,3-disubstituted benzofurans **211** have been synthesized by the Pd(II)-catalyzed cyclization/carbonylation of *o*-(1-alkynyl)phenols **210** using PdI_2/thiourea and CBr_4 as the catalyst system. This system affords good yields of benzofuran-3-carboxylates from both electron-rich and electron-deficient substrates. Benzo[*b*]furo[3,4-*d*]furan-1-ones **213** can also be obtained in good to moderate yields upon reaction of *o*-alkynylphenols **212** with $PdCl_2(PPh_3)_2$/dppp in the presence of CsOAc and acetonitrile under CO pressure (Scheme 87).[99]

Scheme 87

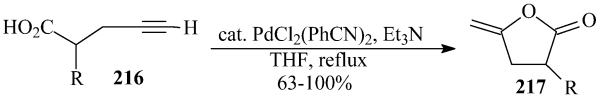


14 examples prepared in 52-92% yields

Scheme 88



R = CH_3, *n*-C_6H_{13}, *n*-C_8H_{17}, Ph



R = H, *n*-C_4H_9, *n*-C_6H_{13}, Ph, $PhCH_2$, $SiMe_3$

3.3.3. Cyclization of Alkynoic Acids

The reaction of 3- and 4-alkynoic acids **214** and **216** with Pd(II) catalysts proceeds by intramolecular *endo* or *exo* addition of the carboxylic acid moiety to the carbon−carbon triple bond to afford unsaturated lactones **215** and **217,** respectively (Scheme 88).[100]

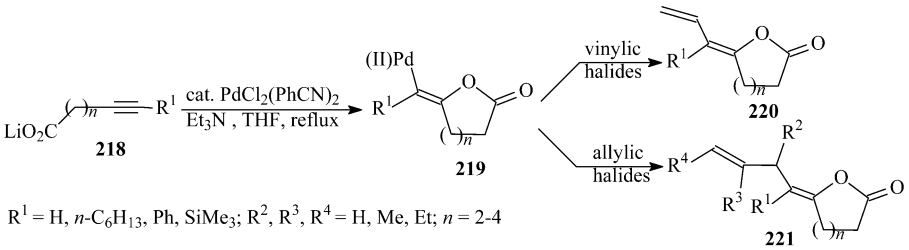
In a similar manner, the lithium alkynoates **218** react with $PdCl_2(MeCN)_2$ to afford alkenylpalladium intermediates **219**, which can react further with vinylic or allylic halides to produce the unsaturated 4-buten-4-olides **220** and **221** (Scheme 89).[101] The lithium 2-alkynyl carbonates **222** react in a similar manner with allyl chloride to afford the cyclic carbonates **223** in good yields (Scheme 90).[102]

The lactones **225** and **226** can be synthesized by the acyloxypalladation of 3-heptynoic acid (**224**) and subsequent trapping with acrolein (Scheme 91).[103] When the reaction is conducted in the presence of an excess of LiBr, the saturated aldehyde **225** is obtained. However, in the presence of only catalytic amounts of LiBr, the major product is the unsaturated aldehyde **226**.

3.3.4. Cyclization of Alkynals and Alkynones

In a couple of recent reports, acetylenes bearing aldehyde functionality have been reported to produce cyclic alkenyl ethers (Scheme 92).[104] The Pd(II) salt is employed as a Lewis acid to induce hemiacetal formation and also to affect cyclization of the alkyne onto the acetal. In this way, aldehydes **227** in the presence of 10 mol % $Pd(OAc)_2$ and benzoquinone afford the five-membered ring acetals **228**, together with a small amount of the six-membered ring products **229**. On the other hand, aryl acetylenic aldehydes **230** when treated with 5 mol % $Pd(OAc)_2$ in methanol produce exclusively the six-membered ring acetals **231** (Scheme 93).

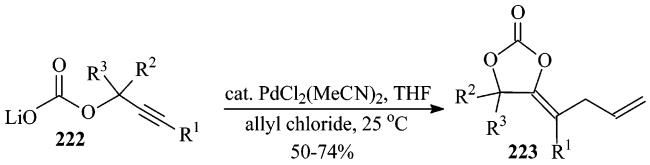
Scheme 89



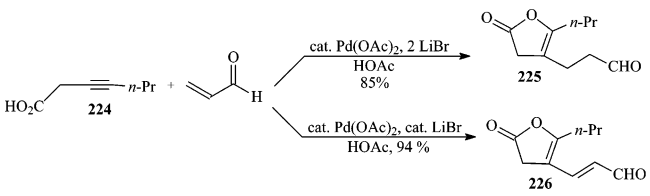
R^1 = H, *n*-C_6H_{13}, Ph, $SiMe_3$; R^2, R^3, R^4 = H, Me, Et; *n* = 2-4

18 examples prepared in 34-94% yields

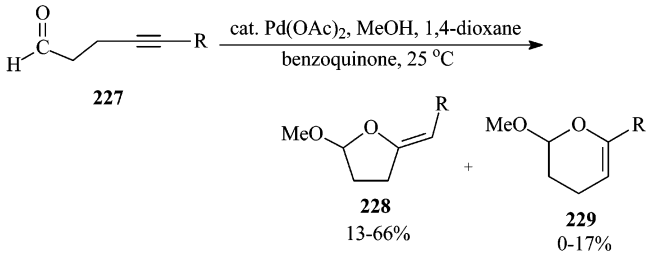
Scheme 90



Scheme 91

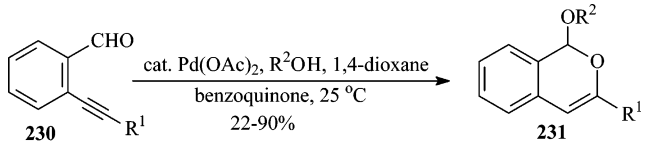


Scheme 92



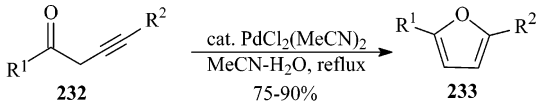
R = Ph, *p*-MeC_6H_4, *p*-$CF_3C_6H_4$, *n*-C_8H_{17}

Scheme 93



R^1 = Ph, *n*-C_4H_9, Me_3Si, H; R^2 = Me, Et, *i*-Pr

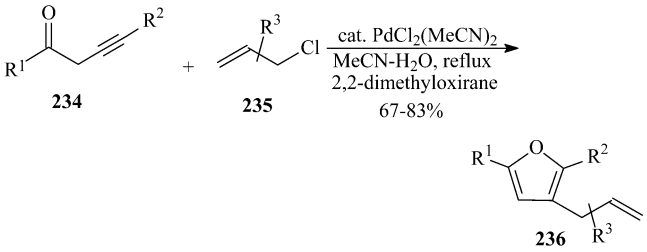
Scheme 94



R^1 = CH_3, C_2H_5, *n*-C_6H_{13}; R^2 = *n*-C_6H_{13}

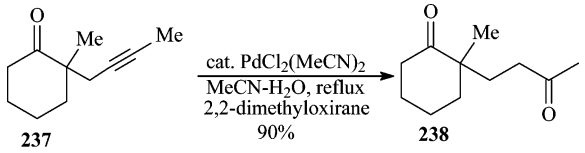
Alkynes containing a ketone group can be cyclized in the presence of a Pd(II) catalyst to a variety of furan and tetrahydrofuran products. For example, 3-alkynones **232** are cyclized to substituted furans **233** in good yields in the presence of a catalytic amount of $PdCl_2(MeCN)_2$ in acetonitrile with a few percent of water added (Scheme 94).[105] When allylic halides **235** are added to the reaction, 3-allylic furans **236** are obtained (Scheme 95). However, under the same reaction conditions, alkynone **237** with no α-hydrogens affords only the 1,4-diketone **238** and no cyclized products were formed (Scheme 96).

Scheme 95

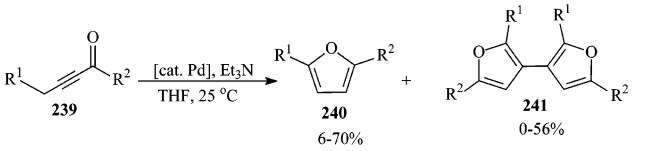


R^1 = CH_3, C_2H_5, *n*-C_6H_{13}; R^2 = *n*-C_6H_{13}; R^3 = H, Me

Scheme 96



Scheme 97



R^1 = Ph, 3-$MeOC_6H_4$; R^2 = *n*-C_8H_{17}, 2-thienyl, *n*-C_5H_{11}; [cat. Pd] = $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$

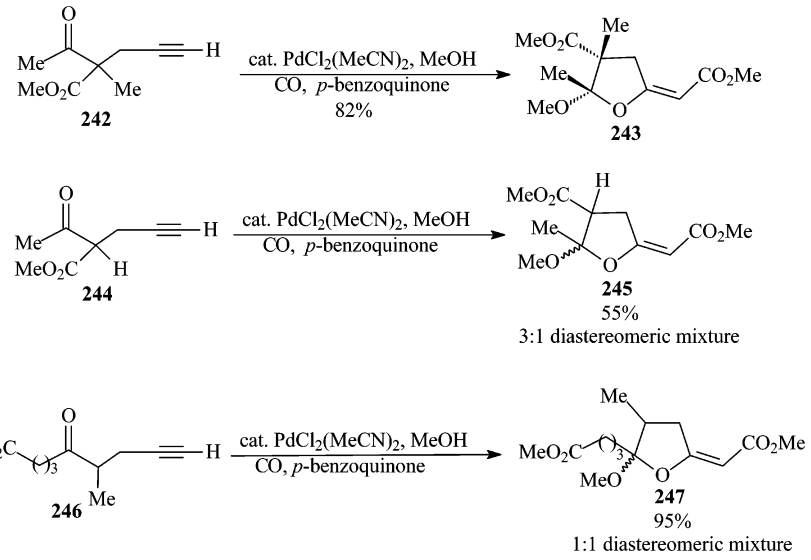
The cyclization of alkynones **239** using Pd(0) or Pd(II) catalysts in the presence of triethylamine forms either simple furans **240** or bifurans **241** (Scheme 97).[106] When the catalyst is a Pd(0) salt, the 2,5-disubstituted furans **240** are obtained. However, catalytic amounts of Pd(II) generate bifurans **241**.

The palladium-catalyzed cyclization of 4-alkynones in the presence of CO produces tetrahydrofuran-containing esters (Scheme 98).[107] Using alkynones **242**, **244,** and **246** and $PdCl_2(MeCN)_2$ as the Pd catalyst in MeOH plus *p*-benzoquinone under CO pressure, the cyclic ketals **243**, **245,** and **247** are formed, respectively, in good yields under mild reaction conditions. The products are the result of *exo*-cyclization and are generally obtained as a diastereomeric mixture.

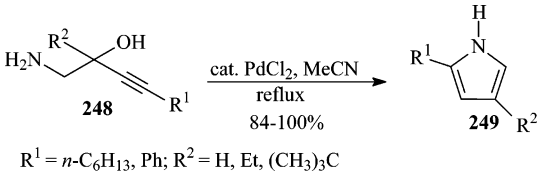
3.3.5. Cyclization of Alkynylamines

The intramolecular reaction of alkynylamines with a Pd(II) catalyst can be a very useful method to prepare a wide variety of nitrogen heterocycles. The

Scheme 98



Scheme 99



first example of nitrogen addition to a triple-bond catalyzed by a Pd(II) complex was described by Utimoto in 1981 (Scheme 99).[108] He reported that the reaction of 1-amino-3-alkyn-2-ols **248** with catalytic amounts of $PdCl_2$ in acetonitrile at reflux affords pyrroles **249** in excellent yields. Under similar reaction conditions using a catalytic amount of $PdCl_2(MeCN)_2$, 1-pyrrolines **251** have been synthesized from 3-alkynylamines **250** (Scheme 100).[109] However, the cyclization of the 4-alkynylamine **252** produced a mixture of five- and six-membered cyclic imines **253** and **254**. On the other hand, the 5-alkynylamine **255** afforded the 2,3,4,5-tetrahydropyridine **256** exclusively.

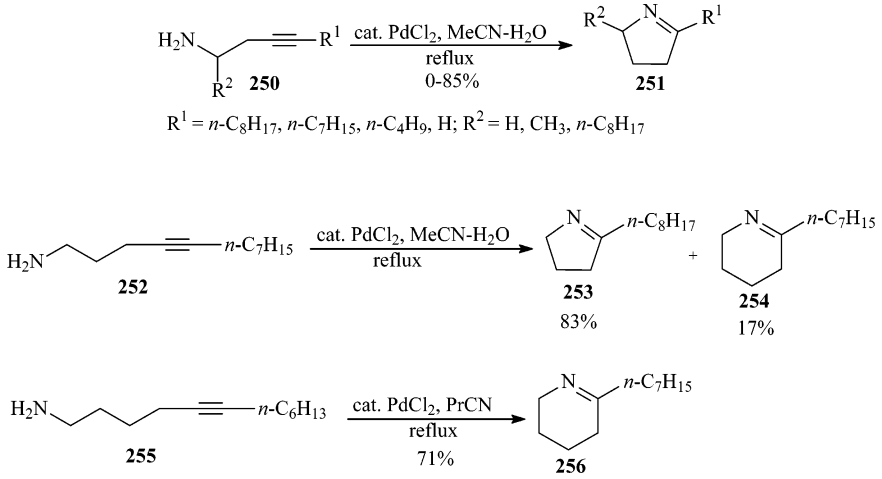
Gabriele and co-workers have shown that *Z*-alkenynols **257** can be readily converted to the corresponding benzylic amines, which cyclize readily at low temperatures to the corresponding pyrroles **258** (Scheme 101).[110] However, when the alkenynylamines **259** contain an internal triple bond, the cyclization requires the addition of a palladium catalyst to produce the corresponding pyrroles **260**. The reaction takes place in good yield using catalytic amounts of $PdCl_2$ plus KCl in anhydrous *N*,*N*-dimethylacetamide.

Cacchi and co-workers cyclized 2-(1-alkynyl)anilines **261** to the corresponding 2-substituted indoles **262** in an acidic two-phase system using $PdCl_2$ and n-Bu_4NCl in CH_2Cl_2/HCl (Scheme 102).[111] This reaction was sensitive to the acid concentration used; in general, 0.5 N HCl gave the best results.

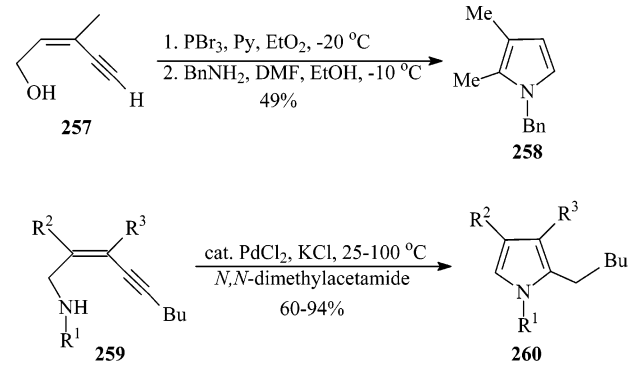
In a subsequent study, the Cacchi group showed that the reaction of *N*-tosyl-*N*-propargylhydrazine **263** with aryl iodides or triflates and a palladium catalyst affords aryl pyrazoles **264** in moderate yields (Scheme 103).[112] This reaction was realized in two steps and one pot by the sequence shown. The first step produces the aromatic acetylene, and the second step affects cyclization. Finally, the tosyl group is removed by base.

The alkynylanilines **265** have also been subjected to Pd(II)-catalyzed cyclization/carbonylation to pre-

Scheme 100

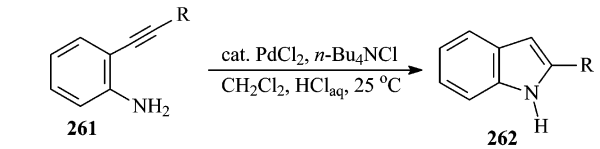


Scheme 101



R^1 = H, Bn; R^2 = H, Et, Ph; R^3 = H, Me

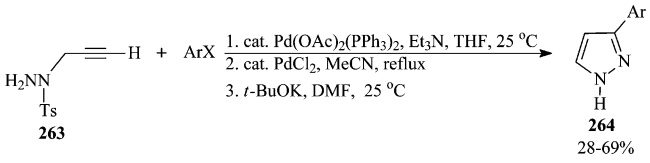
Scheme 102



R = vinyl, aryl

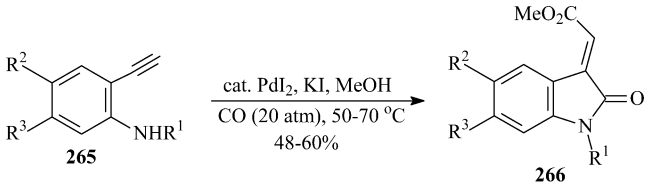
18 examples prepared in 14-98% yields

Scheme 103



Ar = Ph , *p*-$O_2NC_6H_4$, *m*-$O_2NC_6H_4$, *p*-$MeCOC_6H_4$, *m*-$F_3CC_6H_4$, *p*-$EtO_2CC_6H_4$, *m*-$EtO_2CC_6H_4$, *o*-FC_6H_4; X = I, OTf

Scheme 104



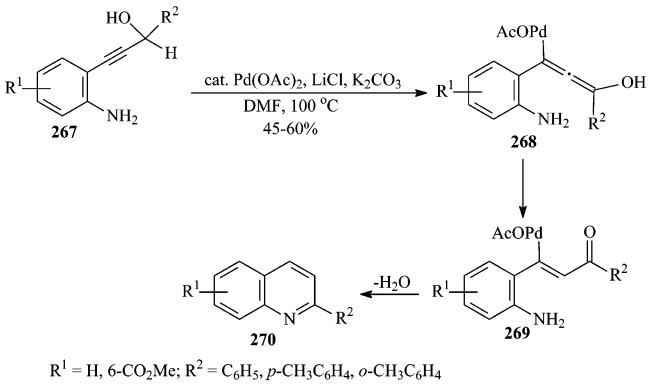
R^1 = H, Bn, *n*-C_4H_9; R^2 = H, Me, Cl; R^3 = H, Cl

pare the dihydroindol-2-ones **266** in moderate to good yields (Scheme 104).[113] The reaction is carried out using catalytic amounts of PdI_2 plus KI in methanol under CO pressure. The stereochemistry of the double bond of the product is exclusively the *E*-configuration.

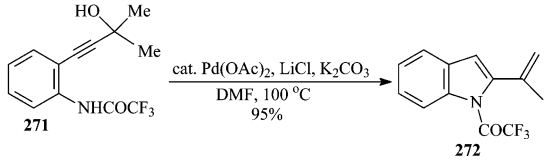
The alcohol-containing alkynylanilines **267** have been cyclized to quinolines **270** using catalytic amounts of $Pd(OAc)_2$ plus LiCl and K_2CO_3 in DMF (Scheme 105).[114] The process is believed to proceed through the allenic palladium intermediate **268**, which tautomerizes to the corresponding enone **269**, which finally cyclizes to the quinoline. If no benzylic proton is present, as in amide **271**, the allenic intermediate does not form and the main products are five-membered ring indoles such as **272**.

Finally, the 1*H*-benzimidazole **273** can be cyclized in the presence of $Pd(OAc)_2$ in refluxing DMF to afford a 1:2 mixture of two isomeric isoquinolines **274** in an 89% yield (Scheme 106).[115]

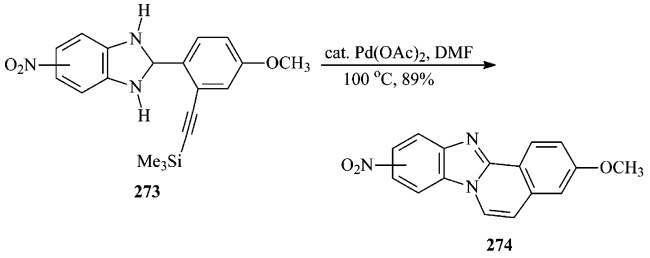
Scheme 105



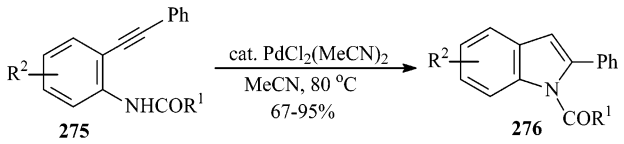
R^1 = H, 6-CO_2Me; R^2 = C_6H_5, *p*-$CH_3C_6H_4$, *o*-$CH_3C_6H_4$



Scheme 106



Scheme 107



R^1 = Ph, CH_3; R^2 = H, 4-CH_3, 5-CH_3, 4-Cl

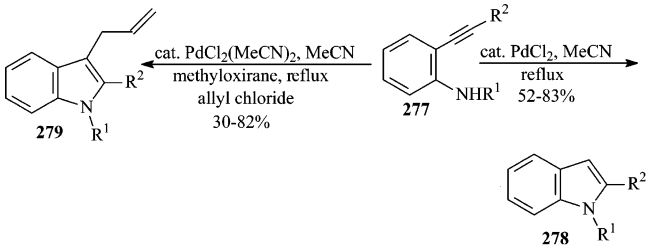
3.3.6. Cyclization of Alkynamides

As one might expect, in analogy to the cyclization of alkynylamines, alkynamides can also be used as substrates for Pd(II)-catalyzed cyclizations. Thus, 2-(*N*-acylamino)tolanes **275** react with catalytic amounts of $PdCl_2(MeCN)_2$ in acetonitrile at 60 °C to afford the 2-substituted indoles **276** (Scheme 107).[116] The reduction of Pd(II) does not take place, and a reoxidant for Pd is therefore not required.

Very useful Pd(II)-catalyzed cyclizations of 2-(1-alkynyl)anilines to indoles have also been developed by Utimoto (Scheme 108).[117] Simple indoles **278** have been obtained in good yields by the reaction of *o*-alkynylanilines **277** with catalytic amounts of $PdCl_2$ in DMF at reflux. In addition, 3-allyl-2-alkylindoles **279** are formed when the reaction is carried out in the presence of allyl chloride and methyloxirane as a proton scavenger.

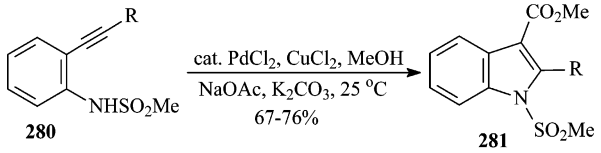
In the presence of CO and a catalytic amount of $PdCl_2$ in methanol at room temperature, using $CuCl_2$ as an oxidant, the alkynylaniline derivatives **280** have been cyclized to indole-3-carboxylates **281** in good yields (Scheme 109).[118]

Scheme 108



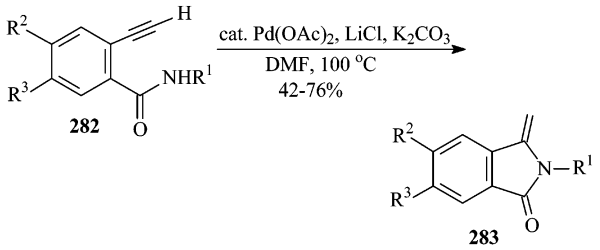
R^1 = H, Ac, CO_2Me; R^2 = Bu, *t*-Bu, CH(Me)Hex, Ph, $SiMe_3$

Scheme 109



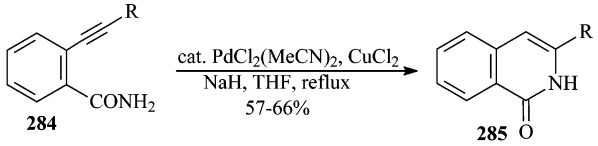
R = Ph, Bu

Scheme 110



R^1= *p*-MeC_6H_4, *m*-ClC_6H_4, *p*-$MeOC_6H_4$, CH_3, Ph, CH_2Ph, H; R^2 = H, OMe; R^3 = OH, NO_2, OMe

Scheme 111



R = Ph, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-MeC_6H_4, *n*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}, *n*-C_6H_{13}

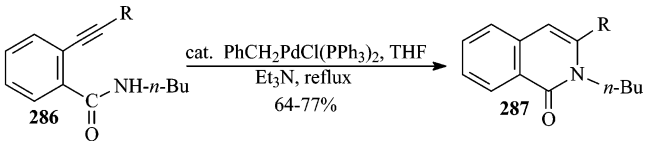
The Pd(II)-catalyzed cyclization of *o*-(ethynyl)benzamides **282** using catalytic amounts of $Pd(OAc)_2$, LiCl, and K_2CO_3 in DMF generate the corresponding isoindolinones **283** in good yields (Scheme 110).[119]

2-(1-Alkynyl)benzamides **284** bearing an internal alkyne are efficiently cyclized to six-membered ring carbostyrils **285** using a palladium reagent and NaH in THF (Scheme 111).[120] The desired products are obtained in good yields using either stoichiometric or catalytic amounts of the Pd complex.

The reaction of *N*-butyl-*o*-(1-alkynyl)benzamides **286** with a catalytic amount of $PhCH_2PdCl(PPh_3)_2$ and Et_3N in refluxing THF also affords isoquinolinones **287** exclusively in good yields by a 6-*endo* cyclization (Scheme 112).[121] Other Pd complexes tested, such as $PdCl_2(MeCN)_2$, were inefficient in this cyclization. The reaction is highly dependent on the substituents on the triple bond. When the R group in the benzamide **286** is a bulky group (*t*-Bu and TMS), the isoquinolinone **287** is not obtained.

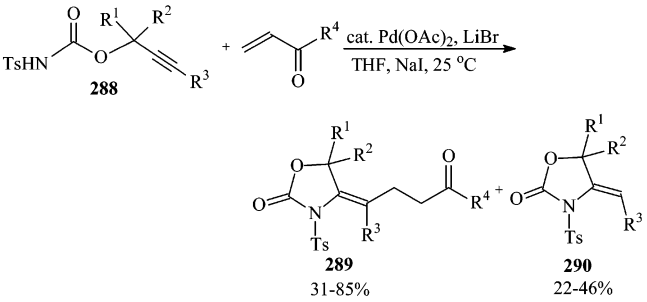
Acetylene-containing carbamates **288** can be cyclized and cross-coupled with unsaturated carbonyl

Scheme 112



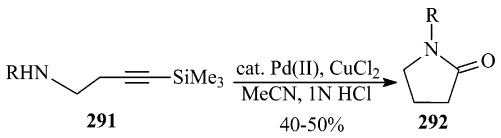
R = Me, Bu, Ph

Scheme 113



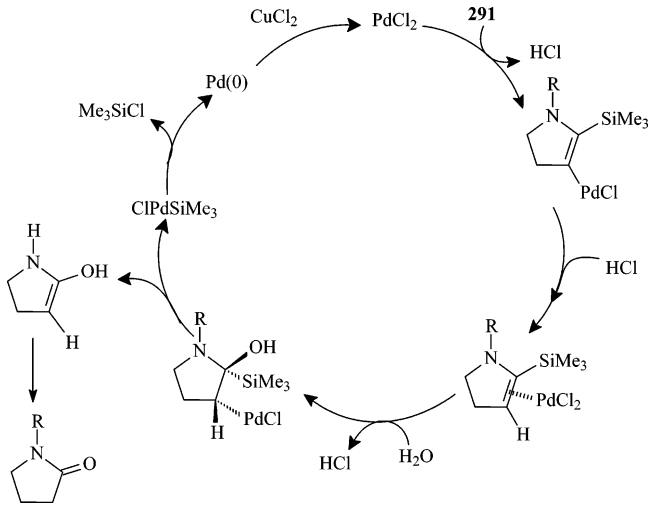
R^1 = H, Me; R^2 = H, Me, Et, *n*-C_5H_{11}, Ph; R^3 = H, Me; R^4 = H, Me

Scheme 114



R = H, Bn, CO_2CH_3, CO_2t-Bu, $COCH_3$

Scheme 115

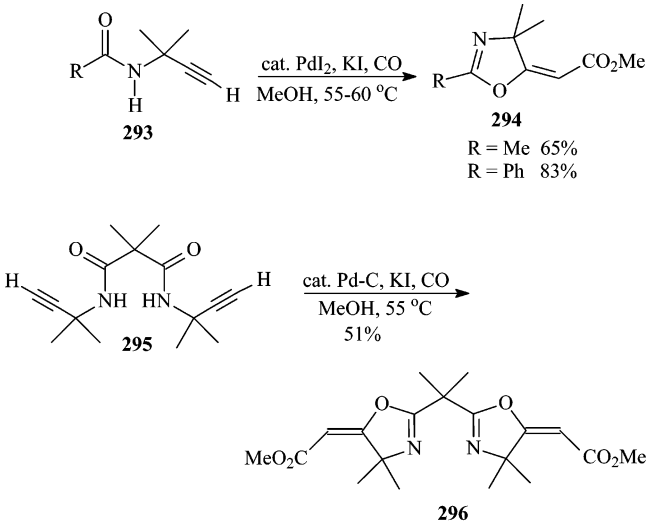


compounds in one step using a palladium catalyst to afford oxazolidinones **289** in good yields (Scheme 113).[122] The oxazolidinones **290** are formed as side products when more highly substituted starting materials are employed.

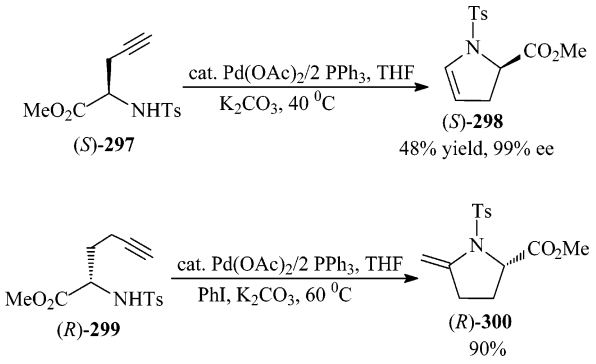
The trimethylsilylalkynes **291** bearing an amide or urethane moiety can be cyclized to the substituted γ-lactams **292** in moderate yields (Scheme 114).[123] These reactions were carried out using 5 mol % of a Pd(II) complex in the presence of $CuCl_2$ as a reoxidant. This reaction appears to involve the sequence described in Scheme 115.

Very recently, prop-2-ynylamides have been subjected to Pd-catalyzed carbonylative cyclization (Scheme 116).[124] Starting from the *N*-(1,1-dimethyl-

Scheme 116



Scheme 117



prop-2-ynyl)amides **293**, the oxazolines **294** are formed as the main product when using catalytic amounts of PdI_2 plus KI in MeOH under CO pressure. The products possess an *E*-configuration and are formed by *exo*-cyclization. The analogous cyclization of acetylenic diamides, such as **295**, to bis-oxazoline **296** has been reported using Pd−C/KI in MeOH, under a CO pressure at 55 °C.

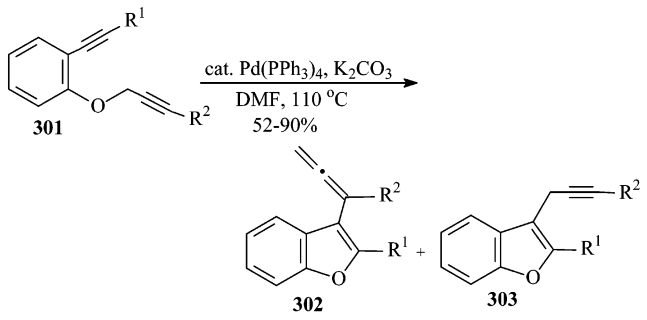
The Pd(II)-catalyzed cyclization of amino acid derivatives has been reported by Rutjes and co-workers (Scheme 117).[125] Nitrogen-containing heterocycles can be obtained in good yields when the nitrogen functionality is protected as a sulfonamide. Thus, the five-membered ring enamide **298** can be obtained from propargylglycine derivative **297**. Conversely, the five-membered ring sulfonamide **300** is produced by the palladium-catalyzed cyclization of sulfonamide **299**.

3.3.7. Miscellaneous Alkyne Reactions

Cacchi and co-workers reported the cyclization of propargylic *o*-(1-alkynyl)phenyl ethers **301** to 3-allenylbenzo[*b*]furans **302** in good yields using $Pd(PPh_3)_4$ as a catalyst (Scheme 118).[126] In some cases, a mixture with small amounts of alkynylbenzofuran **303** is formed. When $R^2 = H$, no allenyl or propargylic products are formed.

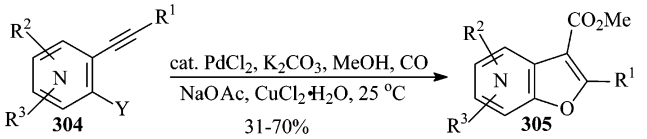
It has recently been shown that *o*-acetoxy- and *o*-(benzyloxy)(1-alkynyl)pyridines **304** can be efficiently cyclized to 2,3-disubstituted furopyridines **305**

Scheme 118



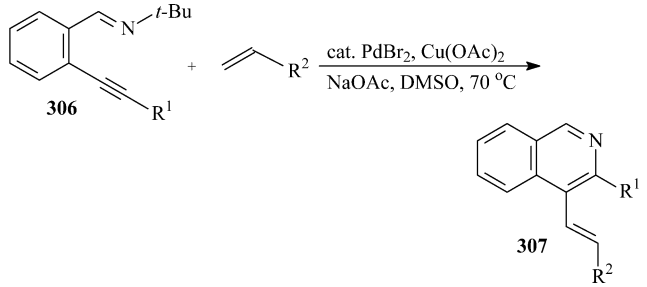
R^1 = Ph, *n*-C_5H_{11}, 4-$MeOC_4H_4$; R^2= 4-MeC_4H_4 , 4-$MeOC_4H_4$, Ph

Scheme 119



Y = OAc, OCH_2Ph

Scheme 120



41 examples prepared in 20-97% yields

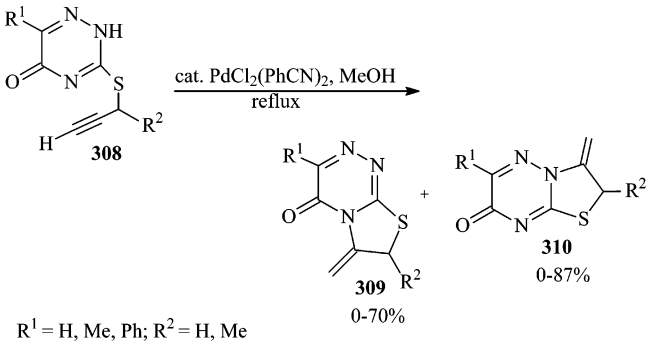
R^1 = C_6H_5, *p*-$MeOC_6H_4$, *o*-$MeOC_6H_4$;
R^2 = CO_2Me, CO_2-*n*-Bu, CO_2-*t*-Bu, CMe_2OH, $CONMe_2$, SO_2CH_3, SO_2Ph, Ph

in good yields (Scheme 119).[127] The best results were obtained using $PdCl_2$ plus $CuCl_2 \cdot 2H_2O$ in the presence of K_2CO_3 and NaOAc in methanol under a CO atmosphere. Using $Pd(PPh_3)_4$ as the catalyst afforded the desired products in low yields.

We observed that 2-(1-alkynyl)benzaldimines **306** can be readily cyclized to a variety of 4-(1-alkenyl)-3-arylisoquinolines **307** in good to excellent yields by Pd(II)-catalyzed cyclization followed by alkenylation (Scheme 120).[128] The introduction of an *o*-methoxy group into the benzaldimine improves the yields substantially. The presence of a chelating methoxy group apparently stabilizes the organopalladium intermediate formed by electrophilic attack of the Pd(II) salt on the alkyne. Subsequent Heck coupling with the olefin produces the final isoquinoline product.

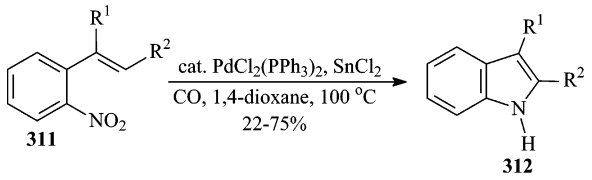
Triazin-5(2*H*)-ones **308** bearing a 3-propargylthio group can be cyclized in the presence of a catalytic amount of $PdCl_2(PhCN)_2$ under CH_3CN reflux to afford a mixture of triazinones **309** and **310** in good yields (Scheme 121).[129] The choice of solvent can change the ratio of the products.

Scheme 121

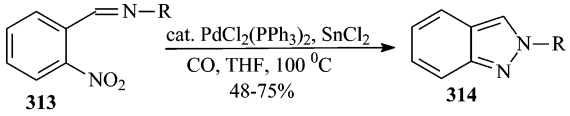


R^1 = H, Me, Ph; R^2 = H, Me

Scheme 122

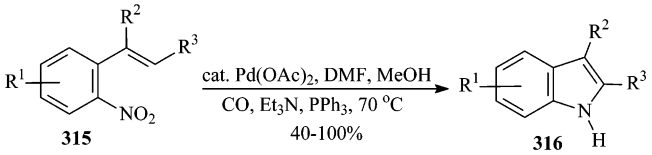


Scheme 123



R = *n*-Pr, *i*-Pr, $(CH_2)_3OCH_3$, 3-ClC_6H_4, *t*-Bu, Ph

Scheme 124



R^1 = H, Me, OMe, OH, OTf, CO_2Me, Br, NO_2; R^2 = H, Me; R^3 = H, Me, Ph

Watanabe and co-workers investigated the scope of the Pd-catalyzed cyclization of nitroarenes **311**, which affords indole derivatives **312** in moderate to good yields (Scheme 122).[130] Using the *N*-(2-nitrobenzylidene)amines **313** as substrates under the same conditions described in Scheme 123, indazole derivatives **314** have been obtained in good yields (Scheme 123). The presence of phosphorus ligands is essential for the success of these processes. When other Lewis acids, such as $SnCl_4$, $CuCl_2$, $FeCl_3$, $ZnCl_2$ or BF_3•Et_2O, were employed, the desired product was not obtained.

More recently, Soderberg and co-workers reported alternative reaction conditions for the cyclization 2-nitrostyrenes **315** to indoles **316** (Scheme 124).[131] The best results using either electron-withdrawing or electron-donating groups on the arene have been obtained using $Pd(OAc)_2/PPh_3$ in acetonitrile under CO pressure (Scheme 124).

4. Conclusion

The Pd(II)-catalyzed cyclization of olefins and alkynes bearing various oxygen- and nitrogen-containing functional groups provides a very valuable method for the synthesis of a wide variety of heterocycles. This chemistry proceeds through initial formation of a π-olefin or π-alkyne complex, which readily undergoes intramolecular nucleophilic attack by a neighboring nucleophile. The resulting heterocyclic organopalladium intermediate can undergo a variety of very useful further transformations, including hydride elimination, protonolysis, or CO or alkene insertion. Many of the most important, medicinally active, heterocyclic ring systems can be readily prepared through this chemistry. The resulting heterocycles have often demonstrated important biological activities, such as cytotoxicity, antitumor, antiviral, anti-inflammatory, and many other pharmaceutically useful properties. In this methodology, the palladium salts can usually be used in only catalytic amounts. The reactions proceed under relatively mild reaction conditions and tolerate a wide variety of functional groups, thus avoiding protection group chemistry. Most palladium-based methodology proceeds stereo- and regioselectively in excellent yields. Thus, we can expect to see many more applications of this useful cyclization methodology soon.

5. Acknowledgments

We gratefully acknowledge financial support of our own research in this area by the National Science Foundation and the Petroleum Research Fund administered by the American Chemical Society.

6. References

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