1
Synthesis of Saturated Five-Membered Nitrogen Heterocycles via Pd-Catalyzed C−N Bond-Forming Reactions

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1.1
Introduction

Saturated five-membered nitrogen heterocycles, such as pyrrolidines, indolines, and isoxazolidines, appear as subunits in a broad array of biologically active and medicinally significant molecules [1]. As such, the synthesis of these compounds has been of longstanding interest. Many classical approaches to the construction of these heterocycles involve the use of C−N bond-forming reactions such as reductive amination, nucleophilic substitution, or dipolar cycloaddition for ring closure [2]. Although these methods have proven quite useful, their substrate scope and functional group tolerance is often limited.

In recent years, a number of powerful new transformations have been developed that involve the use of palladium-catalyzed C−N bond-forming reactions for construction of the heterocyclic ring [3]. These transformations frequently occur under mild conditions, tolerate a broad array of functional groups, and proceed with high stereoselectivity. In addition, the use of palladium catalysis allows for highly convergent multicomponent coupling strategies, which generate several bonds and/or stereocenters in a single process. This chapter describes recent approaches to the synthesis of saturated five-membered nitrogen heterocycles via Pd-catalyzed C−N bond forming reactions.

1.2
Pd-Catalyzed Amination of Aryl Halides

One of the most versatile and widely employed methods for the construction of aryl C−N bonds is the palladium-catalyzed cross coupling of amines with aryl halides and related electrophiles [4]. These reactions are believed to occur as shown in Scheme 1.1, with the coupling initiated by oxidative addition of the aryl halide to a Pd^0 complex. The resulting intermediate **1** is converted to a palladium(aryl)(amido) complex **2** through reaction with the amine substrate in the presence of base. Finally,

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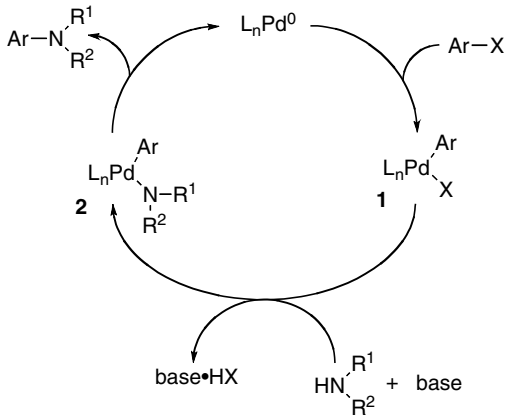
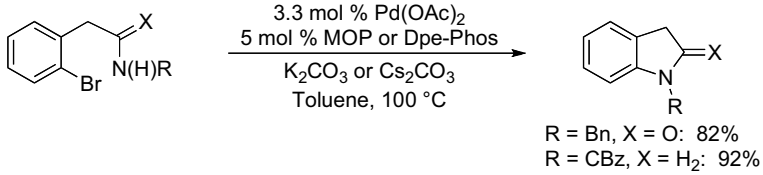


Scheme 1.1

C—N bond-forming reductive elimination affords the desired aniline derivative with concomitant regeneration of the palladium catalyst.

Although these reactions are most commonly used for intermolecular C—N bond formation, intramolecular versions of these reactions have occasionally been employed for the synthesis of saturated nitrogen heterocycles [5]. For example, Buchwald has described the synthesis of oxindoles and indolines through intramolecular reactions of aryl halides bearing pendant amines or amides (Eq. (1.1)) [6]. The conditions are amenable to the generation of indoline derivatives bearing amide, carbamate, or sulfonamide protecting groups. A two-flask sequence involving a four-component Ugi reaction followed by an intramolecular N-arylation that affords 3-amino oxindoles has also been developed (Eq. (1.2)) [7], and a number of other nitrogen heterocycles including ureas [8] and indolo[1,2-*b*]indazoles [9] have been prepared using this method.



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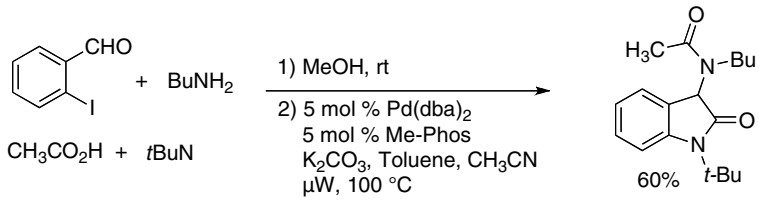
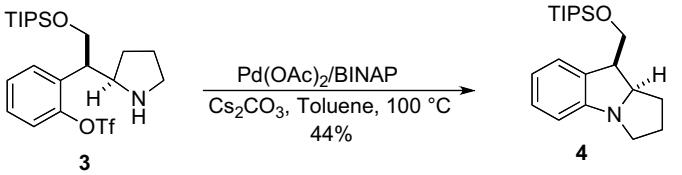


(1.2)

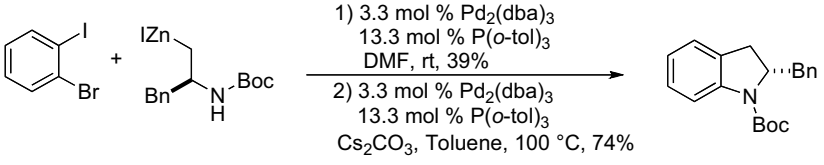
Intramolecular Pd-catalyzed or -mediated N-arylation reactions have been employed in the synthesis of several natural products [5]. For example, pyrroloindoline **4**,

which represents the mitomycin ring skeleton was generated via the intramolecular N-arylation of **3** (Eq. (1.3)) [10]. Other targets generated using this strategy include asperlicin [11], the cryptocarya alkaloids cryptaustoline and cryptowoline [12], and the CPI subunit of CC-1065 [13].



(1.3)

A number of interesting one-pot or two-pot sequences of Pd-catalyzed reactions have been developed that involve intramolecular N-arylation processes [14]. For example, a two flask sequence of Negishi coupling followed by intramolecular C−N bond formation has been employed for the synthesis of substituted indolines (Eq. (1.4)) [14a]. Lautens has recently described an elegant one-flask sequence of intermolecular C−H bond functionalization followed by intramolecular N-arylation for the preparation of substituted indolines [14b]. As shown below (Eq. (1.5)), the Pd-catalyzed coupling of 2-iodotoluene with 2-bromopropylamine **5** in the presence of norbornene provided indoline **6** in 55% yield.



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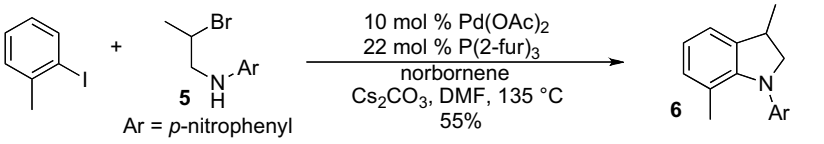

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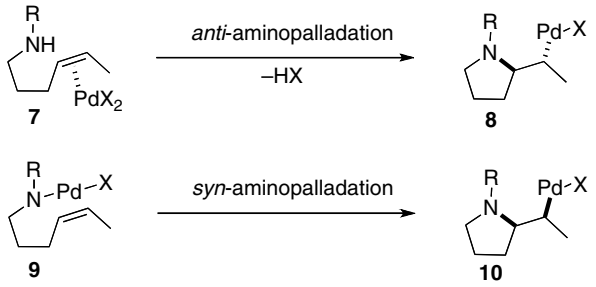
1.3 Synthesis of Saturated Nitrogen Heterocycles via Alkene, Alkyne, or Allene Aminopalladation Reactions

A number of approaches to the synthesis of saturated five-membered nitrogen heterocycles involve alkene, alkyne, or allene aminopalladation as a key step [2b,g].

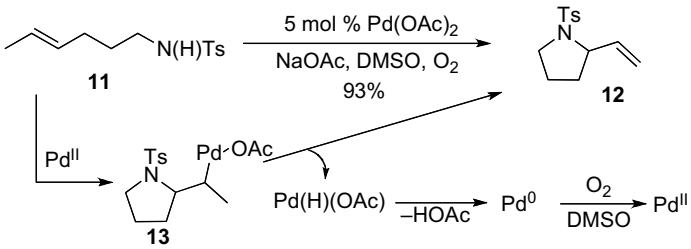


Scheme 1.2

The aminopalladation step can occur by either outer-sphere *anti*-aminopalladation or via inner-sphere *syn*-aminopalladation, and the mechanism can be dependent on substrate structure and reaction conditions. The *anti*-aminopalladation processes generally involve coordination of the unsaturated moiety to Pd^{II}, followed by external attack by a pendant nitrogen nucleophile (e.g., Scheme 1.2, **7** to **8**). In contrast, the *syn*-aminopalladations occur via formation of a palladium amido complex (e.g., **9**), which then undergoes migratory insertion of the alkene into the Pd–N bond to provide **10**. Heterocycle-forming reactions that proceed via aminopalladation of an unsaturated group can be broadly classified into four categories: (i) oxidative amination reactions of alkenes; (ii) hydroamination reactions of alkenes and alkynes; (iii) carboamination reactions of alkenes, alkynes, and allenes; and (iv) haloamination and diamination reactions of alkenes.

1.3.1
Pd^{II}-Catalyzed Oxidative Amination of Alkenes

The first examples of Pd-catalyzed oxidative amination reactions of alkenes were described by Hegedus in 1978 for the construction of indoles [15], and dihydropyrrole derivatives [16]. Although these reactions proceed in good yield with catalytic amounts of palladium, a stoichiometric amount of a co-oxidant, such as benzoquinone (BQ) or $CuCl_2$, was required to facilitate catalyst turnover. In recent years, several groups have explored the extension of this chemistry to the synthesis of saturated nitrogen heterocycles, with a focus on the use of O_2 as a mild, environmentally benign co-oxidant. Early advances in this area were reported independently by Larock and Andersson [17]. For example, treatment of **11** with a catalytic amount of $Pd(OAc)_2$ in the presence of O_2 in DMSO solvent afforded pyrrolidine **12** in 93% yield (Eq. (1.6)). The oxidative amination reactions are believed to proceed via either *syn*- or *anti*-aminopalladation to provide **13**, which then undergoes β-hydride elimination to afford the heterocyclic product. The Pd(H)X intermediate is converted to a Pd^0 complex via loss of HX, and is then subsequently re-oxidized to Pd^{II} by oxygen in the presence of DMSO. This method has also been employed for the generation of indolines and bicyclic pyrrolidines bearing sulfonyl or carbamate protecting groups (Eq. (1.7)) [17, 18].



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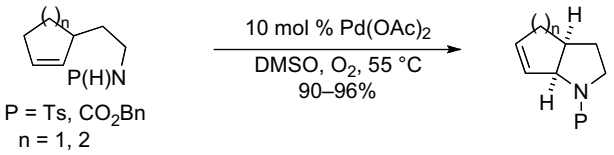
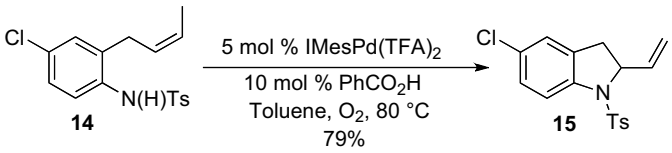


(1.7)

In recent years, there has been a considerable focus on the development of new reaction conditions that use only molecular oxygen as the co-oxidant and do not require DMSO solvent [19]. Considerable progress has been made through the use of palladium catalysts supported by pyridine or N-heterocyclic carbenes as ligands. For example, Stahl has demonstrated that the 2-allylaniline derivative **14** is transformed to indoline **15** in 79% yield upon treatment with 5 mol% $IMesPd(TFA)_2$ and 10 mol% benzoic acid (Eq. (1.8)) [19d]. Stoltz has reported the conversion of amide **16** to lactam **17** under similar reaction conditions (Eq. (1.9)) [19b]. Through elegant mechanistic studies Stahl has shown that the stereochemistry of the aminopalladation step is dependent on reaction conditions, and both *syn*- and *anti*-aminopalladation mechanistic pathways are accessible in oxidative amination reactions [20].



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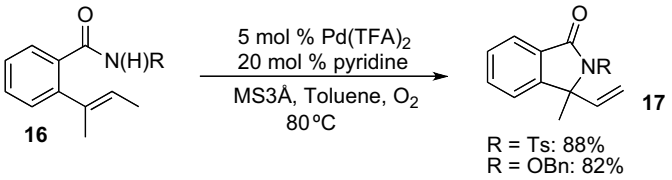
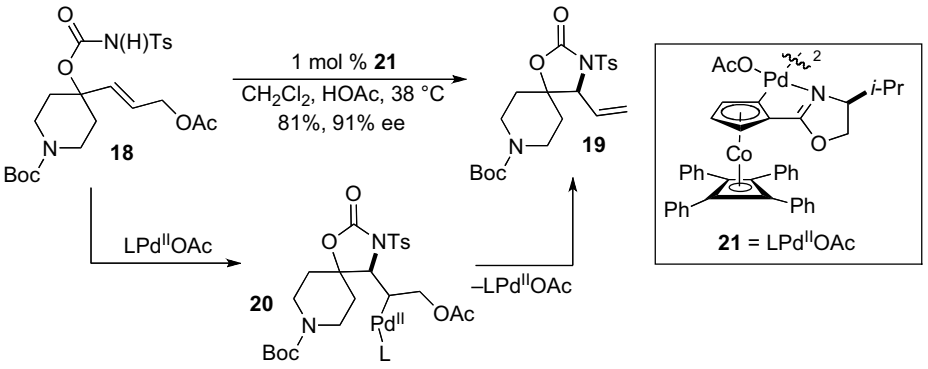


(1.9)

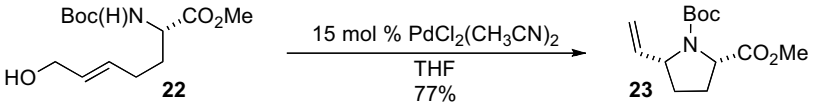
A related approach to the synthesis of nitrogen heterocycles also proceeds via Pd^{II}-catalyzed alkene aminopalladation, but involves substrates bearing allylic acetates or allylic hydroxy groups [21, 22]. In contrast to the oxidative amination reactions described above, these transformations are terminated by β-elimination of the acetate or hydroxy group (rather than β-hydride elimination). This approach alleviates the need for added oxidants, but does require the use of slightly more complex substrates. Nonetheless, this method is quite useful, and has been applied to the synthesis of

several natural products [23]. In addition, a very interesting approach to the asymmetric synthesis of oxazolidinones involves treatment of tosylcarbamate **18** (generated *in situ* from the corresponding alcohol) with a catalytic amount of chiral Pd^{II} catalyst **21** (Eq. (1.10)) [24]. This reaction affords **19** in 81% yield and 91% ee by way of intermediate **20**.



(1.10)

This strategy has also been employed for the synthesis of pyrrolidines [25]. For example, treatment of **22** with 15 mol% $PdCl_2(PhCN)_2$ afforded **23** in 77% yield as a single diastereomer (Eq. (1.11)) [25b]. The mild reaction conditions allow cyclization without epimerization of the amino ester stereocenter.



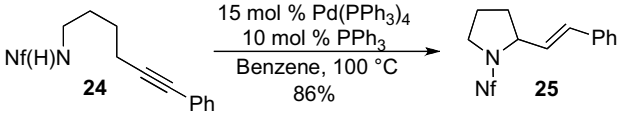
(1.11)

1.3.2
Pd-Catalyzed Hydroamination Reactions of Alkenes and Alkynes

The hydroamination of alkenes and alkynes has been of longstanding interest in organometallic chemistry [26]. Much of the early work in this area focused on early transition metal or lanthanide metal catalyst systems. However, much recent progress has been made in late-metal catalyzed hydroamination chemistry, and several interesting hydroamination reactions that afford nitrogen heterocycles have been developed using palladium catalysts.

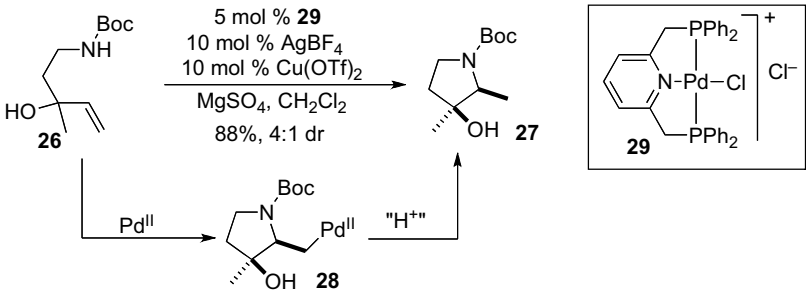
Palladium-catalyzed intramolecular hydroamination reactions of alkynes that afford pyrrolidine derivatives were initially reported by Yamamoto in 1998 [27] and have been the subject of detailed investigation over the past ten years [28]. In a

representative example, alkyne **24** was converted to **25** in 86% yield upon treatment with $Pd(PPh_3)_4$ as catalyst (Eq. (1.12)) [28c]. This transformation has been employed in the synthesis of the natural product indolizidine 209D [29], and asymmetric variants have also been developed that afford pyrrolidine products with up to 95% ee [30]. A related hydroamidation that affords lactam products has also been described [31], and hydroamination reactions of amines bearing tethered allenes are also known [32].



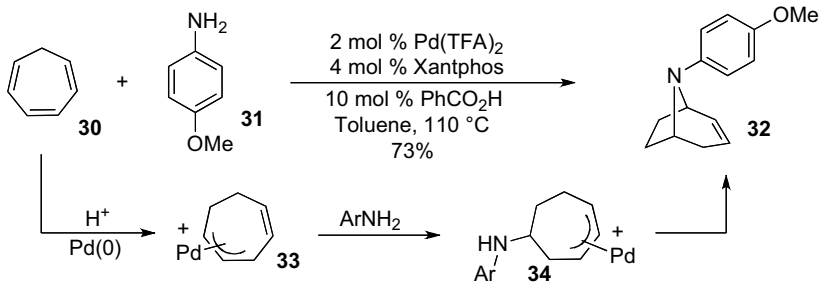
(1.12)

Although Pd-catalyzed intramolecular hydroamination reactions of alkynes have been known for ten years, analogous transformations of unactivated alkenes have only recently been developed [33]. Key to the success of these studies was the use of a cationic palladium complex bearing a pyridine-derived P–N–P pincer ligand (**29**). For example, treatment of **26** with catalytic amounts of **29**, $AgBF_4$, and $Cu(OTf)_2$ led to the formation of pyrrolidine **27** in 88% yield with 4: 1 dr (Eq. (1.13)). Detailed mechanistic studies have indicated these transformations proceed via alkene coordination to the metal complex followed by outer-sphere aminopalladation to provide **28**. Protonolysis of the metal–carbon bond with acid generated *in situ* leads to formation of the product with regeneration of the active catalyst.



(1.13)

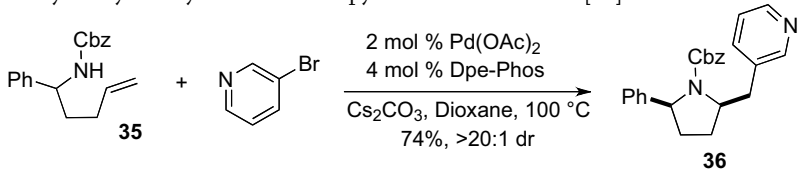
An interesting tandem intermolecular/intramolecular hydroamination reaction of cycloheptatriene with substituted anilines has been developed by Hartwig for the synthesis of tropene derivatives [34]. As shown in Eq. (1.14), the coupling of **30** with **31** provided **32** in 73% yield. The mechanism of this transformation is believed to involve acid-assisted formation of an η^3-pentadienylpalladium complex **33**, which is then captured by the aniline nucleophile to afford the allylpalladium intermediate **34**. Intramolecular attack of the aniline nitrogen on the allylpalladium moiety affords the observed heterocycle.



(1.14)

1.3.3
Pd^0-Catalyzed Carboamination Reactions of Alkenes

Over the past several years our group has been involved in the development of new Pd^0-catalyzed carboamination reactions between aryl or alkenyl halides and alkenes bearing a pendant nitrogen functionality [35, 36]. In a representative example, treatment of Cbz-protected amine **35** with 3-bromopyridine and a catalytic amount of $Pd(OAc)_2$/Dpe-Phos in the presence of Cs_2CO_3 afforded pyrrolidine **36** in 74% yield with >20 : 1 dr (Eq. (1.15)) [36e]. This method has been applied to a stereocontrolled synthesis of (+)-preussin [37], and is also effective with substrates bearing disubstituted alkenes (Eq. (1.16)) [36f]. The reactions appear to proceed via an unusual mechanism involving intramolecular *syn*-aminopalladation of a palladium(aryl)(amido) complex (e.g., **37**) followed by C–C bond-forming reductive elimination of the resulting intermediate **38**. Intramolecular variants of this transformation in which the aryl halide is appended to the alkene have also been described [38], and a one-flask tandem Pd-catalyzed N-arylation/carboamination reaction sequence has been developed for the conversion of primary amine substrates to *N*-aryl-2-arylmethyl indoline and pyrrolidine derivatives [39].



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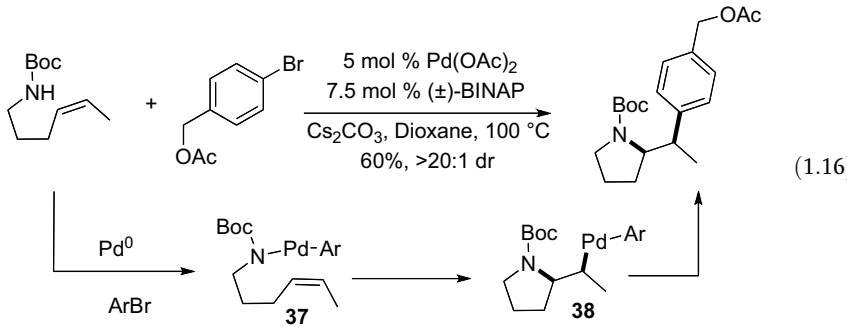
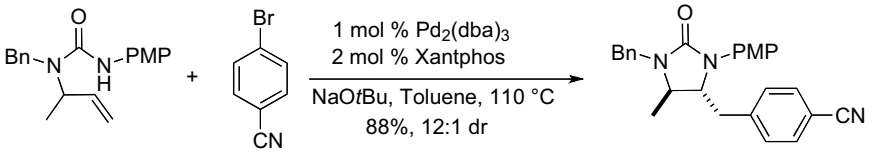


(1.16)

In addition to providing stereoselective access to substituted pyrrolidines, this method has been employed for the construction of a number of different nitrogen heterocycles including imidazolidin-2-ones (Eq. (1.17)) [40], and isoxazolidines [41]. A highly stereoselective synthesis of *cis*- and *trans*-3,5-disubstituted pyrazolidines has been developed in which the presence or absence of an N-1 protecting group controls product stereochemistry [42]. For example, treatment of **39** with 4-bromobiphenyl and a palladium catalyst in the presence of NaO*t*Bu affords the trans-disubstituted product **41** (Eq. (1.18)), whereas subjection of **40** to similar reaction conditions affords the cis-disubstituted product **42** (Eq. (1.19)).



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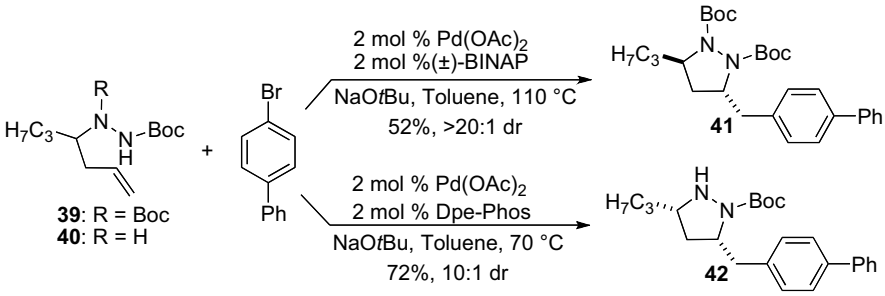
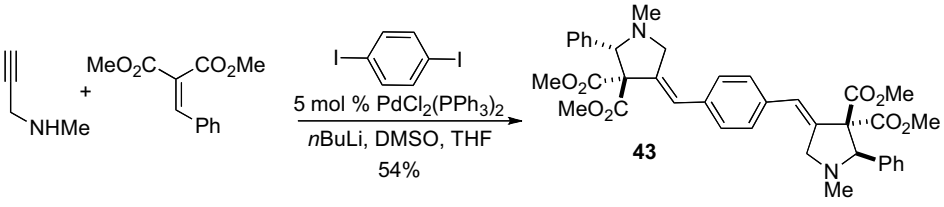


(1.18, 1.19)

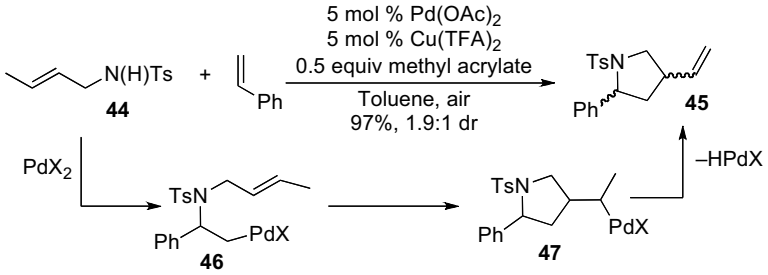
Balme has reported a one-pot three-component alkene carboamination between propargylic amines, alkylidene malonates, and aryl halides [43]. For example, treatment of *N*-methyl propargylamine (2 equiv), dimethyl benzylidene malonate (2 equiv) and 1,4-diiodobenzene (1 equiv) with *n*-BuLi and a palladium catalyst provided **43** as a single diastereomer (Eq. (1.20)) [43a]. The formation of the C−N bond in this process does not appear to be metal catalyzed. Instead, initial conjugate addition of the nitrogen nucleophile to the activated alkene affords a malonate anion, which undergoes carbopalladation followed by reductive elimination to afford the pyrrolidine product.



(1.20)

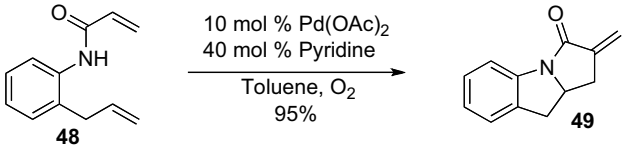
1.3.4
Pd^{II}-Catalyzed Carboamination Reactions of Alkenes

Two recent reports have described Pd^{II}-catalyzed carboamination reactions involving two alkenes that afford pyrrolidine products. Building on early work by Oshima that employed stoichiometric amounts of palladium [44], Stahl has developed an intermolecular Pd-catalyzed coupling of *N*-allylsulfonamide derivatives with enol ethers or styrene derivatives that affords substituted pyrrolidines in high yields with moderate diastereoselectivity [45]. For example, treatment of **44** with styrene in the presence of Pd^{II} and Cu^{II} co-catalysts, with methyl acrylate added for catalyst stability, provided **45** in 97% yield with 1.9: 1 dr (Eq. (1.21)). This reaction proceeds through intermolecular aminopalladation of styrene to afford **46**. Intramolecular carbopalladation then provides intermediate **47**, and subsequent β-hydride elimination yields product **45**.



(1.21)

Yang has reported a related tandem cyclization for the synthesis of pyrroloindoline derivatives that also proceeds though a mechanism involving alkene aminopalladation followed by carbopalladation of a second alkene [46]. As shown below, the 2-allylaniline derivative **48** was converted to **49** in 95% yield through treatment with a catalyst composed of $Pd(OAc)_2$ and pyridine (Eq. (1.22)). Use of (−)-sparteine as a ligand in this reaction provided **49** with up to 91% ee.

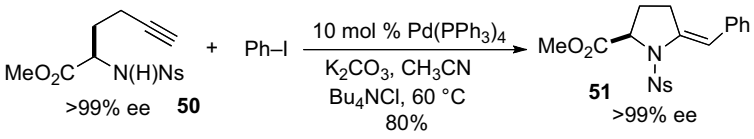


(1.22)

1.3.5
Pd-Catalyzed Carboamination Reactions of Alkynes, Allenes, and Dienes

A few examples of Pd^0-catalyzed carboamination reactions between alkyne-tethered amines and aryl halides have also been reported [28d, 47]. For example, treatment of amino ester derivative **50** with PhI in the presence of K_2CO_3 using $Pd(PPh_3)_4$ as catalyst led to the formation of **51** in 80% yield with complete retention of enantiomeric purity (Eq. (1.23)) [28d]. In contrast to the Pd^0-catalyzed carboamination

reactions of alkenes with aryl halides described above, the reactions of alkynes usually proceed via *anti*-aminopalladation, although products resulting from *syn*-aminopalladation have been obtained in some cases [48]. In addition to carboamination reactions that employ aryl halides as coupling partners, several transformations involving other electrophiles, such as acrylate derivatives, have been described (Eq. (1.24)) [49].



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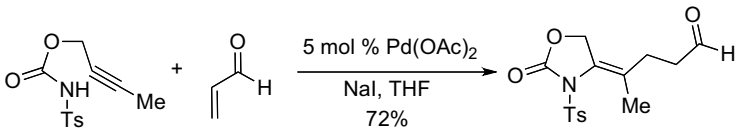
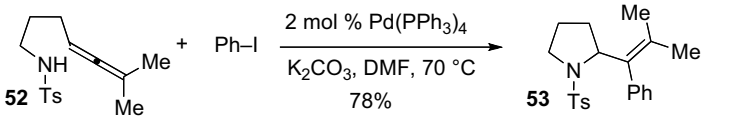


(1.24)

Several examples of Pd^0-catalyzed carboamination reactions between allenes and aryl or alkenyl halides have been reported [50]. For example, treatment of allene **52** with iodobenzene in the presence of K_2CO_3 and 2 mol% $Pd(PPh_3)_4$ afforded pyrrolidine **53** in 78% yield (Eq. (1.25)) [50a]. Mechanisms involving alkene aminopalladation (similar to the reactions of alkynes and alkenes noted above) have occasionally been invoked to explain these reactions. However, in many instances these transformations may involve intermediate π-allylpalladium complexes. Due to this mechanistic ambiguity, these transformations have been included in this section for comparison with the related reactions of alkenes and alkynes. Similar reactions involving allylic halides have also been described (Eq. (1.26)) [51].



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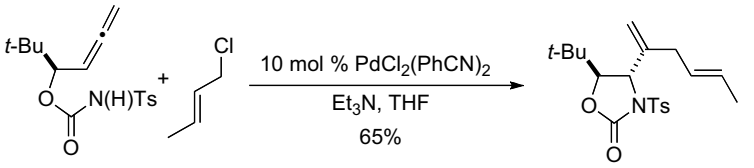
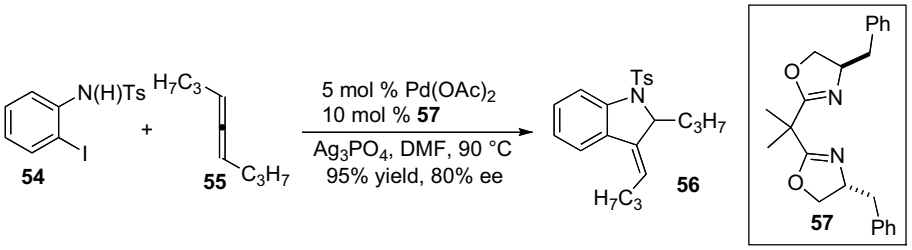


(1.26)

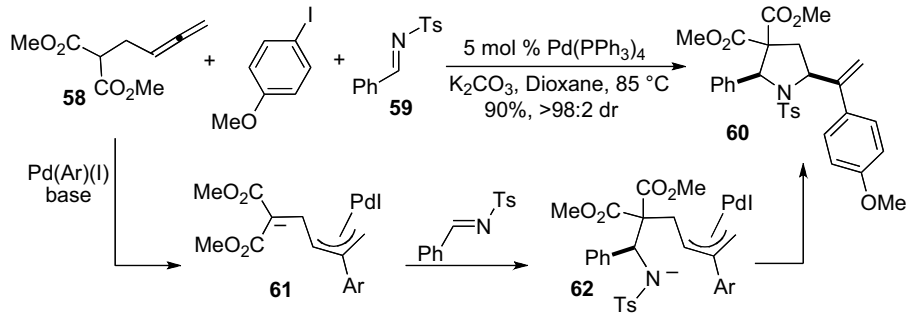
Cross-coupling carboamination reactions between allenes and 2-haloaniline derivatives or halogenated allylic amines have also been employed for the generation of substituted indolines, and use of an appropriate chiral catalyst for these transformations leads to formation of enantioenriched products [52]. For example, Larock has described the synthesis of indoline **56** via the Pd-catalyzed reaction of aryl iodide **54**

with allene **55** (Eq. (1.27)) [52a]. The best asymmetric induction was obtained using chiral bisoxazoline ligand **57**. These reactions appear to proceed via intermediate π-allylpalladium complexes [53].



(1.27)

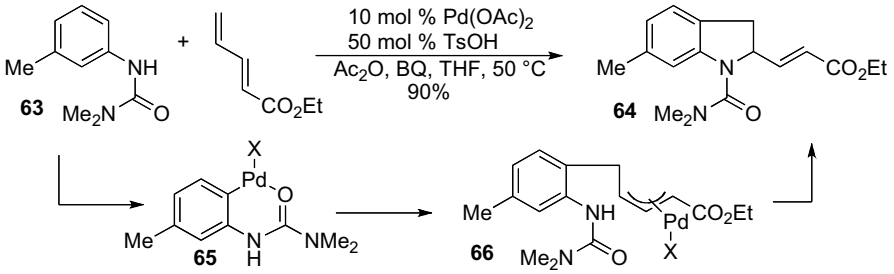
Ma has developed a three-component allene carboamination reaction for the stereoselective synthesis of 2,5-*cis*-disubstituted pyrrolidine derivatives [54]. A representative transformation involving allene **58**, 4-iodoanisole, and imine **59** that generates **60** in 90% yield is shown below (Eq. (1.28)). The reaction is believed to proceed through the intermediate π-allylpalladium complex **62**, which is formed by carbopalladation of the alkene to give **61** followed by addition of the malonate anion to the activated imine. Intramolecular capture of the allylpalladium moiety by the pendant nitrogen nucleophile affords the pyrrolidine product. A related asymmetric synthesis of pyrazolidines that employs azodicarboxylates as one of the electrophilic components has also been reported [55]. The pyrazolidine products are obtained with up to 84% ee when chiral bis oxazolines are employed as ligands.



(1.28)

An interesting Pd-catalyzed diene carboamination reaction that involves urea-directed C−H activation was recently reported [56]. For example, treatment of *N*-aryl urea **63** with an activated diene in the presence of 10 mol% $Pd(OAc)_2$, 50 mol% TsOH, Ac_2O, and benzoquinone provided **64** in 90% yield (Eq. (1.29)). The transformation is initiated by directed palladation of the arene by a palladium tosylate complex (formed

in situ) to yield **65**. Carbopalladation of the diene generates allylpalladium complex **66**, which is then trapped by the urea to afford the observed product.

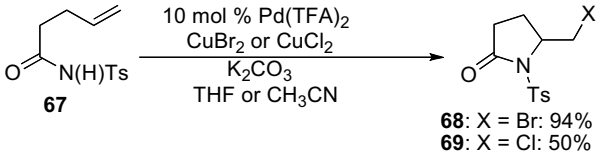


(1.29)

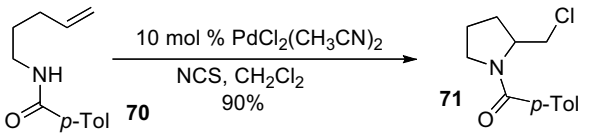
1.3.6
Vicinal Difunctionalization of Alkenes and Allenes

Reactions that effect addition of two heteroatoms across an alkene are very powerful methods for the generation of heterocycles, and have significant potential synthetic utility. Several important advances in this area that involve the use of palladium catalysts have recently been reported [57]. Interestingly, many of these may involve high oxidation state Pd^{IV} complexes as intermediates.

Palladium-catalyzed intramolecular aminobromination and aminochlorination reactions of alkenes have been employed for the conversion of unsaturated amides, carbamates, and sulfonamides to indolines and pyrrolidines [58]. As shown below (Eq. (1.30)), treatment of **67** with 10 mol% $Pd(TFA)_2$ in the presence of excess $CuBr_2$ or $CuCl_2$ affords **68** and **69** in moderate to good yields [58a]. In some cases superior results are obtained using $PdCl_2(CH_3CN)_2$ as the catalyst and NCS as the stoichiometric oxidant, as demonstrated in the conversion of **70** to **71** in 90% yield (Eq. (1.31)) [58b]. The alkene aminohalogenation reactions are believed to proceed via initial aminopalladation of the substrate followed by oxidative halogenation of the resulting alkylpalladium complex.



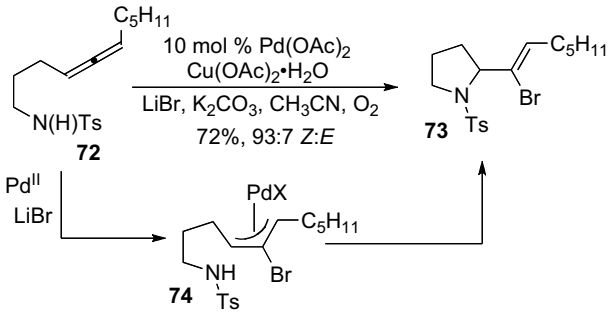
(1.30)



(1.31)

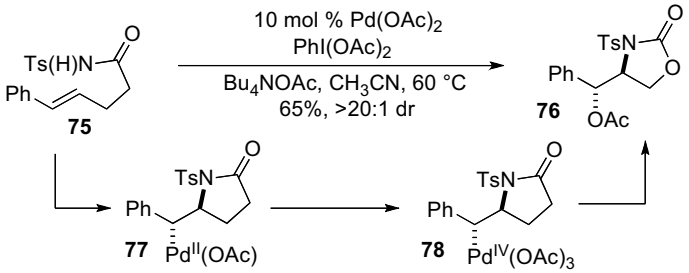
Related aminohalogenation reactions of allenes, such as the conversion of **72** to **73**, can be effected under similar reaction conditions (Eq. (1.32)) [59]. However, these

latter transformations appear to proceed via a different mechanism involving allene bromopalladation followed by nucleophilic trapping of the resulting π-allylpalladium intermediate (e.g., **74**).



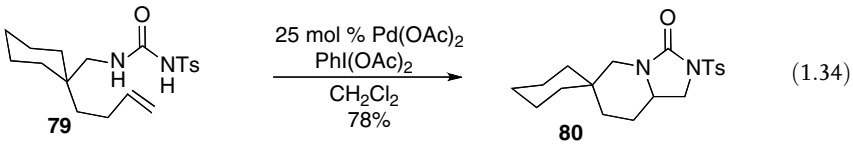
(1.32)

A very interesting Pd^{II}-catalyzed aminoacetoxylation reaction of alkenes was recently developed jointly by the Sorensen and Lee groups [60]. In a representative example, treatment of **75** with $Pd(OAc)_2$ and $PhI(OAc)_2$ provides oxazolidinone **76** in 65% yield with >20: 1 dr (Eq. (1.33)). This transformation is believed to proceed via a Pd^{II}/Pd^{IV} catalytic cycle that is initiated by *anti*-aminopalladation of the alkene to afford **77**. The intermediate Pd^{II} complex is then oxidized by $PhI(OAc)_2$ to alkyl Pd^{IV} intermediate **78**, which undergoes C−O bond-forming reductive elimination to afford **76**.

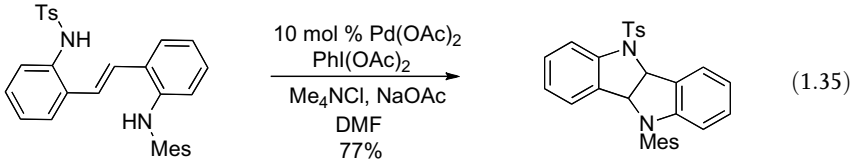


(1.33)

Three different approaches to the synthesis of five-membered cyclic ureas have recently been described that involve Pd-catalyzed alkene diamination reactions. In a series of very interesting papers, Muniz has described the conversion of alkenes bearing pendant ureas to imidizolidin-2-one derivatives using catalytic amounts of $Pd(OAc)_2$ in the presence of an oxidant such as $PhI(OAc)_2$ or $CuBr_2$ [61, 62]. For example, these conditions were used to effect the cyclization of **79** to **80** in 78% yield (Eq. (1.34)) [62a]. These reactions proceed via a mechanism similar to that shown above in Eq. (1.33), except that the heteropalladation may occur in a *syn*- rather than *anti*- fashion, and the reductive elimination occurs with intramolecular formation of a C−N bond rather than intermolecular formation of a C−O bond. The alkene diamination reactions have also been employed for the synthesis of bisindolines (Eq. (1.35)) [63] and bicyclic guanidines (Eq. (1.36)) [64].



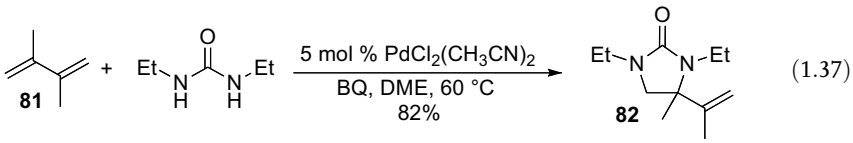
(1.34)



(1.35)

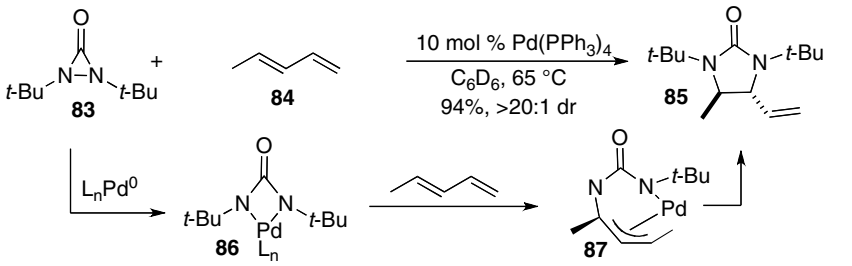
(1.36)

The intermolecular diamination of 1,3-dienes with acyclic ureas to provide monocyclic or bicyclic urea derivatives has been achieved by Lloyd-Jones and Booker-Milburn through use of a palladium catalyst combined with either benzoquinone or O_2 as an oxidant [65]. For example, diene **81** was converted to urea **82** in 82% yield (Eq. (1.37)). These transformations are mechanistically distinct from the reactions described above, and appear to involve intermediate π-allylpalladium complexes.



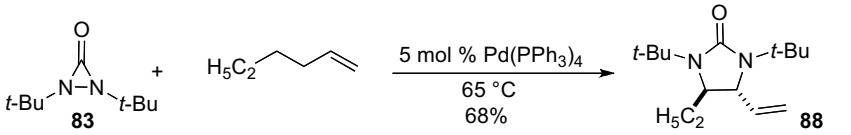
(1.37)

A much different strategy was developed by Shi for the conversion of 1,3-dienes or trienes to cyclic ureas [66]. As shown below, treatment of conjugated diene **84** with di-*t*-butyldiaziridinone **83** and in the presence of $Pd(PPh_3)_4$ as catalyst led to the formation of **85** in 94% yield with >20: 1 dr (Eq. (1.38)). This reaction is believed to occur via oxidative addition of **83** to Pd^0 to generate **86**, which undergoes aminopalladation to afford allylpalladium complex **87**. Reductive elimination from **87** affords the urea product. An asymmetric variant of this transformation that provides products with up to 95% ee has also been reported [67].



(1.38)

The scope of this chemistry has recently been extended to terminal alkene substrates [68]. For example, 1-hexene was transformed to **88** in 68% yield under solvent-free conditions using $Pd(PPh_3)_4$ as catalyst (Eq. (1.39)). Asymmetric induction has also been achieved in these reactions, and ees of up to 94% have been obtained with a catalyst supported by a chiral phosphoramidite ligand [68c]. The mechanism of the terminal alkene diamination reactions has not yet been fully elucidated, but it appears likely that allylic C−H activation/amination is involved.



(1.39)

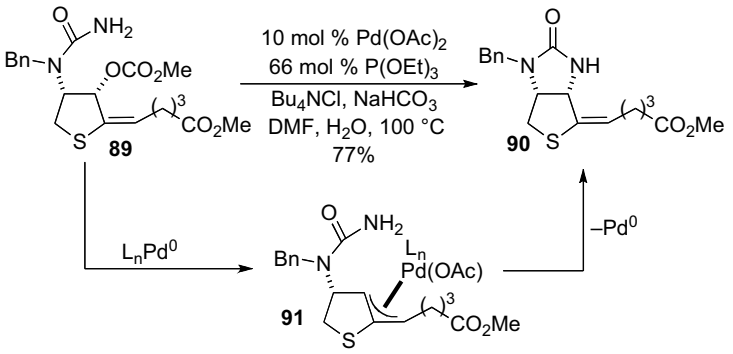
1.4 Synthesis of Nitrogen Heterocycles via Intermediate π-Allylpalladium Complexes

The intramolecular addition of nitrogen nucleophiles to intermediate π-allylpalladium complexes is a valuable method for the synthesis of saturated nitrogen heterocycles [69]. A number of different strategies have been employed for the generation of the reactive intermediate π-allylpalladium complexes, such as oxidative addition of alkenyl epoxides, allylic acetates, allylic carbonates, and related electrophiles to Pd^0. These intermediates have also been accessed through carbopalladation or heteropalladation reactions of allenes (as described above), vinyl cyclopropanes, or 1,3-dienes, and recent approaches involving allylic C−H activation have also been developed.

1.4.1 Reactions Involving Oxidative Addition of Allylic Electrophiles

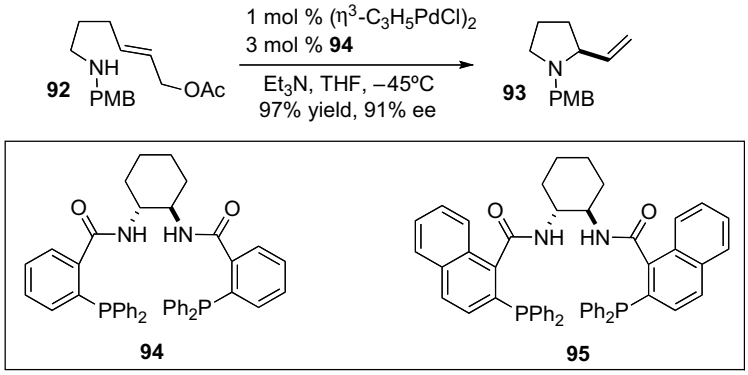
One of the most common methods employed for the generation of allylpalladium complexes involves oxidative addition of allylic electrophiles to Pd^0. This transformation has been explored by several groups, and has been the topic of recent reviews [69]. A representative example of this process was demonstrated in a recent total synthesis of (+)-Biotin [70]. The key step in the synthesis was an intramolecular amination of **89**, which provided bicyclic urea derivative **90** in 77% yield (Eq. (1.40)). In contrast to the Pd^{II}-catalyzed reactions of allylic acetates bearing pendant amines described above (Eq. (1.10)), which proceed via alkene aminopalladation, Pd^0-catalyzed reactions of these substrates occur via initial oxidative addition of the allylic acetate to provide an intermediate π-allylpalladium complex (e.g., **91**). This intermediate is then captured by the pendant nucleophile (e.g., **91** to **90**) in a formal reductive elimination process to generate the product and regenerate the Pd^0 catalyst. Both the oxidative addition and the reductive elimination steps occur with inversion

of configuration when soft nucleophiles are employed, which results in overall retention of configuration at the carbonate-bearing carbon stereocenter. Related transformations of propargylic electrophiles have also been reported [71].



(1.40)

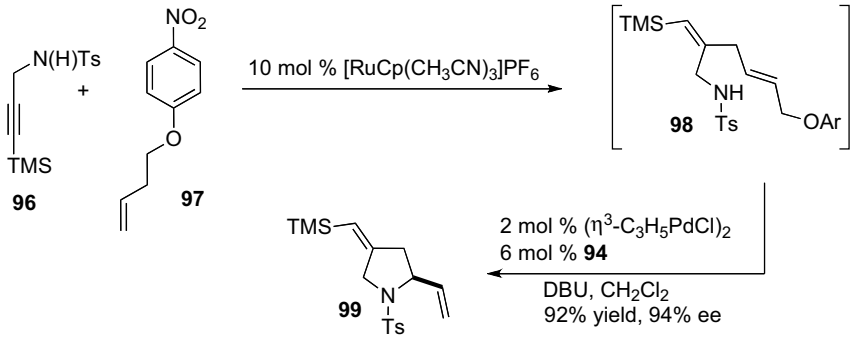
A number of studies have focused on the development and application of asymmetric versions of Pd-catalyzed allylic alkylation reactions [72]. Trost has developed a class of ligands, including **94** and **95**, that provide excellent yields and enantioselectivities for many of these reactions. For example, treatment of allylic acetate **92** with 1 mol% of allylpalladium chloride and 3 mol% of ligand **94** led to the formation of **93** in 97% yield and 91% ee (Eq. (1.41)) [73]. Asymmetric desymmetrization reactions of *meso*-bis-carbamates that provide heterocyclic products have also been described [74].



(1.41)

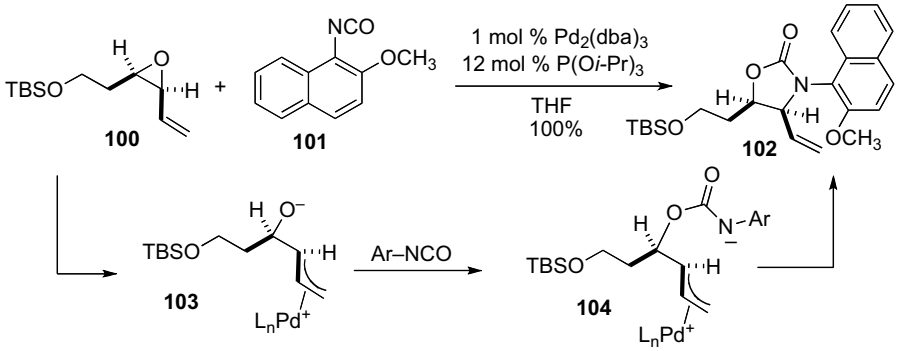
Recently, Trost has employed this methodology in a tandem one-pot ene–yne coupling/enantioselective allylation process [75]. This transformation was used for the construction of pyrrolidine **99**, an intermediate in a formal synthesis of kainic acid [75b]. As shown below (Eq. (1.42)), ruthenium-catalyzed coupling of **96** with **97** provided intermediate allyl ether **98**. Addition of 2 mol% of allylpalladium chloride

and 6 mol% of chiral ligand **94** to the reaction vessel led to the formation of **99** in 92% yield and 94% ee.



(1.42)

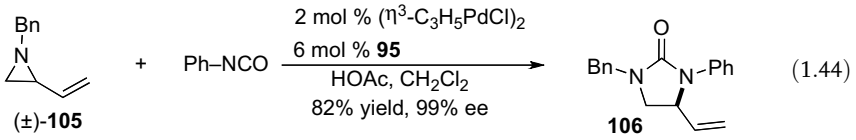
Alkenyl epoxides and aziridines have also been widely utilized as electrophiles in reactions that proceed via intermediate π-allylpalladium complexes [69], including reactions that form five-membered nitrogen heterocycles [76]. In a representative transformation, alkenyl epoxide **100** was coupled with isocyanate **101** in the presence of a catalyst generated *in situ* from $Pd_2(dba)_3$ and $P(O\textit{i}\text{-}Pr)_3$ to afford oxazolidin-2-one **102** in quantitative yield (Eq. (1.43)) [76b]. The reaction is initiated by oxidative addition of **100** to Pd^0 to afford **103**, which reacts with the isocyanate to yield **104**. The product is then generated by trapping the allylpalladium complex with the pendant carbamate anion. Related transformations involving the use of imines in place of isocyanates allow the construction of 1,3-oxazolidines [77], and syntheses of substituted pyrrolidines from 2-vinyloxiranes bearing tethered nitrogen nucleophiles have also been reported [78].



(1.43)

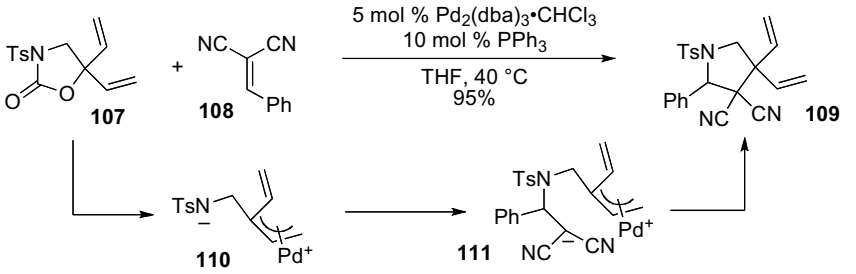
Related reactions of vinylaziridines [79] or activated vinylcyclopropanes [80] with isocyanates and other heterocumulenes have been developed for the construction of cyclic ureas and similar heterocycles. For example, Trost has recently described a dynamic kinetic asymmetric reaction of aziridine **105** with phenylisocyanate that

affords urea **106** in 82% yield with 99% ee (Eq. (1.44)) [81]. The interconversion of stereoisomers occurs via η^3–η^1–η^3 isomerization processes after oxidative addition of the aziridine to Pd^0.



(1.44)

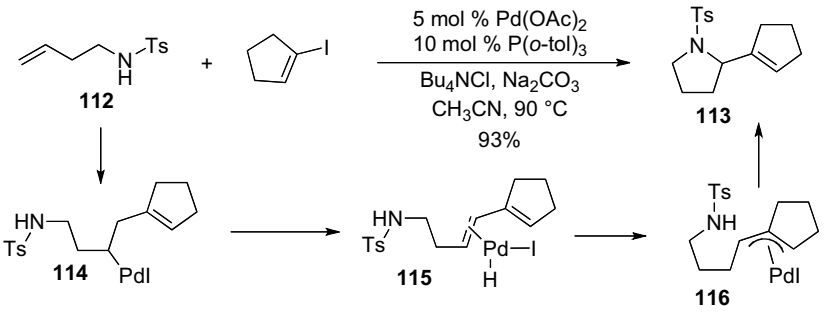
A related strategy has been used for the conversion of 5,5-divinyl oxazolidinones to highly substituted pyrrolidines [82]. For example, treatment of **107** with a Pd^0 catalyst in the presence of activated alkene **108** provides **109** in 95% yield (Eq. (1.45)). The reaction proceeds via oxidative addition followed by decarboxylation to afford the allylpalladium complex **110**. Intermolecular conjugate addition to give **111**, followed by intramolecular trapping of the allylpalladium moiety, affords the observed products.



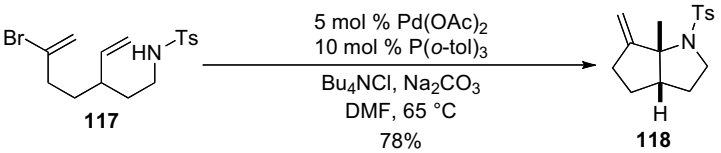
(1.45)

1.4.2
Reactions Involving π-Allylpalladium Intermediates Generated via Alkene Carbopalladation

A number of approaches to the generation of intermediate allylpalladium complexes in heterocycle synthesis involve initial Heck-type carbopalladation of an alkene with an alkenyl halide, followed by rearrangement of the resulting alkylpalladium species via reversible β-hydride elimination processes [83, 84]. For example, treatment of alkenyl sulfonamide **112** with 1-iodocyclopentene in the presence of catalytic amounts of $Pd(OAc)_2$ and $P(o\text{-tol})_3$ provided pyrrolidine **113** in 93% yield (Eq. (1.46)) [84a]. The C−N bond forming step occurs from the π-allylpalladium complex **116**, which results from β-hydride elimination of **114** followed by hydridopalladation of **115**. This strategy has also been employed for the synthesis of lactams from ω-olefinic amides [83b]. In addition, intramolecular versions of the pyrrolidine-forming reactions have been developed, such as the conversion of **117** to **118** (Eq. (1.47)) [84b,c].

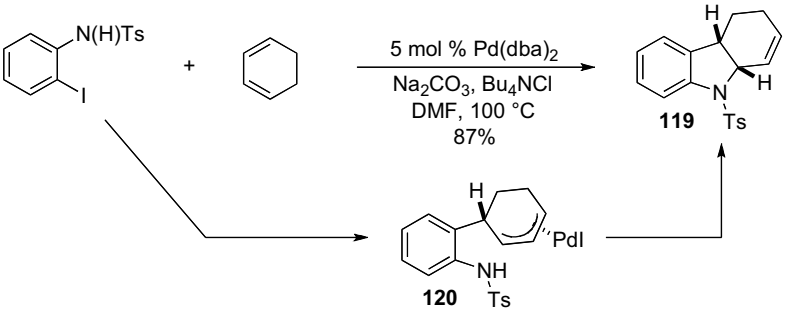


(1.46)



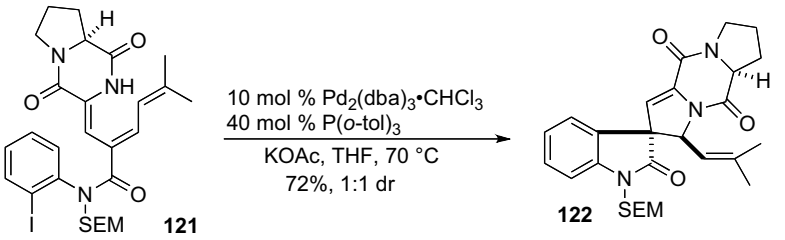
(1.47)

Another approach to the construction of five-membered nitrogen heterocycles by way of intermediate π-allylpalladium complexes involves carbopalladation reactions of 1,3- or 1,4-dienes [85]. For example, Larock has described the coupling of *N*-tosyl-2-iodoaniline with 1,3-cyclohexadiene, which affords **119** in 87% yield (Eq. (1.48)). The allylpalladium complex **120** is a key intermediate in this transformation. Asymmetric versions of these reactions that generate pyrrolidine products have also been described [86]. Related Heck reactions that employ vinylcyclopropanes as diene surrogates have also been reported, although lengthy reaction times (3–4 days) are often required for transformations of these substrates [87].



(1.48)

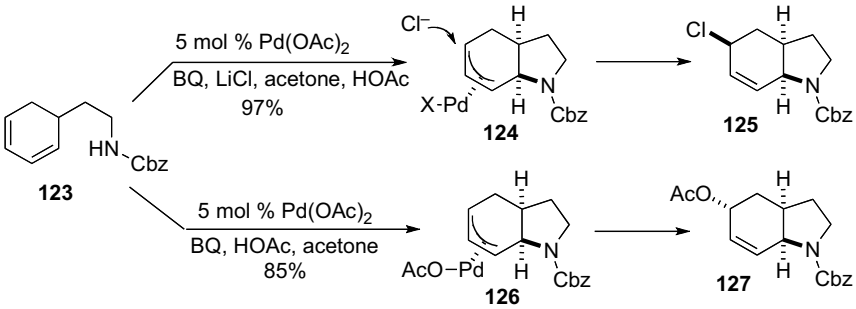
The use of Heck reactions of dienes for the construction of nitrogen heterocycles has been applied to an elegant synthesis of (−)-spirotryprostatin B [88]. As shown below (Eq. (1.49)), the intramolecular Heck reaction of **121** afforded the complex pentacycle **122**, which was converted to the natural product after cleavage of the SEM protecting group.



(1.49)

1.4.3
Reactions Involving Aminopalladation of 1,3-Dienes

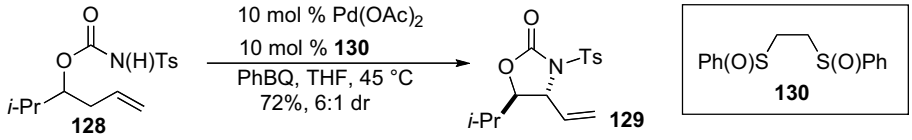
Bäckvall and coworkers have developed a stereoselective palladium catalyzed 1,4-addition to cyclic 1,3-dienes that produces pyrrolidine [89a] or lactam products [89b]. For example, treatment of **123** with catalytic $Pd(OAc)_2$ and excess LiCl affords **125** (Eq. (1.50)). Alternatively, treatment of **123** with catalytic $Pd(OAc)_2$ and excess LiOAc affords **127** (Eq. (1.51)). Both reactions proceed via *anti*-aminopalladation to afford an allylpalladium complex (**124** or **126**), which is then captured by an external nucleophile. Outer-sphere attack of chloride ion on **124** results in net *syn*-addition to the diene to give **125**, whereas inner-sphere attack of acetate results in *anti*-addition to provide **127**.



(1.50, 1.51)

1.4.4
Generation of Allylpalladium Intermediates through C–H Activation

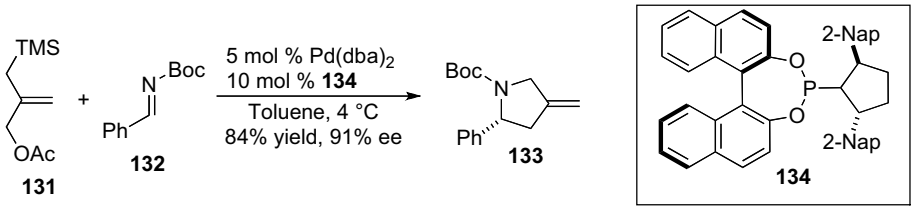
A recent example of isoxazolidine synthesis that involves generation of an allylpalladium complex via allylic C−H activation was reported by the White group [90]. As shown below (Eq. (1.52)), treatment of homoallylic carbamate **128** with $Pd(OAc)_2$ in the presence of sulfoxide ligand **130** and phenylbenzoquinone (PhBQ) provided **129** in 72% yield with 6: 1 dr. A related transformation that affords indoline products has been described by Larock [17a].



(1.52)

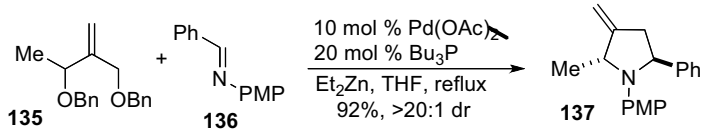
1.5 Synthesis of Nitrogen Heterocycles via Pd-Catalyzed 1,3-Dipolar Cycloaddition Reactions

Although the use of 1,3-dipolar cycloaddition reactions that form carbon–heteroatom bonds is fairly common using traditional synthetic methods [2], palladium-catalyzed dipolar cycloaddition reactions of this type are rather rare. However, a few reports have described an interesting and synthetically useful approach to the synthesis of pyrrolidines via Pd-catalyzed [3 + 2] cycloaddition reactions of trimethylenemethane with imines [91]. In very recent studies, Trost has developed an asymmetric variant of these reactions that provides access to enantioenriched pyrrolidine derivatives [92]. For example, treatment of trimethylenemethane precursor **131** with imine **132** proceeds to afford **133** in 84% yield and 91% ee when a catalyst composed of Pd $(dba)_2$ and ligand **134** is used (Eq. (1.53)).



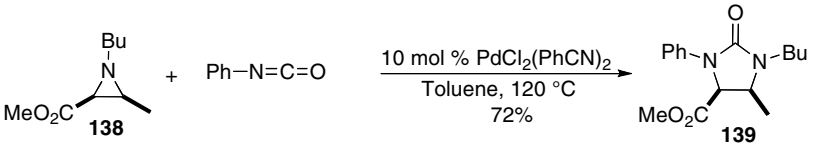
(1.53)

Although many Pd-catalyzed [3 + 2] cycloaddition reactions employ **131** as a trimethylenemethane precursor, readily available 2-methylenepropane-1,3-diols and their corresponding benzyl ethers have also been used as sources of trimethylenemethane [93]. This approach allows construction of more highly substituted pyrrolidine derivatives than can be generated from **131**. For example, treatment of **135** with **136** in the presence of diethylzinc and a palladium catalyst afforded pyrrolidine **137** in 92% yield as a single diastereomer (Eq. (1.54)).



(1.54)

An unusual class of Pd-catalyzed [3 + 2] cycloaddition reactions between activated aziridines and heterocumulenes such as isocyanates and carbodiimides has been extensively examined by Alper and coworkers [94]. These transformations led to the preparation of ureas, carbamates, and other heterocycles in good yields. For example, treatment of **138** with phenylisocyanate afforded urea **139** in 72% yield (Eq. (1.55)) [94a]. The mechanism of these reactions presumably involves oxidative addition of the aziridine to Pd^0, followed by insertion of the isocyanate into the Pd−N bond and C−C bond-forming reductive elimination (similar to the reactions of vinylaziridines described in the section above, although allylpalladium intermediates are obviously not involved).



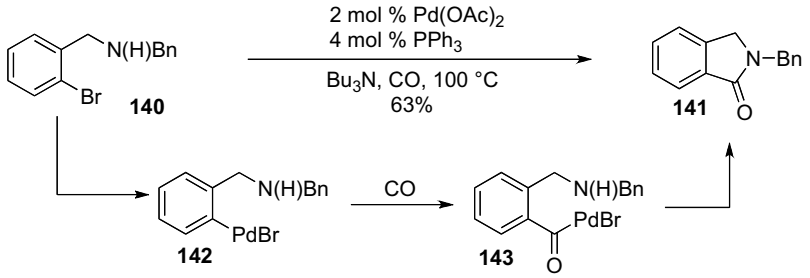
(1.55)

1.6
Synthesis of Nitrogen Heterocycles via Carbonylative Processes

Many of the concepts and strategies outlined above have been employed in carbonylative processes, which provide more highly functionalized heterocyclic products through incorporation of one or more units of CO [95]. Palladium-catalyzed carbonylative transformations that afford saturated five-membered nitrogen heterocycles can be broadly divided into three major categories: (i) processes involving CO insertion into a Pd–C_{Ar} or Pd−$C_{Alkenyl}$ bond, followed by intramolecular capture by a pendant nucleophile; (ii) transformations involving CO insertion into a Pd–heteroatom bond; and (3) Wacker-type processes wherein *anti*-heteropalladation of a carbon–carbon multiple bond precedes CO insertion.

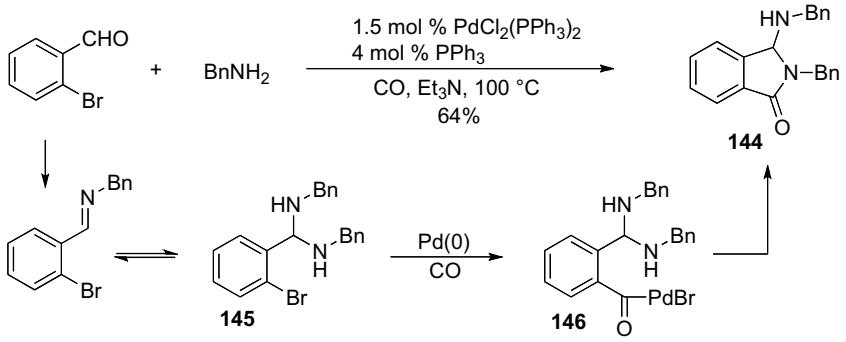
1.6.1
Transformations Involving CO Insertion into Aryl or Alkenyl Pd-Carbon Bonds

Palladium-catalyzed carbonylative reactions of aryl or alkenyl bromides bearing pendant nitrogen nucleophiles have been studied for over 30 years, and have proven useful for the construction of a variety of different heterocyclic compounds [96]. For example, treatment of **140** with catalytic amounts of $Pd(OAc)_2$ and PPh_3 in the presence of Bu_3N under an atmosphere of CO afforded lactam **141** in 65% yield (Eq. (1.56)) [96a]. This transformation presumably occurs via oxidative addition of the aryl bromide to Pd^0 to provide **142**, which undergoes insertion of CO into the Pd−C bond to yield **143**. Intramolecular capture of the acylpalladium intermediate **143** by the tethered amine gives the desired heterocyclic product.



(1.56)

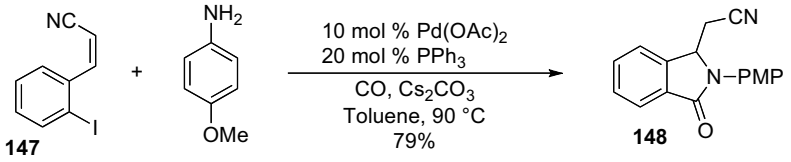
The insertion of CO into Pd–carbon bonds has also been employed in several tandem/cascade reactions that afford five-membered nitrogen heterocycles [97]. A representative example of this approach to the construction of heterocycles involves synthesis of isoindolinones via the Pd-catalyzed coupling of 2-bromobenzaldehyde with two equivalents of a primary amine under an atmosphere of CO [97b]. As shown below (Eq. (1.57)), this method was used for the preparation of **144** in 64% yield. The mechanism of this reaction is likely via initial, reversible condensation of 2-bromobenzaldehyde with 2 equiv of the amine to form an aminal **145**. Oxidative addition of the aryl bromide to Pd^0 followed by CO insertion provides the acylpalladium species **146**, which is then captured by the pendant aminal to afford the observed product. An alternative mechanism involving intramolecular imine insertion into the Pd−C bond of a related acylpalladium species, followed by formation of a palladium-amido complex and C−N bond-forming reductive elimination has also been proposed [97b].



(1.57)

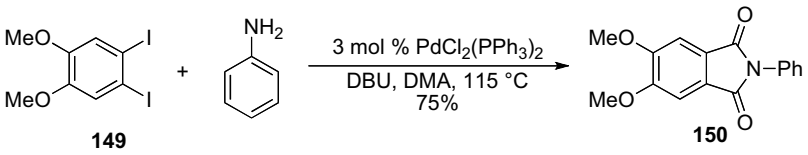
A sequence involving intermolecular Pd-catalyzed carbonylative amidation followed by intramolecular Michael addition has been employed for the construction of isoindolin-1-ones [97d]. For example, treatment of **147** with 4-methoxyaniline under standard conditions for Pd-catalyzed carbonylative coupling gave isoindolinone

148 in 79% yield (Eq. (1.58)). This transformation is effective with a wide array of primary aliphatic and aromatic amine nucleophiles.



(1.58)

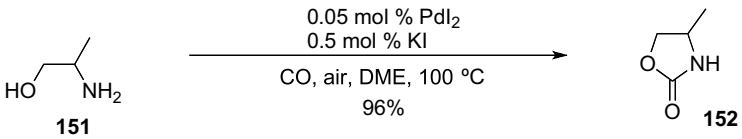
A synthesis of phthalimides via double carbonylative coupling of *ortho*-diiodo arenes with anilines has also been reported [98]. The conversion of **149** to **150** proceeded in good yield using a Pd/PPh_3-based catalyst system (Eq. (1.59)).



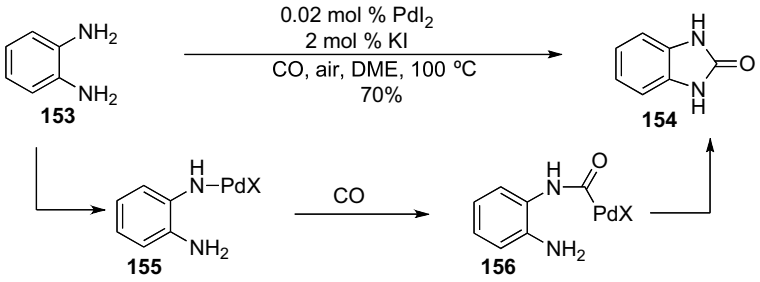
(1.59)

1.6.2
Transformations Involving CO Insertion Into a Pd–Heteroatom Bond

A number of interesting methods for the synthesis of heterocycles that employ palladium carbonylation chemistry involve formal CO insertion into a Pd–heteroatom bond via either an inner-sphere or outer-sphere mechanism [99]. Several groups have employed this strategy for the generation of isoxazolidines and ureas via Pd-catalyzed carbonylation reactions of 1,2-amino alcohols or 1,2-diamines [100]. For example, Gabriele and coworkers have synthesized oxazolidin-2-ones in high yields using a PdI_2/KI/air catalyst system [100b]. Oxazolidin-2-one **152** was obtained in 96% yield from amino alcohol substrate **151** using only 0.05 mol% of PdI_2 (Eq. (1.60)). In a similar fashion, diamine **153** was transformed to 1,3-dihydrobenzoimidazol-2-one **154** in 70% yield (Eq. (1.61)) [100d]. The first carbon heteroatom bond is formed by CO insertion into the palladium amido complex **155**, followed by intramolecular trapping of the resulting acylpalladium intermediate **156** with the second heteroatom. This leads to reduction of the Pd^{II} catalyst to Pd^0, and the presence of air (oxygen) is required to regenerate the catalytically active Pd^{II} species.

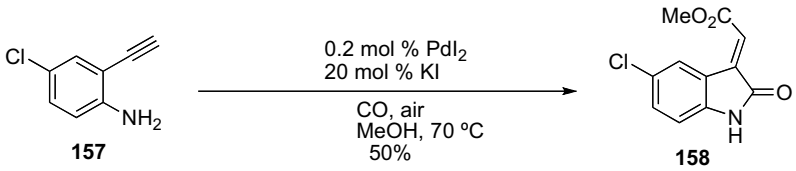


(1.60)

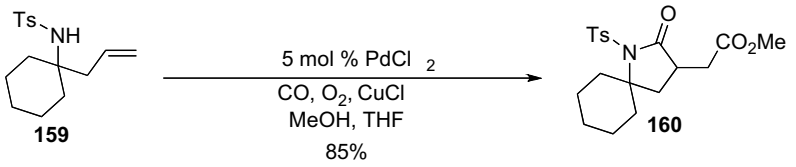


(1.61)

Several transformations involving CO insertion into a Pd–heteroatom bond have been developed that lead to incorporation of two molecules of CO into the heterocyclic product. This approach to heterocycle synthesis is exemplified by a synthesis of dihydroindolones reported by Gabriele [101]. As shown below, treatment of *ortho*-alkynyl aniline **157** with a Pd^{II} catalyst under CO in methanol afforded **158** in 50% yield (Eq. (1.62)). A similar strategy has been employed for the conversion of alkene **159** to pyrrolidinone **160** (Eq. (1.63)) [102].



(1.62)

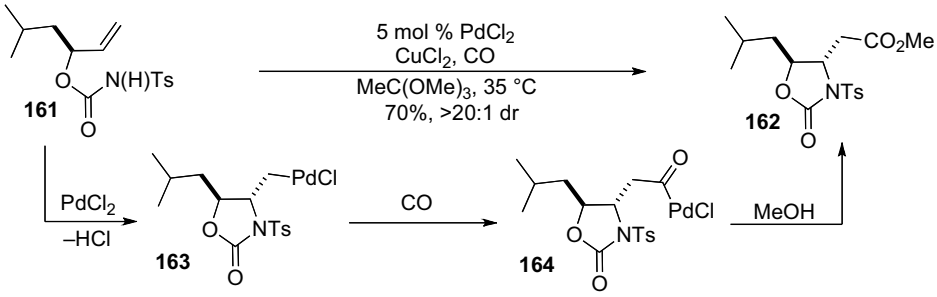


(1.63)

1.6.3
Wacker-Type Carbonylative Processes

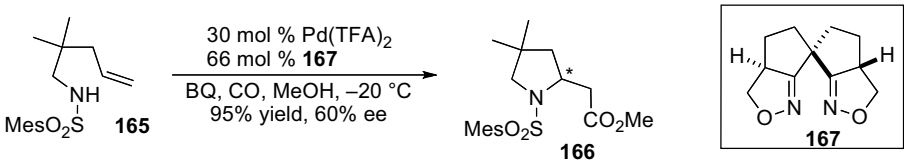
Pd-catalyzed carbonylative processes that involve Wacker-type *anti*-aminopalladation of alkenes, alkynes or allenes have been widely employed in the construction of nitrogen heterocycles. Early studies using stoichiometric amounts of palladium to effect intramolecular alkene aminopalladation followed by carbonylation were reported by Danishefsky in 1983 [103]. A number of elegant studies by Tamaru subsequently led to the development of catalytic versions of these reactions, and extended the scope of this chemistry to allow the generation of a wide array of nitrogen heterocycles, including oxazolidin-2-ones, imidazolidin-2-ones, pyrrolidines, and isoxazolidines [104]. For example, treatment of carbamate **161** with 5 mol% $PdCl_2$ in the presence of $CuCl_2$ under CO using trimethyl orthoacetate as

solvent provides oxazolidin-2-one **162** in 70% yield with >20: 1 dr (Eq. (1.64)) [104e]. The mechanism of this reaction involves *anti*-aminopalladation of the alkene to afford **163**, which undergoes CO insertion to form **164**. Capture of the acylpalladium intermediate **164** with methanol (formed *in situ* from trimethyl orthoacetate) gives the heterocyclic product.



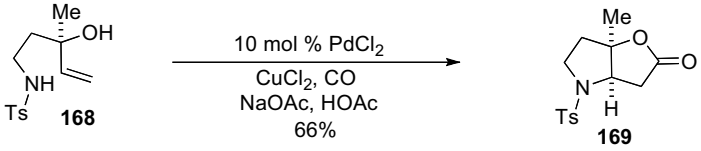
(1.64)

This strategy has been used for the construction of bridged bicyclic nitrogen heterocycles, and has been applied to a formal total synthesis of the alkaloid natural product (±)-ferruginine [105]. In addition, an asymmetric variant of this reaction has been developed by Sasai and coworkers. As shown below (Eq. (1.65)), use of a catalyst composed of $Pd(TFA)_2$ and spiro bis(isoxazoline) ligand **167** effected the conversion of sulfonamide **165** to pyrrolidine **166** in 95% yield and 60% ee [106]. Although this transformation requires high catalyst loadings and very long reaction times (7 days), it is clear that there is potential for achieving asymmetric induction in these systems, and development of new catalysts for these reactions is likely to be an area of future investigation.



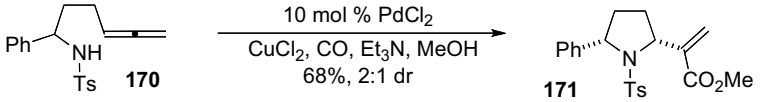
(1.65)

Alkene aminopalladation/carbonylation has also been employed in the synthesis of fused bis(heterocycles) [107]. As shown below, treatment of **168** with 10 mol% $PdCl_2$ in the presence of $CuCl_2$ under CO provided **169** in 66% yield (Eq. (1.66)) [107a]. This strategy has been used for the preparation of 1,4-iminoglycitols [107b], and has been applied to a concise synthesis of the Geissman–Waiss Lactone, which is a key intermediate in the synthesis of necine bases [107c].

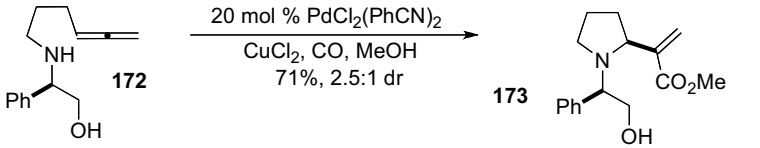


(1.66)

A number of Pd-catalyzed carbonylative processes have employed allenes as substrates for the synthesis of nitrogen heterocycles [108]. For example, subjection of substituted allene **170** to reaction conditions similar to those employed in related reactions of alkenes led to the formation of pyrrolidine **171** in 68% yield with 2: 1 dr (Eq. (1.67)) [108d]. Modest asymmetric induction has been achieved in these transformations using simple chiral auxiliaries [108b,d]. This strategy was employed in an asymmetric synthesis of pumiliotoxin 251 D, which involved the aminocarbonylation of allene **172** to pyrrolidine **173** as a key step (Eq. (1.68)) [108b].



(1.67)



(1.68)

1.7 Summary and Future Outlook

Over the past several decades, research in the field of palladium catalysis has resulted in the development of a myriad of transformations that provide access to saturated nitrogen heterocycles. Many of these transformations effect the formation of several bonds, and/or proceed with good to excellent levels of stereocontrol. Despite the many advances made in this field, discoveries of new reactivity are still being reported with great frequency, and this promises to remain a fruitful area of research for many years to come. In particular, the development of new palladium catalysts will likely lead to improvements in the scope of existing transformations, and will also open up new reaction pathways that can be applied to unsolved problems in heterocyclic chemistry.

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