Synthesis of Heterocycles via Palladium-Catalyzed Oxidative Addition

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Contents

1. Introduction

Palladium-catalyzed processes have proven to be a powerful and useful tool for the synthesis of heterocycles. Palladium has found such wide utility because it affects 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 papers[2] have been published on various aspects of organopalladium chemistry, including one book devoted exclusively to heterocyclic synthesis.[1f]

In this review, we shall cover a wide range of palladium-catalyzed processes involving oxidation addition/reductive elimination 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, as well as the synthesis of heterocycles via intramolecular cyclization of palladium π-olefin and π-alkyne complexes, will not be discussed in this review, since they have recently been reviewed elsewhere.

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 chemistries. Palladium(0) complexes are fairly nucleophilic and rather labile and are 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 the focus of this review.

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 has recently been reviewed elsewhere. 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(II) complexes are often added to reactions as precatalysts, since they are readily reduced by various species to Pd(0), which then catalyzes the desired process.

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Gilson Zeni was born 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 Prof. A. L. Braga, and his Ph.D. (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. In 2003, he received a CNPq Postdoctoral Fellowship to work with Prof. R. C. Larock at Iowa State University. 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.

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. 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 electrophilic cyclization of alkynes, plus the synthesis of industrially useful oils and polymers from natural oils, such as soybean oil.

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-catalyzed oxidative addition chemistry directed toward heterocyclic synthesis.

There are a large number of organic reactions, which palladium catalyzes, that generate heterocycles. This review will cover these basic processes from a mechanistic standpoint, with each new section providing some overall comments and a general mechanism for the processes to be discussed. The focus will be on the more recent developments in this field with particular emphasis on palladium-catalyzed cyclization and annulation processes involving oxidative addition.

3. Heterocycles via Palladium-Catalyzed Oxidative Addition Reactions. General Comments

Cyclization by palladium-catalyzed oxidative addition/reductive elimination is a powerful method for the construction of heterocycles. This process generally involves the addition of a covalent molecule to a Pd(0) complex, with cleavage of the covalent bond and oxidation of Pd(0) to Pd(II), to afford a σ-organopalladium(II) halide or triflate complex. The σ-bonded species, once formed, generally undergoes rapid insertion of an unsaturated species or other reactions as outlined in Scheme 1. Subsequent reductive elimination affords the desired heterocycle and Pd(0), which reenters the catalytic cycle directly, in contrast to Pd(II)-catalyzed reactions, which usually require an additional reoxidation step. The mechanistic details of these processes have been reviewed a number of times.[1]

The palladium-catalyzed cyclization of vinylic/aryl halides or triflates containing neighboring alkenes, dienes, alkynes, and arenes via oxidative addition/reductive elimination reactions provides a very valuable approach to a wide range of heterocycles, which will be discussed in the following sections.

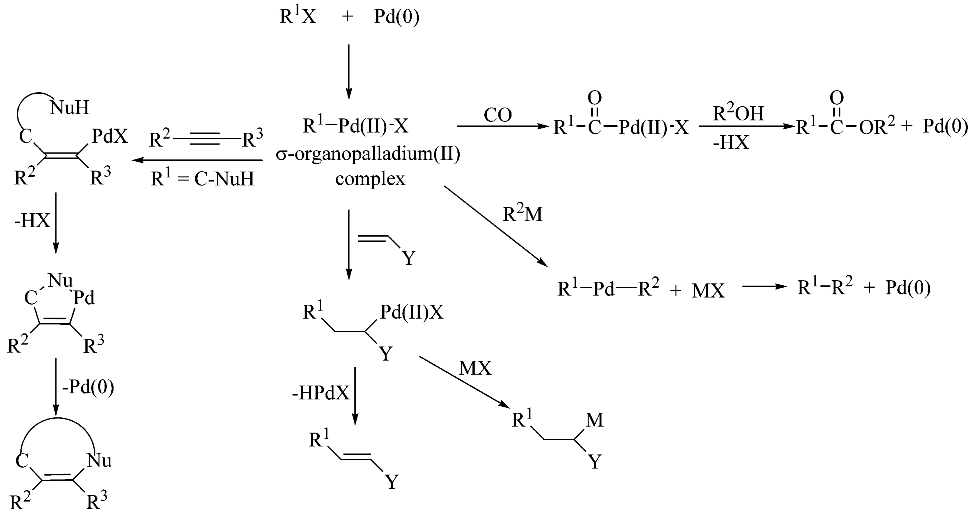
4. Heterocycles via Alkene Cyclizations

4.1. Heterocycles via Intramolecular Heck Cyclization of Aryl Halides

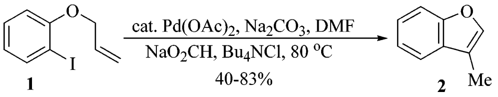
The palladium-catalyzed coupling of aryl or alkenyl halides or triflates with alkenes to provide more highly substituted alkenes is generally known as the Heck reaction.[7] Intramolecular versions of the Heck reaction have become a versatile tool in heterocyclic synthesis. Early applications focused on the preparation of heterocycles from haloarenes. More recently, a wide range of vinylic or aryl halides or triflates bearing appropriate heteroatoms and neighboring carbon−carbon double bonds have been employed in this process. Thus, we have reported the use of *o*-iodoaryl allyl ethers **1** as starting materials in the preparation of benzofurans **2** via intramolecular Heck cyclization (Scheme 2).[8] This cyclization proceeds under mild conditions and in reasonably good isolated yields when catalytic amounts of $Pd(OAc)_2$, Na_2CO_3, HCO_2Na, and *n*-Bu_4NCl in DMF are employed at 80 °C. Mechanistically, these reactions appear to proceed as indicated in Scheme 3. The addition of HCO_2Na improves the overall yields of benzofurans, presumably by reducing any π-allylpalladium intermediates **3** formed by carbon−oxygen insertion back to Pd(0), which can then reenter the desired catalytic cycle.

Similar conditions were employed by Kozikowski and co-workers in their preparation of benzofurans **5** from the 2-bromoanilines **4** (Scheme 4).[9] The benzofurans **5** were key intermediates in the synthesis of the indolactams **6**. Yum and co-workers also used formate in their preparation of 3-alkylfuropyridines **8** from iodopyridinyl allyl ethers **7** (Scheme 5).[10] Allylic ethers **7** with longer side chains and a

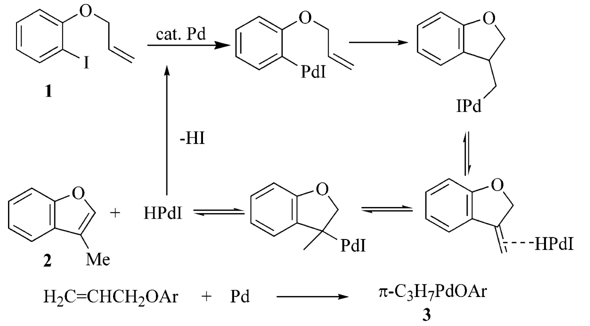
Scheme 1. Reaction Pathways for σ-Organopalladium(II) Complexes



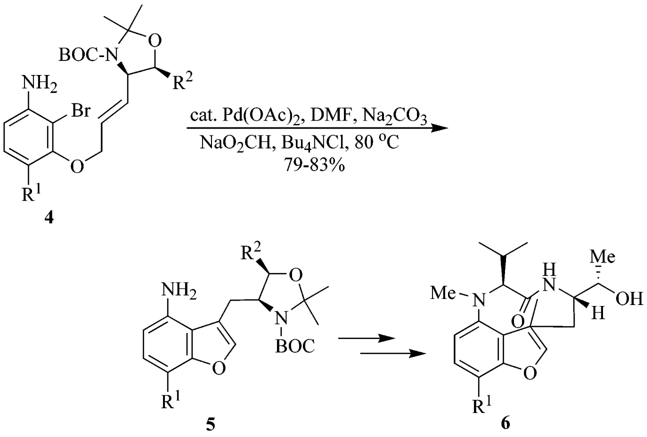
Scheme 2



Scheme 3

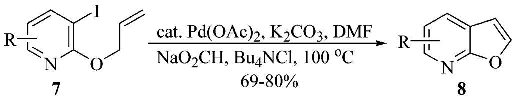


Scheme 4



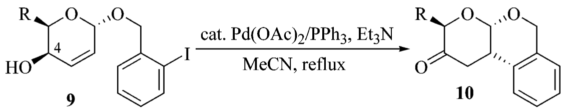
R^1 = H, *n*-hexyl; R^2 = H, Me

Scheme 5



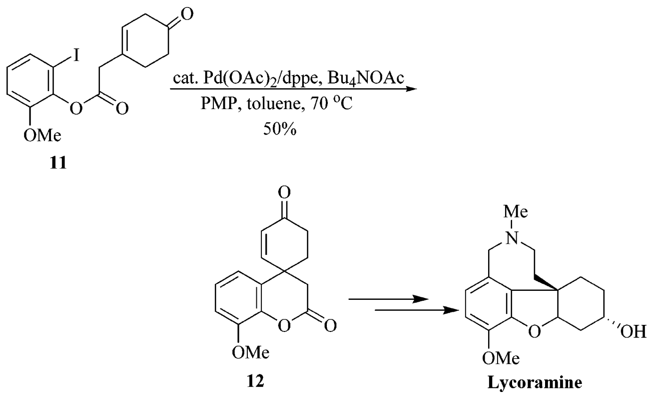
R = alkyl group

Scheme 6



10a R = CH_2OH 78%
10b R = Me 70%

Scheme 7



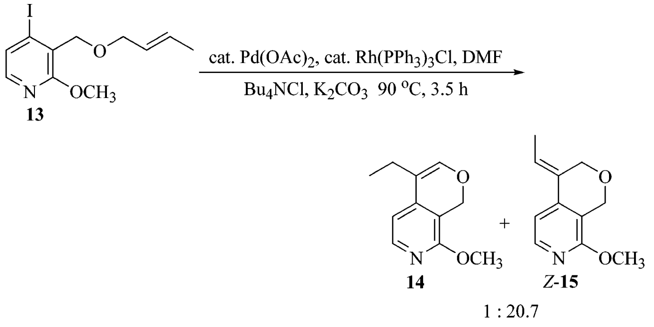
2-cyanopyridyl allyl ether provided lower yields of the desired products.

Carbohydrate derivatives bearing a fused pyran or furan ring have also been prepared by intramolecular Heck cyclization. Thus, the reaction of hex-2-enopyranosides **9** with catalytic $Pd(OAc)_2/PPh_3$, Et_3N, and MeCN or toluene as solvent give the *cis*-fused pyran or furan derivatives **10** in good yields (Scheme 6).[11] The configuration at C(4) was crucial for the cyclization, and only 1,4-*trans*-hex-2-enopyranosides could be cyclized efficiently.

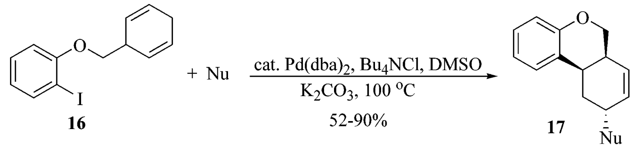
Guillou and co-workers utilized an intramolecular Heck cyclization to prepare a benzopyran ring in their synthesis of the alkaloid lycoramine (Scheme 7).[12] The tricyclic benzopyran **12** was obtained from iodide **11** in 50% yield using catalytic $Pd(OAc)_2$/dppe in the presence of 1,2,2,6,6-pentamethylpiperidine (PMP), tetrabutylammonium acetate, and toluene as the solvent. In the absence of Bu_4NOAc or when $Pd(OAc)_2$ and MeCN were used at reflux, the product **12** was isolated in lower yields.

The use of a catalytic couple composed of Rh(I) and Pd(II) to prepare enol ether **14** and allylic ether **15** has been described by Bankston and co-workers (Scheme 8).[13] They found that a catalyst consisting of Rh(I) and Pd(II) gives the desired product in better yields than the use of Pd(II)

Scheme 8

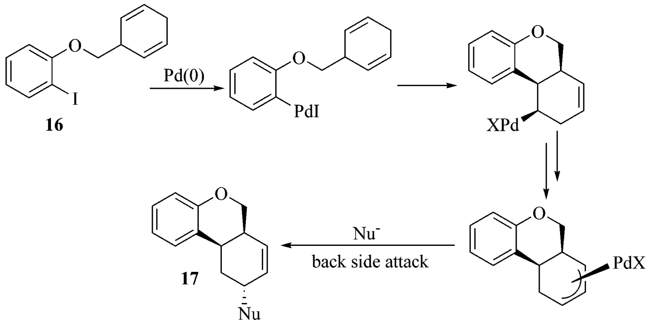


Scheme 9

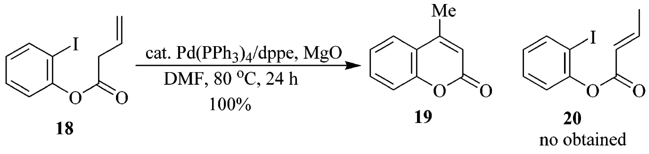


Nu = $CH(CO_2Et)_2$, $TsNCH_2Ph$, $HC(CO_2\text{-}t\text{-}Bu)_2$, NHPh, SO_2Ph, OAc, OPh

Scheme 10



Scheme 11

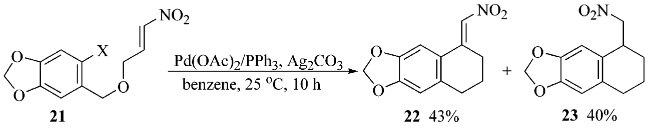


alone. In the presence of Rh(I) *endo* cyclization was preferred. Other parameters, such as dilution, temperature, and the palladium ligand can also effect the rate and selectivity.

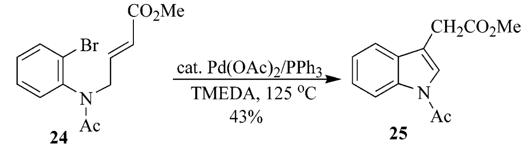
We have utilized the intramolecular Heck cyclization of 2,5-cyclohexadienyl-substituted aryl iodides to prepare functionalized heterocycles (Scheme 9).[14] The reaction of a variety of carbon, nitrogen, oxygen, and sulfur nucleophiles with aryl iodides, such as **16**, in the presence of catalytic $Pd(dba)_2$ in DMSO at 100 °C afforded the heterocyclic compounds **17** in good yields and high diastereoselectivity. The reaction is believed to proceed via (1) oxidative addition of the aryl halide to Pd(0), (2) organopalladium addition to one of the carbon−carbon double bonds, (3) palladium migration along the carbon chain on the same face of the ring to form a π-allylpalladium intermediate, and (4) nucleophilic displacement of the resulting π-allylpalladium species (Scheme 10).

Catellani and co-workers have prepared 4-methylcoumarin (**19**) in a quantitative yield from *o*-iodophenyl 3-butenoate (**18**) (Scheme 11).[15] Isomerization of the carbon−carbon double bond in **18** to the internal position (**20**) was controlled by the appropriate choice of ligand, solvent, and base.

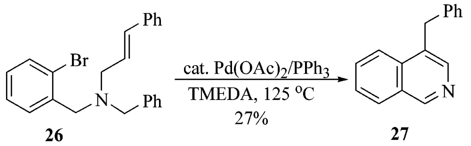
Scheme 12



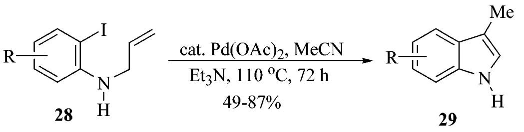
Scheme 13



Scheme 14



Scheme 15



R = CH_3, CH_3O, CH_3CH_2O, $c\text{-}C_6H_{11}$

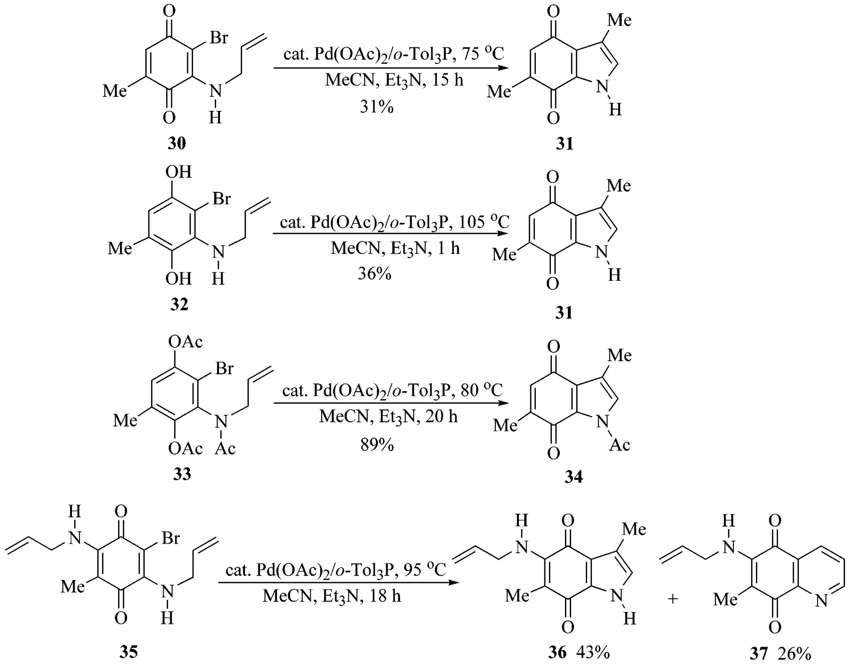
Iodoarene **21** was found by Denmark and Schnute to undergo Pd-catalyzed intramolecular Heck cyclization in the presence of stoichiometric amounts of $Pd(OAc)_2$ and PPh_3 at room temperature to afford exocyclic pyran derivative **22** (Scheme 12).[16] The use of Ag_2CO_3 as a base and the nonpolar solvent benzene are crucial for the success of the reaction. The product was obtained as a single geometrical isomer along with the corresponding saturated nitroalkane **23**.

Nitrogen heterocycles are also readily prepared by intramolecular Heck cyclization. Thus, indoles have been synthesized by the reaction of aryl halides bearing a neighboring olefin (Scheme 13).[17] The reaction of aryl bromide **24** with a catalytic amount of $Pd(OAc)_2$ and PPh_3 in the presence of tetramethylethylenediamine at 125 °C afforded indolyl acetate **25** in a moderate yield. The aryl bromide gave better results than the corresponding aryl iodide, and the analogous aryl chloride did not afford any indole. Analogous reaction conditions were applied by the same group to prepare the isoquinoline **27** from aryl bromide **26** (Scheme 14).[18]

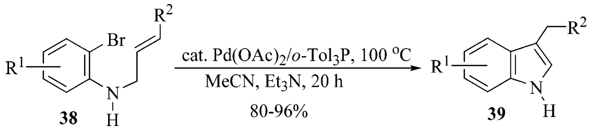
Hegedus and co-workers have also reported the preparation of indoles using intramolecular Heck cyclization (Scheme 15).[19] Thus, the reaction of 2-iodoanilines **28** with catalytic $Pd(OAc)_2$, Et_3N, and MeCN at 110 °C affords indoles **29** in good yields. Better results were obtained by addition of the catalyst in portions. The authors used similar reaction conditions to prepare indoloquinones **31** and **34** from bromo derivatives **30**, **32**, and **33** (Scheme 16). The cyclization of the quinone **30** or hydroquinone **32** afforded the cyclization product in lower yields than when the acetyl hydroquinone **33** was employed. The regiochemistry of cyclization depends on the substitution pattern present in the starting material. For example, the substituted diaminoquinone **35** afforded a mixture of indole **36** and quinoline **37** (Scheme 16).[20]

Kasahara and co-workers have reported that arylamino ketones and esters such as **38** react in the presence of catalytic

Scheme 16

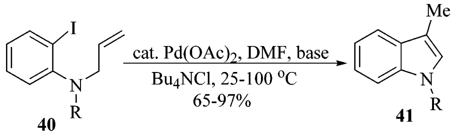


Scheme 17



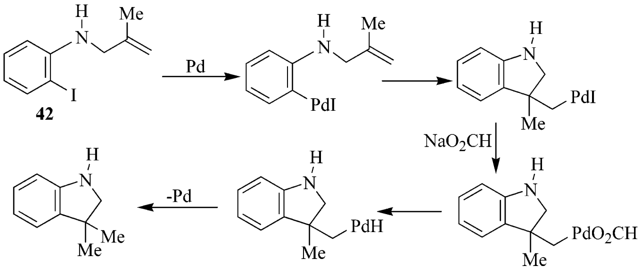
R^1 = H, 6-OMe, 4-CO$_2$Me, 5-CO$_2$Me, 6-CO$_2$Me; R^2 = COCH$_3$, CO$_2$Et

Scheme 18

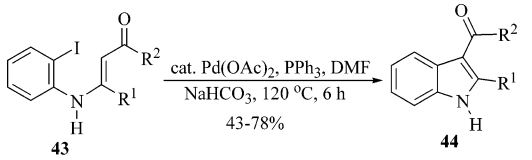


R = H, CH$_3$; base = Na$_2$CO$_3$, Et$_3$N or NaOAc

Scheme 19



Scheme 20



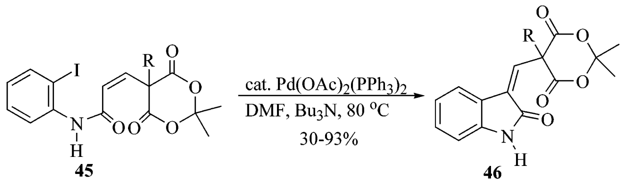
R^1 = H, CH$_3$, CH$_2$CO$_2$Et; R^2 = CH$_3$, OEt, Ph, OMe

amounts of Pd(OAc)$_2$ and tri-*o*-tolylphosphine in acetonitrile to afford 3-substituted indoles **39** in high yields (Scheme 17).[21]

We have also reported the preparation of indoles by intramolecular Heck cyclization. A catalytic amount of Pd(OAc)$_2$ in the presence of Bu$_4$NCl, DMF, and an appropriate base (Na$_2$CO$_3$, NaOAc, or Et$_3$N) rapidly cyclizes nitrogen-containing *o*-iodoaryl alkenes **40** to indoles **41** under mild temperatures and in high yields (Scheme 18).[22] Substitution on the nitrogen and/or the double bond slowed the reaction, but good yields of indoles could still be obtained. The cyclization of *N*-methallyl-*o*-iodoaniline (**42**) in the presence of sodium formate affords a good yield of an indoline (Scheme 19).[23] The sodium formate presumably reduces the initial organopalladium cyclization product to the indoline and Pd(0).

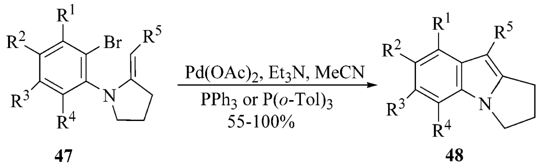
β-(2-Iodophenyl)amino unsaturated ketones or esters **43** can be readily cyclized to 2,3-disubstituted indoles **44**

Scheme 21



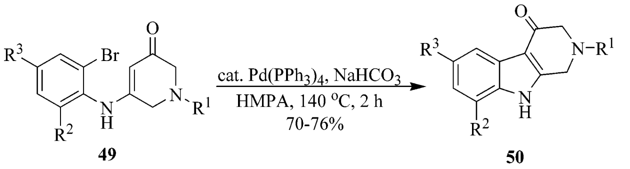
R = CH$_3$, CH$_2$CH$_2$COCH$_3$, CH$_2$CH$_2$CO$_2$CH$_3$, CH$_2$CH$_2$Ph, CH$_2$Ph

Scheme 22



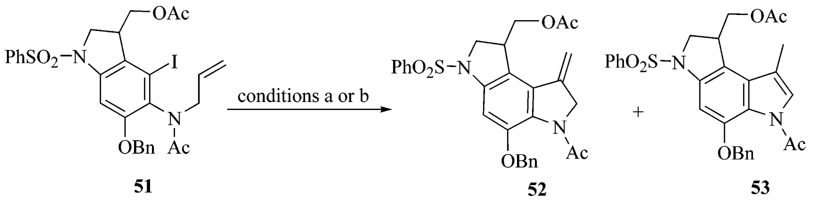
R^1 = R^2 = R^3 = R^4 = H, Me, OMe; R^5 = CO$_2$Et, COCH$_3$, CN

Scheme 23



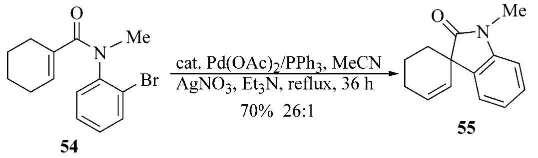
R^1 = CH$_2$Ph, CO$_2$Et; R^2, R^3 = H, Me

Scheme 24

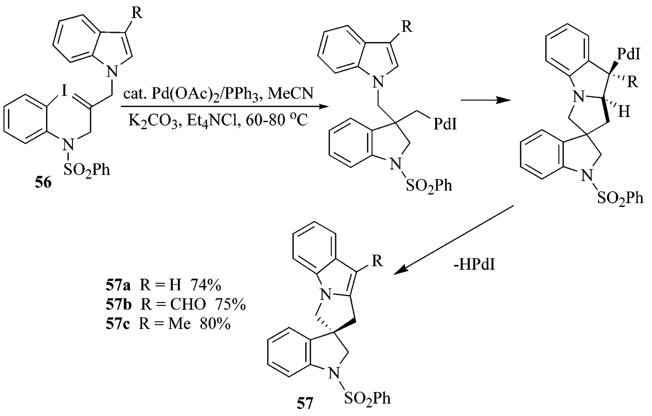


conditions a - cat. $Pd(OAc)_2$, NaOAc, Bu_4NCl, DMF - 64% : 30%
conditions b - cat. $Pd(PPh_3)_4$, Et_3N - 10% : 70%

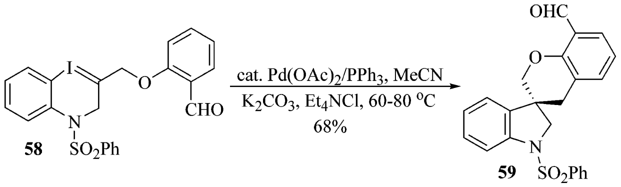
Scheme 25



Scheme 26



Scheme 27



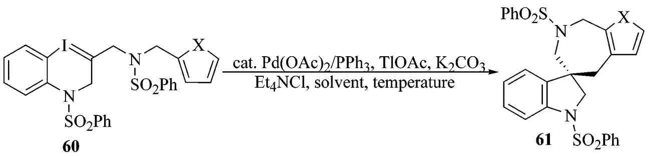
(Scheme 20).[24] The best yields of indoles were obtained when catalytic $Pd(OAc)_2$, $NaHCO_3$, and DMF were employed at 120 °C. When Et_3N was used instead of $NaHCO_3$, cyclization did not occur, and use of the bromide in place of the iodide gave the 2,3-disubstituted indoles in lower yields.

Cacchi and co-workers have prepared oxindoles **46** via intramolecular Heck cyclization of the Meldrum acid derivatives **45** (Scheme 21).[25] Moderate to high yields of the *Z* isomers of the alkylideneoxindoles **46** were obtained in all cases.

The enamines **47** have been cyclized in good yields to the pyrrolo[1,2-*a*]indoles **48** using $Pd(OAc)_2/PPh_3$ and Et_3N in acetonitrile (Scheme 22).[26] This cyclization was sensitive to the nature of the phosphine and the quantity of $Pd(OAc)_2$ used. The best result was obtained using PPh_3 or $P(o\text{-Tol})_3$ as the ligand and a stoichiometric amount of $Pd(OAc)_2$.

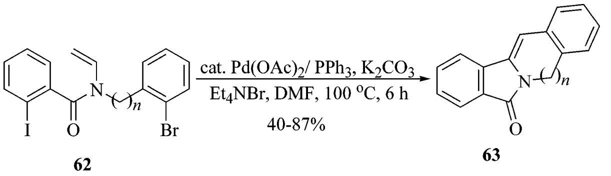
Chen and co-workers have also used bromoenaminones to prepare indoles via intramolecular Heck cyclization (Scheme 23).[27] When the bromoenaminones **49** were treated with catalytic $Pd(PPh_3)_4$ and $NaHCO_3$ in HMPA, the indoles **50** were obtained in good yields.

Scheme 28



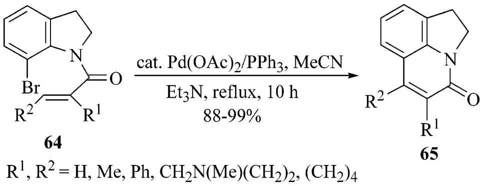
61a - X = O 64%; MeCN, 80 °C
61b - X = S 41%; DMF, 100 °C

Scheme 29



n = 0, 1, 2

Scheme 30



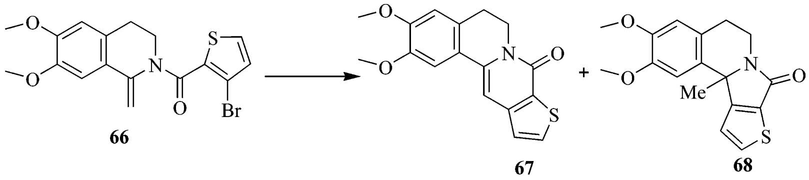
R^1, R^2 = H, Me, Ph, $CH_2N(Me)(CH_2)_2$, $(CH_2)_4$

An intramolecular Heck cyclization has been employed to prepare indole intermediates in the synthesis of the antitumor antibiotic CC-1065 (Scheme 24).[28] When the reaction of aryl iodide **51** was carried out with $Pd(OAc)_2$ in NaOAc, Bu_4NCl, and DMF, a mixture of the 8-methylene-7,8-dihydro-6*H*-indole **52** and 8-methylindole **53** was obtained in 64% and 30% yields, respectively. However, **52** and **53** were obtained in a ratio of 1:7 and 80% yield using catalytic $Pd(PPh_3)_4$ and Et_3N in acetonitrile at 78 °C.

The addition of silver salts has been reported by Overman and co-workers to reduce the amount of double bond isomerization during the synthesis of spirooxindoles (Scheme 25).[29] The reaction of carboxamide **54** with catalytic $Pd(OAc)_2$ in the presence of PPh_3 and Et_3N in refluxing acetonitrile provided a 1:1 mixture of oxindole **55** and a double bond regioisomer. The addition of Ag_2CO_3 or $AgNO_3$ afforded a 26:1 mixture of **55** and its alkene regioisomer in 70% yield. Replacement of the bromine by iodine in the substrate **54** gave the cyclized product more rapidly and with less $Pd(OAc)_2$ catalyst, but afforded a 1:1 mixture of **55** and its double bond regioisomer.

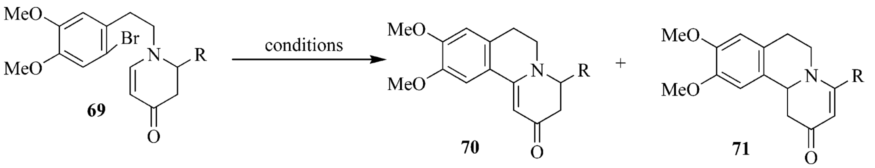
Grigg and co-workers have described the preparation of spiroindolines and spiroindoles by Heck cyclization (Scheme 26).[30] The spirocyclic product **57** was obtained in a good yield from **56** by two successive 5-*exo*-trig processes. Under similar reaction conditions, the spiroheterocycles **59** (Scheme 27) and **61** (Scheme 28) have been prepared in good yields.

Scheme 31



cat. $Pd(OAc)_2/PPh_3$, Na_2CO_3 MeCN, Et_4NCl - 47% 99:1
cat. $Pd(OAc)_2/PPh_3$, HCO_2Na, MeCN, Et_4NCl - 62% 4:96

Scheme 32



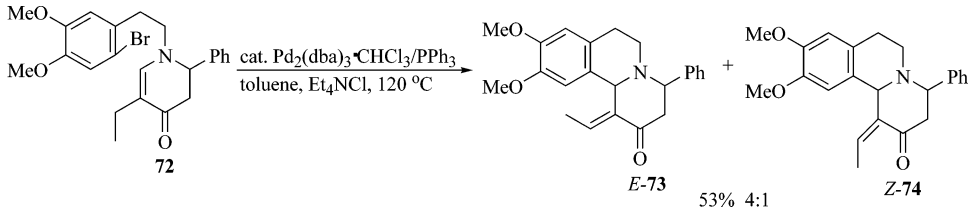
conditions - cat. $Pd_2(dba)_3$•$CHCl_3/PPh_3$, DMF, EtN(i-Pr)$_2$, 100 °C

R= Ph **70a** - 67%
R= C_6H_5OMe-p **70b** - 87%
R= $C_6H_5ONO_2$-o **70c** - 65%
R= H **70d** - 12%
R= i-Pr **70e** - 12%
R= n-Pr **70f** - 9%

conditions - cat. $Pd_2(dba)_3$•$CHCl_3/PPh_3$, DMF, K_2CO_3, Et_4NCl, 100 °C

R= Ph **70a** - 87%
R= p-OMePh **70b** : **71b** - 76% : 9%
R= H **70d** : **71d** - 17% : 35%
R= i-Pr **70e** : **71e** - 20% : 38%
R= n-Pr **70f** : **71f** - 26% : 42%

Scheme 33



Note that these reactions are terminated by palladium-promoted alkylation of the internal arene.

Isoindole derivatives have been prepared from the dihalobenzamides **62** by a tandem intramolecular Heck reaction (Scheme 29).[31] The first cyclization takes place regioselectively in the more favored 5-*exo* mode, leading to the isoindole nucleus, while the second takes place in the *endo* mode to afford the tetracyclic product **63**.

Bromoindolines **64** have been cyclized to quinolones **65** using $Pd(OAc)_2$ as the catalyst (Scheme 30).[32] The products were obtained via 6-*endo-trig* cyclization. However, increasing substitution of the double bond under the same reaction conditions provided a mixture of 6-*endo* and 5-*exo* cyclization products.

Sageot and Bombrum have studied the 6-*exo* versus 5-*endo* cyclization of enamides **66** (Scheme 31).[33] Those studies indicate that the catalytic system $Pd(OAc)_2/PPh_3$, Na_2CO_3, and Et_4NCl in acetonitrile affords mainly 6-*exo* cyclization product **67**. However, addition of the hydride source HCO_2Na provided mainly the 5-*endo* cyclization product **68**.

The cyclization of enaminones **69** in the presence of catalytic $Pd_2(dba)_3$•$CHCl_3/PPh_3$, DMF, and EtN(i-Pr)$_2$ at 100 °C produced only benzoquinolizine **70** (Scheme 32).[34] However, using K_2CO_3 and Et_4NCl at 120 °C, the cyclization produced benzoquinolizine **70**, plus its regioisomer **71**, in moderate yields. The enaminone **72** affords a mixture of **73** and **74** in moderate yield, with the *E* isomer formed preferentially (Scheme 33).

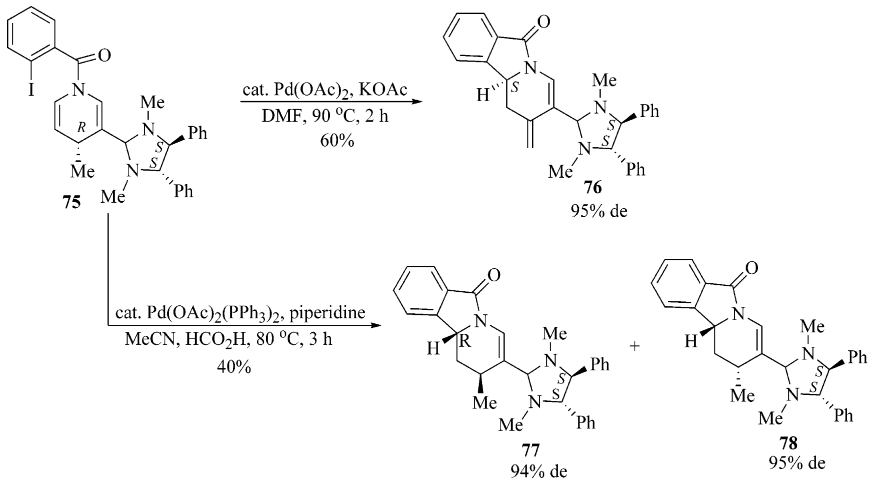
The chiral 1,4-dihydropyridines **75** have been cyclized to isoindolones **76** (Scheme 34).[35] Using catalytic $Pd(OAc)_2$ and KOAc in DMF at 90 °C, the dihydropyridine **75** was converted into **76** in 60% yield and 95% de by *anti* carbopalladation, then a *syn* β-elimination, and an isomerization of the double bound. When catalytic $Pd(OAc)_2(PPh_3)_2$ and piperidinium formate as a hydride reagent were used, the reaction afforded two diastereomeric products, **77** (94% de) and **78** (95% de), in a 7:3 ratio.

The use of chiral unsaturated amido esters **79** in the intramolecular Heck cyclization affords isoquinolones **80** (Scheme 35).[36] Of the various experimental parameters examined, the use of catalytic $Pd(OAc)_2/PPh_3$ and Et_3N gave the best overall results, and the isoquinolones **80** were obtained in good yields as a single stereo- and regioisomer. Using similar reaction conditions, but adding a silver(I) salt, the aryl iodide **81** can be cyclized in 98% yield to enantiomerically pure isoquinolone (S)-**82** by an *exo* cyclization (Scheme 36).

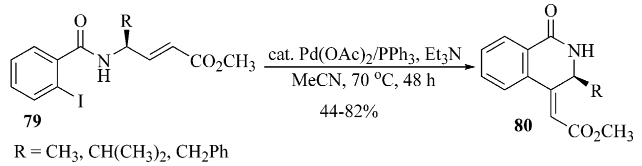
In a similar manner, chiral benzamides have been used to obtain 3,4-dihydroisoquinolinones (Scheme 37).[37] The reaction of benzamide **83** carried out in the presence of catalytic $Pd(OAc)_2/PPh_3$ and tetrapropylammonium bromide (TPAB) in DMF afforded a mixture of isoquinolinones **84** and **85** in 66−82% yields with high diastereo- and regioselectivity. The selectivity increases with increasing bulk of the substituent at the stereogenic center.

An *endo*-selective cyclization in the intramolecular Heck reaction of hydroindolinones has been reported by Rigby and co-workers (Scheme 38).[38] Treatment of hydroindolinone **86** under standard intramolecular Heck conditions [catalytic $Pd(OAc)_2$/o-Tol_3P, Et_3N, $MeCN/H_2O$, 80 °C] afforded a mixture of the expected *exo* product **87** together with a small amount of the unexpected *endo* product **88**. On the other hand, use

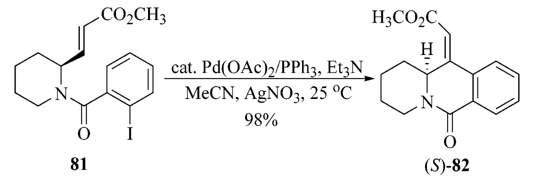
Scheme 34



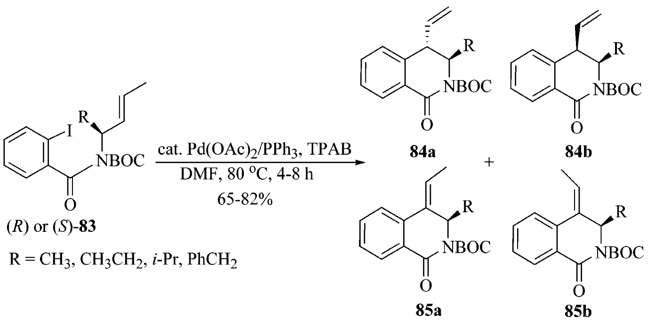
Scheme 35



Scheme 36



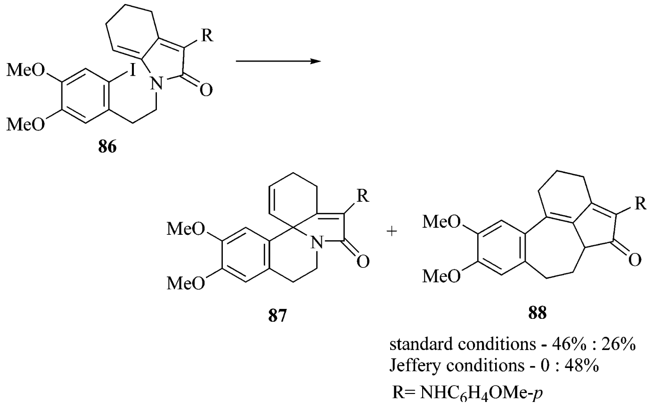
Scheme 37



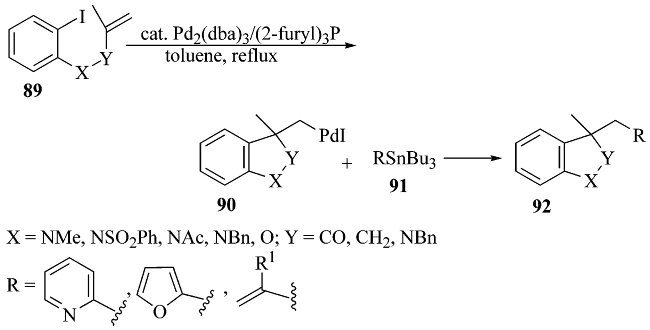
of the Jeffery Pd catalyst system[39] [catalytic Pd(OAc)$_2$, Bu$_4$NCl, KOAc, DMF] provides only product **88** resulting from an *endo* cyclization pathway.

Grigg and co-workers have employed a sequence involving Pd-catalyzed cyclization, followed by anion capture to prepare heterocycles. This process replaces the β-hydride elimination step of an intramolecular Heck cyclization with a group- or atom-transfer step, which results in the formation of one or more rings with simultaneous introduction of a wide range of functionality. The aryl iodide derivatives **89** undergo cyclization, followed by Stille coupling of **90** with the stannanes **91**, to give heterocycles **92** (Scheme 39).[40] Cyanide has also been used as an anion capture reagent (Scheme 40),[41] as has CO/MeOH (Scheme 41).[42] Similarly, the polycyclic olefin **93** undergoes cyclization to produce the heterocycles **94** and **96** as the main products via Stille coupling with or without incorporation of CO (Scheme 42).[43]

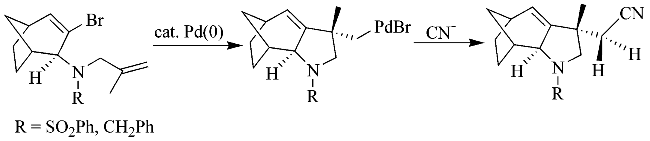
Scheme 38



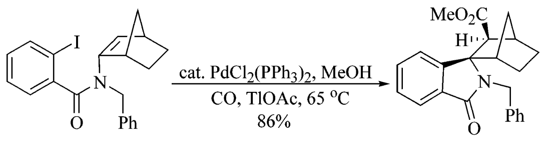
Scheme 39



Scheme 40

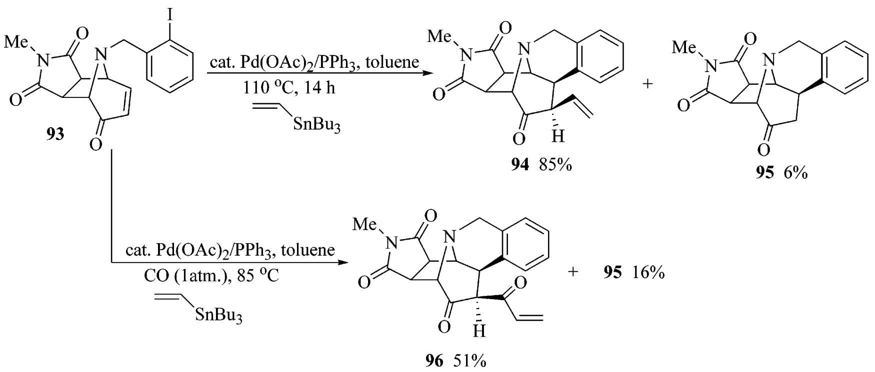


Scheme 41

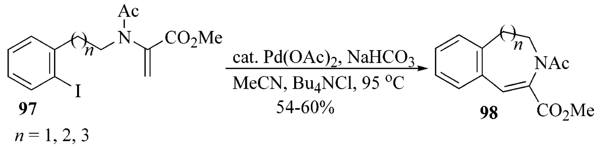


Heterocycles ranging from seven- to nine-membered rings can also be synthesized by intramolecular Heck cyclization. Aryl iodide **97** bearing a neighboring enamide afforded the corresponding 7-, 8-, and 9-*endo* cyclization products **98**

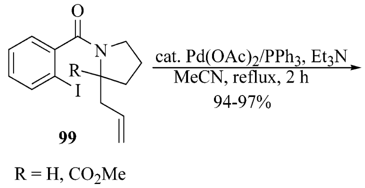
Scheme 42



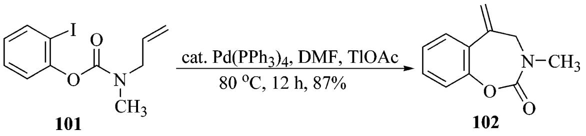
Scheme 43



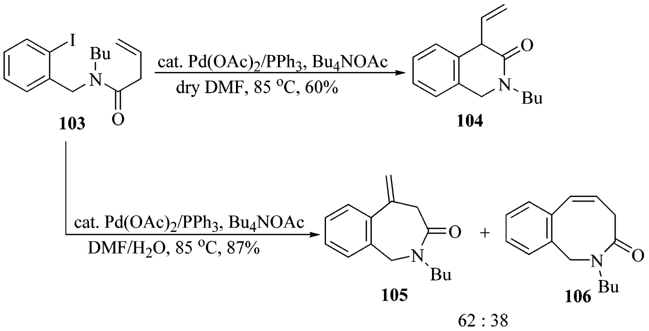
Scheme 44



Scheme 45



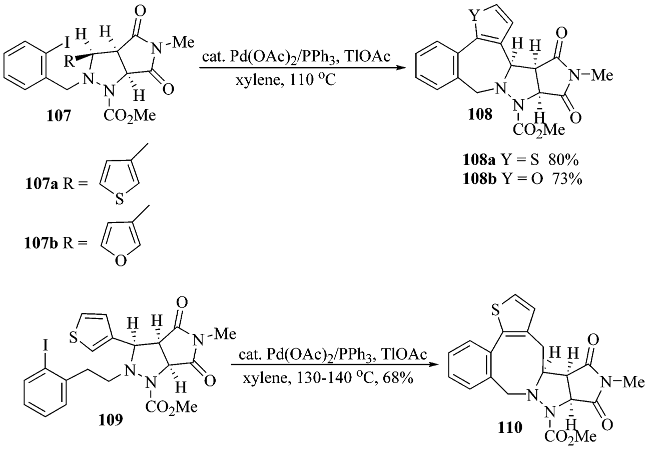
Scheme 46



(Scheme 43).[44] The pyrrolidines **99** have been cyclized to the tricyclic amide **100** containing a seven-membered ring (Scheme 44).[45] The seven-membered *N*,*O*-heterocycle **102** has also been obtained from carbamate **101** via intramolecular Heck cyclization using $Pd(PPh_3)_4$ as the catalyst (Scheme 45).[46]

The reaction of 3-butenamide **103** generates six-, seven-, and eight-membered ring heterocycles depending on the reaction conditions employed (Scheme 46).[47] When $Pd(OAc)_2$/PPh_3 is utilized as the catalyst, the regiochemistry of the cyclization is largely dependent on the presence or absence of water. Anhydrous DMF affords the six-membered ring product **104** exclusively, while aqueous DMF produces a mixture of lactams **105** and **106**.

Scheme 47



Pyrazolidines **107** and **109** bearing an aryl iodide substitution allowed Pd-catalyzed cyclization in the presence of $Pd(OAc)_2$/PPh_3 and TlOAc in xylene at 110 °C to give seven (**108**) and eight (**110**) membered heterocycles, respectively, in good yields (Scheme 47).[48]

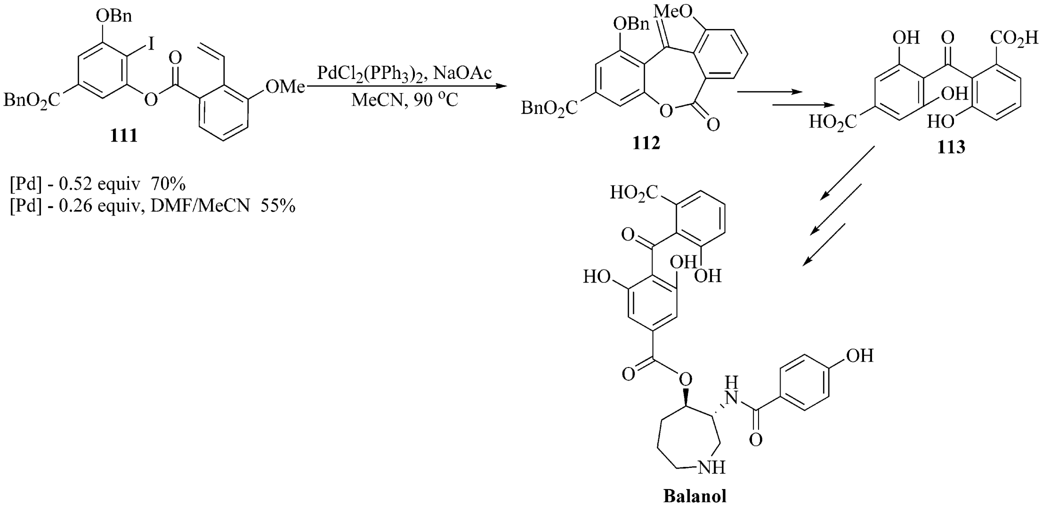
The intramolecular Heck cyclization of aryl iodide **111** to a seven-membered ring lactone (**112**) has been employed in the synthesis of a benzophenone fragment (**113**) of balanol (Scheme 48).[49] The lactone was obtained in 55−70% yields and converted to the ketone by oxidation and ring opening.

The intramolecular Heck cyclization of trifluoracetamide **114** using a catalytic amount of $Pd(OAc)_2$ and PPh_3 in the presence of Pr_4NBr and KOAc gives the seven-membered ring product **115** in a high yield (Scheme 49).[50] The addition of PPh_3 was crucial to drive the reaction to completion. In the absence of PPh_3, no cyclized product was obtained.

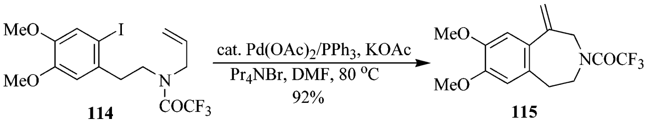
Intramolecular Heck cyclizations in the solid phase have been described by De Mesmaeker and co-workers (Scheme 50).[51] The enamines **116** on a polystyrene support produced heterocyclic products **117** via 6-*exo* cyclization, while the allylic amines **118** afforded the 6-*endo*-cyclized products **119**, after treatment with NaOMe.

The *erythro*-carbohydrate derivatives **120** can be readily cyclized to the corresponding bicyclic derivatives **121** in moderate to good yields using an intramolecular Heck cyclization (Scheme 51).[52] Using the same reaction conditions, the *threo* derivatives **122** produced the tetrahydrofurans **123** in 30−51% yields. The difference in yields in these cyclization reactions stems from the fact that the OEt group is a better leaving group than the aryl ether substituent. In a similar manner, the tricyclic derivatives **125**, containing six-membered rings, have been prepared from the unsaturated pyranosides **124** (Scheme 52).[53]

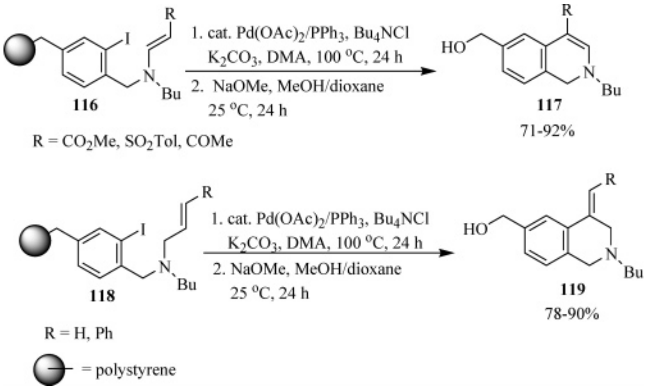
Scheme 48



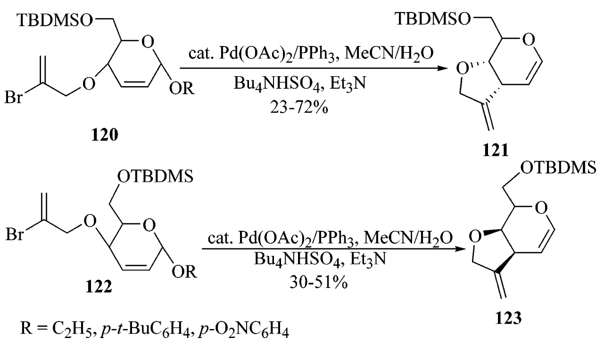
Scheme 49



Scheme 50



Scheme 51

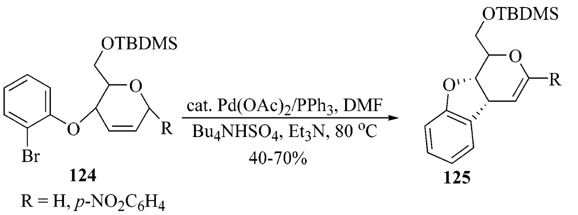


The intramolecular Heck cyclization of vinylic sulfones by catalytic Pd(0) in the presence of $AgNO_3$ generates polycyclic sulfones (Scheme 53).[54] The vinylic sulfone **126** bearing an iodide provides a much higher yield of the cyclization product than the corresponding bromide. The absence of $AgNO_3$ afforded the cyclized products **127** accompanied by the allylic isomer **128**.

The cyclization of sulfides **129** produces benzothiophenes **130** in good yields (Scheme 54).[55]

A curious stereochemical inversion of the (*Z*)-enol ether **131** during Heck cyclization has been noted by Danishefsky and co-workers (Scheme 55).[56] They have suggested that the (*Z*)-enol ether **131** is isomerized to the more reactive *E* isomer **135** via ring opening of **131** to the transitory intermediates **132** and **133**. Rotation about the σ-bond affords the *E* isomer **135**, via intermediate **134**, and cyclization produces the aldehyde **136**.

Scheme 52



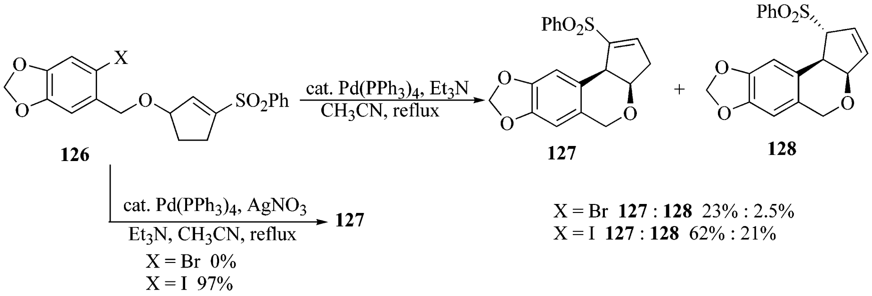
4.2. Heterocycles via Intramolecular Heck Cyclization of Vinylic Halides

There are far fewer examples of the intramolecular Heck cyclization of vinylic halides than aryl halides. Thus, the cyclization of vinylic bromides **137** and **140** in the presence of piperidine leads to the formation of five (**138**) and six (**139**) membered ring oxygen and nitrogen heterocycles (Scheme 56).[57] The amines **140** cyclize predominantly to the five-membered ring amines **141**, but the *N*-acetyl derivative afforded equal amounts of the five (**141**) and six (**142**) membered ring amides. These reactions apparently proceed by intramolecular carbopalladation of the neighboring double bond and subsequent rearrangement to the corresponding π-allylpalladium intermediate, which then undergoes displacement of the palladium by the amine.

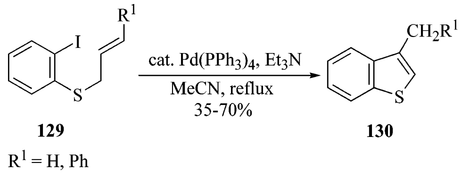
The intramolecular Heck cyclization of the dienyne **143** with a methyl substituent provided the tetracyclic product **145** in a good yield via 5-*exo-trig* cyclization of intermediate **144** and eventual β-hydride elimination (Scheme 57).[58] On the other hand, when the hydrogen-substituted dienyne **143** was cyclized, it afforded tricyclic diene **147** in 52% yield via *endo* cyclization of **146** and subsequent β-hydride elimination.

An intramolecular Heck cyclization of a vinylic iodide has been employed in the synthesis of *Strychnos* alkaloids (Scheme 58).[59] Dehydrotubifoline (**149**) can be obtained from iodide **148** in 79% yield. However, the presence of a carbamate group in **148** afforded the alkaloid **150** in an 84%

Scheme 53



Scheme 54



yield.[60] None of the anticipated alkaloid **151** was observed. The same reaction conditions were employed to produce isostrychnine (**153**) from vinylic iodide **152** (Scheme 59).[61]

The Heck cyclization of vinyl bromides **154** with R = H afforded *cis*-fused bicyclic ethers **155** in 16−73% yields (Scheme 60).[62] No cyclized product was obtained from **154** with a methyl substituent on the double bond.

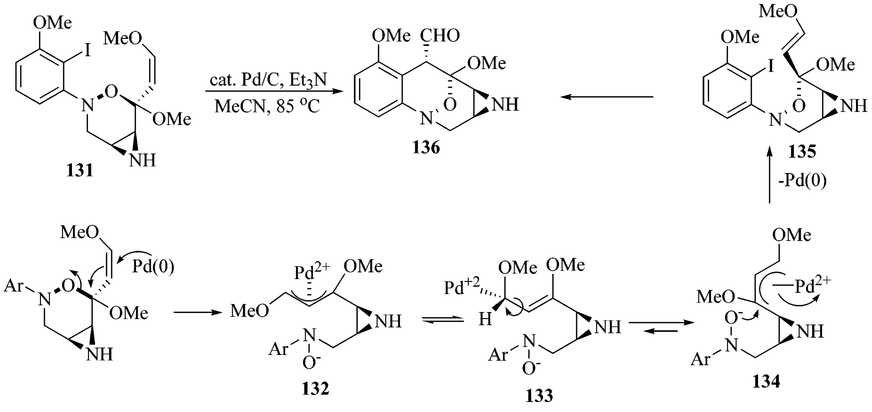
Closely related intramolecular Heck cyclizations have been carried out in an aqueous medium (Scheme 61).[63] Employing vinylic bromide **156**, both 6-*endo-trig* and 5-*exo-trig* cyclization products **157** and **158** have been obtained, with the former predominating. However, when anhydrous conditions were employed, only the five-membered ring heterocycle **158** was obtained.

Recent work has indicated that the product of an intramolecular Heck cyclization can be readily trapped by arylboronic acid cross-coupling (Scheme 62).[64] The reaction of tosylamide **159** with arylboronic acids in the presence of catalytic $Pd(PPh_3)_4$ and Na_2CO_3 afforded pyrrolidine derivatives **160** in good yields. It is believed that the alkylpalladium intermediate **161** is stabilized by coordination to the neighboring sulfonamide, which results in suppression of β-hydride elimination.

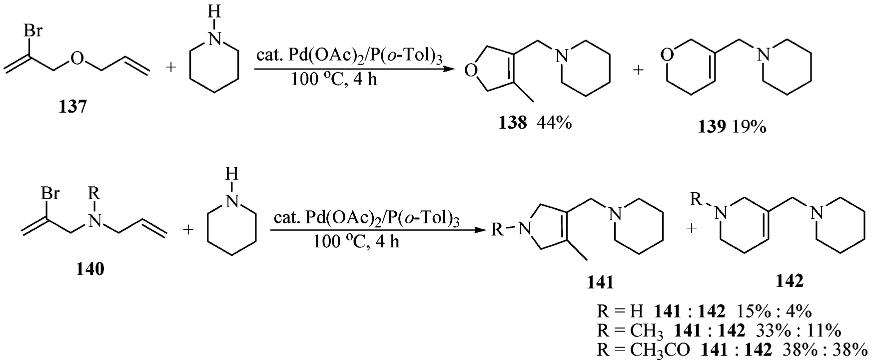
The 1,1-dibromo-1-alkenes **162** have been cyclized to the bicyclic ethers **163** and **164** via intramolecular Heck cyclization (Scheme 63).[65] Reaction with the phenyl-substituted starting triene required different reaction conditions and resulted in a much lower yield.

The vinyl bromides **165** bearing an enamine group have been cyclized to pyrroles **166** in moderate to good yields (Scheme 64).[66] From a mechanistic point of view (Scheme 65), the cyclization apparently proceeds through oxidative addition of the vinylic bromide to Pd(0) and coordination to the neighboring double bond to give intermediate **167**. This is followed by the formation of intermediates **168** and **169**. Reductive elimination of the latter and isomerization afford the observed pyrroles **166**.

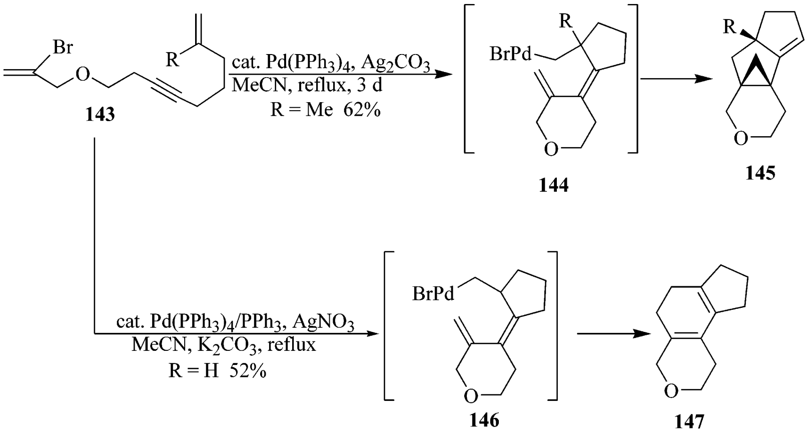
Scheme 55



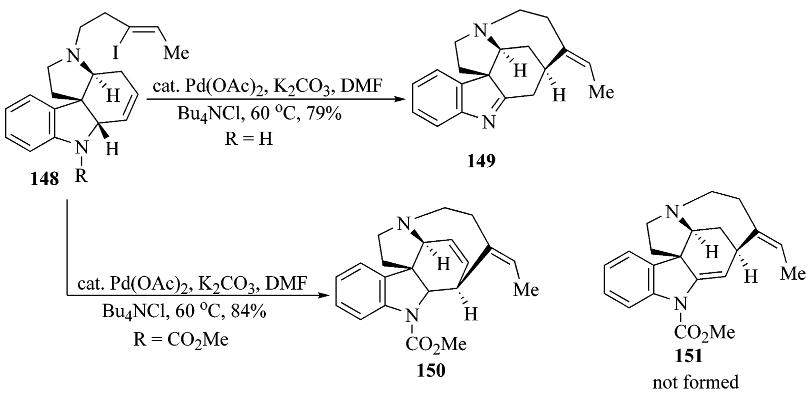
Scheme 56



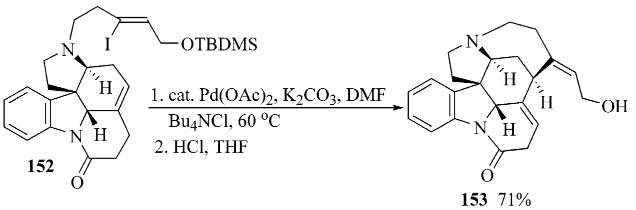
Scheme 57



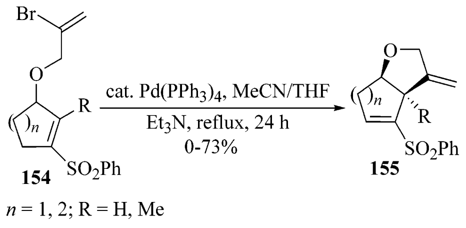
Scheme 58



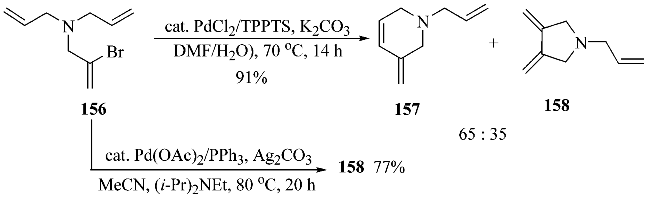
Scheme 59



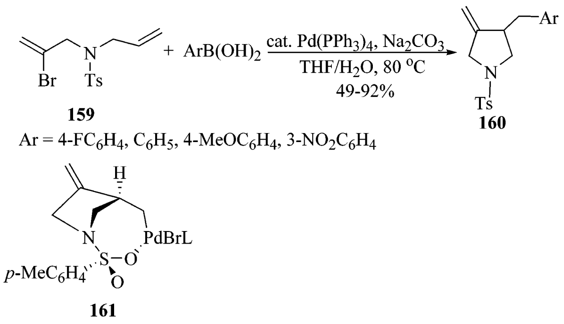
Scheme 60



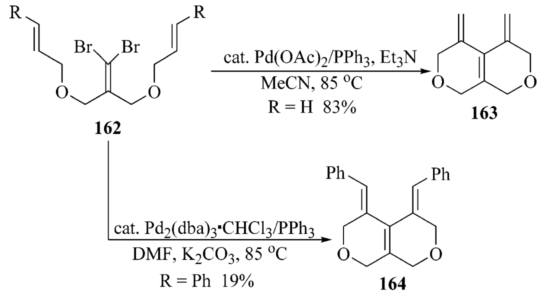
Scheme 61



Scheme 62



Scheme 63

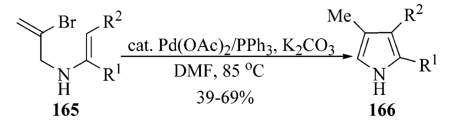


4.3. Heterocycles via Intramolecular Heck Cyclization of Vinylic and Aryl Triflates

Most of the work employing vinylic or aryl triflates as substrates for the intramolecular Heck reaction has focused on the synthesis of carbocycles. Very little work has been reported on the synthesis of heterocycles. However, the cyclization of aryl triflates **170** and **172** has produced anabasine analogues **171** and **173**, respectively, in moderate yields, after hydrogenation with catalytic Pd/C (Scheme 66).[67]

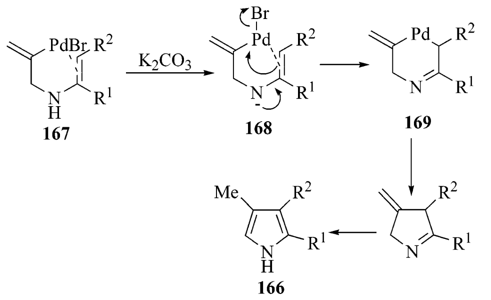
Naphthopyrrolocarbazoles have been synthesized by intramolecular arylation using aryl triflates (Scheme 67).[68] For example, the reaction of aryl triflate **174** with a stoichiometric

Scheme 64

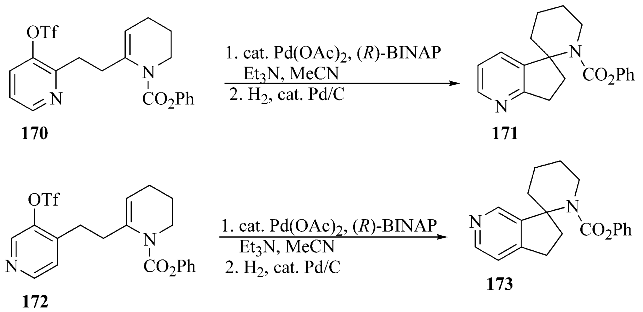


R^1 = H, Me, n-C_6H_{13}, CH_2OMe, Ph; R^2 = p-$MeC_6H_4SO_2$

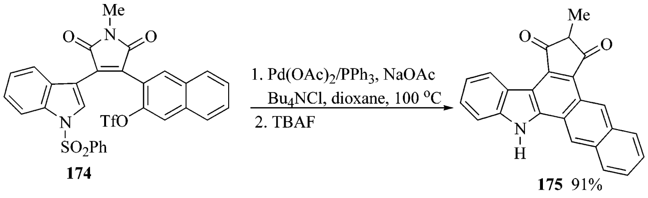
Scheme 65



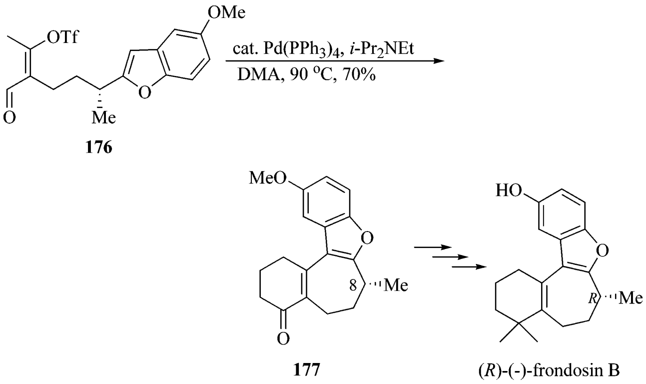
Scheme 66



Scheme 67



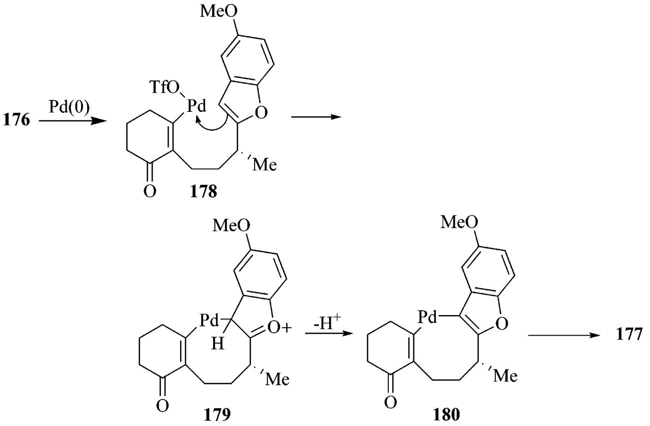
Scheme 68



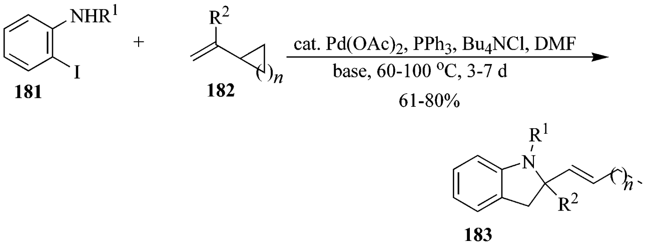
amount of Pd(OAc)$_2$ gave **175** in a high yield after tratment with TBAF.

Similarly, the reaction of vinylic triflate **176** has been used to prepare a seven-membered ring furan derivative (**177**) from vinyl triflate **176**, which is an intermediate in the synthesis of (−)-frodosin B (Scheme 68).[69]

Scheme 69

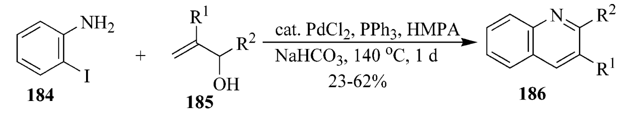


Scheme 70



R^1 = H, Ts; R^2 = H, Me, Ph; base = KOAc, Na_2CO_3, K_2CO_3, Et_3N; n = 1, 2

Scheme 71



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

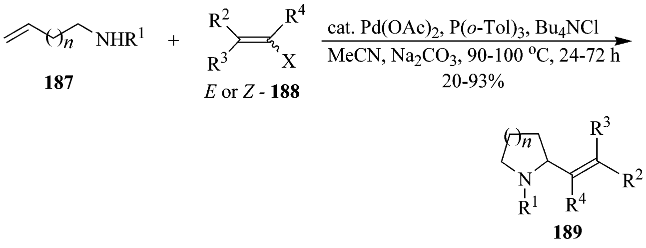
4.4. Heterocycles via Intermolecular Annulation

The palladium-catalyzed intermolecular cross-coupling of simple alkenes with functionally substituted aryl or vinylic halides or triflates provides another useful route to a wide variety of heterocycles.[70] For example, we have described the preparation of the indolines **183** by the cross-coupling of *o*-iodoanilines **181** with vinylic cyclopropanes or cyclobutanes **182** (Scheme 70).[71] The process is reasonably general with regard to the types of substituents on the arene that can be employed and the substitution pattern allowed in the unsaturated cyclopropane or cyclobutane. This process appears to involve (cyclopropylcarbinyl)- or (cyclobutylcarbinyl)palladium intermediates, which rapidly ring open to olefinic palladium species in which the palladium moiety subsequently migrates to the allylic position by a palladium hydride elimination/readdition process. The resulting π-allylpalladium intermediate then undergoes intramoleccular displacement by nitrogen.

In 1991, we reported a convenient synthesis of quinolines **186** by the cross-coupling of *o*-iodoaniline (**184**) and allylic alcohols **185** (Scheme 71).[72] The reactions are generally quite clean, affording a single predictable product in reasonable isolated yields.

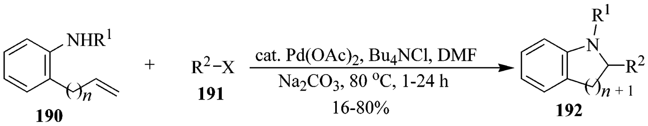
We and Weinreb and co-workers have also reported a simple, direct method for the synthesis of unsaturated pyrrolidines and piperidines by the reaction of the readily available vinylic halides **188** and olefinic sulfonamides **187** (Scheme 72).[73] A wide variety of vinylic halides can be employed in this process, including bromides and iodides with a range of substitution patterns. The (*E*)- and (*Z*)-1-halo-1-alkenes both give exclusively the *E*-substituted product.

Scheme 72



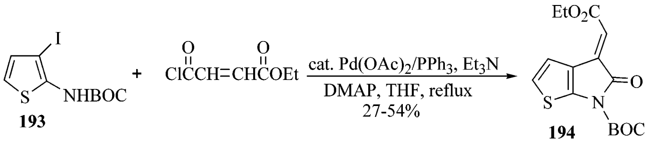
R^1 = Ts, Tf; R^2 = H, CO_2Me, Ph, *n*-Bu, Et; R^3 = H, Me; R^4 = H, Me, Et;
X = Br, I; *n* = 0, 1

Scheme 73

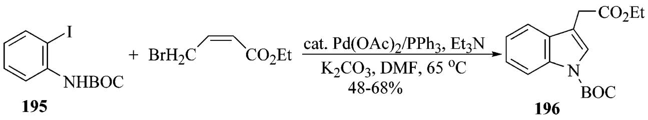


R^1 = Ts, $COCF_3$, H; R^2 = vinylic; X = I, Br, OTf; *n* = 0, 1

Scheme 74



Scheme 75



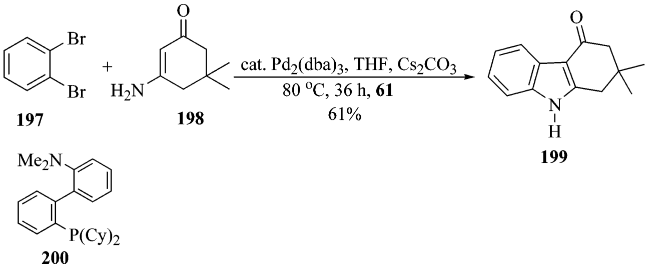
We have also been able to prepare a range of dihydroindoles and dihydroquinolines **192** by the palladium-catalyzed cross-coupling of unsaturated anilide derivatives **190** and vinylic halides or triflates **191** (Scheme 73).[74] This process again proceeds via π-allylpalladium intermediates and intramolecular displacement.

Heterocycles have also been prepared by a one-pot process involving substitution on a nitrogen moiety and subsequent palladium-catalyzed cyclization. For example, acylation and cyclization of the BOC-protected iodothiophene derivative **193** by ethoxyfumaroyl chloride afforded the heterocycle **194** in moderate yield (Scheme 74).[75] In a similar manner, the allylation/cyclization of *o*-iodoaniline derivative **195** by ethyl 4-bromocrotonate produced the indole **196** (Scheme 75). In both cases, only 5-*exo* cyclization was observed.

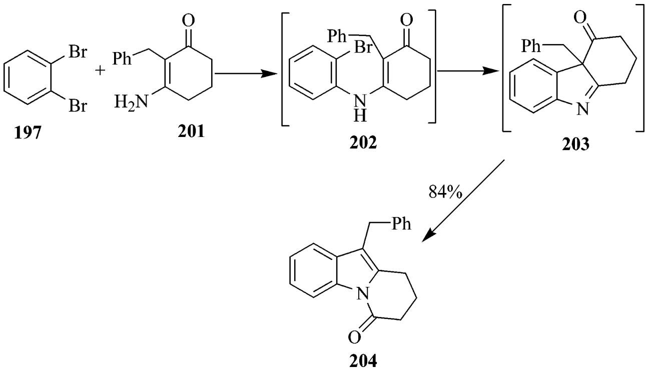
Palladium-catalyzed cross-couplings with 1,2-dibromobenzene have proven to be a useful way to generate indoles. Thus, the reaction of 1,2-dibromobenzene (**197**) with enaminone **198** in the presence of catalytic $Pd_2(dba)_3$, ligand **200**, and Cs_2CO_3 in THF afforded indole **199** in 61% yield (Scheme 76).[76] However, when enaminone **201** was allowed to react with 1,2-dibromobenzene under the same conditions, the cyclized product **204** was produced in 84% yield via intermediates **202** and **203** (Scheme 77).

In a related study, Shim and co-workers showed that isoindolinones **207** could be prepared in moderate yields from *o*-iodobenzoyl chloride (**205**), CO, and aldimines **206** by a one-step intermolecular cyclization (Scheme 78).[77] None of the desired cyclization product could be obtained when R^1 = *t*-Bu or Ph.

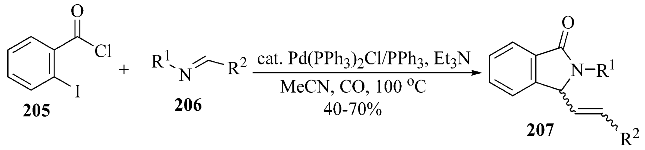
Scheme 76



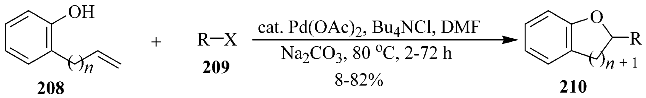
Scheme 77



Scheme 78

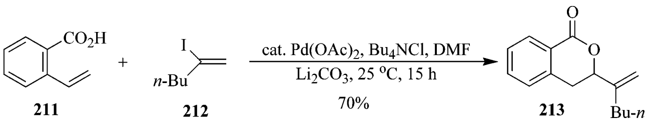


Scheme 79



R = vinylic; X = I, Br, OTf; *n* = 1, 2

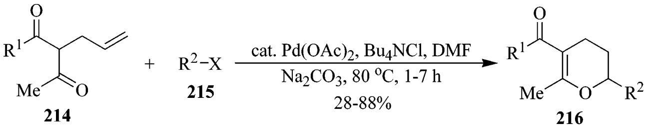
Scheme 80



The intermolecular cross-coupling of alkenes bearing a OH group at an appropriate distance with aryl or vinylic halides or triflates is a versatile way to generate a wide variety of oxygen heterocycles under mild reaction conditions. Thus, we have found that the reactions of *o*-allylic and *o*-vinylic phenols **208** with vinylic halides or triflates **209** produces substituted dihydrobenzopyrans and dihydrobenzofurans **210**, respectively, in good yields (Scheme 79).[78]

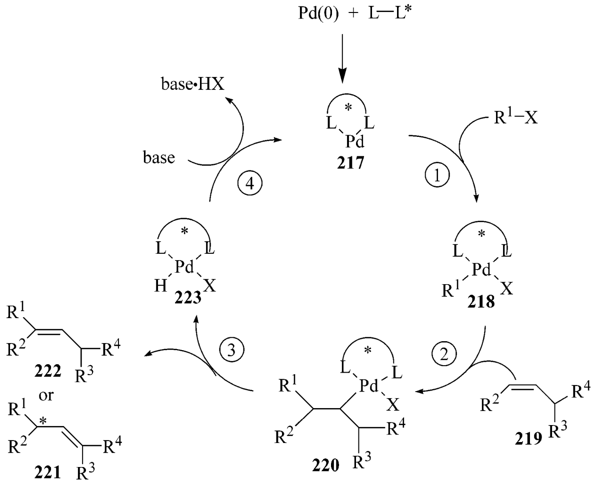
The intermolecular reaction of *o*-(1-alkenyl)benzoic acids with vinylic halides and triflates in the presence of a palladium catalyst produces the corresponding 3,4-dihydroisocoumarins (Scheme 80).[79] For example, the treatment of *o*-vinylbenzoic acid (**211**) and a vinylic halide such as **212** afforded the dihydroisocoumarin **213** in a 70% yield. Various *o*-(1-alkenyl)benzoic acids and vinylic substrates, including *E* and *Z* isomers, have been successfully employed in this process. No matter what the stereochemistry of the vinylic substrate, only products with *E* stereochemistry are

Scheme 81



R^1 = OEt, Me; R^2 = vinylic; X = I, Br, OTf

Scheme 82



produced. This is consistent with the formation of a π-allylpalladium intermediate.

In a similar manner, the intermolecular palladium-catalyzed cross-coupling of 2-allyl-1,3-dicarbonyl compounds **214** with vinylic halides or triflates **215** generates dihydropyran derivatives **216** in good yields (Scheme 81).[80]

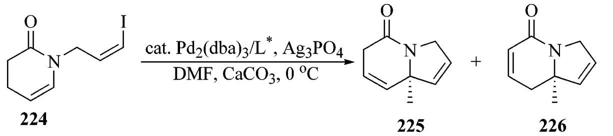
4.5. Heterocycles via Asymmetric Heck Cyclization

Asymmetric versions of the palladium-catalyzed Heck reaction have provided a very useful new route to heterocycles, which are enantiomerically enriched.[81] Three different mechanistic pathways—cationic,[82] anionic,[83] and neutral[84]—have been reported for these reactions.[85] However, in general it appears that the asymmetric Heck reaction proceeds through oxidative addition of the organic halide to a Pd(0)—phosphine species (**217**) (step 1) to give a Pd(II) intermediate (**218**) (Scheme 82). Coordination and insertion of the alkene **219** then gives **220** (step 2). Asymmetric induction occurs during the addition step, which leads to **220**. β-Hydride elimination from **220** affords **221** or **222** (step 3) and a palladium hydride (**223**). Subsequent reductive elimination of HX from **223** regenerates the starting Pd(0)—phosphine species **217** (step 4). Over the years, a number of chiral ligands have been utilized in this process. However, the best enantiomeric purities in this reaction have generally been obtained using the chiral bidentate phosphine ligand BINAP.

In an attempt to induce chirality in the Heck cyclization of alkenyl iodide **224**, Shibasaki and co-workers used chiral palladium ligands, such as (*R*)-BINAP, (*R*,*R*)-MOD-DIOP, (*S*,*S*)-BCPM, and (*R*,*S*)-BPPFOH in DMF along with Ag$_3$PO$_4$ to obtain a mixture of functionalized indolizidines **225** and **226** in moderate yields (6—67%) and enantioselectivities (34—64%) (Scheme 83).[86] However, considerable improvement was observed when using silver-exchanged zeolites in a mixture of DMSO—DMF as solvent.

Overman and co-workers have carried out a series of asymmetric Heck cyclizations using aryl iodide **227** and (*R*)-(+)-BINAP in the presence of a silver salt (Scheme 84).[87] Heck cyclization using catalytic Pd$_2$(dba)$_3$ and (*R*)-BINAP in *N*,*N*-dimethylacetamide in the presence of Ag$_3$PO$_4$ afforded the (*S*)-3,3-spirooxindole **228** in 81% yield and 71% enantiomeric excess. The use of 1,2,2,6,6-pentamethylpiperidine (PMP) instead of the silver salt gave the (*R*)-3,3-spirooxindole **229** in 77% chemical yield and 66% enantiomeric excess.

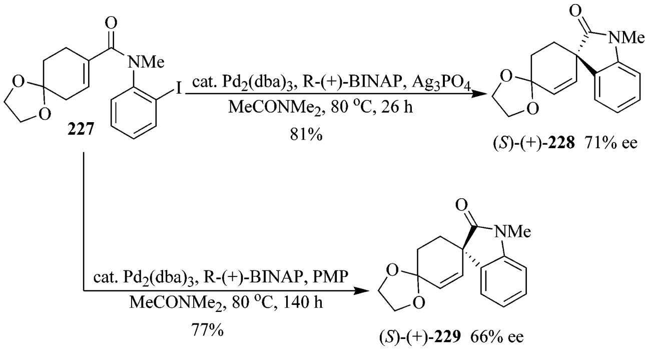
Scheme 83



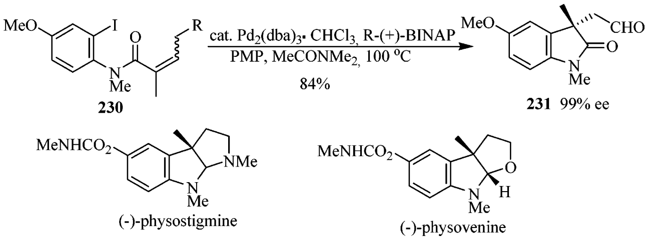
L* = silver-exchanged zeolite

94% yield, 86% ee

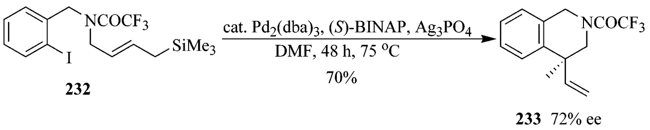
Scheme 84



Scheme 85



Scheme 86

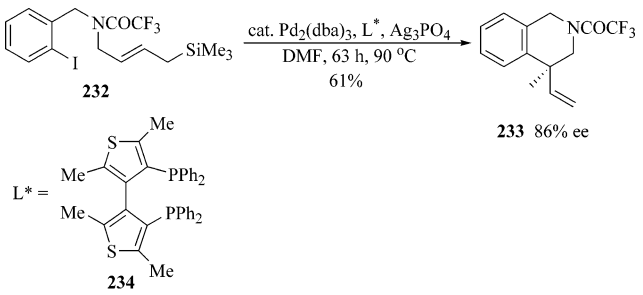


They employed similar reaction conditions to synthesize the indole derivative **231** from the 2-iodoanilide **230** (Scheme 85).[88] This intermediate was subsequently converted into the natural products physostigmine and physovenine.

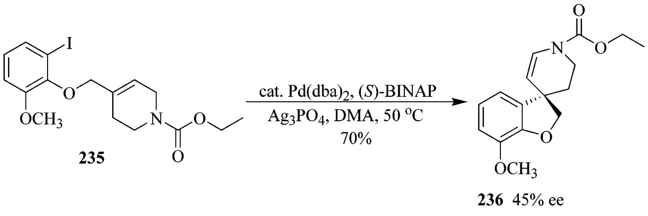
In a similar manner, the allylsilane **232** undergoes asymmetric Heck cyclization in the presence of (*S*)-BINAP and Ag$_3$PO$_4$ to produce the tetrahydroisoquinoline **233** in a good yield and moderate enantiomeric excess (Scheme 86).[89] A significant improvement in this reaction was later reported using (+)-TMBTP (**234**) as the ligand instead of (*S*)-BINAP (Scheme 87).[90]

Cheng and co-workers have employed an asymmetric Heck cyclization to prepare a morphine fragment from aryl iodide **235** (Scheme 88).[91] Using Pd(dba)$_2$ as the catalyst and (*S*)-BINAP as the chiral ligand in the presence of Ag$_3$PO$_4$, they obtained spiro derivative **236** with low stereoselectivity. Employing similar reaction conditions, Wipf and Yokokawa synthesized the benzofuranone fragment **238** of

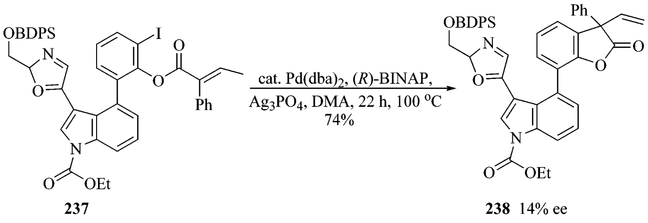
Scheme 87



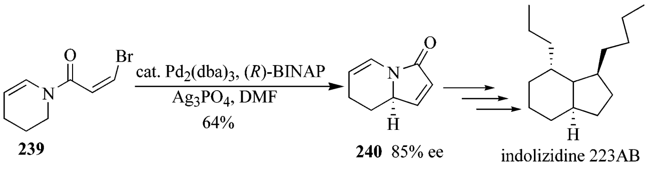
Scheme 88



Scheme 89



Scheme 90



diazoamide A[92] in good chemical yield, but low enantioselectivity (Scheme 89).[93] Better results were obtained by Sulikowski and co-workers in the preparation of indolizidone (**240**), an intermediate in their synthesis of the alkaloid indolizidine 223A (Scheme 90).[94]

The asymmetric Heck cyclization of aryl iodide **241** in the presence of (*S*)-(−)-**243** gave the cyclized product **242** in a higher yield and ee than when (*S*)-BINAP was employed as the ligand (Scheme 91).[95] However, when aryl triflate **244** was used in the synthesis of the tetracycle **245**, (*S*)-BINAP gave better results.

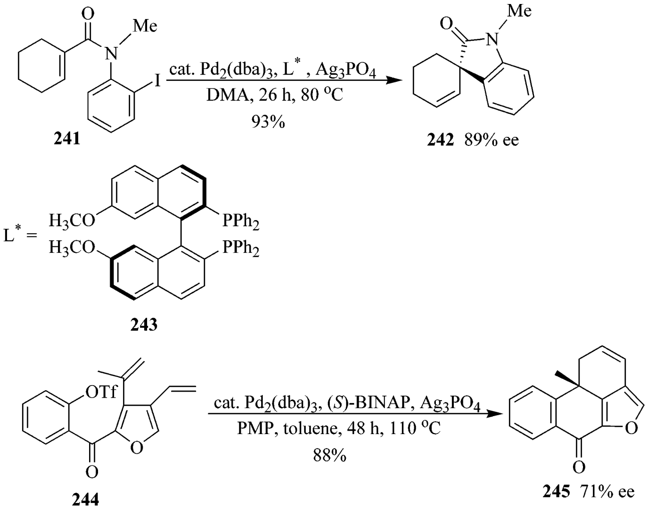
The chiral monodentate ligand **248** has been very effective in the asymmetric cyclization of **246** to cyclohexadiene **247** (Scheme 92).[96]

4.6. Heterocycles by the Annulation of Dienes

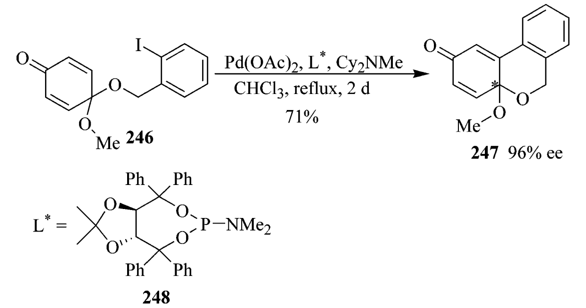
4.6.1. Heterocycles by the Annulation of 1,2-Dienes

The Pd-catalyzed heteroannulation of 1,2-dienes has proven to be a very versatile method for the synthesis of a wide variety of heterocycles.[21] Thus, we have reported that the aryl iodides **249**, bearing various heteroatom-containing functionality in the ortho position, react regioselectively with the 1,2-dienes **250** in the presence of a catalytic amount of a palladium complex to afford the five- and six-membered ring heterocycles **251** in high yields (Scheme 93).[97] This reaction most likely proceeds as illustrated in Scheme 94. The first step is the reduction of Pd(II) to Pd(0), which undergoes subsequent oxidative addition of the aryl halide to form arylpalladium intermediates, which in turn readily undergo carbopalladation of the 1,2-diene, producing π-allylpalladium compounds, which readily undergo intramolecular nucleophilic substitution.

Scheme 91



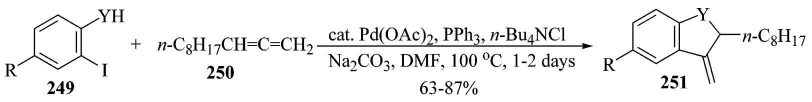
Scheme 92



We have also described the Pd-catalyzed asymmetric heteroannulation of 1,2-dienes, using functionally substituted aryl iodides (Scheme 95).[98] Aryl iodides **252** with a nucleophilic substituent in the *ortho* position or vinylic iodides **256** with a pronucleophile in the allylic position react with the 1,2-dienes **253** in the presence of various palladium catalysts and a chiral bisoxazoline ligand (**255**) to afford the *O*- and *N*-heterocycles **254** and **257**, respectively, in good yields and in 46−88% enantiomeric excess. The generality of this process was demonstrated by the use of nucleophilic substituents ranging from tosylamides and alcohols to carboxylic acids.

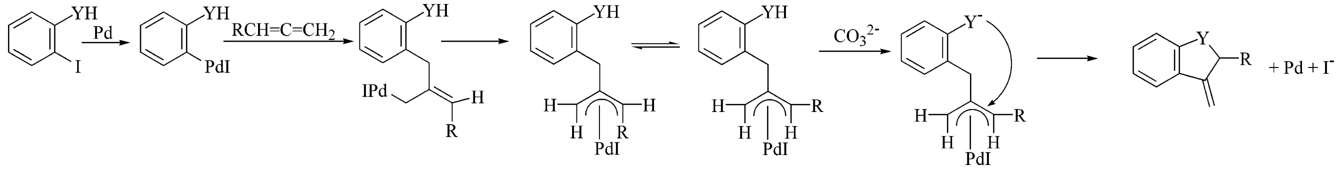
We have also reported that palladium catalyzes the regio- and stereoselective annulation of the 1,2-diene **259** by vinylic halides such as **258**, bearing alcohol, amine, sulfonamide, carboxylic acid, and carboxamide groups, to produce a variety of unsaturated heterocycles with five- and six-membered rings (**260**) (Scheme 96).[99] Six-membered rings are formed more readily than five-membered rings. The regioselectivity is generally high, with vinylic halides bearing alcohol, carboxylic acid, and carboxamide groups predominantly but not exclusively, affording the product of intramolecular attack on the more substituted end of the π-allylpalladium intermediate, while amines selectively attack only at the less substituted end of the π-allylpalladium intermediate.

Scheme 93

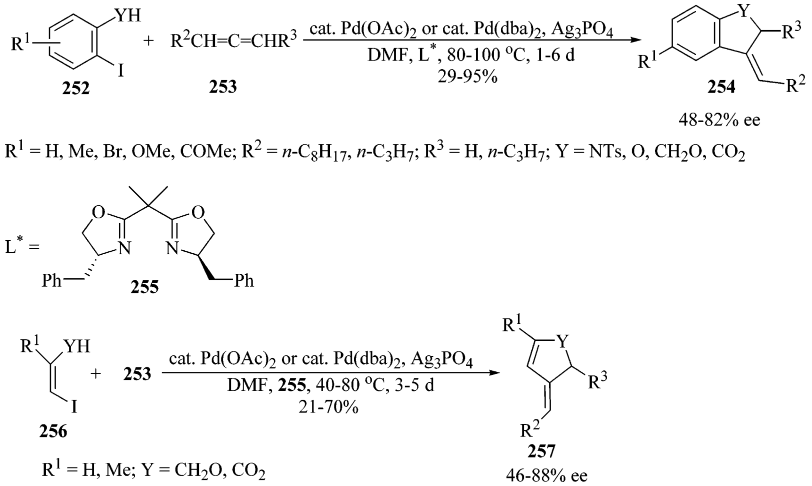


R = H, COMe; Y = O, NTs, CH_2NTs

Scheme 94



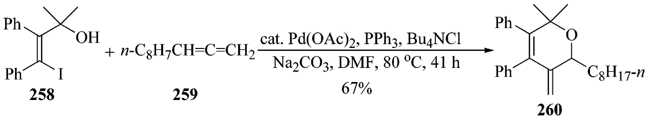
Scheme 95



R^1 = H, Me, Br, OMe, COMe; R^2 = n-C_8H_{17}, n-C_3H_7; R^3 = H, n-C_3H_7; Y = NTs, O, CH_2O, CO_2

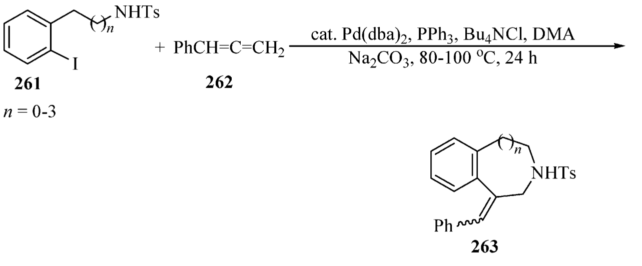
R^1 = H, Me; Y = CH_2O, CO_2

Scheme 96



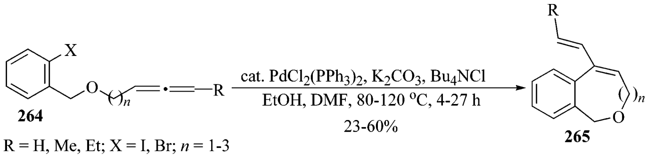
36 examples prepared in 34-95% yields

Scheme 97



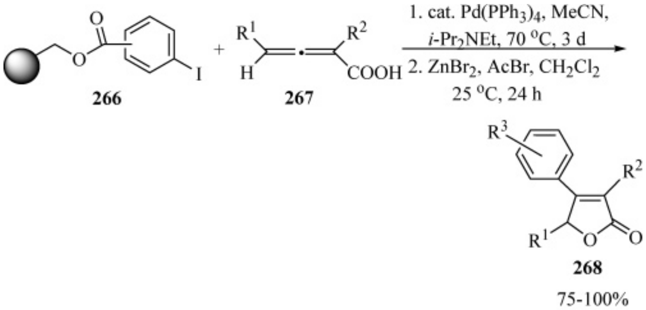
22 examples prepared in 23-94% yields

Scheme 98



R = H, Me, Et; X = I, Br; n = 1-3

Scheme 99



R^1; R^2 = n-C_4H_9, n-C_5H_{11}, n-C_6H_{13}, c-C_6H_{13}; R^3 = CO_2H, $AcOCH_2$

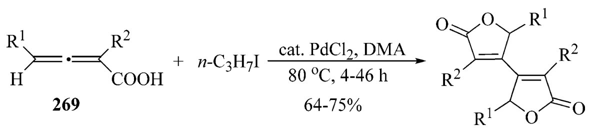
In 1998, we described the synthesis of medium-ring nitrogen heterocycles by the Pd-catalyzed heteroannulation of 1,2-dienes (Scheme 97).[100] Nitrogen heterocycles with seven-, eight-, and nine-membered rings (**263**) are readily prepared by the Pd-catalyzed annulation of a variety of 1,2-dienes such as **262**, by a range of aryl and vinylic halides **261** containing tosylamide and amine functionality. The ease of ring formation is seven > eight > nine, and better results were obtained using aryl rather than vinylic halides and tosylamide rather than amine functionality.

Negishi and Ma demonstrated that the 1,2-dienes **264** can be readily cyclized to the corresponding medium- and large-ring oxygen heterocycles **265** (Scheme 98).[101] The reaction of **264** with a catalytic amount of $PdCl_2(PPh_3)_2$, using K_2CO_3 as the base, in EtOH or DMF, afforded the corresponding heterocycles in moderate to good yields.

Ma and co-workers have also described the Pd-catalyzed coupling of 2,3-alkadienoic acid and polymer-supported aryl iodides (Scheme 99).[102] This process affords the butenolides **268** in high purities and yields, after cleavage of the resin by a Lewis acid-catalyzed process.

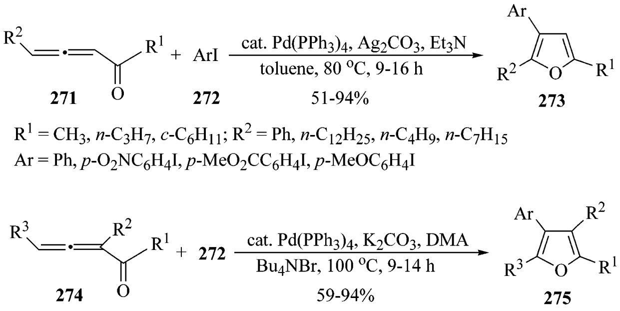
In a similar manner, Ma and co-workers have studied the synthesis of butenolide dimers by the Pd-catalyzed cycliza-

Scheme 100



R^1 = Ph, CH_3, α-naphthyl; R^2 = CH_3, $PhCH_2$, n-C_3H_7

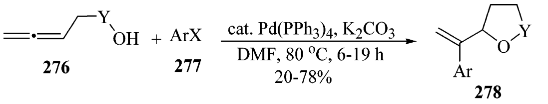
Scheme 101



R^1 = CH_3, n-C_3H_7, c-C_6H_{11}; R^2 = Ph, n-$C_{12}H_{25}$, n-C_4H_9, n-C_7H_{15}
Ar = Ph, p-$O_2NC_6H_4I$, p-$MeO_2CC_6H_4I$, p-$MeOC_6H_4I$

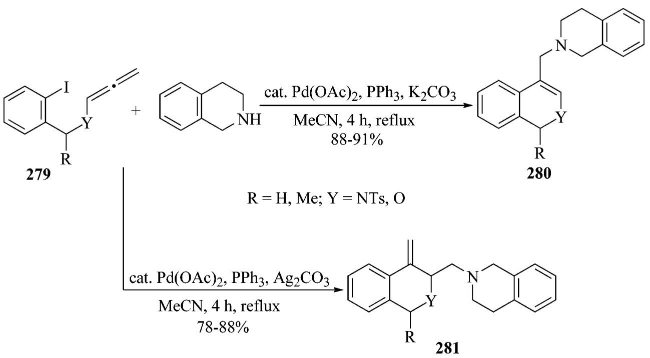
R^1 = CH_3, i-C_3H_7; R^2 = n-C_4H_9, n-C_5H_{11}; R^3 = n-C_5H_{11}, n-C_4H_9, 2-pentyl

Scheme 102



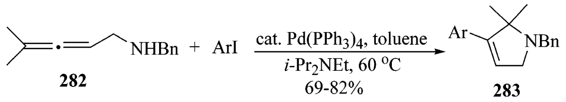
Y = CH_2, C=O; Ar = C_6H_5, p-$O_2NC_6H_4$, p-$CH_3COC_6H_4$, m-$CH_3C_6H_4$, p-$CH_3OC_6H_4$, p-$O_2NC_6H_4$, p-BrC_6H_4, p-IC_6H_4; X = Br, I

Scheme 103



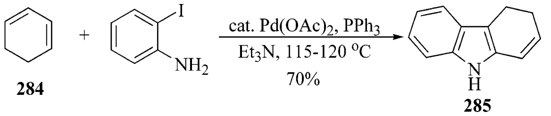
R = H, Me; Y = NTs, O

Scheme 104

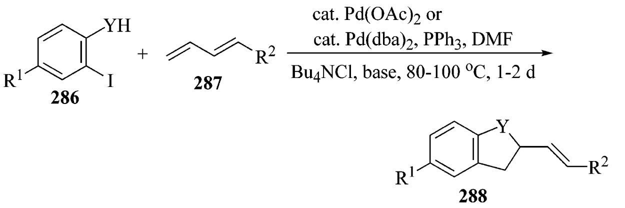


Ar = Ph, 4-$MeOC_6H_4$, 4-$EtO_2CC_6H_4$

Scheme 105



Scheme 106



22 examples prepared in 24-87% yields

R^1=H, COMe, CHO;
R^2=OAc, C_4H_9, Me; Y=O, CH_2O, NTs, CH_2NTs; base=Na_2CO_3, NaOAc, KOAc

tion reaction of 2,3-alkadienoic acids (Scheme 100).[103] Oxidative cyclization of the acids **269** when carried out in the presence of propyl iodide and a catalytic amount of $PdCl_2$ in DMA leads to butenolide dimers **270** in good yields. In this process the Pd(0) species is oxidized by oxygen in the presence of the alkyl iodide to regenerate the Pd(II) species.

Recently, Ma and co-workers have also demonstrated that allenic ketones can be cyclized to the corresponding tri- and tetrasubstituted furans.[104] In the preparation of the trisubstituted furans **273**, the most promising results were obtained when the ketones **271** were allowed to react with the aryl iodides **272** and $Pd(PPh_3)_4$ in the presence of Et_3N and Ag_2CO_3 (Scheme 101). The best results in the preparation of the tetrasubstituted furans **275** have been obtained through the reaction of the allenic ketones **274** with aryl iodides **272** in the presence of $Pd(PPh_3)_4$, K_2CO_3, TBAB, and DMA (Scheme 101).

A variety of functionally substituted furanones and tetrahydrofurans have been prepared by Walkup and co-workers by the palladium-catalyzed coupling of aryl halides and allenic alcohols and acids (Scheme 102).[105] The reaction of 1,2-dienes **276** bearing a hydroxyl or carboxyl group with aryl halides **277** in the presence of $Pd(PPh_3)_4$, K_2CO_3, and DMF affords the cyclized products **278** in moderate yields. The process is more efficient using aryl bromides than aryl iodides.

Two types of allylic amines (**280** and **281**) have been obtained from the same 1,2-diene (**279**), with only a slight variation in the catalytic system employed (Scheme 103).[106] In each of the two procedures, both $Pd(OAc)_2$ and PPh_3 are necessary to effect the reaction. In the formation of product **281**, Ag_2CO_3 was used as the base. On the other hand, replacing Ag_2CO_3 with K_2CO_3 afforded the product **280**.

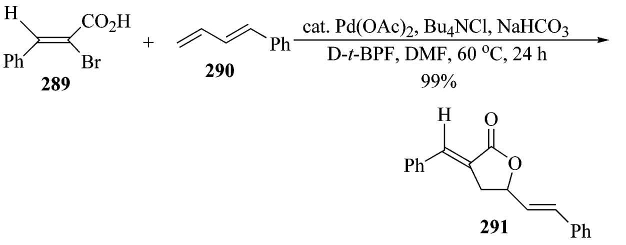
The Pd-catalyzed synthesis of pyrrolines from 1,2-dienamines and aryl iodides has been described by Shibata and co-workers (Scheme 104).[107] Thus, the reaction of allenic amine **282** and several aryl iodides in the presence of a catalytic amount of $Pd(PPh_3)_4$, using a bulky amine (i-Pr_2NEt) as the base and CH_2Cl_2 as the solvent, generates pyrrolines **283** in good yields. The cyclized products were formed in low yields when an inorganic base, such as K_2CO_3, was employed, instead of i-Pr_2NEt.

4.6.2. Heterocycles via Cyclization of 1,3-Dienes

An early investigation by Dieck and co-workers reported the Pd-catalyzed annulation of 1,3-cyclohexadiene by o-iodoaniline (Scheme 105).[108] 1,3-Cyclohexadiene (**284**) affords tetrahydrocarbazole (**285**) in a 70% yield, using a catalytic amount of $Pd(OAc)_2/PPh_3$, o-iodoaniline, and Et_3N as the base. When other amines, such as diethylamine, pyrrolidine, and piperidine, as well as other phosphine ligands, such as $(Tol)_3P$ and $(Ph_2PCH_2)_2$, were used, the cyclized product was obtained in a lower yield.

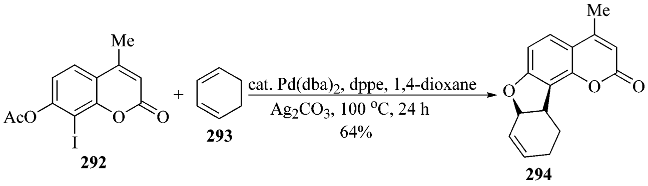
We have reported that aryl iodides bearing a wide range of oxygen and nitrogen functionality react with 1,3-dienes in the presence of a palladium catalyst and an appropriate base to afford a variety of O- and N-heterocycles (Scheme 106).[109] Optimal conditions for this cyclization utilize the aryl iodides **286**, 1,3-dienes **287**, $Pd(OAc)_2$ or $Pd(dba)_2$ as a source of palladium in the presence of a base (Na_2CO_3, NaOAc, KOAc), PPh_3, n-Bu_4NCl, and DMF as the solvent.

Scheme 107



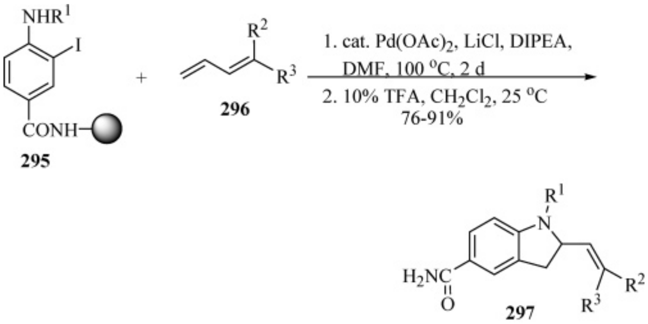
16 examples prepared in 50-99% yields

Scheme 108



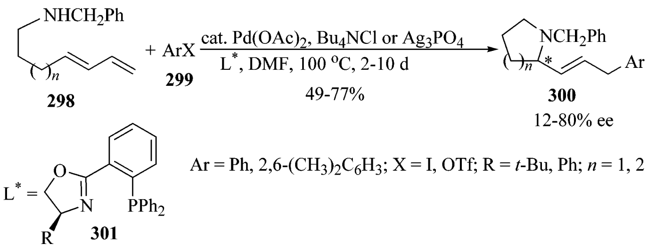
23 examples prepared in 10-83% yields

Scheme 109



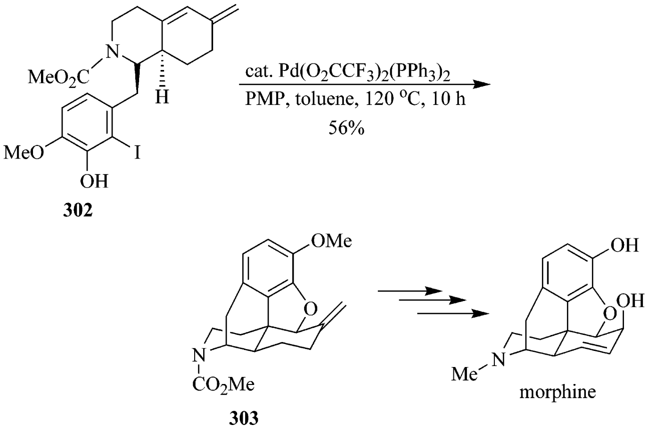
R^1 = p-$CH_3C_6H_4SO_2$, p-$ClC_6H_4SO_2$, p-$AcNHC_6H_4SO_2$, CH_3CO; R^2; R^3 = H, Et, Me, CO_2Me

Scheme 110

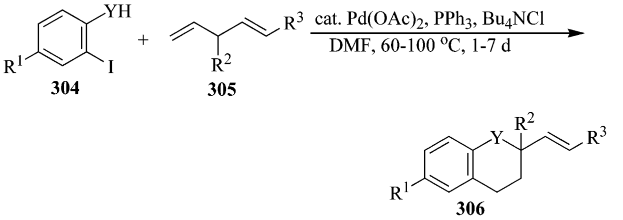


Ar = Ph, 2,6-$(CH_3)_2C_6H_3$; X = I, OTf; R = t-Bu, Ph; n = 1, 2

Scheme 111



Scheme 112



14 examples prepared in 52-85% yields

R^1 = H, COMe; R^2, R^3 = Me, H; Y = O, NH, NTs

The heterocycles **288** are formed in good yields, accommodating considerable substitution in the aryl and diene moieties.

In 2000, we demonstrated that the Pd-catalyzed heteroannulation of 1,3-dienes by α-iodo- and *β*-bromoacrylic acids provides α-alkylidene-*γ*-butyrolactones such as **291** (Scheme 107).[110] The best results were obtained by the reaction of 1,3-dienes such as **290** with carboxylic acids such as **289**, employing a catalytic amount of both $Pd(OAc)_2$ and sterically hindered chelating (di-*tert*-butylphosphino)ferrocene (D-*t*-BPF). For most substrates, this process is highly regio- and stereoselective. Annulation predominantly occurs at the less hindered end of the diene, and in the case of acyclic dienes, the *E* isomer is the main product.

Recently, we also described an efficient method to prepare dihydrofurocoumarins such as **294** by the Pd-catalyzed annulation of 1,3-dienes such as **293** using *o*-iodoacetoxycoumarins such as **292** (Scheme 108).[111] The presence of the acetyl group on the phenolic oxygen and the use of Ag_2CO_3 as the base are crucial for this process. This reaction is very general and quite regio- and stereoselective. A variety of *o*-iodoacetoxycoumarins, as well as symmetrical, unsymmetrical, cyclic, and internal 1,3-dienes can be utilized.

Solid-phase-linked *o*-iodoanilines **295** have been employed in the Pd-catalyzed annulation of 1,3-dienes **296** in the presence of a catalytic amount of $Pd(OAc)_2$, LiCl, diisopropyllethylamine (DIPEA) as base, and DMF as solvent (Scheme 109).[112] Heterocycles **297** are formed in good yields. Cleavage of the product from the resin was achieved by reaction with 10% TFA in methylene chloride.

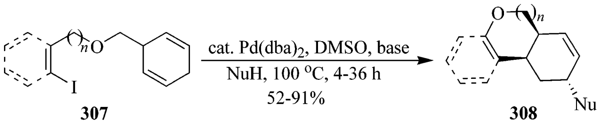
The palladium-promoted cyclization of the amino-1,3-dienes **298** and aryl halides or triflates **299** provides a very useful route to chiral *N*-protected pyrrolidine or piperidine derivatives **300** (Scheme 110).[113] Enantiomeric excesses of up to 80% have been achieved using a catalytic amount of $Pd(OAc)_2$ and the chiral phosphinooxazolines **301** as the ligand, in DMF as the solvent. Compared to aryl iodides, the aryl triflates gave higher enantioselectivities, but longer reaction times were required.

Overman and Hong have employed a Pd-catalyzed cyclization of 1,3-dienes as the key step in this formal total synthesis of morphine (Scheme 111).[114] Thus, the reaction of diene **302** with a catalytic amount of $Pd(O_2CCF_3)_2(PPh_3)_2$ and pentamethylpiperidine (PMP) in refluxing toluene afforded pentacyclic opiate **303** in a 56% yield.

4.6.3. Heterocycles via Cyclization of 1,4-Dienes

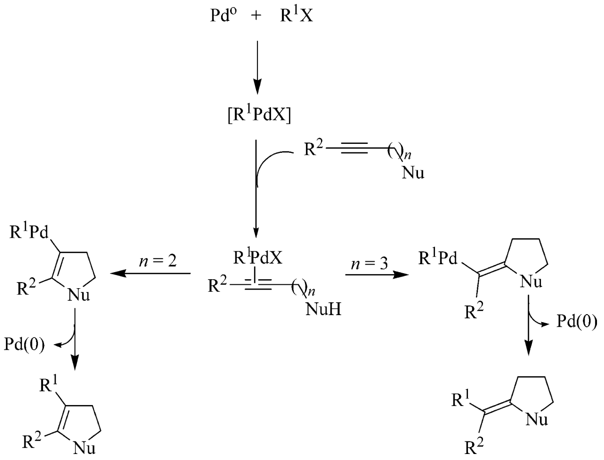
We have reported that the Pd-catalyzed annulation of the 1,4-dienes **305** by aryl halides **304** bearing an *o*-heteroatom affords heterocycles containing monocyclic and bicyclic six-membered rings (Scheme 112).[115] Optimal conditions for this cyclization utilize a catalytic amount of $Pd(OAc)_2/PPh_3$,

Scheme 113

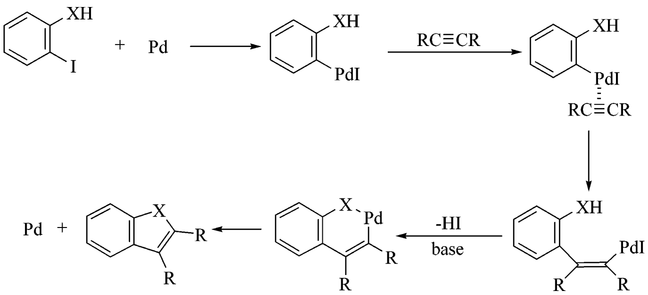


Nu = $CH(CO_2Et)_2$, $N(Ts)CH_2Ph$, $NH(CO_2$-*t*-Bu), OAc, NHPh; *n* = 0, 1

Scheme 114



Scheme 115



n-Bu_4NCl, Na_2CO_3 as base, and DMF as the solvent. The annulation produces the heterocycles **306** in high yields either in the presence or in the absence of PPh_3. In general, cleaner reactions were observed when the *o*-iodophenols were replaced by *o*-iodoaniline. This process involves arylpalladation of the less hundered carbon−carbon double bond, palladium migration to form a π-allylpalladium intermediate, and intramolecular nucleophilic displacement of the palladium with the regeneration of the Pd(0) catalysts.

In 1998, we described the preparation of highly functionalized polycyclics by the Pd-catalyzed intramolecular coupling of aryl or vinylic iodides, 1,4-dienes, and various nucleophiles (Scheme 213).[116] Aryl and vinylic iodides **307** bearing a 1,4-cyclohexadienyl moiety, readily undergo sequential intramolecular carbopalladation, Pd migration, and nucleophilic displacement by the cross-coupling with a heteroatom or carbon nucleophile to produce a wide variety of diastereomerically pure polycyclic products **308** in good to excellent yields.

5. Heterocycles via Cyclization and Annulation of Alkynes

The palladium-catalyzed cyclization and annulation of alkynes have proven to be extraordinarily useful for the synthesis of a wide variety of heterocycles.[117] This catalytic annulation process can follow two distinctly different reaction pathways. If the alkyne contains an internal nucleophile, the process proceeds by coordination of the organopalladium species to the carbon−carbon triple bond, followed by regioselective addition of the aryl/vinylic palladium intermediate to the carbon−carbon triple bond of the alkyne to produce a cyclic adduct (Scheme 114). Subsequent reductive elimination produces the heterocyclic or carbocyclic product and regenerates the Pd(0) catalysts. Both *endo* and *exo* cyclization products can be obtained depending on the number of carbon atoms between the triple bond and the nucleophilic center.

Alternatively, the aryl or vinylic halide may bear a neighboring nucleophile (Scheme 115). After *cis* carbopalladation of the alkyne, the internal nucleophile may effect intramolecular displacement of the palladium, most likely by prior palladacycle formation and reductive elimination. A number of examples of alkyne cyclizations and annulations of these types have been reported in the preparation of *N*- and *O*-heterocycles, as will be discussed in the following sections.

5.1. Heterocycles via Cyclization and Annulation of Internal Alkynes

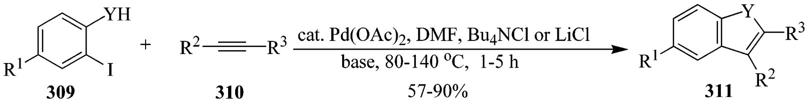
The palladium-catalyzed annulation of internal alkynes by aryl/vinylic halides bearing an oxygen nucleophile is a versatile way to generate a wide variety of oxygen heterocycles.[118] Thus, in 1995, we reported that this chemistry provides a valuable route to benzofurans, benzopyrans, and isocoumarins (Scheme 116).[119] The reaction of aryl iodides **309** with internal alkynes **310**, using $Pd(OAc)_2$ as a catalyst, in the presence of base and DMF as the solvent, gives the *O*-heterocycles **311** in good yields. Alkynes containing aryl or carbonyl groups generally gave the best results and proved to be highly regioselective.

In 1997, Cacchi showed that the 2,5-disubstituted furans **314** are formed through palladium-catalyzed annulation of the alkyl 3-oxo-6-heptynoates **312** (Scheme 117).[120] The cyclization takes place in good yields using the *para*-substituted aryl halides **313**, a catalytic amount of $Pd(PPh_3)_4$, and K_2CO_3 as the base in DMF. This cyclization produces good results with aryl halides bearing both electron-withdrawing and electron-donating substituents.

The same group reported the preparation of the substituted coumarin **316** upon reaction of a catalytic amount of $Pd(OAc)_2$, the alkyne **315**, and *p*-iodoanisole (Scheme 118).[121] The coumarin **316** was obtained in a 40% yield.

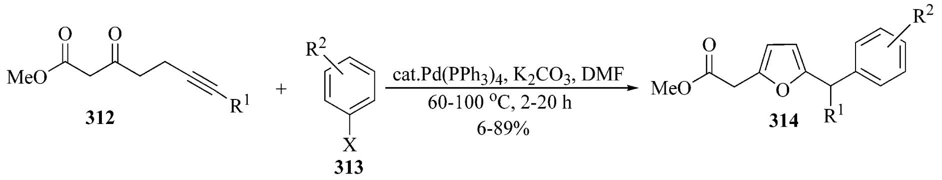
We have described the synthesis of the 3,4-disubstituted isocoumarins **319** in good yields by treating the halogen-containing aromatic esters **317** with internal alkynes **318** in

Scheme 116



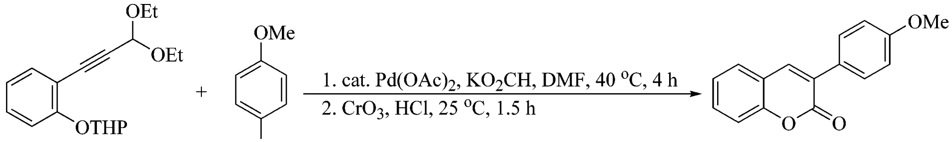
R^1 = H, Ac; R^2 = Me, *t*-Bu, Et, Ph; R^3 = Ph, Me, CHO, CO_2Et, $Si(i\text{-}Pr)_3$, $SiMe_3$; YH = O, $C(CH_3)_2OH$, CO_2Me; base = Na_2CO_3, NaOAc, KOAc

Scheme 117



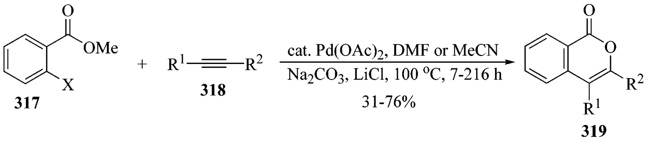
R^1 = aryl; R^2 = *m*-F_3C, *p*-CHO, *m*-CHO, *m*-MeCO, *p*-CO_2Me, *m*-CO_2Me, *m*-NO_2, *p*-NO_2, *p*-F, *m*-F, *p*-MeO; X = Br, I

Scheme 118



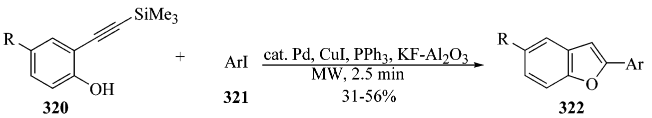
316 40% yield

Scheme 119



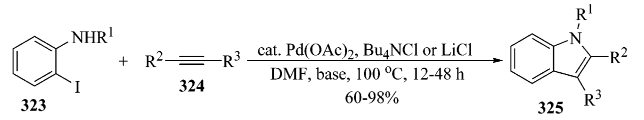
R^1 = Me, Et, *n*-Bu, Ph; R^2 = Me_3C, Me_2COH, Ph, Me_3Si, *i*-Pr_3Si; X = I, Br

Scheme 120



R = H, CH_3, CH_3CO; Ar = C_6H_5, *m*-FC_6H_4, *p*-$CH_3OC_6H_4$, *p*-$CH_3C_6H_4$

Scheme 121



R^1 = H, Me, Ac, Ts; R^2 = *n*-Pr, *t*-Bu, *c*-C_6H_{11}, CMe_2OH, Me_3Si, CH_2OH, Ph; R^3 = *n*-Pr, Me, Et, CH_2OH; base = K_2CO_3, KOAc, Na_2CO_3

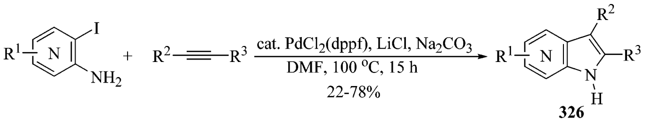
the presence of a palladium catalyst (Scheme 119).[122] Synthetically, this methodology provides an especially simple and convenient regioselective route to isocoumarins containing aryl, silyl, ester, *tert*-alkyl, and other hindered groups.

The phenols **320**, bearing a silylethynyl group in the *ortho* position, have been subjected to coupling/cyclization by aryl iodides **321**, using a catalytic amount of palladium powder, CuI, and PPh_3 (Scheme 120).[123] The reaction is carried out under solvent-free conditions and microwave irradiation to give 2-substituted benzofurans **322** in moderate yields.

A large number of nitrogen heterocycles can also be synthesized by the palladium-catalyzed cyclizations and annulation using aryl/vinylic halides and internal alkynes. Thus, we and others have reported the palladium-catalyzed coupling of *o*-haloaniline and the corresponding *N*-methyl, -acetyl, and -tosyl derivatives **323** with a wide variety of internal alkynes **324** (Scheme 121).[124] This methodology provides a very valuable route to the corresponding 2,3-disubstituted indoles **325** in good to excellent yields. In general, this process is very regioselective, placing the aryl group of the aniline on the less sterically hindered end of the triple bond and the nitrogen moiety on the more sterically hindered end.

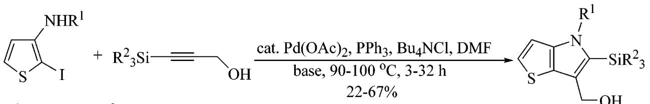
Our indole synthesis has been employed by others to prepare various heteroatom-substituted analogues, including

Scheme 122



R^1 = H, Me, CO_2Me, Cl, CF_3; R^2 = H, CH_2CH_2OH, *n*-Pr, Ph; R^3 = Ph, *n*-Pr, Me_3Si, Et_3Si

Scheme 123



R^1 = Ac, Boc; $R^2{}_3Si$ Me$_3$, *t*-$BuMe_2Si$

327

5-, 6- and 7-azaindoles **326** (Scheme 122),[125] thienopyrroles **327** (Scheme 123),[126] and tryptophan derivatives **328** (Scheme 124). The development of solid-phase resin-bound versions of this chemistry in the preparation of trisubstituted indoles **329** has also been described (Scheme 125).[127]

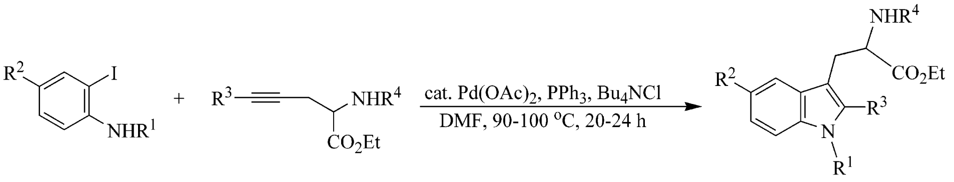
Scammells and co-workers reported the preparation of indole derivatives using *N*-(*tert*-butoxycarbonyl)-2-iodo-3-methoxyaniline (**330**) as the substrate in a palladium annulation/cyclization (Scheme 126).[128] The reaction of **330** with internal alkynes **331**, using $Pd(OAc)_2/PPh_3$ as the catalyst system in the presence of Et_4NCl and *i*-Pr_2NEt in DMF, produced the indoles **332** in good yields. When tri-2-furylphosphine was used instead of PPh_3, lower yields of the desired indoles were obtained. The use of LiCl and Na_2CO_3 gave indoles in low yields and poor regioselectivities.

The cyclization of alkynyltrifluoroacetanilides with various organic halides has been described by Cacchi (Scheme 127).[129] For example, the reaction of acetanilides **333** with halides **334** in the presence of Cs_2CO_3 and a catalytic amount of $Pd(PPh_3)_4$ in MeCN afforded 2-substituted 3-aryl- and 3-heteroarylindoles **335** in excellent yields.

Pfeffer and Beydoun have reported the synthesis of *N*-methylbenzo[*d*,*e*]quinolines **338** by the palladium-catalyzed annulation of internal alkynes **337**, using 1-iodo-8-(dimethylamino)naphthalene (**336**) (Scheme 128).[130] This is an interesting example of demethylation during annulation.

We have reported that this alkyne heteroannulation chemistry can be readily extended to vinylic halides to produce a variety of interesting nitrogen and oxygen heterocycles. For example, the reaction of vinylic halide **339** with diphenylacetylene afforded the *N*-heterocycle **340** (Scheme 129).[131] Optimal reaction conditions for this cyclization utilize $Pd(OAc)_2$ as the catalyst in the presence of

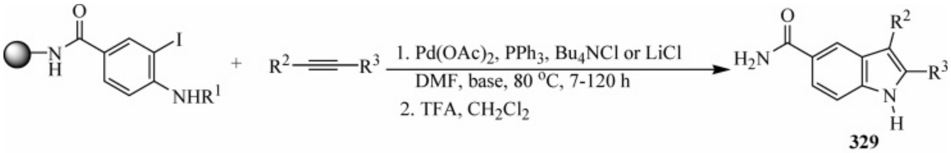
Scheme 124



328

R^1 = H, Ac; R^2 = H, NO_2, Br, Cl, F, NH_2; R^3 = TMS, TBDMS; R^4 = Ac, Boc

Scheme 125

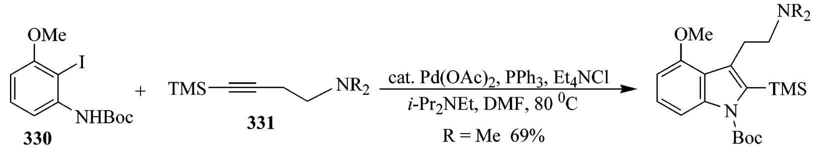


329

38-100%

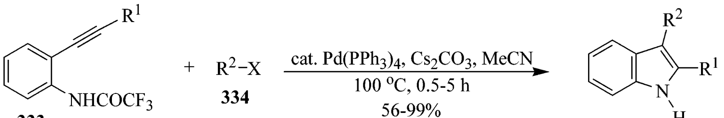
R^1 = H, MeCO, Me_2CHCO; R^1 = *n*-Pr, Me, Ph, CO_2Et, CH_2CH_2OH, CH_2CH_2Cl; R^3 = *n*-Pr, *t*-Bu, Ph, Me_3Si

Scheme 126



330 **331** **332**

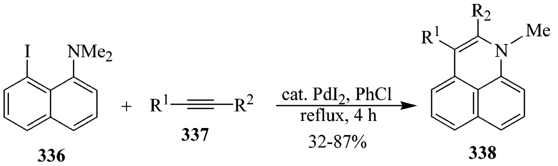
Scheme 127



333 **334** **335**

R^1 = *p*-$CH_3OC_6H_4$, *p*-$CH_3COC_6H_4$, *p*-$NO_2C_6H_4$, *n*-C_5H_{11}; R^2 = C_6H_5, *p*-NCC_6H_4, *m*-$HCOC_6H_4$, *p*-$HCOC_6H_4$, *p*-$CH_3COC_6H_4$, *p*-$NO_2C_6H_4$, 2-thiazolyl, 2-pyridyl, 5-indolyl, 5-pyrimidinyl, CH_2CO_2Et, CH_2CN, $CH_2COC_6H_4$-*p*-Br; X = I, Br

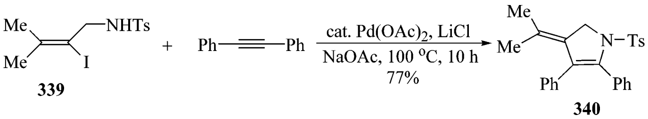
Scheme 128



336 **337** **338**

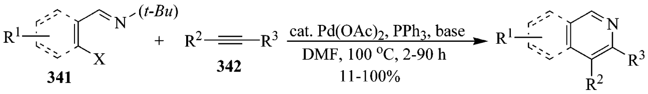
R^1 = Ph, CO_2Me; R^2 = C_6H_5, *p*-$NO_2C_6H_4$, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *m*-$F_3CC_6H_4$, CO_2Me, CO_2Et

Scheme 129



339 **340**

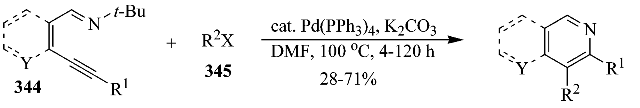
Scheme 130



341 **342** **343**

R^1 = H, HC=N(*t*-Bu), OMe, Me_2N; R^2; R^3 = Me, Et, *n*-Pr, CH_2OH, Ph, CO_2Et

Scheme 131



344 **345** **346**

R^1 = C_6H_5, *n*-Bu, *p*-$MeOC_6H_4$, 1-cyclohexenyl; R^2 = C_6H_5, *p*-$O_2NC_6H_4$, *m*-$O_2NC_6H_4$, *o*-$O_2NC_6H_4$, *m*-$EtO_2CC_6H_4$, *p*-$EtO_2CC_6H_4$, *o*-$EtO_2CC_6H_4$, *m*-$F_3CC_6H_4$, *o*-$F_3CC_6H_4$, 3-iodopyridyl, allylic, vinylic, 1-alkynyl; Y = N, H.

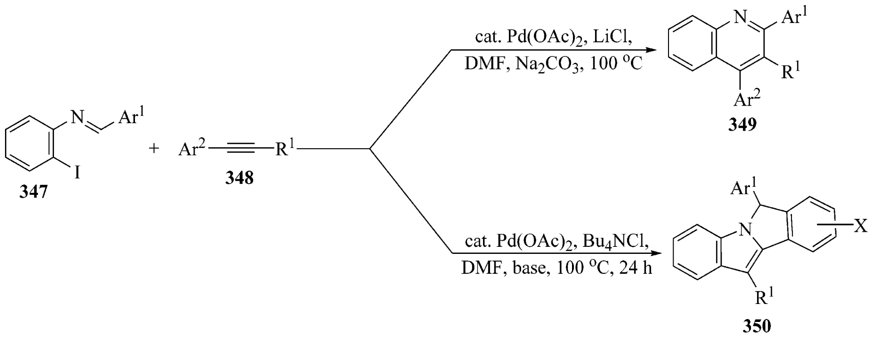
LiCl, a base, and DMF as the solvent. This annulation process is highly regioselective for alkynes containing hindered alkyl, trialkylsilyl, and other similar groups with a quaternary center.

We have discovered that the palladium-catalyzed iminoannulation of internal alkynes **342** by the *tert*-butylimines **341** of *o*-iodobenzaldehyde readily affords isoquinoline and pyridine derivatives **343** in good to excellent yields (Scheme 130).[132] This annulation methodology is particularly effective for aryl- or alkyl-substituted alkynes. When electron-rich imines are employed, this chemistry can be extended to alkyl-substituted alkynes.

We have also prepared isoquinoline derivatives **346** by the palladium-catalyzed cross-coupling of *N*-*tert*-butyl-2-(1-alkynyl)benzaldimines **344** and aryl halides **345** (Scheme 131).[133] This synthetic strategy exhibits considerable structural flexibility in the type of iminoalkynes and aryl halides that can be employed. Allylic, benzylic, and alkynyl halides could also be used in this process.

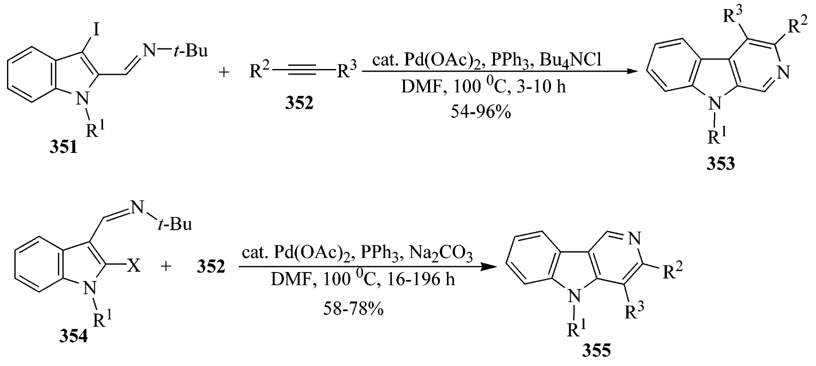
We have observed that imines **347** derived from *o*-iodoaniline and benzaldehyde react with internal aryl alkynes **348** under the appropriate reaction conditions, to give either isoquinoline **349** (only one successful example, R^4 = Ar^2 = Ph) or more commonly the tetracyclic indoles **350**

Scheme 132



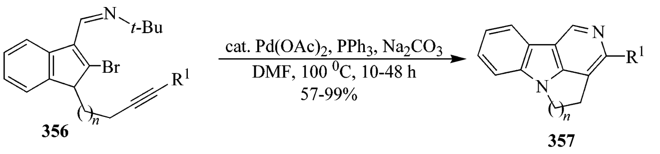
$Ar^1 = C_6H_5$, p-ClC_6H_4; $Ar^2 = C_6H_5$, m-MeC_6H_4, m-$MeOC_6H_4$, m-$F_3CC_6H_4$, m-$Et_2OCC_6H_4$, 2-thienyl;
R^1 = Et, n-Bu, CO_2Et, CH_2OH, CH_2OMe, $(CH_2)_4OH$, C_6H_5; base = Na_2CO_3, i-Pr_2NEt.

Scheme 133



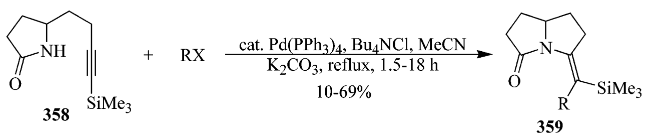
R^1 = Me, MOM, Bn, Ts; R^2; R^3 = Me, n-Pr, t-Bu, Ph, CH_2OH, CO_2Et, TMS; X = Br, I

Scheme 134



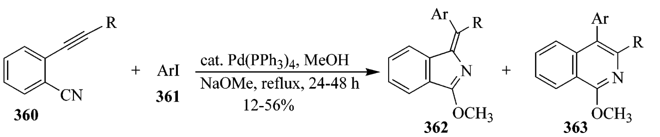
R^1 = Ph, n-C_6H_{13}, n-C_4H_9, $SiMe_3$, (E)-CH=CHPh, H; n = 0, 1, 2

Scheme 135



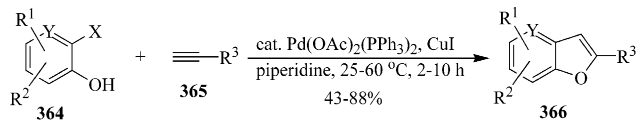
R = C_6H_5, p-$O_2NC_6H_4$, p-$MeOC_6H_4$, 2-thienyl, 2-pyridyl, $(CH_3)_2C$=CH; X = Br, I

Scheme 136



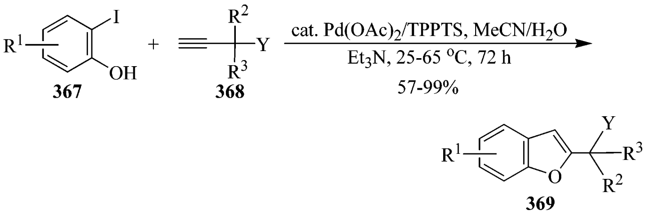
R = Ph, n-Bu; Ar = C_6H_5, p-$CH_3C_6H_4$, p-$CH_3OC_6H_4$

Scheme 137



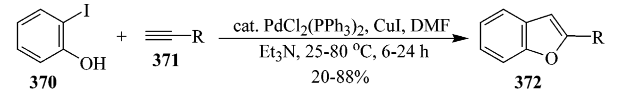
R^1 = H, 2-CH_3, 1-CHO; R^2 = H, 3-OCH_3; R^3 = n-C_4H_9, n-C_5H_{11}CH(OH), CH_2OH,
$C_2H_5C(CH_3)(OH)$; X = I, Br; Y = CH, N

Scheme 138



R^1 = H, CHO; R^2; R^3 = H, CH_3, C_2H_5, n-C_5H_{11}; Y = OH, NH_2

Scheme 139



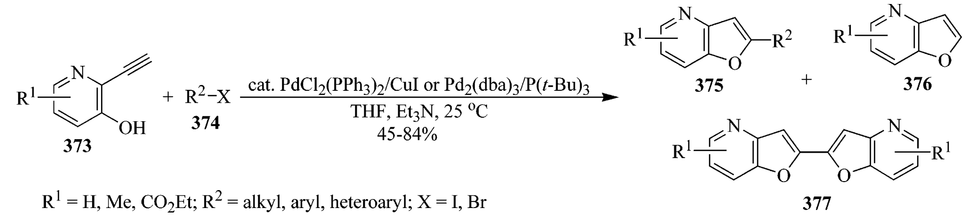
R = C_6H_5, m-C_6H_4, CH_2OH, CMe_2OH, CH(OH)HC=CHMe, CH(OH)Ph,
CH(OH)C_6H_4-o-Me, CH(OH)MeC_6H_4-p-Me, CH(OH)C_6H_4-m-Me

(Scheme 132).[134] A variety of internal alkynes have been employed in this annulation process, in which the aromatic ring of the alkyne contains either a phenyl or a heterocyclic ring.

In 2001, we described the preparation of substituted β-**353** and γ-carbolines **355** by the palladium-catalyzed annulation of internal alkynes **352**, using the *tert*-butylimines of *N*-substituted 3-iodoindole-2-carboxaldehydes **351** and 2-haloindole-3-carboxaldehydes **354**, respectively (Scheme 133).[135] This annulation chemistry is effective for a wide range of alkynes, including aryl-, alkyl-, hydroxymethyl-, ethoxycarbonyl-, and trimethylsilyl-substituted alkynes. When an unsymmetrical internal alkyne is employed, this method generally gives two regioisomers.

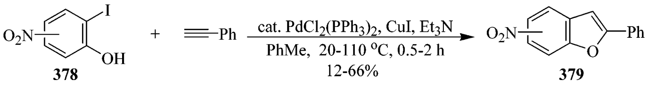
The γ-carbolines **357** can also be prepared by iminoannulation of the *N*-alkynyl-2-bromo-1*H*-indole-3-*tert*-butylimines **356** (Scheme 134).[136] The best results were obtained by using 5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, and Na_2CO_3 in DMF. Using this method, various γ-carboline derivatives,

Scheme 140

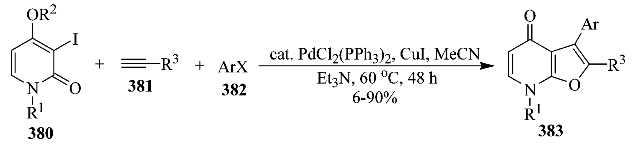


R^1 = H, Me, CO_2Et; R^2 = alkyl, aryl, heteroaryl; X = I, Br

Scheme 141

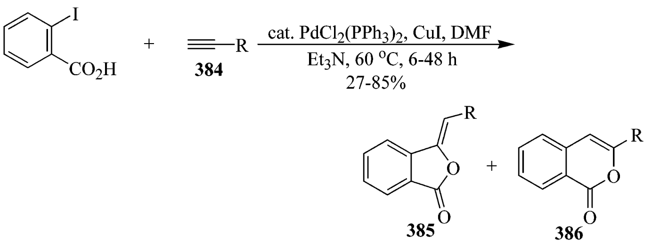


Scheme 142



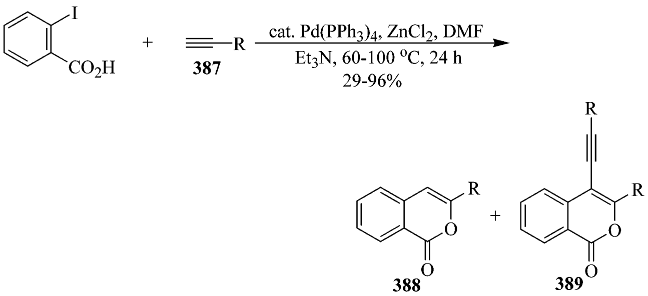
R^1; R^2 = Me, Bn; R^3 = C_6H_5, *p*-$MeO_2CC_6H_4$, *n*-C_4H_9; Ar = *p*-$MeO_2CC_6H_4$, *m*-$MeO_2CC_6H_4$, *p*-IC_6H_4, *m*-$CF_3C_6H_4$, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$, *p*-FC_6H_4; X = I, Br

Scheme 143



R = H, *m*-ClC_6H_4, CH(OH)C_6H_4-*o*-Me, 1-naphthyl, CH_2OH, CMe_2OH, CH(OH)CH=CHMe, CH(OH)Ph, CO_2Me

Scheme 144



R = H, *n*-C_4H_9, *n*-C_3H_7, *c*-C_6H_{11} CH_2OH, CH_2OCH_3, $C(CH_3)_2OH$, C_6H_5, *p*-$CH_3OC_6H_4$, *o*-$H_2NC_6H_4$

with an additional ring fused across the 4- and 5-positions, could be obtained in good yields.

Hiemstra and co-workers have used the palladium coupling/cyclization of lactams **358** containing a 3-butynyl side chain and aryl or vinylic halides to prepare bicyclic enamides **359** (Scheme 135).[137] A catalytic procedure was developed using MeCN as the solvent and $Pd(PPh_3)_4$ as the catalyst. The enamides **359** were obtained in 10−69% yields with the aryl or vinylic moiety and the nitrogen nucleophile introduced *cis* to one another.

Recently, Wu and co-workers have demonstrated that 2-(2-phenylethynyl)benzonitrile **360** can be cyclized by aryl iodides **361** in the presence of $Pd(PPh_3)_4$, NaOMe, and MeOH to give 3-diarylmethylideneisoindoles **362** as the sole product in moderate yields (Scheme 136).[138] When 2-(1-hexynyl)benzonitrile was employed, isoindole derivatives **362** were obtained together with isoquinolines **363**.

5.2. Heterocycles via Cyclization of Terminal Alkynes

The palladium-catalyzed annulation of terminal alkynes by aryl halides containing a neighboring oxygen nucleophile has proven to be a powerful and useful tool for the construction of the benzofuran nucleus. Preparation of the benzo[*b*]furan ring by the reaction of 2-hydroxyaryl and 2-hydroxyheteroaryl halides and terminal alkynes has been reported by Cacchi (Scheme 137).[139] When carried out in the presence of a catalytic amount of $Pd(OAc)_2(PPh_3)_2$ and CuI, the reaction of the halides **364** with terminal alkynes **365** produces the benzo[*b*]furans **366** in good yields.

The efficient water-soluble catalyst system $Pd(OAc)_2$/TPPTS has been used by Amatore and co-workers in the preparation of benzofuran derivatives (Scheme 138).[140] The reaction of propargylamines or propargylic alcohols **368** with the 2-iodophenols **367** in the presence of 2.5% $Pd(OAc)_2$/TPPTS catalyst and Et_3N produced the benzofuran derivatives **369** in excellent yields.

The palladium-catalyzed heteroannulation of terminal alkynes by *o*-iodophenol affords 2-substituted benzofurans (Scheme 139).[141] $PdCl_2(PPh_3)_2$ was the best catalyst for this cyclization process. Other catalysts, such as $Pd(OAc)_2$, led to lower yields. The addition of further PPh_3 completely suppressed product formation.

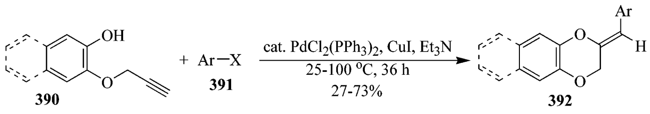
Cacchi has also observed that the ethynylpyridinols **373** react with the aryl or heteroaryl halides **374** to afford furopyridines **375** by a coupling/cyclization process (Scheme 140).[142] Both the structure of the alkyne and the organic halide play an important role in determining the products formed. Depending on their nature, variable amounts of 2-unsubstituted furopyridines **376** and bifuropyridines **377** are formed together with **375**.

Dai and co-workers have reported that the reaction of the nitrophenol **378** and phenylacetylene affords nitrobenzo[*b*]furans **379** when catalyzed by 10% $PdCl_2(PPh_3)_2$ and CuI in toluene as the solvent (Scheme 141).[143] In this case, the benzofurans **379** are obtained in modest yields.

Balme and co-workers have described the synthesis of the furo[2,3-*b*]pyridones **383** in a single step through the sequential coupling of three starting materials: the 3-iodo-2-pyridones **380**, the terminal alkynes **381**, and the aryl iodides **382** (Scheme 142).[144] This one-pot procedure was optimized using a catalytic amount of $PdCl_2(PPh_3)_2$ and CuI in the presence of Et_3N and MeCN. Following this protocol, furo[2,3-*b*]pyridones **383** were obtained in good to excellent yields.

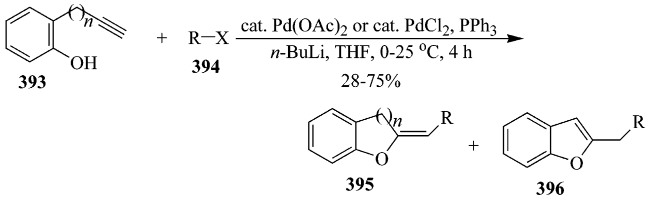
Kundu and co-workers have shown that the reaction of *o*-iodobenzoic acid with the terminal alkynes **384** in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$, CuI, and Et_3N in DMF leads to phthalide isobenzofuranones **385** in

Scheme 145



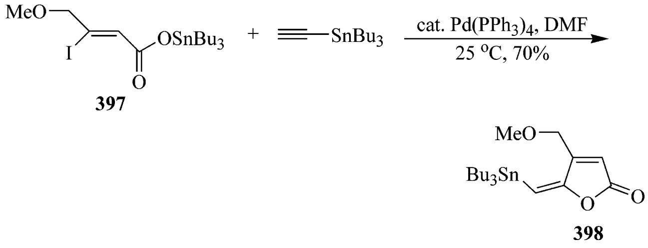
R = C_6H_5, 2-$MeOC_6H_4$, 3-ClC_6H_4, 2-$NO_2C_6H_4$, 2-$MeO_2CC_6H_4$, 4-IC_6H_4, 2-IC_6H_4, 1-naphthyl, 2-thienyl; X = Br, I

Scheme 146

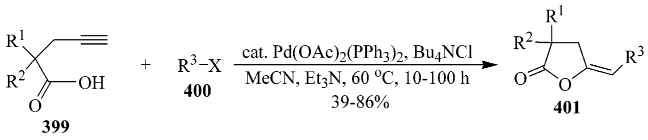


R = Me, Ph, 2-thienyl, benzyl; X= I, Br; n = 1, 2

Scheme 147

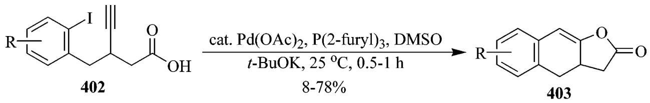


Scheme 148



R^1; R^2 = H, CO_2Me, alkyl; R^3 = vinylic, aryl; X = Br, I, OTf

Scheme 149



R = H, Me, methylenedioxy

good yields (Scheme 143).[145] The process was found to be highly stereospecific since only the *Z* isomers of **385** were obtained. In some cases, isocoumarins **386** were obtained as minor products.

o-Iodobenzoic acid reacts with various terminal alkynes **387** in the presence of $Pd(PPh_3)_4$, Et_3N, and $ZnCl_2$ in DMF to give the corresponding 3-substituted isocoumarins **388** (Scheme 144).[146] In some cases the substituted isocoumarins **389** were isolated in low yields. In contrast to the results described in Scheme 143, the addition of $ZnCl_2$ instead of CuI exhibits greater selectivity for isocoumarins than phthalides.

The acetylenic phenols **390** undergo stereoselective palladium-catalyzed cyclization by aryl halides **391** to give aryldioxin derivatives **392** in moderate yields (Scheme 145).[147] The best cyclization results were obtained using a catalytic amount of $PdCl_2(PPh_3)_2$, CuI, and Et_3N as the base and solvent. The cyclization produced only *Z* isomers as the product.

The stereodefined 2-alkylidenetetrahydrofurans or -pyrans **395** have been synthesized from terminal-alkyne-containing phenols and the aryl or alkyl halides **394** (Scheme 146).[148] Good yields have been obtained by treatment of the acetylenes **393** with *n*-BuLi in THF, followed by the addition of a solution containing a catalytic amount of $Pd(OAc)_2$ or $PdCl_2$, PPh_3 in THF, and the organic halide. The choice of base and solvent significantly affects the yields of cyclization. The use of $NaHCO_3$ or NaOMe as base and DMF, $CHCl_3$, benzene, or toluene as the solvent gave the cyclized products only in low yields. In some cases, a double bond migration product (**396**) was observed as a minor product.

The coupling of the tributylstannyl iodopropenoate **397** and tributytin acetylene to produce the butenolide **398** has been described by Parrain and co-workers (Scheme 147).[149] The catalyst $Pd(PPh_3)_4$ in DMF gave (*E*)-5-(tributylstannylmethylidene)-5*H*-furanone **398** in 70% yield. No isomerization of the double bond was observed, and no cyclization to a pyran ring occurred.

Cacchi in 1992 reported the conversion of 4-alkynoic acids to butyrolactones (Scheme 148).[150] Reaction of the substituted 4-pentynoic acids **399** with aryl/vinylic halides or triflates regio- and stereoselectively produced the corresponding (*E*)-butyrolactones **401** in good to high yields. The reaction was catalyzed by $Pd(OAc)_2(PPh_3)_2$ in the presence of n-Bu_4NCl and Et_3N. The presence of the chloride anion was essential to obtain the butyrolactones in good yields.

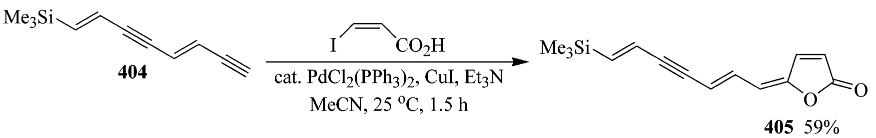
Subsequently, in 1996, Balme and co-workers published an intramolecular version of the protocol described by Cacchi, which provides γ-arylidenebutyrolactones **403** from pentynoic acids **402** (Scheme 149).[151]

Employing different reaction conditions, Fiandanese and co-workers have also described the preparation of (*Z*)-γ-alkylidene butenolides **405** in good yields and high stereoselectivity from (*Z*)-3-iodo-2-propenoic acid and the silylated polyunsaturated terminal alkyne **404** (Scheme 150).[152] The best results in this cyclization were obtained using $PdCl_2(PPh_3)_2$/CuI and Et_3N as the catalyst system.

Cacchi and we have demonstrated that the 2-propynyl-1,3-dicarbonyl compounds **406** and organic halides **407** can be cross-coupled to give the corresponding highly substituted furans **408**, using only a catalytic amount of $Pd(PPh_3)_4$ and K_2CO_3 as the base (Scheme 151).[153] The nature of the base strongly affects the reaction course. Other bases, such as Et_3N, gave the desired furans in only low yields. This methodology can tolerate a wide variety of important functional groups, in both the alkyne and the organic halide.

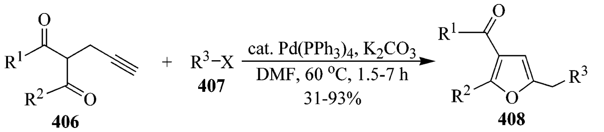
The Cacchi group has also shown that *N*-propargylamides readily undergo palladium-catalyzed cyclization with aryl iodides, affording disubstituted oxazoles (Scheme 152).[154] The reaction of aryl iodides **410** with the *N*-propargylamides **409**, using a catalytic amount of $Pd_2(dba)_3$/P(2-furyl)$_3$, in the presence of NaO-*t*-Bu and MeCN, gave 2,3-disubstituted oxazoles **411** in good yields. Other solvents, such as DMF and THF, and other bases, such as K_2CO_3, gave lower yields

Scheme 150



405 59%

Scheme 151



R^1 = Me, OEt, Ph, PhHN; R^2 = Me, Ph; R^3 = alkyl, aryl, heteroaryl; X = Br, I, OTf

of the desired oxazoles. In some cases, the oxazoles **412** were observed as a minor product.

(*Z*)-3-Aryl-2-bromopropenoic acids have also been found to undergo palladium-catalyzed cyclization by the Rossi group (Scheme 153).[155] In this case, the reaction of the 2-bromopropenoic acid **413** with phenylacetylene and a catalytic amount of $Pd(PPh_3)_4$ and CuI in MeCN gave the 3*H*-furanone **414** as the sole product in a modest yield. Conversely, an analogous reaction of **413** with 1-hexyne gave a mixture of furanone **415** and its double bond isomerization product **416**, which were isolated in 11% and 34% yields, respectively.

As might be expected, nitrogen nucleophiles have been well studied in these processes for the preparation of *N*-heterocycles. For example, the treatment of pyridyl iodide **417** with propyne, catalyzed by $Pd(OAc)_2$ and PPh_3, affords the azaindole **418** in a 65% yield (Scheme 154).

Several *o*-trifluoroacetanilides have been successfully converted into the corresponding indoles by Cacchi (Scheme 155).[156] When carried out in the presence of $Pd_2(dba)_3$, K_2CO_3, and DMSO, the reaction of *o*-ethynyltrifluoroacetanilide (**419**) with the aryl iodides **420** produced 3-arylindoles **421** in good yields. The influence of both the ligand in the palladium salt and the solvent has been investigated.

Applications of this palladium cyclization of terminal alkynes to the solid phase to prepare indole derivatives have been described (Scheme 156).[157] In general, substituted indoles **424** are obtained in excellent yields by the palladium-catalyzed coupling of resin-bound sulfonamide **422** with the terminal alkynes **423**, followed by cleavage of the sulfonamide linkage. The best catalyst system for this cyclization was found to be a catalytic amount of $PdCl_2(PPh)_2$ and CuI, plus Et_3N in DMF.

The propargyl tosylcarbamates **425** undergo stereoselective heterocyclization with aryl iodides or vinylic triflates **426** to give tosyloxazolidin-2-ones **427**, in moderate to good yields (Scheme 157).[158] The best results in this cyclization were obtained using $Pd(PPh_3)_4$ as the catalyst in the presence of K_2CO_3 as the base, or using $Pd(OAc)_2$ as the catalyst, in the presence of TEBA as the chloride source. This reaction gave solely *Z* stereoisomers and five-membered cyclic carbamates.

In a related study, Kundu showed that (*E*)-tetrahydroquinoxalines **430** are formed through a regio- and stereoselective palladium-catalyzed heterocyclization of tosylamide **428** and aryl iodides **429** (Scheme 158).[159] The cyclization takes place in good yields using $Pd(OAc)_2$ as the catalyst in the presence of Bu_4NBr and K_2CO_3. The reaction exhibits high stereoselectivity with sole formation of the *E* product, instead of the usually expected *Z* configuration.

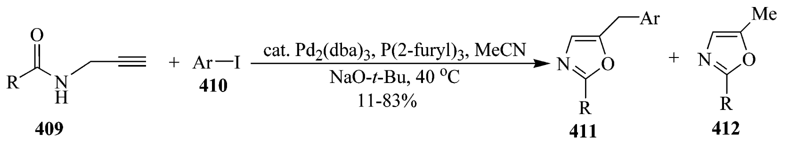
Rutjes and co-workers have reported the preparation of the chiral cyclic amino esters **433** from the optically active α-amino acid **431** and aryl halides **432** (Scheme 159).[160] In general, the best results were obtained using $Pd(PPh_3)_4$, TBAC, and K_2CO_3. The presence of TBAC is essential in generating the higher yields in these cyclization reactions.

We have described the use of *tert*-butylimine nucleophiles in the palladium-catalyzed annulation of terminal alkynes to prepare isoquinolines and pyridines (Scheme 160).[161] Thus, a one-pot reaction of the aryl-, alkenyl-, and alkyl-substituted terminal alkynes **435** with the *tert*-butylimines of *o*-iodobenzaldehydes **434**, in the presence of $PdCl_2(PPh_3)_2$ and CuI, gave the *N*-heterocycles **436** in excellent yields.

5.3. Heterocycles via Cyclization of Alkynes plus CO

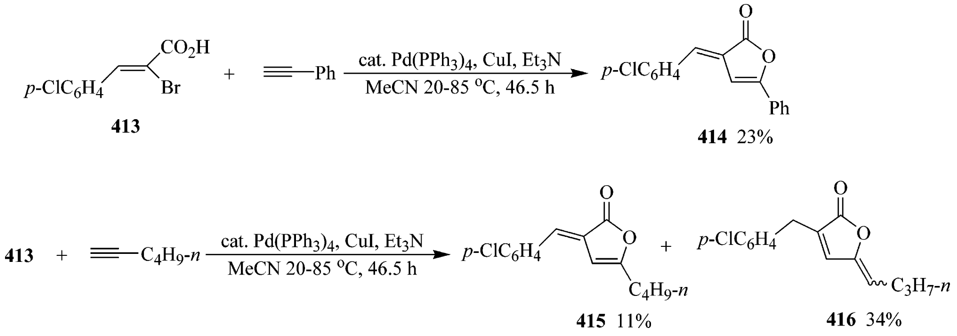
The palladium-catalyzed cyclization of alkynes with aryl/vinylic halides and CO insertion is a valuable and highly effective method for the synthesis of heterocycles containing a carbonyl group. The mechanism shown in Scheme 161 is proposed for this process. It consists of the following key steps: (1) oxidative addition of the organo halides to the palladium catalyst, followed by CO insertion, (2) coordination of the resulting acylpalladium intermediate **A** to the alkyne triple bond to form complex **B**, which activates the triple bond toward nucleophilic attack, (3) nucleophilic attack of the nitrogen or oxygen atom on the activated carbon–

Scheme 152

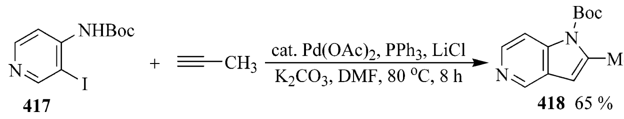


R = C_6H_5, *p*-$MeOC_6H_4$, *m*-$CF_3C_6H_4$, *p*-MeC_6H_4, CF_3; Ar = *o*-MeC_6H_4, *m*-$MeOC_6H_4$, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *p*-ClC_6H_4, *m*-$CF_3C_6H_4$, *p*-FC_6H_4, *p*-$MeOCC_6H_4$.

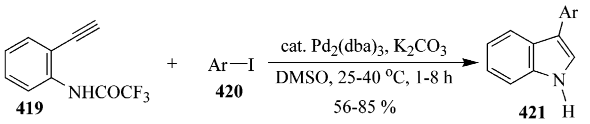
Scheme 153



Scheme 154

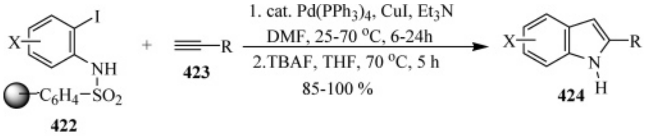


Scheme 155



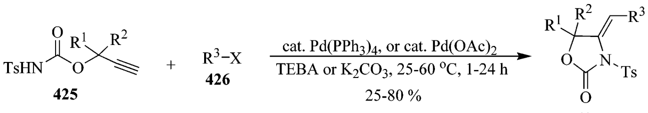
Ar = C_6H_5, p-$MeOC_6H_4$, p-$MeCONHC_6H_4$, p-FC_6H_4, m-FC_6H_4, p-ClC_6H_4, m-$CF_3C_6H_4$, p-$MeOCC_6H_4$, m-$MeOCC_6H_4$, p-$EtO_2CC_6H_4$, m-$EtO_2CC_6H_4$, 3-NO_2, 4-MeC_6H_3, m-$NO_2C_6H_4$, p-MeC_6H_4

Scheme 156



R = C_6H_5, o-MeC_6H_4, o-FC_6H_4, o-$MeOC_6H_4$, o-$NO_2C_6H_4$, 2-pyridyl, $PhSCH_2$, n-Bu, $MeOCH_2$; X = H, 3-F, 3-OMe, 4-CO_2Me

Scheme 157



R^1; R^2 = H, Me, Et, c-C_6H_{11}, c-C_5H_9; R^3 = aryl, vinylic; X = I, OTf

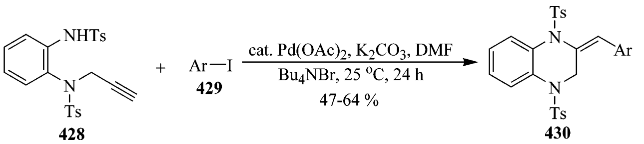
carbon triple bond to afford intermediate **C**, and (4) reductive elimination to form the carbon−carbon bond between the carbonyl group and the heterocyclic ring in **D** with simultaneous regeneration of the palladium catalyst. Many closely related carbonylative coupling processes are also known as will be discussed below.

The palladium-catalyzed addition of an acylpalladium to an alkyne, followed by nucleophilic attack of the oxygen atom, provides an efficient route to *O*-heterocycles. Thus, the reaction of internal alkynes **437** with aryl iodides **438** in the presence of the palladium−phosphine catalyst under CO pressure gives a mixture of butenolides **439** and **440** in moderate yields and good stereoselectivity (Scheme 162).[162] The yields are higher when using aryl iodides containing an electron-donating group.

We have reported that a catalytic amount of $Pd(OAc)_2$, under a 1 atm pressure of carbon monoxide, provides excellent methodology for the annulation of internal alkynes **442** with substituted *o*-iodophenols **441** to form coumarins **443** (Scheme 163).[163] The synthesis employs mild reaction conditions and can accommodate a wide variety of functional groups both in the alkyne and in the phenol. Unsymmetrical alkylarylalkynes also afford the desired products in good yields. However, such compounds afford a mixture of coumarins **443** and **444** with only modest regioselectivity (∼75:25).

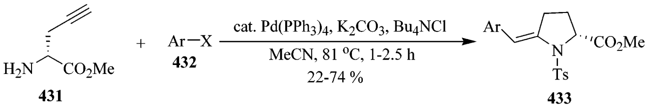
Recently, Yang and co-workers have demonstrated that the *o*-alkynylphenol **445** can be cyclized to the corresponding 3-aroylbenzo[*b*]furans **447** in good yields (Scheme 164).[164] The best results were obtained with a combination of aryl iodides **446**, *o*-alkynylphenol **445**, $Pd(PPh_3)_4$, and K_2CO_3 in MeCN under a 1 atm pressure of CO. In this cyclization, aryl iodides substituted with electron-donating groups gave better yields than iodides with electron-withdrawing groups.

Scheme 158



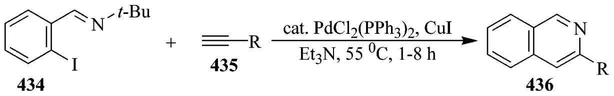
Ar = C_6H_5, m-ClC_6H_4, p-MeC_6H_4, o-MeC_6H_4, p-$MeOCC_6H_4$, o-$MeOCC_6H_4$, o-$NO_2C_6H_4$, 1-naphthyl, 2-thienyl

Scheme 159



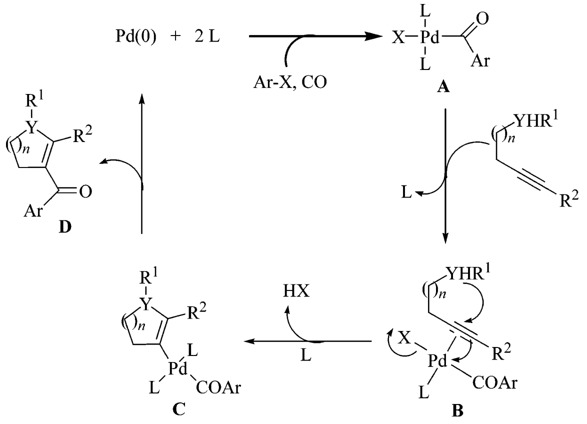
Ar = C_6H_4, p-$NO_2C_6H_4$, p-$MeOC_6H_4$; X = Br, I

Scheme 160



R = C_6H_5, $(CH_2)_2OTHP$, $CH(OEt)_2$, $(CH_2)_3CN$, n-Bu, c-C_6H_{11}

Scheme 161

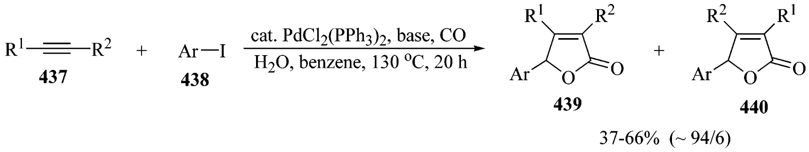


Yang and co-workers have reported the annulation of terminal arylalkynes **449** with *o*-iodophenol acetates **448** under a 1 atm pressure of CO to prepare flavones **450** (Scheme 165).[165] The reactions were conducted in Et_2NH, using $PdCl_2(PPh_3)_2$/dppp as the catalyst system in the presence of thiourea and DBU under a 1 atm pressure of CO. The annulation proceeds at 40 °C with high regioselectivity, and the flavones are formed in good to excellent yields. Electron-donating groups on the aromatic rings of the arylalkynes give flavones in lower yields than the corresponding unsubstituted aromatic rings.

The *o*-ethynylphenols **451** and vinylic triflates **452** under carbon monoxide pressure have been employed by Cacchi to synthesize the 2-coumaranones **453** (Scheme 166).[166] The reaction using $Pd(PPh_3)_4$ and KOAc in MeCN under a balloon of carbon monoxide gave a *Z*/*E* mixture of coumarin isomers in 40−79% yields.

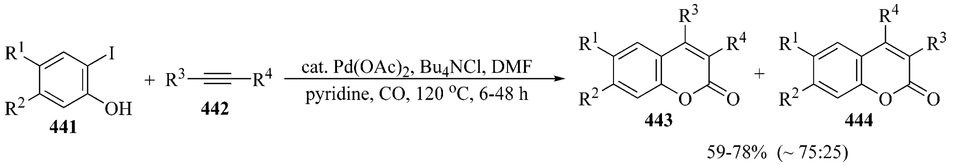
The palladium-catalyzed cyclization of alkadione **454** with aryl iodides **455** under a carbon monoxide atmosphere provides a very useful synthetic route to trisubstituted dihydrofurans, such as **456** and **457** (Scheme 167).[167] The alkyne and aryl iodide ratio will determine whether the process gives the dihydrofurans **456** or **457**. When the reaction is conducted in the presence of $Pd(OAc)_2$ and P(*o*-Tol)$_3$ in MeCN under a CO atmosphere using 0.66 as the **455**:**454** ratio, the dihydrofurans **456** are obtained. However,

Scheme 162



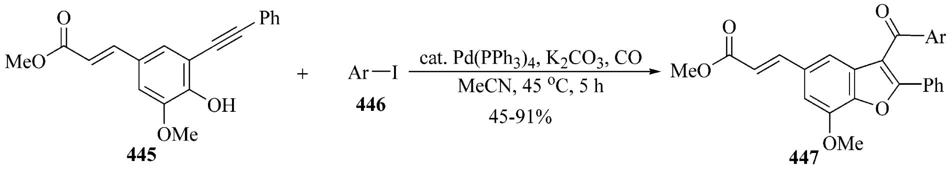
R^1 = *n*-Pr, *n*-Bu, Me_3Si, Bn; R^2 = *n*-Pr, Bn; Ar = Ph, *m*-MeC_6H_4, *p*-ClC_6H_4, *p*-$MeO_2CC_6H_4$;
base = Et_3N, $NaHCO_3$

Scheme 163



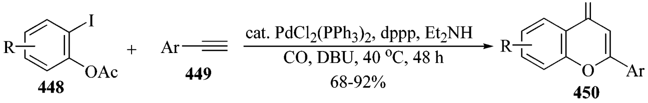
R^1 = H, CO_2Et, OMe; R^2 = H, CO_2Me; R^3 = Ph, Me, Et, *n*-Pr, CH_2OBn; R^4 = Ph, *n*-Pr, *t*-Bu, CH_3CO, Me_3Si

Scheme 164



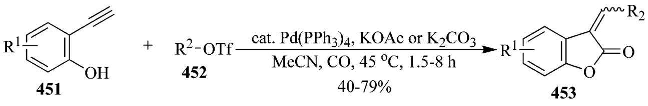
Ar = C_6H_5, *p*-$MeOCC_6H_4$, *p*-$CF_3CC_6H_4$, 2-thienyl

Scheme 165



R = MeO, $TBSOCH_2$, $MeO_2CHC{=}CH$, MeOC, MeO_2C; Ar = C_6H_4, *m*-OBn-*p*-OMe

Scheme 166



R^1 = H, Me, PhOC; R^2 = vinylic

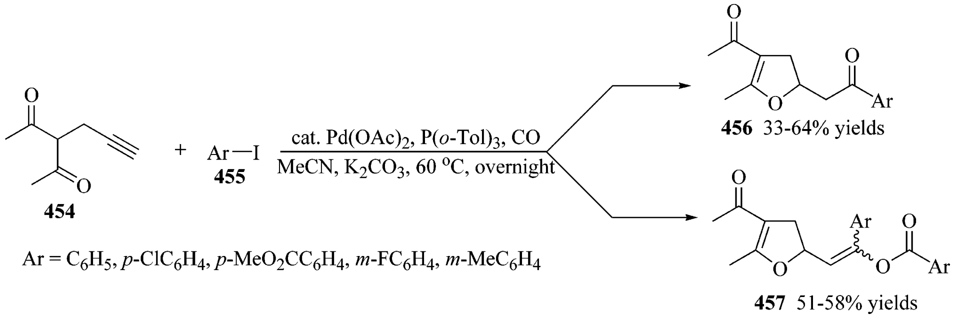
under the same reaction conditions, but using a **455**:**454** ratio of 3, the dihydrofurans **457** are obtained.

The palladium-catalyzed reaction of alkynes bearing a nitrogen atom at an appropriate distance from the carbon–carbon triple bond with aryl/vinylic halides or triflates generates a wide variety of nitrogen heterocycles containing a carbonyl group. Thus, the palladium-catalyzed reaction of alkynyltrifluoroacetanilides **458** with the aryl iodides or vinylic triflates **459** under a CO atmosphere in the presence of K_2CO_3 produces 3-acylindoles **460** in good yields (Scheme 168).[168] The acidity of the nitrogen–hydrogen bond in **458** proved to be of crucial importance for the success of this cyclization process.

Recently, Cacchi has studied the palladium-catalyzed cyclocarbonylation of bis(*o*-trifluoroacetamidophenyl)acetylene (**461**) with aryl/vinylic halides or triflates **462** as a useful route to acylindolo[1,2-*c*]quinazolines **463** (Scheme 169).[169] The pressure of carbon monoxide, the solvent, and the nature of the organic halide or triflate were found to influence the yields and selectivity of the cyclization between acylindoloquinazoline **463** and aryllindoloquinazoline **464**. The best conditions developed to obtain **463** as the main product employ $Pd(PPh_3)_4$ as the catalyst and K_2CO_3 as the base in MeCN under 5 atm of carbon monoxide at 50 °C. In the case of vinylic triflates, the addition of *n*-Bu_4NBr or *n*-Bu_4NI is also necessary.

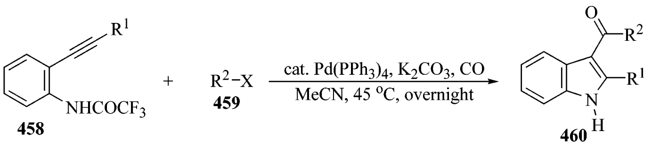
Negishi has reported the carbonylative amidation of nitrogen-containing iodoalkynes **465** to obtain lactams **466** (Scheme 170).[170] In the case of carboxamides or sulfonamides, this process affords good yields using only a catalytic amount of $PdCl_2(PPh_3)_2$ and Et_3N in MeOH under 1 atm of carbon monoxide. When free amines are employed as the substrate, the use of *i*-PrOH, instead of MeOH, as well as a temperature of 75 °C, is necessary.

Scheme 167



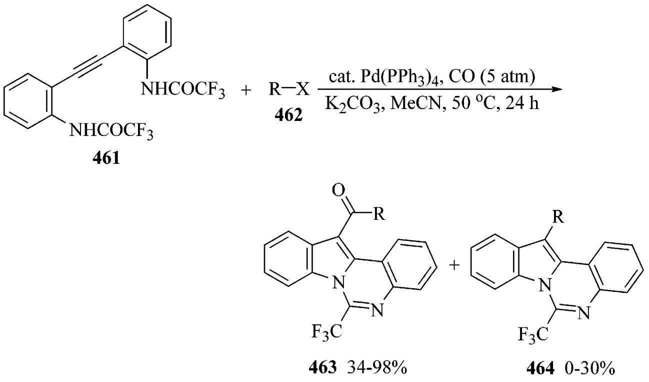
Ar = C_6H_5, *p*-ClC_6H_4, *p*-$MeO_2CC_6H_4$, *m*-FC_6H_4, *m*-MeC_6H_4

Scheme 168



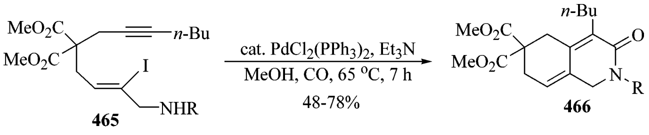
R^1 = alkyl, aryl, heteroaryl; R^2 = vinylic, p-MeOC$_6$H$_4$, p-MeCONHC$_6$H$_4$, p-ClC$_6$H$_4$, m-MeC$_6$H$_4$, m-FC$_6$H$_4$; X = I, OTf

Scheme 169



R = aryl, vinylic; X = I, Br, OTf

Scheme 170



R = H, Ac, Ts

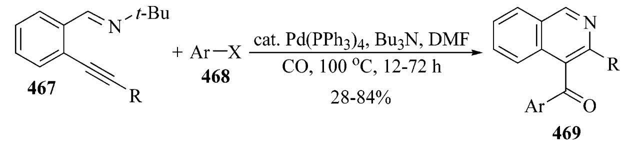
We have developed an efficient synthetic method for the carbonylative cyclization of *N-tert*-butyl-2-(1-alkynyl)benzaldimines **467** and aryl halides **468** to the corresponding 4-aroylisoquinolines **469** (Scheme 171).[171] A number of aroylisoquinolines have been prepared in good yields using a catalytic amount of Pd(PPh$_3$)$_4$ under a 1 atm pressure of carbon monoxide. This methodology can tolerate a wide variety of important functional groups both in the alkyne and in the aryl halide.

The preparation of 2-substituted chromones and quinolones **472** has been carried out by a palladium-catalyzed carbonylation of *o*-iodophenols or *o*-iodoanilines **470** in the presence of terminal alkynes (Scheme 172).[172] The reaction involves the carbonylative coupling of the aryl halides and terminal alkynes **471**, followed by cyclization, in a one-pot procedure. The choice of solvent and base is crucial in obtaining the cyclized product in good yields and high selectivity. In general, secondary amines, such as Et$_2$NH, are the better solvent/base for the carbonylation, rather than primary amines. The best results were obtained with PdCl$_2$(dppf) and PdCl$_2$(PPh$_3$)$_2$ as catalysts.

6. Heterocycles via Carbonylative Cyclization

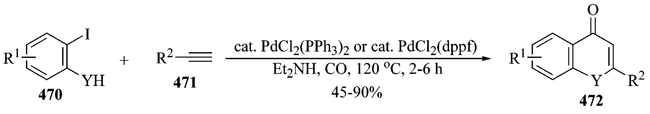
The palladium-catalyzed reaction of aryl/vinylic halides with carbon monoxide in the presence of a nucleophilic heteroatom proceeds by an initial oxidative addition of palladium to the carbon−halogen bond, followed by carbon monoxide insertion to give an acylpalladium intermediate. This acylpalladium intermediate can react with various nucleophiles, including oxygen and nitrogen atoms, with formation of an *O*- or *N*-heterocycle. This palladium-catalyzed reaction provides a very valuable approach to a wide range of *O*- and *N*-heterocycles, which will be discussed in the following sections.

Scheme 171



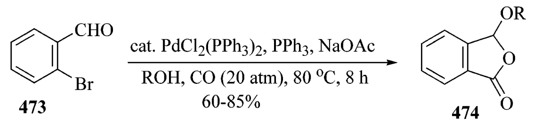
R = C$_6$H$_5$, 1-cyclohexenyl, 3-cyanopropyl, n-Bu; Ar = C$_6$H$_5$, p-MeOC$_6$H$_4$, m-MeOC$_6$H$_4$, o-MeOC$_6$H$_4$, o-MeC$_6$H$_4$, m-MeC$_6$H$_4$, p-MeC$_6$H$_4$, p-BrC$_6$H$_4$, m-EtO$_2$CC$_6$H$_4$, m-MeO$_2$CC$_6$H$_4$, o-F$_3$CC$_6$H$_4$, m-CF$_3$C$_6$H$_4$, p-F$_3$CC$_6$H$_4$, p-NO$_2$C$_6$H$_4$, m-NO$_2$C$_6$H$_4$, o-NO$_2$C$_6$H$_4$; X = Br, I, COCl

Scheme 172



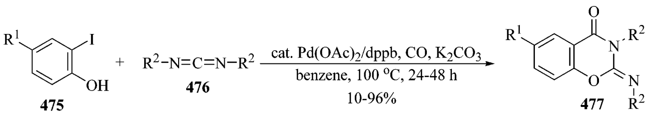
R^1 = H, Me; R^2 = n-C$_5$H$_{11}$, n-C$_6$H$_{13}$, CH$_2$OTHP, (CH$_2$)$_3$OAc, (CH$_2$)$_3$OTHP, 2-thienyl, p-MeOC$_6$H$_4$, m-MeOCC$_6$H$_4$, p-EtO$_2$CC$_6$H$_4$; Y = O, NH

Scheme 173



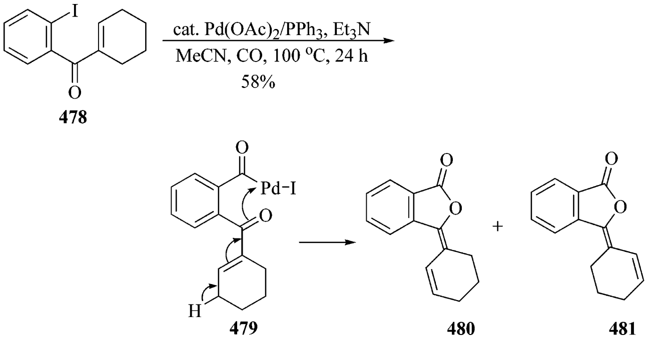
R = Me, Et, n-Pr, n-Bu, t-Bu, i-Bu

Scheme 174

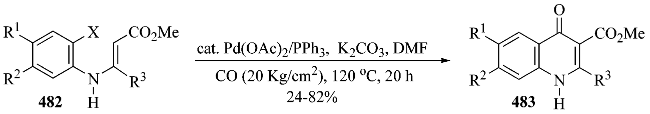


R^1 = H, CH$_3$, Cl; R^2 = C$_6$H$_5$, p-ClC$_6$H$_4$, p-CH$_3$C$_6$H$_4$, p-BrC$_6$H$_4$, p-CH$_3$OC$_6$H$_4$, i-C$_3$H$_7$

Scheme 175



Scheme 176

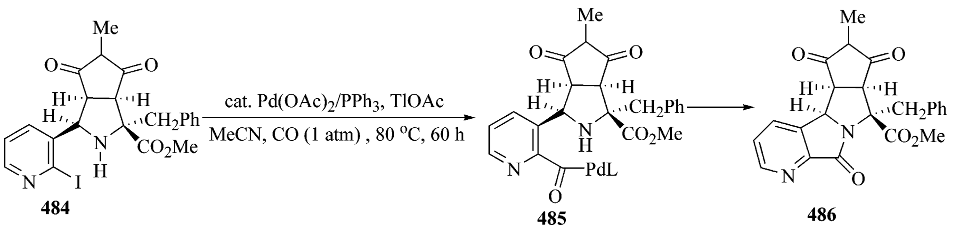


R^1 = H, F; R^2 = H, Cl, F; R^3 = Me, CH$_2$CO$_2$Me, CO$_2$Me; X = Br, I

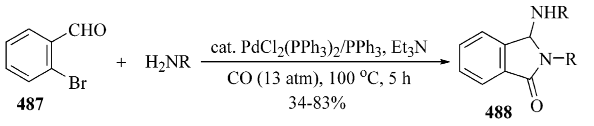
6.1. Heterocycles via Carbonylative Cyclization of Aryl Halides

The palladium-promoted carbonylative cyclization of *o*-bromobenzaldehyde (**473**) in an alcohol solvent provides a very useful route to 3-substituted phthalides **474** (Scheme 173).[173] The use of a catalytic amount of PdCl$_2$(PPh$_3$)$_2$/PPh$_3$ and NaOAc in an alcoholic medium under a 20 atm pressure

Scheme 177

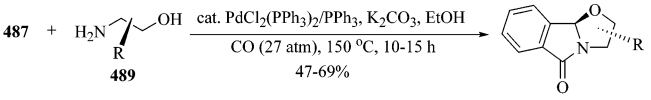


Scheme 178



R = CH_2CH_3, $CH_2(CH_2)_2CH_3$, $CH_2(CH_2)_{10}CH_3$, $CH(CH_3)_2$, $CH(CH_3)(CH_2)_4CH_3$, CH_2Ph, $CH_2C_6H_4OMe$-*p*, *c*-C_6H_{11}, $CH_2CH{=}CH_2$

Scheme 179



R = Me, CH_2Ph

490 > 99 % de

of carbon monoxide produces the best yields of phthalides. The use of other palladium complexes, such as $PdCl_2/PPh_3$, $Pd(OAc)_2/PPh_3$, or $Pd(PPh_3)_4$, gave lower catalytic activity.

Alper and co-workers have shown that the *o*-iodophenols **475** react with carbodiimides **476** in the presence of a $Pd(OAc)_2$/dppb catalyst in benzene to afford benzo[*e*]-1,3-oxazinone derivatives **477** in excellent yields (Scheme 174).[174] Both electron-donating and electron-withdrawing groups on the aromatic ring of the *o*-iodophenols afforded **477** in good yields.

Treatment of the *o*-iodoaryl alkenyl ketone **478** with carbon monoxide in MeCN in the presence of a catalytic amount of $Pd(dba)_2$ and Et_3N led to the formation of a 1:1 mixture of heterocycles **480** and **481** in a 58% yield (Scheme 175).[175] In this reaction, Et_3N is used in excess as the base to induce the *endo* cyclization of **479**, which is formed as an intermediate.

The palladium-catalyzed insertion of carbon monoxide into 3-substituted 3-[2-(haloaryl)amino]propenoates **482** results in heterocyclization to form a variety of 2-substituted 1,4-dihydro-4-oxoquinoline-3-carboxylates **483** in 24−82% yields (Scheme 176).[176] The best yields in this cyclization are obtained using the combination of $Pd(OAc)_2/PPh_3$ and K_2CO_3 in DMF under 20 kg/cm^2 of carbon monoxide. When the reaction was carried out under 1 atm of carbon monoxide, the quinolines **483** were obtained in lower yields, together with the usual Heck reaction product produced without insertion of the carbon monoxide.

The cyclization of 2-iodopyridine **484** to the corresponding lactam in the presence of a palladium catalyst and carbon monoxide has been described by Grigg and co-workers (Scheme 177).[177] Treatment with $Pd(OAc)_2/PPh_3$ and 1 atm of carbon monoxide in the presence of TlOAc afforded the lactam **486** by carbonylative insertion and subsequent intramolecular capture of the acylpalladium(II) species **485** by the pyrrolidine nitrogen. The palladium(0) required is generated in situ from $Pd(OAc)_2$ and PPh_3.

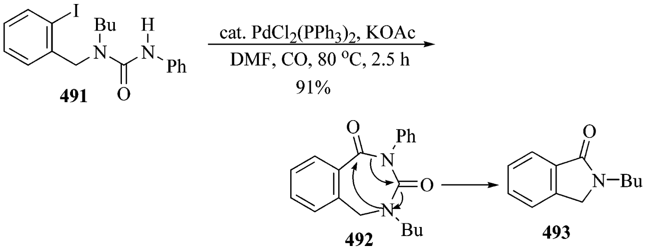
Shim and co-workers have reported that 3-(alkylamino)-isoindolinones **488** can be obtained in moderate to good yields by the palladium-catalyzed carbonylation of *o*-bromobenzaldehyde (**487**) with primary amines under carbon monoxide pressure (Scheme 178).[178] The best results are obtained using a catalyst system consisting of $PdCl_2(PPh_3)_2/PPh_3$ in Et_3N under a 13 atm pressure of carbon monoxide. Employing inorganic bases, such as NaOAc, K_2CO_3, and $NaHCO_3$, in place of Et_3N resulted in lower yields of **488**.

In a closely related investigation, Shim and co-workers reported the use of **487** and chiral alkanolamines **489** as precursors to tricyclic chiral isoindolinones **490** in moderate yields and high diasteroselectivity (Scheme 179).[179] This reaction was conduced in ethanol using $PdCl_2(PPh_3)_2/PPh_3$ as the catalyst, K_2CO_3 as the base, and a 27 atm pressure of carbon monoxide.

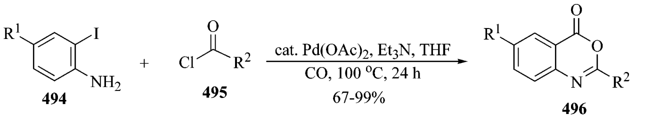
In 1999, Catellani and co-workers demonstrated that urea **491** can be cyclized to the corresponding benzodiazepine-1,3-dione **492** in 91% yield using a catalytic amount of $Pd(PPh_3)_4$ and KOAc in DMF (Scheme 180).[180] The yields and selectivity are strongly affected by the solvent. When the cyclization was carried out in anisole, under the same reaction conditions, the seven-membered ring product **492** was transformed to **493** by rearrangement and ring contraction.

The one-pot reaction of *o*-iodoanilines **494** with acid chlorides **495** and carbon monoxide, in the presence of a

Scheme 180

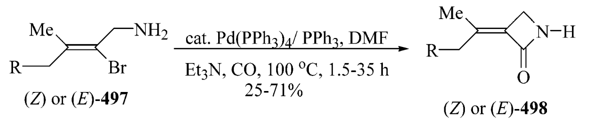


Scheme 181



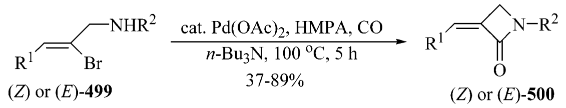
R^1 = H, CH_3, CN, Cl, OH; R^2 = CH_3, $CHPh_2$, CH_2SPh, C_6H_5, *p*-ClC_6H_4, *o*-$CH_3OC_6H_4$, *t*-Bu

Scheme 182



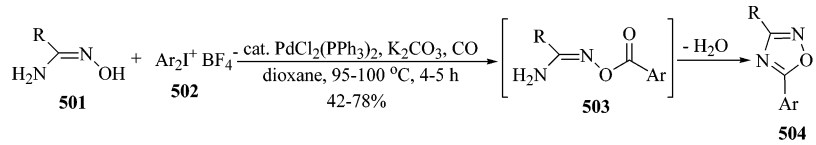
R = H, $OSiMe_2t$-Bu, $OSiPh_2t$-Bu

Scheme 183



R^1 = H, Ph; R^2 = CH_2CH_2Ph, $CH_2CH_2CO_2Me$, CH_2Ph

Scheme 184



R = C_6H_5, *p*-$CH_3OC_6H_4$, *p*-ClC_6H_4, CH_2Ph; Ar = C_6H_5, *p*-$CH_3OC_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, *m*-$NO_2C_6H_4$, MeC_6H_4

palladium catalyst and *i*-Pr_2NEt, regioselectively affords benzoxazinones **496** in excellent yields (Scheme 181).[181] Both electron-rich and electron-poor *o*-iodoanilines react with acid chlorides to form **496** in good yields. The reaction proceeds via in situ amide formation, followed by oxidative addition of the aryl halide to the palladium(0) species, CO insertion, and intramolecular cyclization to give **496**.

6.2. Heterocycles via Carbonylative Cyclization of Vinylic Halides

The 2-bromoallylic amines **497** can be cyclized in the presence of a palladium catalyst under carbon monoxide pressure to produce β-lactams (Scheme 182).[182] Thus, the stereoselective reaction of (*Z*)- or (*E*)-2-bromoallylic amines **497** with $Pd(PPh_3)_4$ in DMF under 1 atm of carbon monoxide gave β-lactams **498** in good yields.

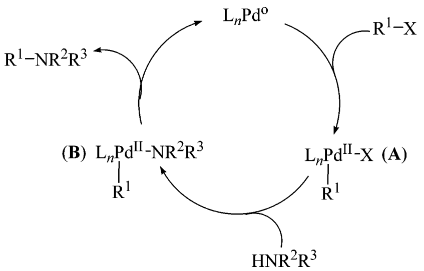
Employing different reaction conditions, Ban and coworkers have also described the preparation of β-lactams via palladium-catalyzed carbonylation, using amine-containing vinylic bromides (Scheme 183).[183] Thus, the insertion of carbon monoxide into various vinylic bromides **499** in the presence of a catalytic amount of $Pd(OAc)_2$ and PPh_3 gave the corresponding β-lactams **500** in good yields.

Recently, Chen and co-workers reported that 3,5-disubstituted oxadiazoles **504** can be prepared in a one-pot procedure by the palladium-catalyzed carbonylation of diaryliodonium salts **502** and amidoximes **501** under 1 atm of carbon monoxide (Scheme 184).[184] The acylpalladium coupling with the amidoximes produces the intermediate **503**, which, via intramolecular dehydrative cyclization, affords the oxadiazoles in good yields.

7. Heterocycles via Palladium-Catalyzed Aryl/Vinylic Amination. Hartwing−Buchwald C−N Bond Formation

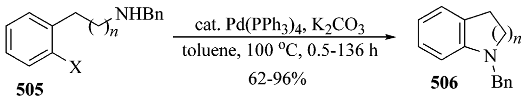
The palladium-catalyzed coupling reaction of aryl/vinylic halides with the nitrogen atom from amines or amides is generally known as the Hartwing−Buchwald reaction.[185] The general mechanism for the reaction involves initial oxidative addition of the aryl/vinylic halide to a palladium(0) species to give the palladium(II) intermediate **A**. The coordination and substitution of the halide by a nitrogen atom in **A** gives the intermediate **B**, which undergoes reductive elimination to afford the aryl/vinylic amine or amide and regenerates the palladium(0) catalyst (Scheme 185).

Scheme 185



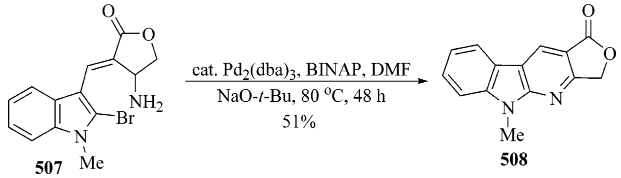
The direct palladium-catalyzed C−N bond formation was first reported by Buchwald[186] and Hartwing[187] for the preparation of arylamines. After this discovery, a number of reports describing the formation of amines or amides, including nitrogen heterocycles, by this process were reported. For example, the treatment of the amine-containing aryl halides **505** with a palladium catalyst and a base in toluene promoted heterocyclization to the cyclic amines **506** (Scheme 186). To complete conversion, it was necessary to utilize $Pd(PPh_3)_4$ as the catalyst and K_2CO_3 as the base in toluene at 100 °C. Other bases, such as Na_2CO_3, NaOAc, KOAc, Li_2CO_3, Ag_2CO_3, and $CaCO_3$, are less effective for the cyclization. The formation of six- and seven-membered rings required a longer reaction time than was necessary for the formation of five-membered rings.

Scheme 186

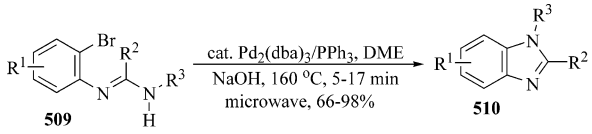


X = Br, I; *n* = 1-3

Scheme 187



Scheme 188



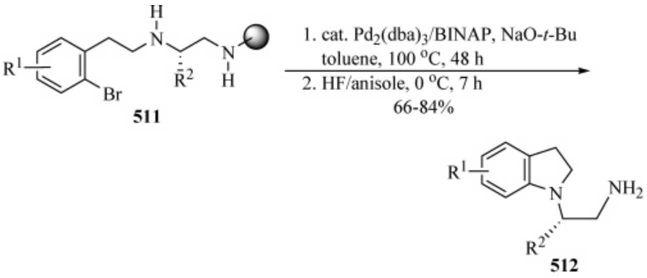
R^1 = H, 5-NO_2, 5-MeO, 3-Me; R^2 = Me, Ph; R^3 = Me, Ph, *i*-Pr

Dodd and Abouabdellah performed the cyclization of bromide **507** with a $Pd_2(dba)_3$/BINAP catalyst to furnish, after air oxidation, the pyrido[2,3-*b*]indole **508** in 51% yield (Scheme 187).[188] When this reaction was carried out in the absence of palladium/BINAP, only the starting material was recovered, even after prolonged heating.

The use of an amidine in a palladium-catalyzed aryl amination has been reported by Brain and Steer (Scheme 188).[189] When the reaction of amidine **509** was carried out in the presence of $Pd_2(dba)_3/PPh_3$, with DME as the solvent, and heated in a microwave reactor, benzimidazoles **510** were produced in excellent yields and in a relatively short reaction time.

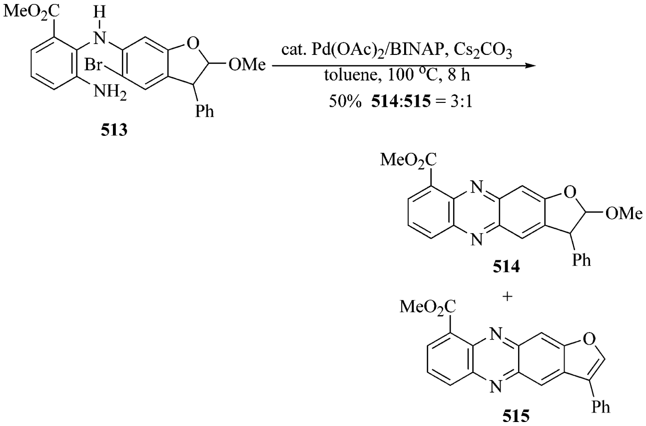
Very recently, Houghten and co-workers have employed a palladium-catalyzed intramolecular aryl amination in the preparation of indolines **512**, using solid-phase synthesis

Scheme 189

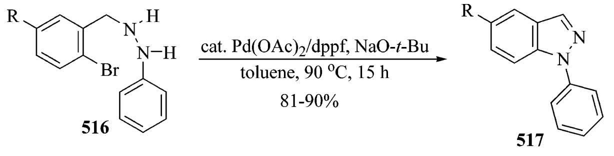


R^1 = H, 5-Cl, 5,6-di-CH_3O; R^2 = H, CH_3, $HC(CH_3)_2$, $CH_2CH(CH_3)_2$, CH_2Ph

Scheme 190



Scheme 191



R = H, F, OMe

(Scheme 189).[190] The amines **511** bonded to a resin were converted to indolines **512** by a $Pd_2(dba)_3$/BINAP catalyst system, followed by cleavage from the resin using HF and anisole.

The *N*-arylation of the 2-bromoaniline derivative **513** to the corresponding phenazine has been described (Scheme 190).[191] Using Buchwald's conditions,[192] phenazine **514** was produced together with the elimination product **515** in moderate yield.

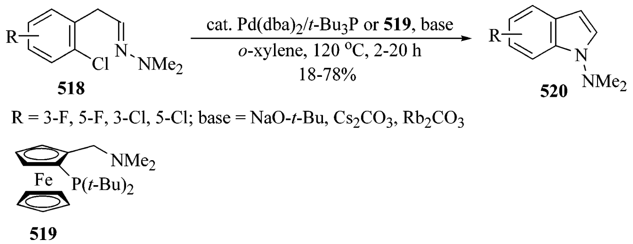
Song and Yee have described the preparation of indazoles **517** from hydrazines **516** via palladium-catalyzed C−N bond formation (Scheme 191).[193] The cyclization took place in good yields, using $Pd(OAc)_2$/dppf as the catalyst, NaO-*t*-Bu as the base, and toluene as the solvent.

In a related study, Watanabe showed that *t*-Bu_3P or the ferrocenylphosphine ligand **519** can be used in the palladium-catalyzed cyclization of unreactive aryl chlorides to form aminoindoles (Scheme 192).[194] Thus, the cyclization of the hydrazones **518** in the presence of $Pd(dba)_2$, a ligand, and a base gives 1-aminoindoles **520** in moderate to good yields.

Buchwald has shown that secondary amides or carbamates **521** react in the presence of $Pd(OAc)_2$, a ligand, and K_2CO_3 or Cs_2CO_3 as the base to afford five-, six-, and seven-membered *N*-heterocycles **522** in excellent yields (Scheme 193).[195]

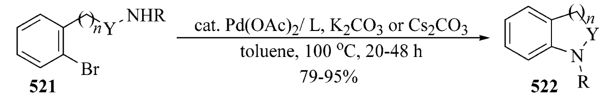
This chemistry was subsequently employed by Katayama and co-workers for the synthesis of indazole derivatives (Scheme 194).[196] When indolines **523** are employed as the substrate in a palladium-catalyzed aromatic amination, the indolo[1,2-*b*]indazoles **524** are formed. This cyclization is effective for the synthesis of indoles having either an electron-donating or an electron-withdrawing group present in either of the two aromatic rings.

Scheme 192



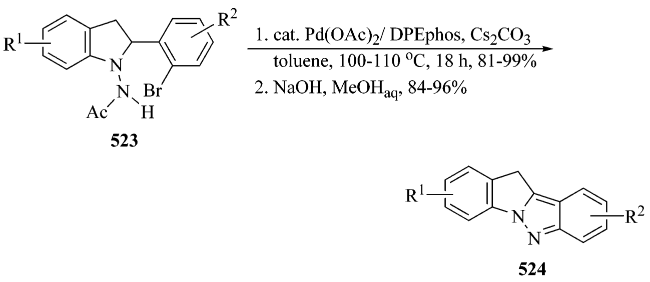
R = 3-F, 5-F, 3-Cl, 5-Cl; base = NaO-*t*-Bu, Cs_2CO_3, Rb_2CO_3

Scheme 193



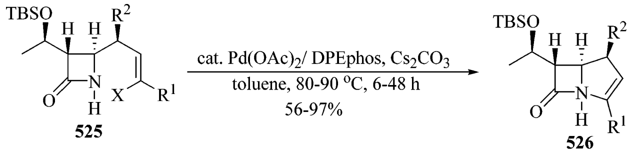
R = Ac, Bn, Boc, Cbz; Y = CH_2, C=O; *n* = 1-3; L = BINAP, MOP, DPEphos, xantphos, BINAP

Scheme 194



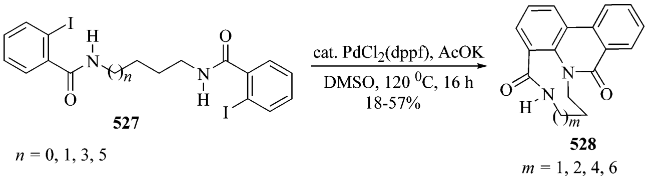
R^1 = H, 5-Me, 7-Me, 5-Cl, 5-F; R^2 = H, 4-OMe, 3-Me, 5-F

Scheme 195



R^1 = CH_2OTBS, CO_2Me, CO_2Et; R^2 = H, Me; X = Br, I, OTf

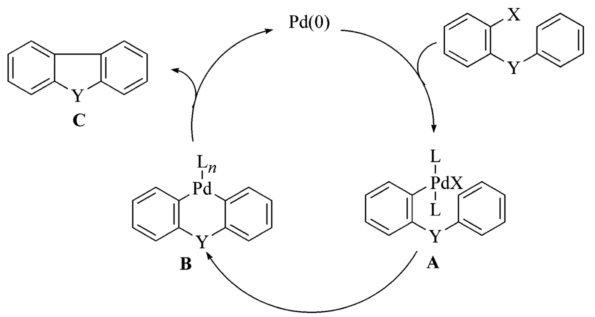
Scheme 196



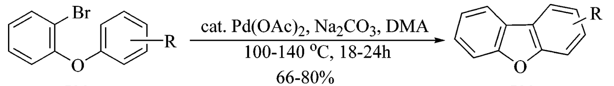
Mori and Kozawa have used the vinylic halides **525** bearing an amide group as a substrate to produce the corresponding carbapenems **526** in good yields (Scheme 195).[197] When $Pd(OAc)_2$ was used in the presence of other ligands, such as BINAP and P(*o*-Tol)$_3$, good results were not obtained.

Finally, very recently, Zhu and co-workers have developed an interesting one-pot procedure involving intramolecular amination, C−H activation, and aryl−aryl bond formation for the preparation of poly-*N*-heterocycles **528** from diamides **527** (Scheme 196).[198] Thus, the reaction of the linear diamides **527** with a catalytic amount of $PdCl_2$(dppf) and

Scheme 197



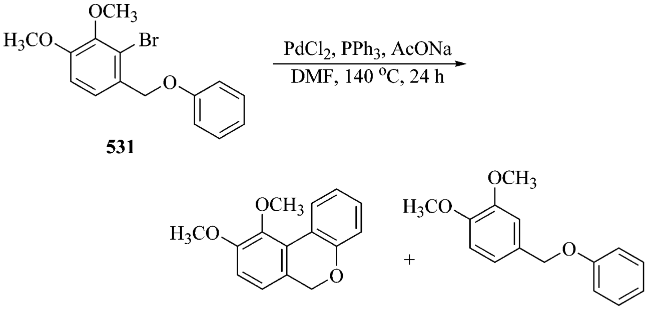
Scheme 198



529 **530**

R = 2-NO$_2$, 3-NO$_2$, 4-NO$_2$, 4-CN, 4-CH$_2$OH, 3-CH$_3$, 4-CO$_2$H

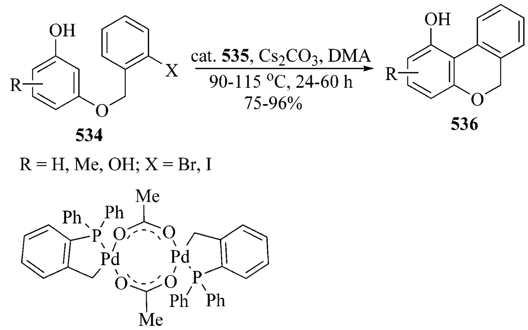
Scheme 199



531

532 66% yield **533** 5% yield

Scheme 200



534 **536**

R = H, Me, OH; X = Br, I

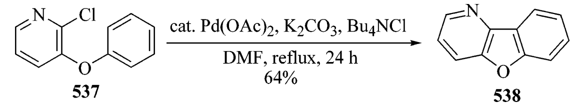
535

KOAc in DMSO at 120 °C produced diamides **528** fused with a macrocyclic ring in moderate yields. This reaction is highly temperature dependent. Higher yields are only obtained when the reaction is carried out at a higher temperature.

8. Heterocycles via Palladium-Catalyzed Intramolecular Biaryl Cross-Coupling

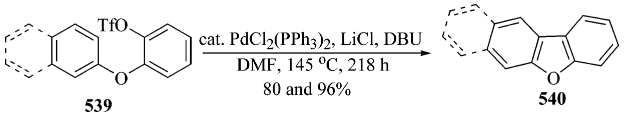
The palladium-catalyzed intramolecular cross-coupling of aryl halides or triflates bearing another aromatic ring is a versatile way to generate a wide variety of *N*- and *O*-heterocycles under mild reaction conditions. From a mechanistic point of view, the cyclization proceeds through the oxidative addition of palladium to the aryl halide or triflate to give a σ-arylpalladium intermediate (**A**). Electrophilic attack on the aromatic or heteroaromatic ring leads to diarylpalladium species **B**, which after reductive elimination of palladium, affords heterocycle **C** (Scheme 197).

Scheme 201



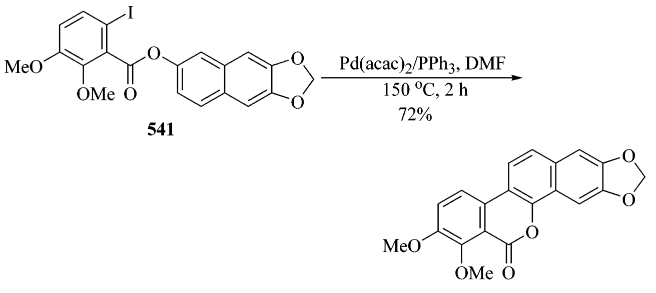
537 **538**

Scheme 202



539 **540**

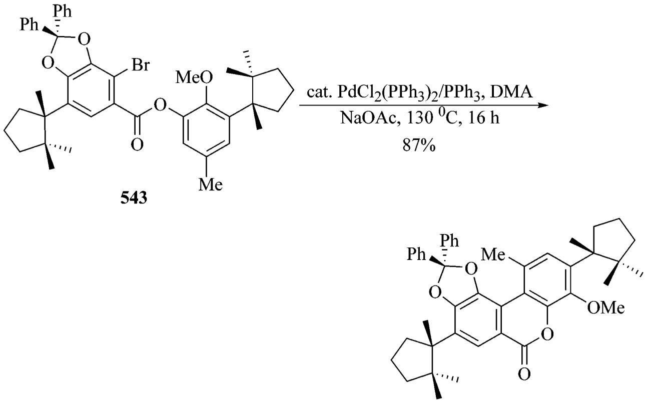
Scheme 203



541

542

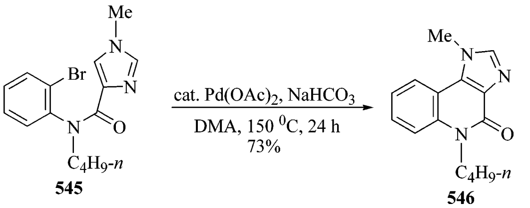
Scheme 204



543

544

Scheme 205

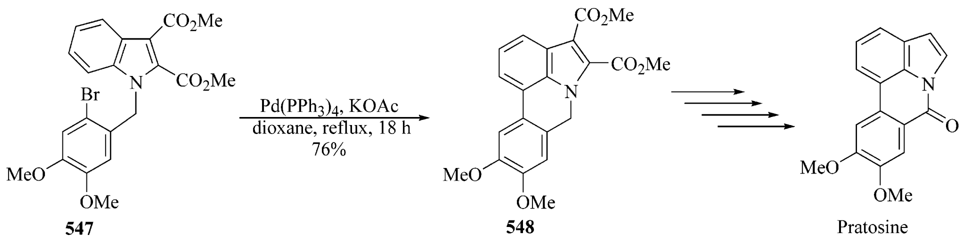


545 **546**

The palladium-catalyzed cross-coupling of 2-bromophenyl phenyl ethers affords substituted furans under basic conditions (Scheme 198).[199] Thus, the benzofurans **530** have been prepared in moderate to good yields by heating the 2-bromophenyl phenyl ethers **529** with Pd(OAc)$_2$ in dimethylacetamide while using Na$_2$CO$_3$ as a base. The reaction tolerates strongly electron-withdrawing as well as electron-donating groups.

In a closely related investigation, Schäfer and Wiegand reported the cyclization of 2-aryl ether **531** to the cyclic aryl ether **532** by an intramolecular aryl−aryl coupling reaction (Scheme 199).[200] When the reaction was carried out in the presence of PdCl$_2$/PPh$_3$ and NaOAc, the ether **532** was obtained in a 66% yield together with the noncyclized product **531** in a 5% yield. It was found that substituents on

Scheme 206



the aromatic ring bonded directly to the oxygen atom exhibit a great influence on the formation of product **532**. This influence can be seen by the fact that when the substituent is a methyl group, none of the cyclized product is observed.

Rawal and co-workers have also described the synthesis of cyclic aryl ethers **536** by an intramolecular coupling of phenols bearing aryl halides **534** (Scheme 200).[201] When the reaction was performed in the presence of 5 mol % palladacycle **535**, Cs_2CO_3, and DMA, the ethers **536** were formed in excellent yields. Other catalysts, such as $Pd(OAc)_2$, $Pd_2(dba)_3$, and $PdCl_2$, as well as other bases, such as K_2CO_3 and KO-*t*-Bu, afforded the desired product in only low yields.

The heteroaryl ether **537** has also been shown to undergo heteroaryl−aryl bond formation when subjected to a palladium catalyst (Scheme 201).[202] Thus, benzo[4,5]furopyridine (**538**) can be obtained in a 64% yield by the cross-coupling of diaryl ether **537**, when catalyzed by $Pd(OAc)_2$ under ligand-free conditions.

An intramolecular aryl−triflate−arene cross-coupling reaction catalyzed by palladium has been employed by Harvey and Wang in the synthesis of polycyclic aromatic furan derivatives (Scheme 202).[203] Thus, the palladium-catalyzed reaction of aryl triflate ethers **539** with LiCl and DBU in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ in DMF at 145 °C gave benzo[*b*]naphtha[2,3-*d*]furan or dibenzofuran **540** in 96% and 80% yields, respectively.

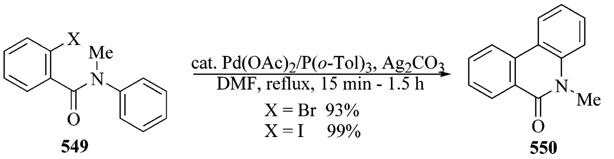
Harayama and Yasuda have utilized an intramolecular aryl−aryl palladium cross-coupling as the key step in a synthesis of arnottin I (**542**) (Scheme 203).[204] Thus, the reaction of *o*-iodoester **541** with a catalytic amount of $Pd(acac)_2/PPh_3$ and NaOAc in DMF provided **542** in 72% yield. Other palladium catalysts, such as $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$, gave the desired product, however, in lower yields than $Pd(acac)_2$.

Bringmann and co-workers have reported the use of bromoester **543** as a substrate in a palladium-catalyzed cross-coupling to prepare lactone **544** (Scheme 204).[205] To completely convert bromoester **543** to lactone **544**, it was necessary to utilize $PdCl_2(PPh_3)_2/PPh_3$ and NaOAc in dimethylacetamide. Under these conditions, the desired lactone was prepared in an 87% yield without any major side products.

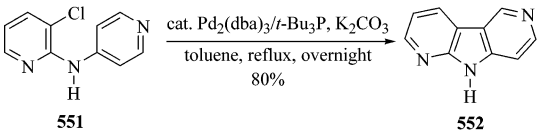
A number of nitrogen heterocycles have also been synthesized by a palladium-catalyzed aryl−aryl cross-coupling. Suzuki and Kuroda showed that the reaction of aryl bromide **545** with a catalytic amount of $Pd(OAc)_2$ and $NaHCO_3$ in dimethylacetamide afforded the corresponding tricyclic quinolinone **546** in a 60% yield (Scheme 205).[206]

The palladium-catalyzed cyclization of indole **547** in the presence of a catalytic amount of $Pd(PPh_3)_4$ and KOAc in dioxane gave the phenanthridine derivative **548** in a 76% yield, which, after four steps, was converted to the alkaloid pratosine (Scheme 206).[207]

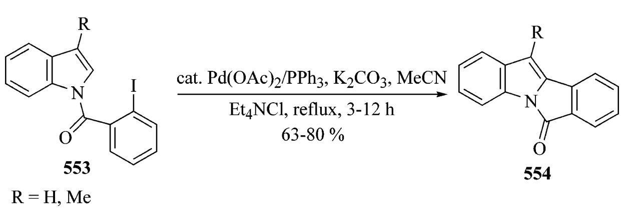
Scheme 207



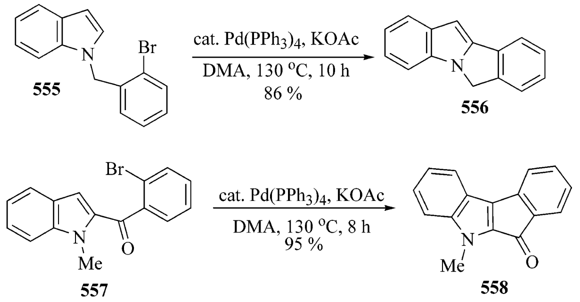
Scheme 208



Scheme 209



Scheme 210



Harayama and co-workers have been able to prepare the benzo[*c*]phenanthridine derivative **550** by the reaction of benzamides **549** with a palladium catalyst, a phosphine ligand, and a base (Scheme 207).[208] Excellent yields of the desired product were obtained when the reaction was performed using a catalytic amount of $Pd(OAc)_2$, $P(o\text{-}Tol)_3$, and Ag_2CO_3 in DMF as the solvent.

Maes and co-workers have recently reported that $Pd_2(dba)_3$, *t*-Bu_3P, and K_3PO_4 in dioxane are effective in the intramolecular arylation of 3-chloro-2-(4-pyridylamino)pyridine (**551**) to form 11*H*-indolo[3,2-*c*]quinoline **552** (Scheme 208).[209] This reaction affords heterocycle **552** in a 80% yield.

Grigg has described the preparation of fused nitrogen heterocycles using the 1-aroylindoles **553** as substrates in an intramolecular palladium coupling (Scheme 209).[210] Thus, the 1-aroylindoles were cyclized using a catalytic amount of $Pd(OAc)_2/PPh_3$, Et_4NCl, and K_2CO_3 in boiling acetonitrile to give isoindoles **554** in good yields.

Using somewhat different reaction conditions, the palladium-catalyzed intramolecular cyclization of indole **555** to annelated indole **556** has been described by Kozikowski and Ma (Scheme 210).[211] This process has been carried out using $Pd(PPh_3)_4$ and KOAc in DMA as the catalytic system to afford the polycyclic indole **556** in a 86% yield. When the same reaction conditions were employed for *N*-methylindole **557**, the product **558** was obtained in a 95% yield.

9. Conclusion

In this review, we have presented numerous very useful processes for the synthesis of heterocycles, which involve palladium-catalyzed cyclizations or annulations via oxidative addition reactions. This chemistry generally involves initial oxidative addition of an organic halide or triflate to the palladium(0) complex, which readily undergoes intramolecular nucleophilic attack by a neighboring nucleophile or addition to an alkene, alkyne, or carbon monoxide. The resulting organopalladium intermediate can undergo a variety of very useful subsequent transformations to give heterocycles. In this methodology, 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 methodologies proceed stereo- and regioselectively in excellent yields. In the next few years we are likely to see many new and exciting cyclization strategies in palladium chemistry developed for the construction of a wide range of heterocycles. Thus, we hope with this review to have provided appropriate background for such developments and the encouragement to synthetic organic chemists to employ this valuable methodology in important new heterocyclic and medicinal chemistry.

10. Acknowledgments

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