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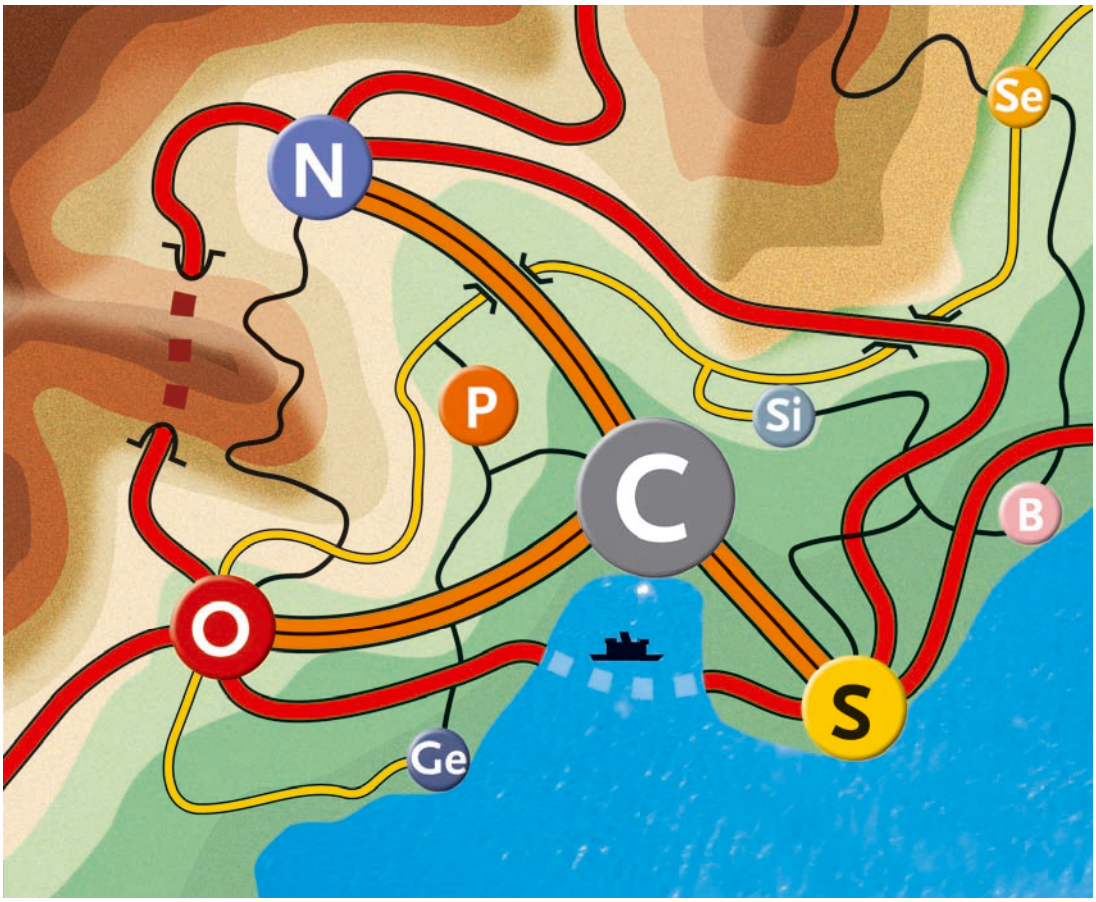
Catalyzed Carbon-Heteroatom Bond Formation

With a Foreword by John F. Hartwig



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Contents

Preface

Metal catalyzed carbon-heteroatom bond forming processes constitute a vibrant area of research that continues to serve as an unmatched source of challenges. The cover of the book you hold in your hands provides a pictorial representation of a typical landscape in transition metal catalysis. The roads connecting the carbon center with heteroatoms depict catalyzed pathways. These roads are often indirect, they go via valleys and they climb over steep hills. There is almost always more than one way to connect the nodes on this map. Continuing effort in this important area is a testament to how difficult finding an optimal solution to a given bond forming reaction really is. I owe a great deal of gratitude to an outstanding cast of authors who wrote 11 outstanding chapters you will find in this book. I am grateful to these individuals for agreeing to participate in this important undertaking and for delivering superb and comprehensive chapters. I would also like to express gratitude to my students, Igor Dubovyk and Lawrence Cheung, for proof reading some of the chapters.

May 2010 *Andrei Yudin*
Toronto, Canada

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

John P. Wolfe, Joshua D. Neukom, and Duy H. Mai

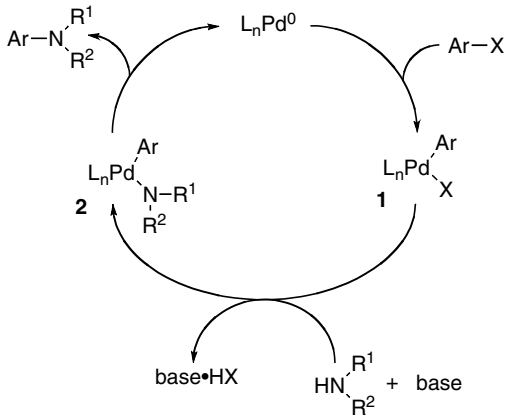
1.1
Introduction

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

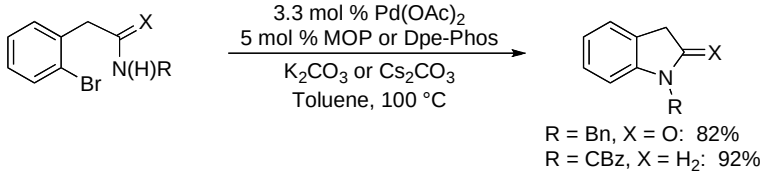
One of the most versatile and widely employed methods for the construction of aryl C−N bonds is the palladium-catalyzed cross coupling of amines with aryl halides and related electrophiles [4]. These reactions are believed to occur as shown in Scheme 1.1, with the coupling initiated by oxidative addition 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,



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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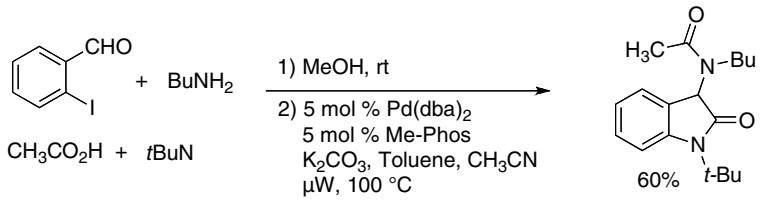
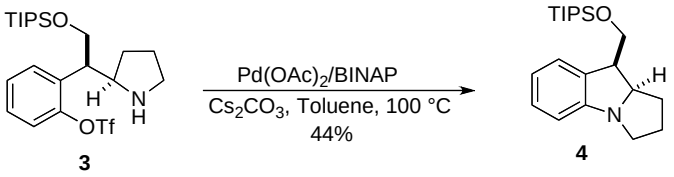


(1.2)

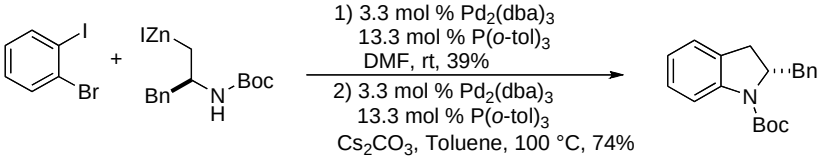
Intramolecular Pd-catalyzed or -mediated N-arylation reactions have been employed in the synthesis of several natural products [5]. For example, pyrroloindoline **4**,

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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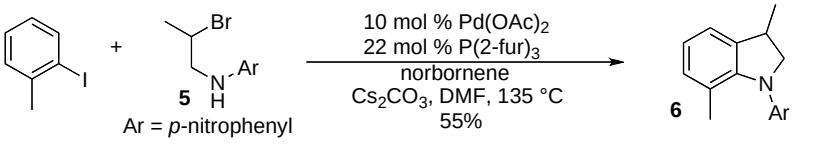
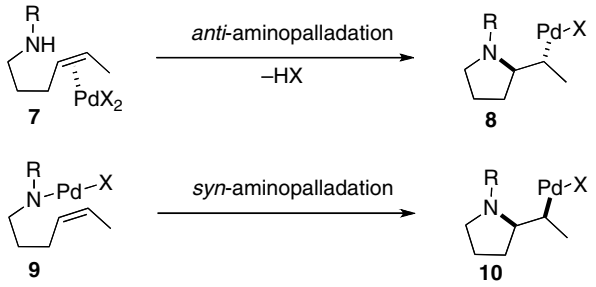


(1.5)

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].

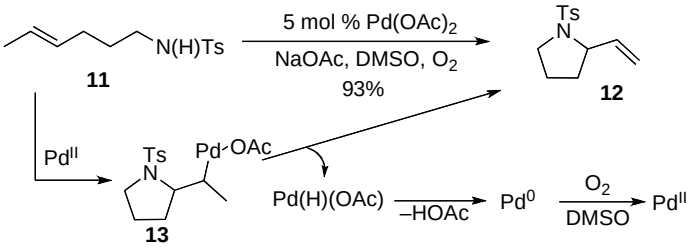


Scheme 1.2

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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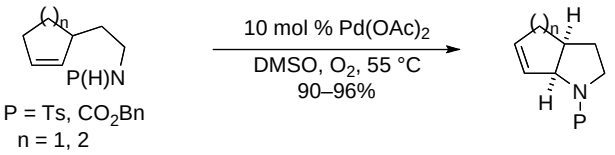
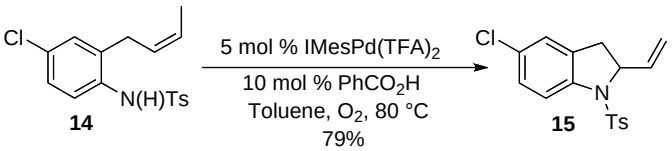


(1.7)

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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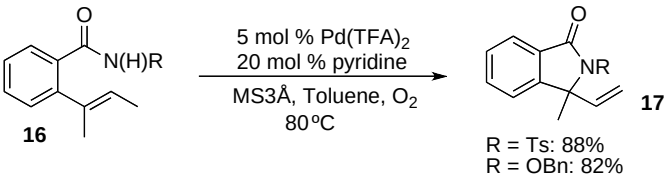
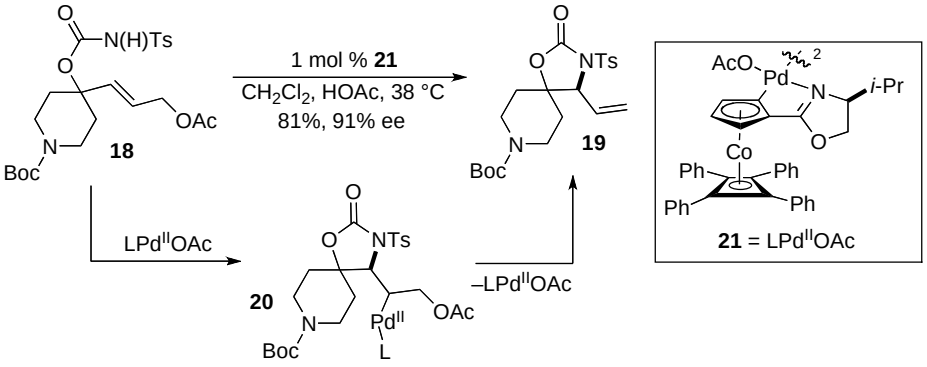


(1.9)

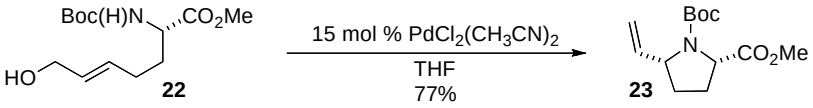
A related approach to the synthesis of nitrogen heterocycles also proceeds via Pd^{II}-catalyzed alkene aminopalladation, but involves substrates bearing allylic acetates or allylic hydroxy groups [21, 22]. In contrast to the oxidative amination reactions described above, these transformations are terminated 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.



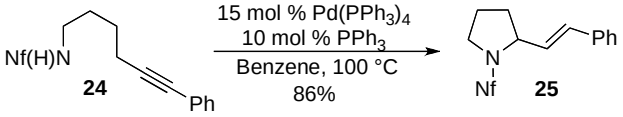
(1.11)

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.

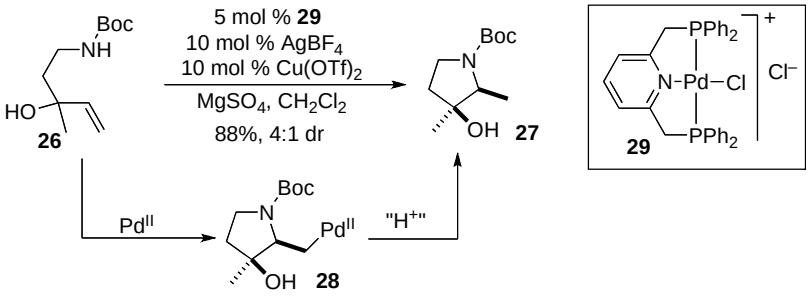
Palladium-catalyzed intramolecular hydroamination reactions of alkynes that afford pyrrolidine derivatives were initially reported by Yamamoto in 1998 [27] and have been the subject of detailed investigation over the past ten years [28]. In a

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].



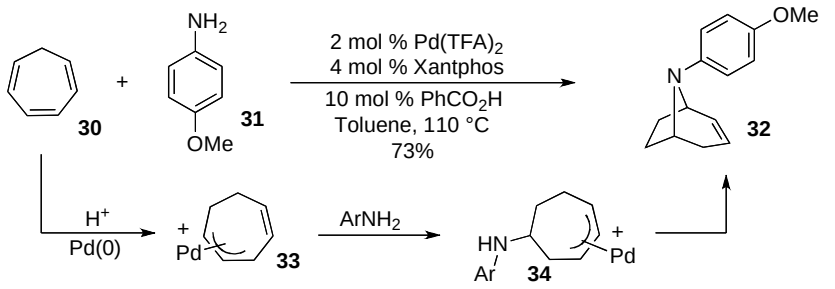
(1.12)

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)

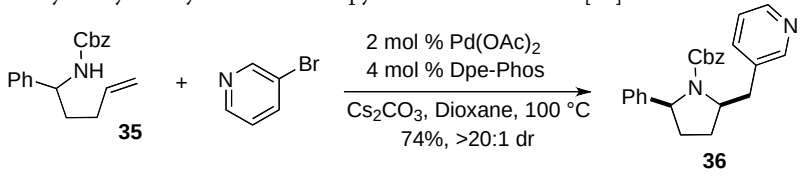
An interesting tandem intermolecular/intramolecular hydroamination reaction of cycloheptatriene with substituted anilines has been developed by Hartwig for the synthesis of tropene derivatives [34]. As shown in Eq. (1.14), the coupling of **30** with **31** provided **32** in 73% yield. The mechanism 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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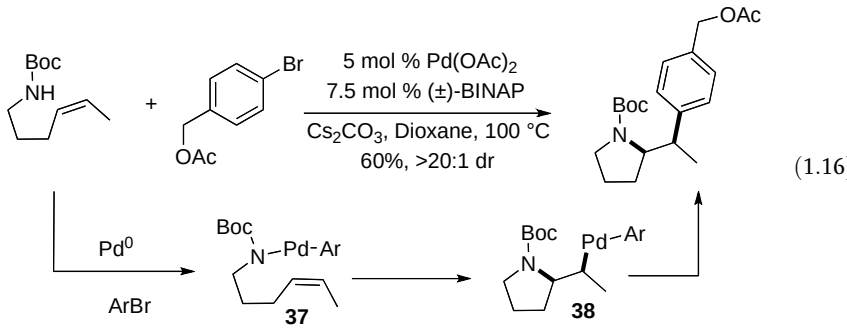
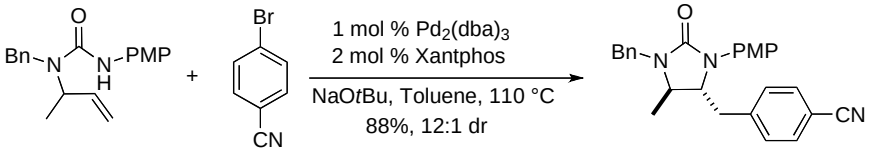


(1.16)

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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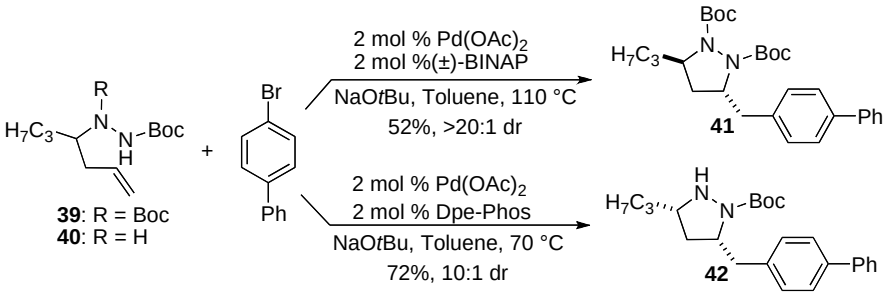
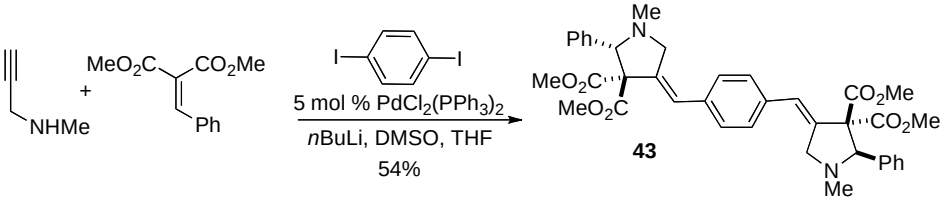


(1.18, 1.19)

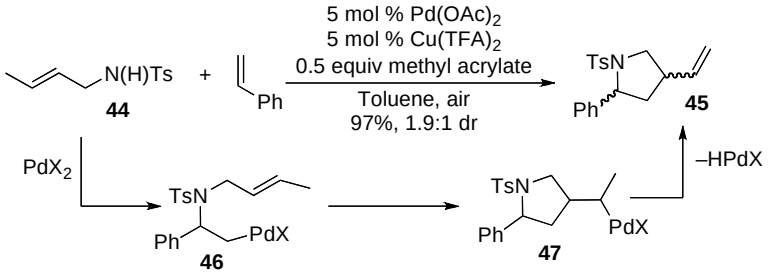
Balme has reported a one-pot three-component alkene carboamination between propargylic amines, alkylidene malonates, and aryl halides [43]. For example, treatment of *N*-methyl propargylamine (2 equiv), dimethyl benzylidene malonate (2 equiv) and 1,4-diiodobenzene (1 equiv) with *n*-BuLi and a palladium 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)

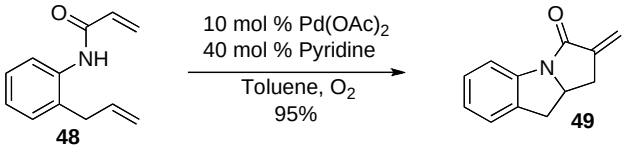
1.3.4
Pd^{II}-Catalyzed Carboamination Reactions of Alkenes

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.

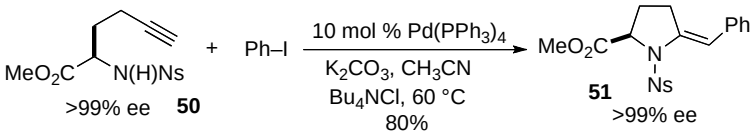


(1.22)

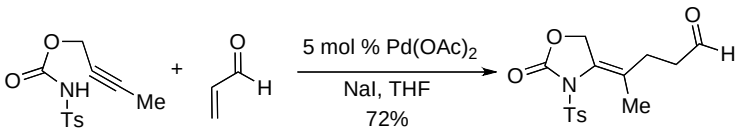
1.3.5
Pd-Catalyzed Carboamination Reactions of Alkynes, Allenes, and Dienes

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].

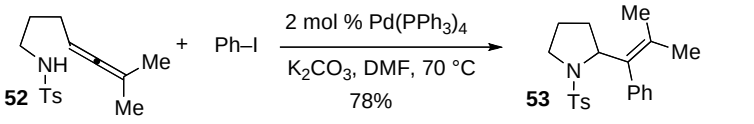


(1.23)

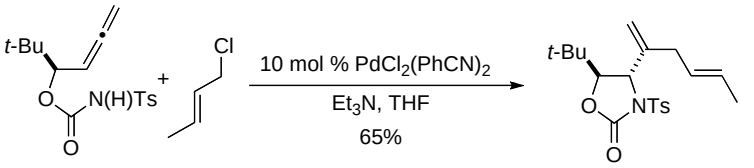


(1.24)

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].



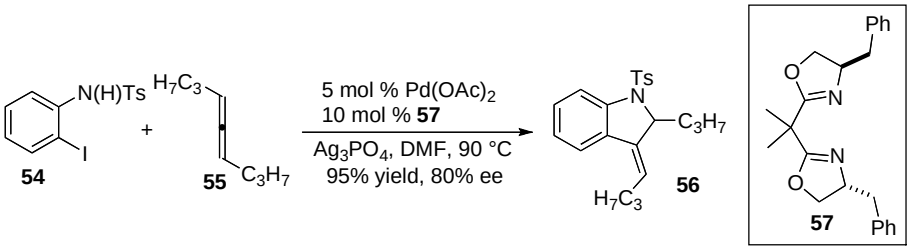
(1.25)



(1.26)

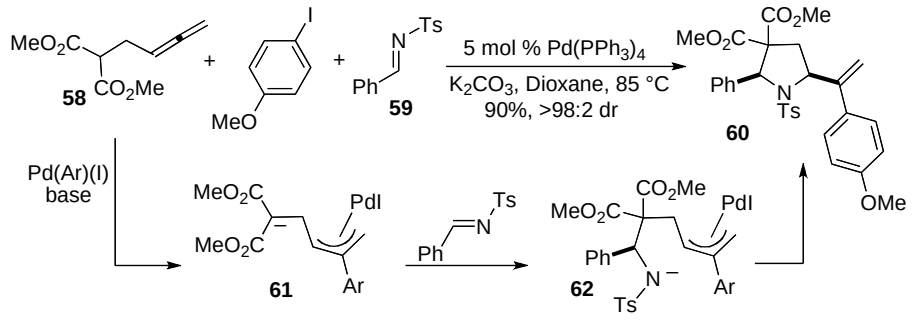
Cross-coupling carboamination reactions between allenes and 2-haloaniline derivatives or halogenated allylic amines have also been employed for the generation of substituted indolines, and use of an appropriate chiral catalyst for these transformations leads to formation of enantioenriched products [52]. 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