HETEROCYCLES, Vol. 81, No. 4, 2010, pp. 795 - 866. © The Japan Institute of Heterocyclic Chemistry
Received, 20th October, 2009, Accepted, 8th January, 2010, Published online, 15th January, 2010
DOI: 10.3987/REV-09-662-2

RECENT DEVELOPMENT IN PALLADIUM-MEDIATED SYNTHESIS OF NITROGEN HETEROCYCLES

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Abstract - This review describes the synthesis of nitrogen heterocycles by palladium-mediated cyclization. This report covers literature published during 2003 to 2007.

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1. INTRODUCTION

Recently, there is flurry of activities in the synthesis of heterocyclic compounds due to their pharmacological and biological activities. Synthetic organic chemists are continuously after the development of novel and more effective synthetic methodologies. Many of the methodologies involve the formation of carbon-heteroatom bond from the corresponding acyclic precursors. Among newly

developed protocols, the application of palladium catalysis in the synthesis of heterocycles is extremely useful and are now routinely considered in planning of complex target molecules.

A good number of books[1] and reviews[2] covering general, particular and limited aspects of the chemistry of organopalladium are available. Organopalladium chemistry has already resulted in a large number of name reactions for the formation of C-C, C-O, and C-N bonds under relatively mild conditions. The catalysts are generally air stable, tolerant of a wide range of functionalities which avoids protection-deprotection processes. The use of chiral ligands[3] in asymmetric transformation for the synthesis of heterocycles and the palladium catalyzed domino reactions[4] are quite significant in organopalladium chemistry.

Palladium in three oxidation states, Pd(0), Pd(II) and Pd(IV) can exist in palladium complexes. Fortunately, there is facile interconversion between Pd(0) and Pd(II) oxidation states due to small energy difference between them. The ability of interconversion between the aforesaid two oxidation states is responsible for wide use of palladium in organic synthesis. Palladium(0) oxidation state is synthetically most useful and is also very important for the synthesis of heterocyclic compounds. Palladium(II) complexes are very important in organopalladium chemistry. They are stable in air, soluble in most common organic solvents and electrophilic in character. Electron-rich olefins, alkynes and arenes are the common substrates for Palladium(II). Some useful Pd(II) complexes are $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $PdCl_2(RCN)_2$, $Pd(PPh_3)_4$. Usually Pd(II) complex is added to the reaction mixture which is readily reduced by various species to Pd(0) and catalyzes the reaction.

The synthesis of various heterocycles and new protocols involving palladium has been the central goal in recent years. Therefore, our objective is to provide a complete and updated summary of palladium-catalyzed protocols for the preparation of nitrogen heterocycles developed from 2003 onwards with the emphasis on the underlying principle following each synthetic procedure, the results and the appropriate choice of reaction conditions. We have also avoided a thorough review of the patent literature which is beyond the scope of this review.

2. INTRAMOLECULAR REACTIONS WITH ALKYNES, ALKENES, ALLENES, ARENES AND HETEROARENES: HECK, SUZUKI, STILLE AND SONOGASHIRA TYPE REACTIONS

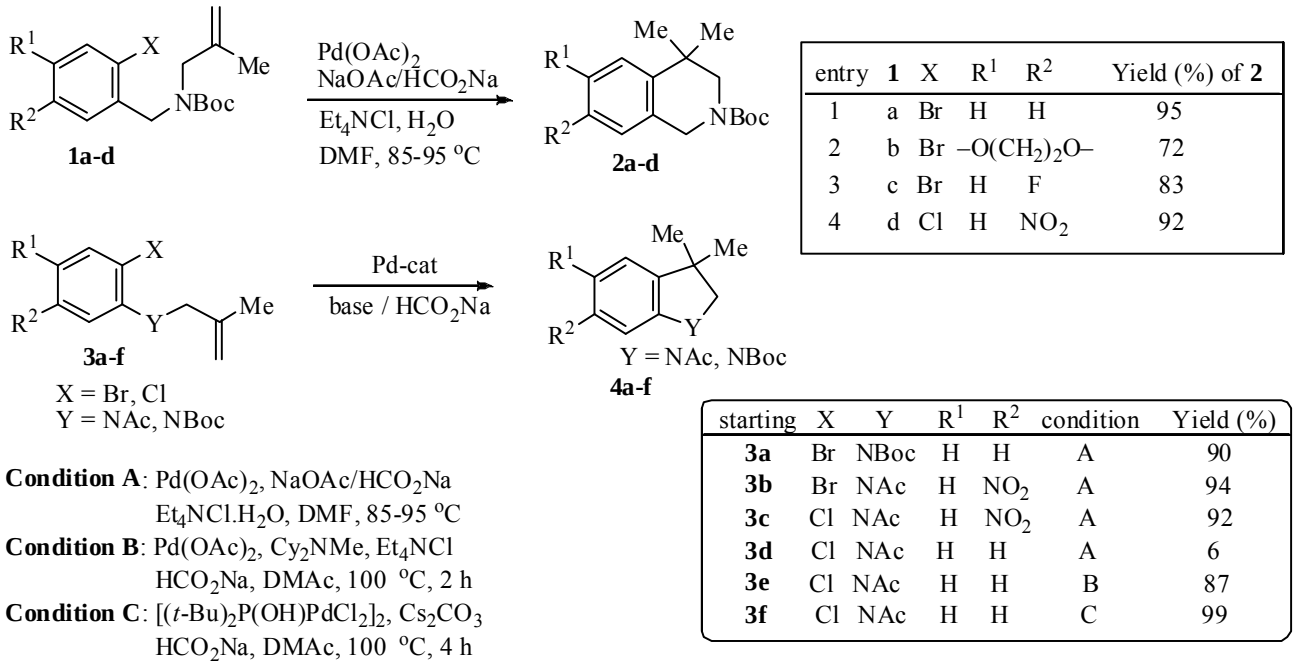
The potentiality of C-C unsaturated bond as carbon source to get coupled with aryl- and vinyl halides or organometallics in a palladium mediated reaction is well documented.[2,5] Heck reaction[1a,2a,6] is significant in the synthesis of heterocycles. The intramolecular version of this reaction with aryl or vinyl halides generally proceeds through a sequence of oxidative addition to C-X (X = halogen) bond, insertion and β-elimination (for olefins) or protonolysis (for alkynes) to generate the heterocycles ranging from small to macrocyclic compounds. The observed rate of oxidative addition with C-X bonds decreases according to the following order: C-I> C-Br> C-Cl> C-F.[7] The reactivity of aryl triflates is in between that of aryl iodides and aryl bromides. Additives also play a important role in controlling the results of palladium-

catalyzed reactions.[8] Recently intramolecular reactions have been developed involving related carbopalladation reactions followed by trapping with nucleophilic reagents.[9]

For macrocyclization via C-C bond formation with olefin or alkyne, the well-known Heck, Suzuki, Sonogashira and Stille reactions are now routinely considered.[10] A different approach to C-C bond formation involving the palladium-catalyzed intramolecular reaction of enolate derived from ketones, esters and amides with aryl or vinyl halide[11] or oxidative coupling with olefin[12] has been utilized for the synthesis of five- and six-membered heterocyclic compounds.

2.1. REACTIONS OF ARYL HALIDES

In palladium-catalyzed Heck reaction, aryl iodide has been found to be the most commonly used halide source.[13,14] In an investigation, Liu *et al*. reported the use of aryl bromide and chloride **1a-d** and **3a-f** for the synthesis of a number of 1,2,3,4-tetrahydroisoquinolines **2a-d**, indolines **4a-f** under ligand free $Pd(OAc)_2$–catalyzed reductive Heck[15] cyclization (**Scheme 1**).[16] The reaction was robust in the presence of water as up to 5% water. Although the ligand free condition was efficient for bromobenzene, chlorobenzene showed low reactivity in the absence of an activating group on the aromatic ring. However, an excellent improvement in the yield of **4e** (87%) was observed under the Buchwald condition.[17] By employing various palladium complexes $[(t\text{-Bu})_2P(OH)]_2\text{-}PdCl_2$, $[(t\text{-Bu})_2P(OH)(t\text{-Bu})]_2\text{-}PdCl_2$ and $[(t\text{-Bu})_2P(OH)\text{-}PdCl_2]_2$ developed by Li,[18] a 99% yield of **4f** was obtained from **3f**.



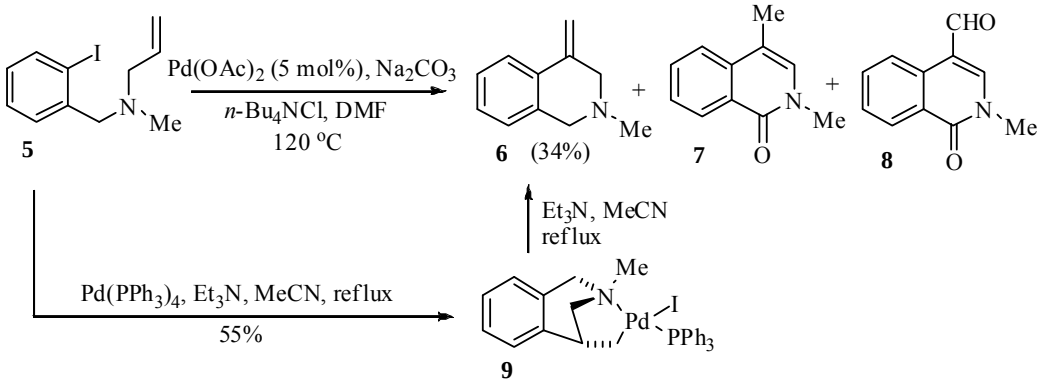
entry	**1**	X	R^1	R^2	Yield (%) of **2**
1	a	Br	H	H	95
2	b	Br	$-O(CH_2)_2O-$		72
3	c	Br	H	F	83
4	d	Cl	H	NO_2	92

starting	X	Y	R^1	R^2	condition	Yield (%)
3a	Br	NBoc	H	H	A	90
3b	Br	NAc	H	NO_2	A	94
3c	Cl	NAc	H	NO_2	A	92
3d	Cl	NAc	H	H	A	6
3e	Cl	NAc	H	H	B	87
3f	Cl	NAc	H	H	C	99

Condition A: $Pd(OAc)_2$, $NaOAc/HCO_2Na$
$Et_4NCl.H_2O$, DMF, 85-95 °C
Condition B: $Pd(OAc)_2$, Cy_2NMe, Et_4NCl
HCO_2Na, DMAc, 100 °C, 2 h
Condition C: $[(t\text{-Bu})_2P(OH)PdCl_2]_2$, Cs_2CO_3
HCO_2Na, DMAc, 100 °C, 4 h

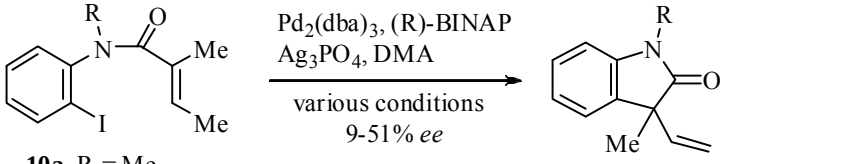
Scheme 1

The compound **5** when subjected to intramolecular Heck reaction using $Pd(OAc)_2$ as catalyst, afforded the cyclized product **6** in 34% yield along with sizable amount of 2,4-dimethylisoquinolin-1(2*H*)-one **7** and 4-formyl-2-methylisoquinolin-1(2*H*)-one **8** (**Scheme 2**).[19]



Scheme 2

Stephenson *et al*. extensively investigated the intramolecular asymmetric Heck reaction[3,20] of *o*-iodoanilide **10** for the synthesis of oxindoles **11** by employing a wide range of conditions (**Scheme 3**).[21] The conversion rate and *ee* data clearly indicated a general tendency for high *ee*'s at high temperature and relatively low *ee*'s at low temperature. The limiting *ee*'s at 100 °C indicated the generation of catalytically active Pd(0) particles by thermal decomposition of $Pd_2(dba)_3$ [(R)-BINAP] intermediates resulting in a competing racemic cyclization over time.

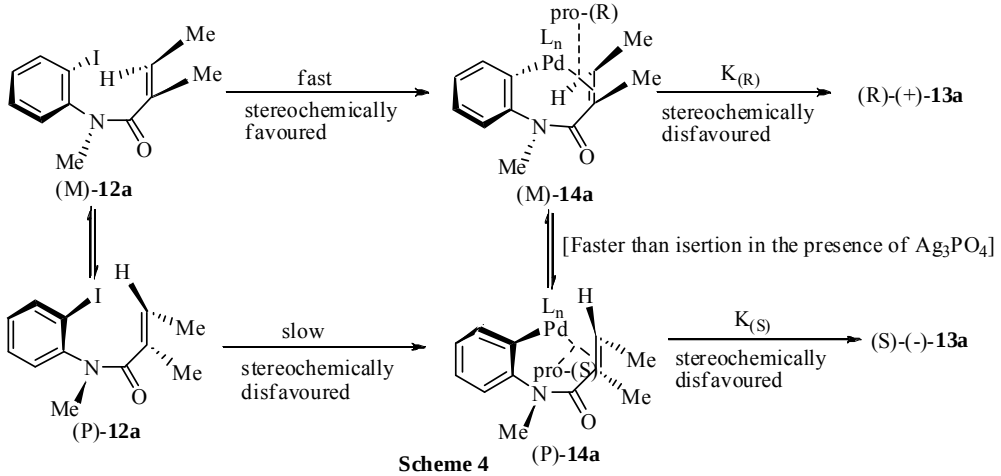


10a, R = Me
10b, R = COC(Me)=CHMe

11a, R = Me
11b, R = COC(Me)=CHMe

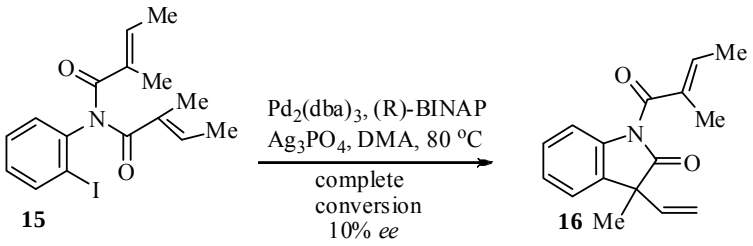
Scheme 3

The X-ray crystallographic study of the substrate **22a** revealed the presence of enantiomerically pure (P)- and (M)-helical structures (**Scheme 4**). Here it is important to note that Curran and co-workers[22] also synthesized 2-oxindole by radical-mediated intramolecular cyclization and found that the stable amide atropisomers play a significant role in the control of intramolecular Heck reaction. The dynamic kinetic resolution of interconverting helical iodide (P)- and (M)-**12a** must favor the oxidative addition of (M)-helix to promote the pro-(R) pathway to product **13a**. However, in the case of Ag_3PO_4 protocol, the rationalization for the opposite stereochemical preference is due to the equilibrium between palladium bound oxidative addition complexes of the (P)- and (M)-helices [(P)/(M)-**14a**]. The (S)-(-)-**13a** product was formed through the pro-(S) catalytic intermediate, the access of which has been enhanced by Ag_3PO_4.



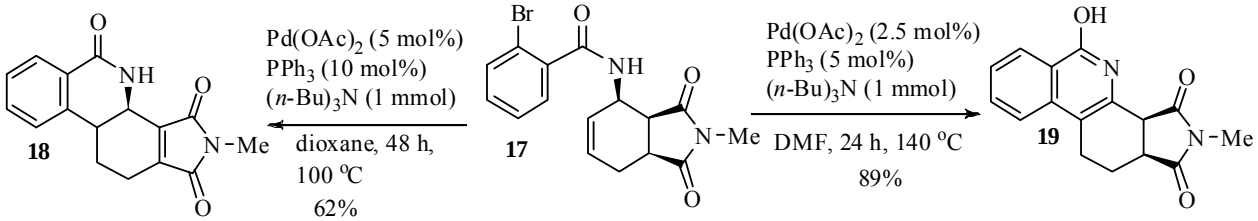
Scheme 4

The equilibrium between the two atropisomeric forms of **12a** is crucial for an efficient asymmetric induction in the Heck cyclization which is evident from the formation of product **16** with an *ee* of only 10% from the imide substrate **15** containing two 2-methylbut-2-enyl groups (**Scheme 5**).



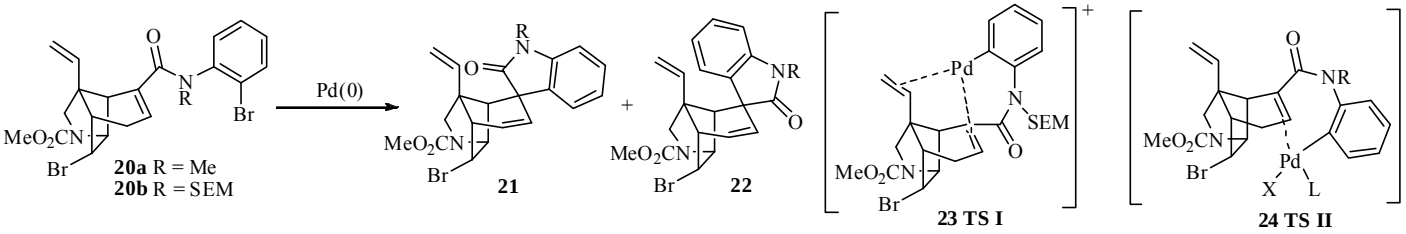
Scheme 5

Intramolecular Heck reaction of 2'-bromo-*N*-(2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindol-4-yl)benzamide **17** was investigated under two different conditions.[23] In both the conditions the imide **17** underwent 6-*exo-trig* cyclization. In dioxane, 2-methyl-3b,9b,10,11-tetrahydro-1*H*-pyrrolo[3,4-*c*]-phenanthridine-1,3,5-(2*H*,4*H*)-trione **18**, was obtained. Whereas the reaction in DMF afforded 2-methyl-4,10,11,11a-tetrahydro-1*H*-pyrrolo[3,4-*c*]phenanthridine-1,3,5(2*H*,3*H*)-trione **19** (**Scheme 6**).



Scheme 6

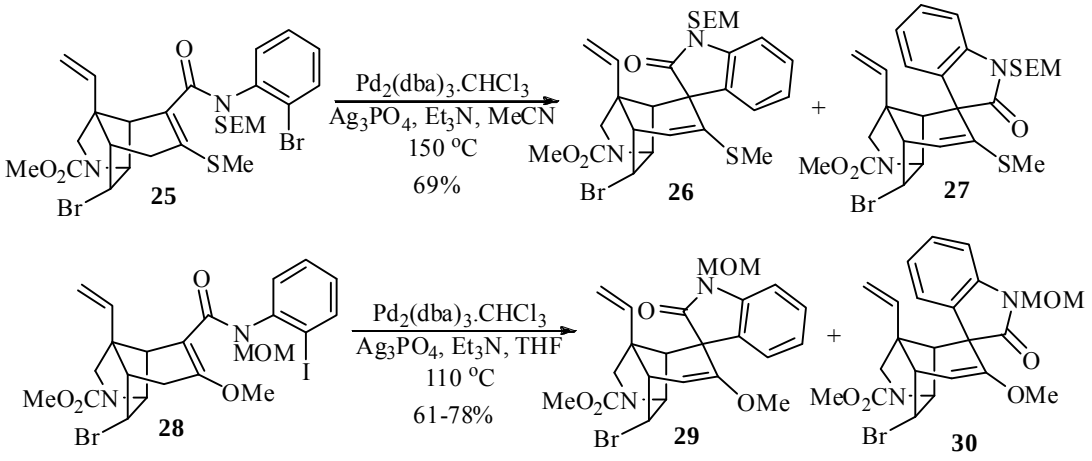
The intramolecular Heck reaction of *α,β*-unsaturated 2-haloanilides derived from azatricyclo[4.4.0.0^{2,8}]decanone was used to introduce the congested spirooxindole functionality of gelsemine.[24] Depending upon the reaction conditions, two epimeric products **21** and **22** were obtained from anilides **20a** and **20b** possibly via migratory insertion from the *α*-face (**TS I**) and *β*-face (**TS II**) (**Figure 1**) respectively (**Scheme 7**). The extra stability of **TS-II** is due to the coordination with angular vinyl group. An examination of the catalytic conditions revealed that anilides **20a** and **20b** when subjected to catalytic system $Pd(PPh_3)_4/Et_3N$/MeCN afforded spiro oxindoles **21** and **22** in 66:34 and 60:40 ratios. However, cyclization of *α,β*-unsaturated anilide **20b** catalyzed by tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] in the absence of phosphine ligands was more selective. In contrast, Heck cyclization of the precursor **20b** conducted in the presence of Ag_3PO_4 and in the absence of phosphine ligands occurred with virtually complete selectivity to give the epimeric oxindole **22**.



Scheme 7

Figure 1. Possible two transition states

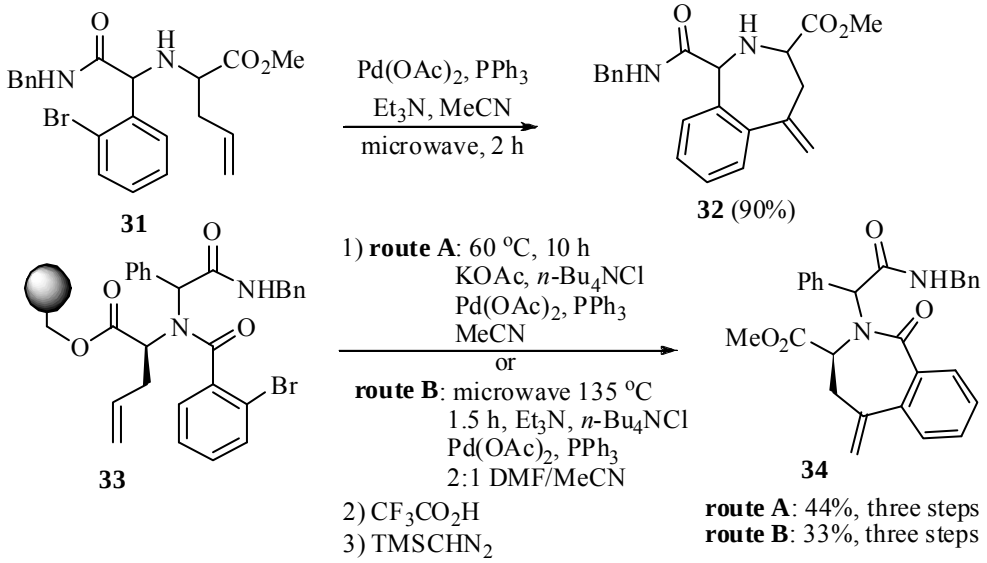
The intramolecular Heck reaction of *β*-methylthio-*α,β*-unsaturated anilide **25** and *β*-methoxy-*α,β*-unsaturated anilide **28** was also examined. Under forcing conditions (150 °C) using $Pd_2(dba)_3.CHCl_3$ as the catalyst, the intramolecular Heck reaction of **25** produced a 1:2 mixture of stereoisomeric tetracyclic products **26** and **27** in 69% yield. (**Scheme 8**). However, in the case of **28**, a high preference for the formation of **29** was observed using 35 mol% $Pd_2(dba)_3$ and Ag_3PO_4 in refluxing THF.



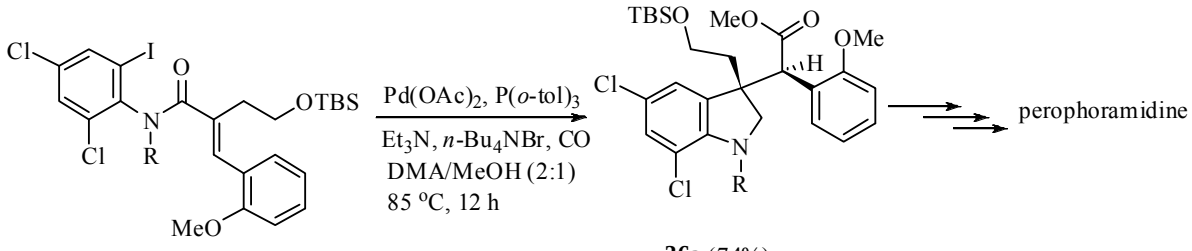
Scheme 8

The intramolecular Heck reaction of the amide **31** under microwave irradiation and employing the same combination of catalysts gave benzoazepine **32** in excellent yield. In contrast, the intramolecular Heck reaction of resin bound amide **33**, performed under microwave and standard heating conditions, afforded the benzolactam **34** in moderate yield after washing of the resin followed by methylation (**Scheme 9**).[25]

Weinreb and Artman[26] reported a halogen-selective domino intramolecular Heck/carbonylation reaction for the construction of an indole moiety with quaternary stereocenter, found in metabolite perophoramidine. The $Pd(OAc)_2$-catalyzed process worked efficiently and compounds **36a**,**b** were obtained from the precursors **35a**,**b** as single diastereomers (**Scheme 10**).



Scheme 9

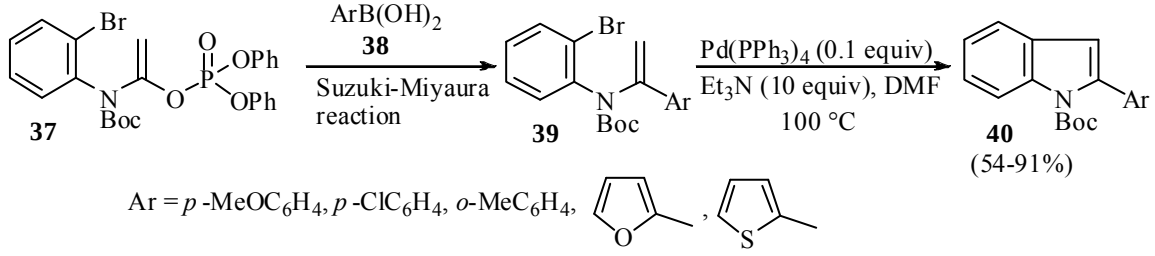


35a, R - Me
35b, R = MOM

36a (74%)
36b (88%)

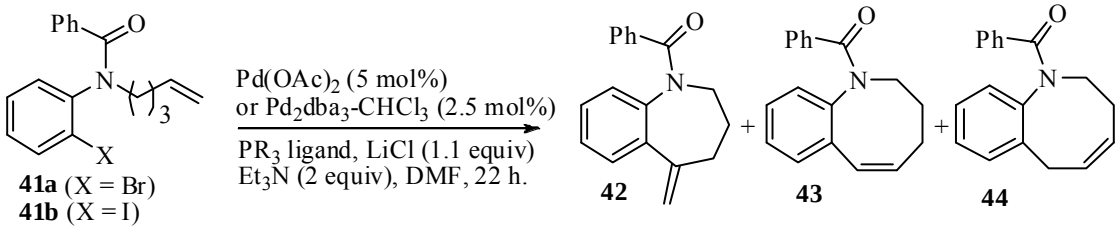
Scheme 10

Fuwa *et al*. recently reported the first application of acyclic *α*-phosphoryloxy enecarbamates to the synthesis of indole-2,3-quinodimethanes and 2-(*N*-alkoxycarbonylamino)-1,3-dienes and demonstrated their efficiency in the Heck reaction.[27] The same group, in a recent investigation, has reported the use of *α*-phosphoryloxy enecarbamates **37** in Pd(0)-catalyzed intramolecular Heck[2,28] reaction for the preparation of indole derivatives **40**. Thus, *N*-(*o*-bromophenyl) enecarbamates **39**, prepared from the acyclic *α*-phosphoryloxy enecarbamates **37** by Suzuki-Miyaura cross coupling afforded 2-phenylindole derivatives **39** when subjected to $Pd(PPh_3)_4$, Et_3N in DMF (**Scheme 11**).[29]



Scheme 11

Regioselective construction of medium-sized benzolactams has been successfully achieved by intramolecular Heck reaction.[30] The regiochemistry of the reaction is highly dependent on the catalytic condition as both *exo*[30a,b] and *endo*[30c] products can be formed. An interesting example of ligand and temperature effect on the regioselectivity of the intramolecular Heck reaction was reported by Hii *et al*.[31] The 7-*exo-trig* cyclized product benzazepine **42** was obtained exclusively when the amides **41a**,**b** were subjected to $Pd(OAc)_2$ or $Pd_2(dba)_3.CHCl_3$ as catalyst at 140 °C employing ligands PPh_3 or dppp or dppf (**Scheme 12**). A competitive formation of 8-*endo-trig* cyclized products **43** and **44** as an inseperable mixture along with compound **42** was observed by employing 3 equiv of PPh_3 (51-60%). Replacement of PPh_3 with the P(*o*-tol)$_3$ ligand led to an improvement in the yield of **42** (80%). An exclusive formation of **42** in excellent yield was observed by using 4 equiv of PPh_3 at 130 °C (88%).

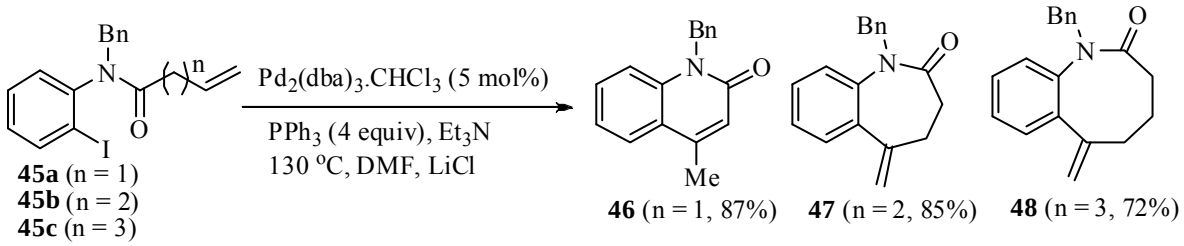


41a (X = Br)
41b (X = I)

42 **43** **44**

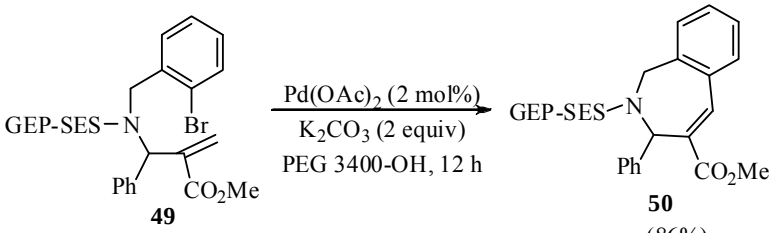
Scheme 12

Similarly, compounds **45a-c** in the presence of $Pd_2(dba)_3.CHCl_3$ as catalyst and PPh_3 as ligand in a ratio 1:4 underwent cyclization in an *exo*-manner to afford quinolinone **46**, 1-benzazepinone **47** and 1-benzazocinone **48** (**Scheme 13**).[32] However, under ligand free Jeffery's condition, compound **45b** afforded an inseparable mixture of benzapinone and its double bond isomer **47** in a 1:1 ratio.



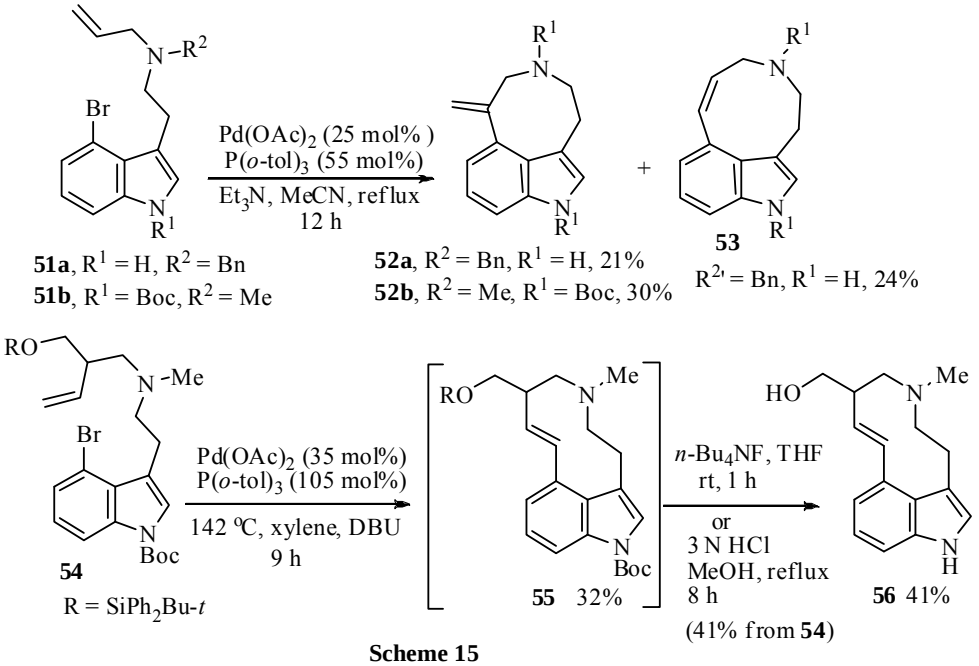
Scheme 13

The intramolecular Heck reaction for the synthesis of a series of a novel benzazepines **50** (**Scheme 14**)[33] was carried with $Pd(OAc)_2$ catalyst and K_2CO_3 in the absence of any posphine ligand. The amine **49** afforded the benzazepine **50**. Interestingly, PEG 3400 acted both as solvent as well as a stabilizer for in situ generation of nanoparticles, thus influencing the outcome of the reaction in terms of selectivity.



Scheme 14

The intramolecular Heck reaction of indole derivative **51a** in the presence of $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N, afforded both 9-*endo*-**53** and 8-*exo*-**52a** products.[34] The substrate **51b** under the same reaction conditions afforded 8-*exo*-**52b** as the isolable product. Moreover, the intramolecular Heck reaction of compound **54** employing $Pd(OAc)_2$, P(*o*-tol)$_3$, DBU afforded 10-membered *trans*-macrocycle **55** (**Scheme 15**).

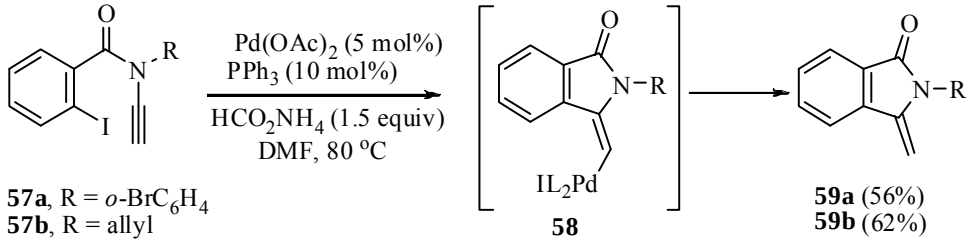


Scheme 15

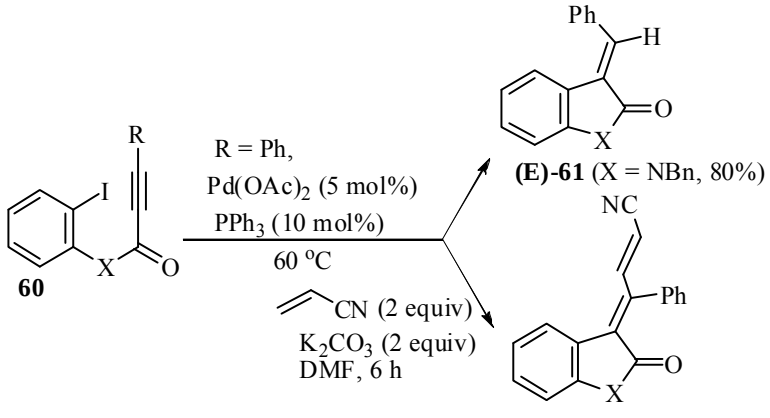
N-Aryl and *N*-ethynyl-2-iodobenzamides **57a**,**b** underwent intramolecular hydroarylation reaction on treatment with a catalytic amount of $Pd(OAc)_2$ and PPh_3 to afford 3-methyleneisoindolin-1-ones **59a**,**b** via the intermediate **58** (**Scheme 16**).[35,36] Here ammonium formate (HCO_2NH_4) acts as the reducing agent in order to regenerate the Pd(0) catalyst from the intermediate **58**. Similarly, by the application of domino-coupling[37] the same type of products with terminally aryl substitution may be obtained.

An efficient $Pd(OAc)_2$-PPh_3-catalyzed method for the domino reaction of alkynamides **60** was demonstrated by Takemoto *et al*.[38] The efficiency of the catalytic system was explored in the synthesis of various (*E*)-, (*Z*)-, and disubstituted 3-alkylideneoxindoles **61** and **62** in excellent yields (**Scheme 17**).

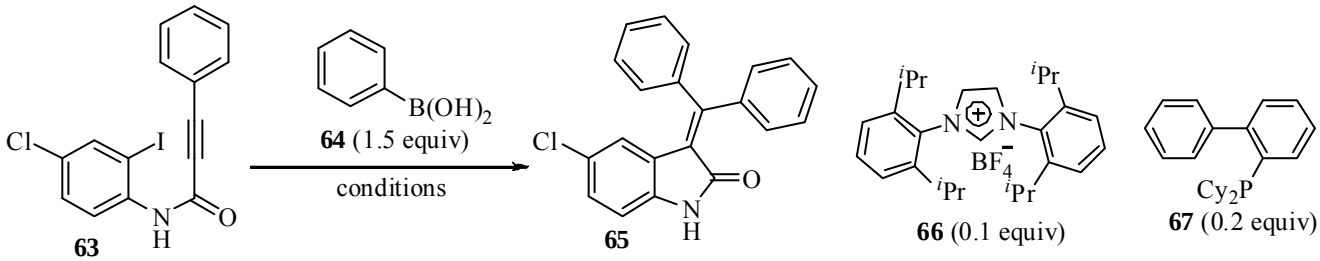
Using a small screening set of different catalysts Player *et al*.[39] demonstrated that domino carbocyclization/Suzuki coupling of alkynylamide **63** under both microwave and ambient temperature afforded the desired (*E*)-3,3-(diarylmethylene)indolines **65** in 48-78% yields. More activating carbene ligand precursor **66**[40] and Buchwald's ligand, 2-dicyclohexylphosphinobiphenyl ligand **67**[41] were found to be less effective to promote the reaction even under the microwave condition (**Scheme 18**).



Scheme 16



Scheme 17

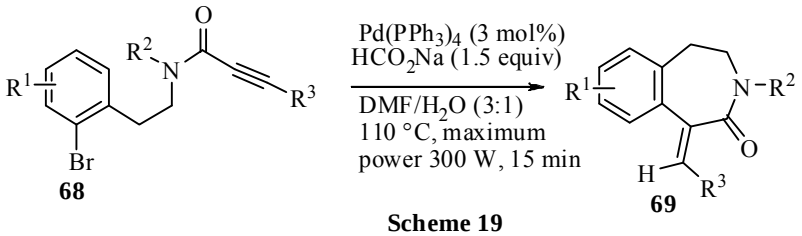


Scheme 18

A new synthetic strategy based on the microwave-assisted intramolecular hydroarylation was developed for the synthesis of medium-sized nitrogen heterocycles.[42] Thus seven-membered heterocycles **69** were

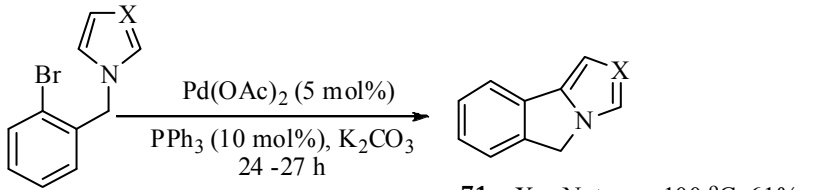
synthesized in moderate-to-good yields starting from propynoic acid amides **68** using $Pd(PPh_3)_4$ and HCO_2Na (**Scheme 19**).

$Pd(OAc)_2$-PPh_3-catalyzed intramolecular carbopalladation of 1-(2-bromobenzyl)-1*H*-imidazole **70a** was carried out to afford fused heteroaromatic compounds, 5*H*-imidazo[5,1-*a*]isoindole **71a**.[43] Attempted reaction at higher temperature afforded better yield of **71a** (**Scheme 20**). Similarly, 5*H*-imidazolo[2,1-*a*]-isoindoles[44] may also be synthesized by intramolecular Heck reaction sequence.



68 **69**

Scheme 19

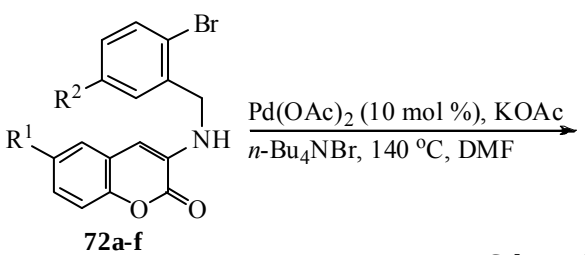


70a, X = N
70b, X = CH

71a, X = N, temp: 100 °C, 61%
temp: 140 °C, 77%
71b, X = CH, temp: 100 °C, 82%

Scheme 20

We have utilized the Jeffery's two-phase protocol for the construction of a number of tetracyclic coumarin-annulated nitrogen heterocycles from **72a-f** (**Scheme 21**).[45] By using $Pd(OAc)_2$ as catalyst, KOAc as base, and *n*-Bu_4NBr as additive in DMF a series of tetrahydropyrido[2,3-*c*]coumarin derivatives **73a-f** were synthesized.

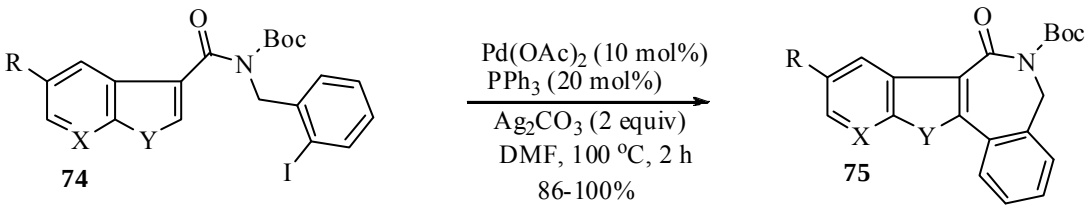


72a-f

73a, $R^1 = R^2 = H$, 88%
73b, $R^1 = H$, $R^2 = OMe$, 81%
73c, $R^1 = OMe$, $R^2 = H$, 77%
73d, $R^1 = R^2 = OMe$, 86%
73e, $R^1 = Me$, $R^2 = H$, 82%
73f, $R^1 = Me$, $R^2 = OMe$, 80%

Scheme 21

An efficient route for the construction of complex heterocycle **75** containing benzazepine moiety has been achieved via an intramolecular biaryl coupling reaction at position 2 of the heterocyclic systems such as **74** (**Scheme 22**).[46]



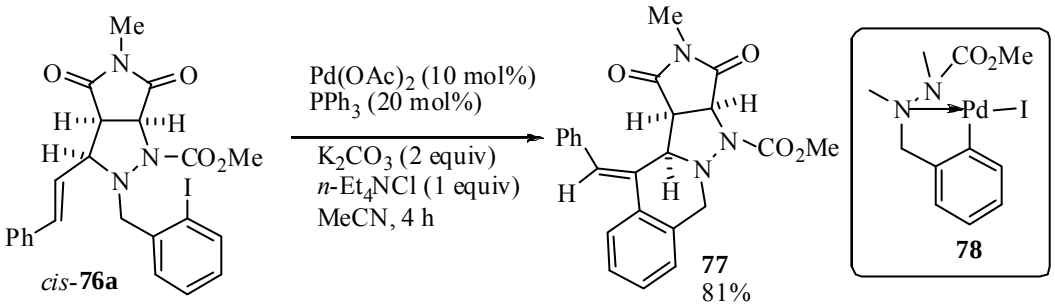
74

R = H, OMe; X = CH, N; Y = NTs, S

75

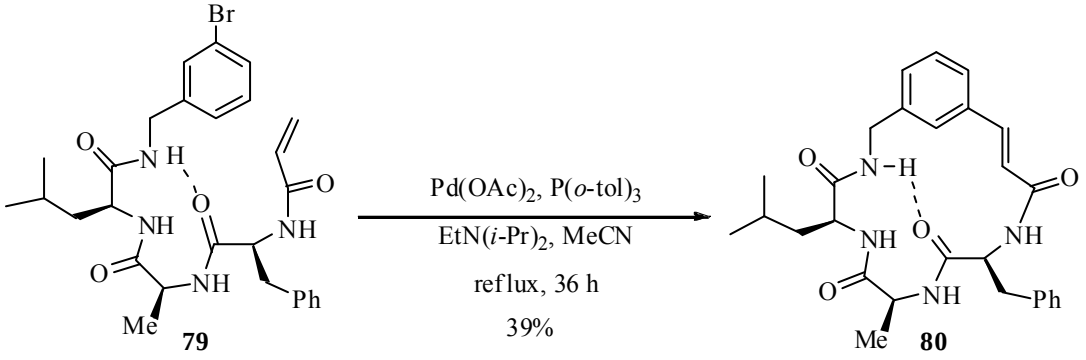
Scheme 22

Grigg and co-workers recently reported[47] an interesting observation during the course of cyclization of the substrates *cis*-**76a** and *trans*-**76b** by the palladium-catalyzed intramolecular Heck reaction. When the *cis*-isomer **76a** was treated with a catalytic system comprising $Pd(OAc)_2$, PPh_3, *n*-Et_4NCl and K_2CO_3, the corresponding *exo*-cyclized product **77** was obtained with exclusively (*Z*)-configuration due to the *cis*-addition of ArPdI to the styryl moiety followed by *cis*-*β*-hydride elimination. The possible explanation is that the conformational differences in the pyrazolidine moiety of the chelated oxidative addition product **78** may destabilize *trans*-isomer to the extent that the cyclization is disfavored (**Scheme 23**).



Scheme 23

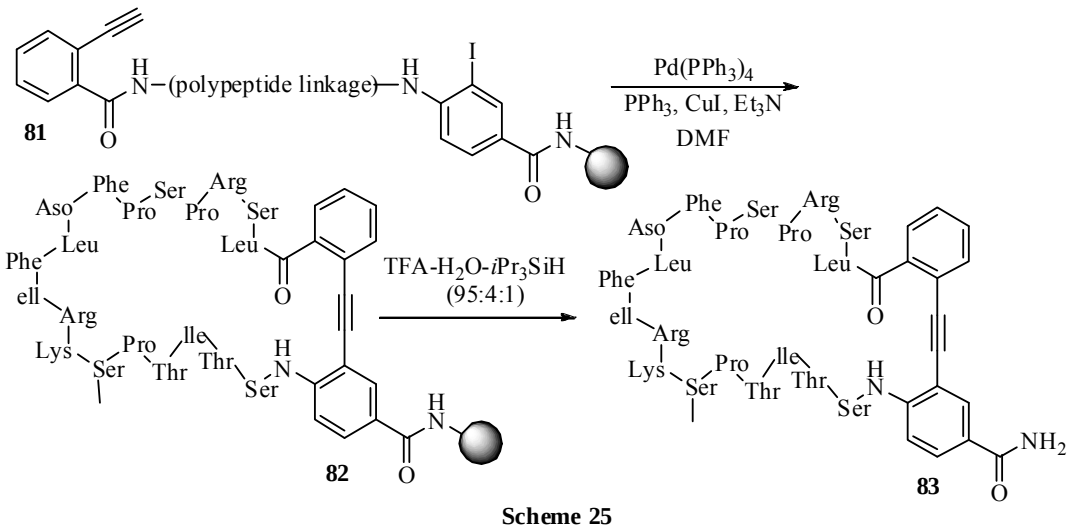
Similarly, tripeptides having 3-bromobenzylamino group at the C-termini and an acryloyl group at the *N*-termini **79** underwent intramolecular Heck reaction utilizing $Pd(OAc)_2$/P(*o*-tol)$_3$/EtN(*i*-Pr)$_2$ to afford the corresponding cyclic peptide **80** (**Scheme 24**).[48]



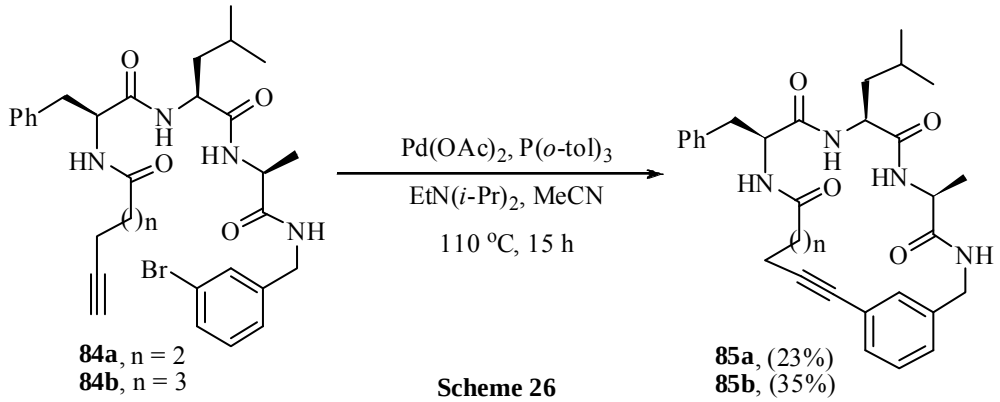
Scheme 24

Sonogashira[10] coupling was exploited for the solid-phase synthesis of a cyclic peptide containing 21-residue epitope present in the A-B loop of the C-3 domain of human immunoglobulin E.[49] The key step to construct the 65-membered ring **82** was achieved in 13% yield from the corresponding acyclic precursor **81** on treatment with $Pd(PPh_3)_4$-CuI-PPh_3-Et_3N catalytic system in DMF (**Scheme 25**).

Copper-free Sonogashira coupling was utilized for the macrocylization of di- and tri-peptides **84** to give cyclic peptides **85** with rigid linkers leading to unusual peptidometrics[50] (**Scheme 26**).

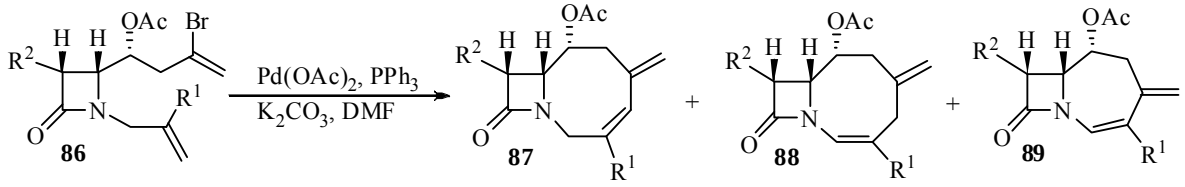


Scheme 25



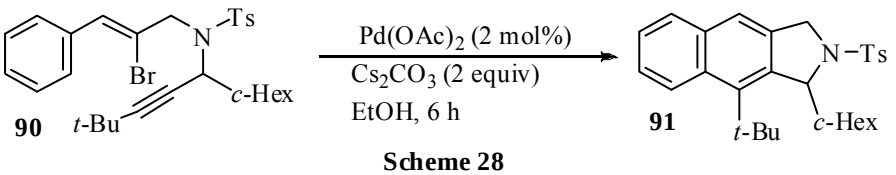
Scheme 26

An efficient route for the stereocontrolled synthesis of bicyclic *β*-lactams via palladium-catalyzed intramolecular Heck reaction[51] was best performed using $Pd(OAc)_2$, PPh_3 and K_2CO_3 in DMF. The regiochemistry of the reaction was observed to be highly influenced by the reaction temperature (**Scheme 27**). At lower temperature exclusive formation of 8-*endo-trig* cyclized product **87** along with very little or no formation of 7-*exo-trig* cyclized product **89** was obtained from the precursors **86**. At higher temperature, the reaction afforded isomeric bicycle **88** along with **89**.



Scheme 27

Ohno and Tanaka demonstrated that bromoenyne **90** when treated with $Pd(OAc)_2$ and Cs_2CO_3 in EtOH underwent tandem cyclization to give the tricyclic heterocycles **91** in good yields (**Scheme 28**).[52]



Scheme 28

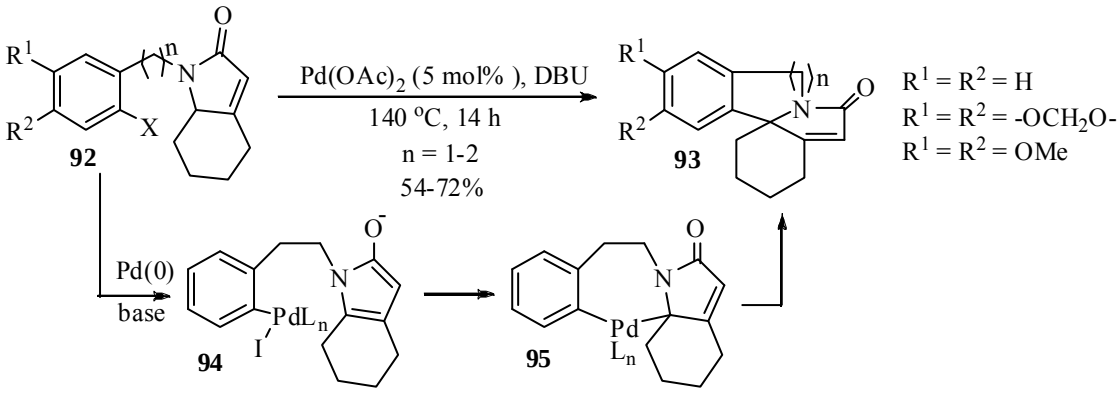
2.2 REACTIONS OF ENOLATES

Palladium-catalyzed intramolecular coupling reaction of tethered vinyl or aryl halides and ketone enolates provides a useful route to a wide variety of heterocycles.[11,53]

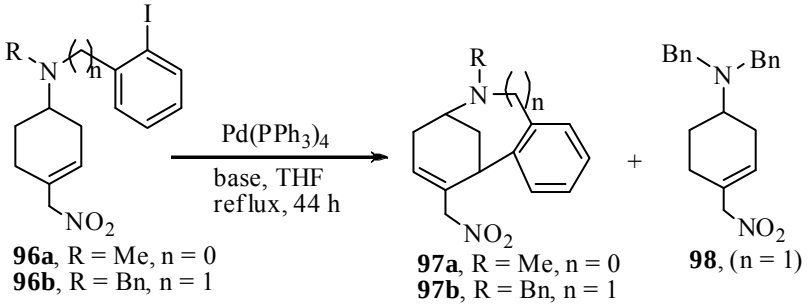
2.2.1 REACTIONS OF ARYL HALIDES

α,β-Unsaturated-*γ*-lactam **92** containing a haloaryl moiety tethered to nitrogen on treatment with $Pd(OAc)_2$ in DBU underwent cyclization to afford five- and six-membered ring conpounds **93** (**Scheme 29**).[54] A plausible mechanism[55] for this reaction involves the formation of the palladium complex **94** followed by transmetallation to give **95** and reductive elimination to afford **93**.

Intramolecular Heck reaction of aryl iodide **96a** and **96b** on to *β,γ*-unsaturated nitro-derivative in with $Pd(PPh_3)_4$ as catalyst gave different results depending on the nature of the base used (**Scheme 30**).[56] While KOPh gave the cyclized compounds **97a**, **97** and **97b** in good yields KO*t*-Bu proved completely ineffective, giving either complex reaction mixtures or the dehalogenation product **98** instead of the cyclized product **97b**.



Scheme 29

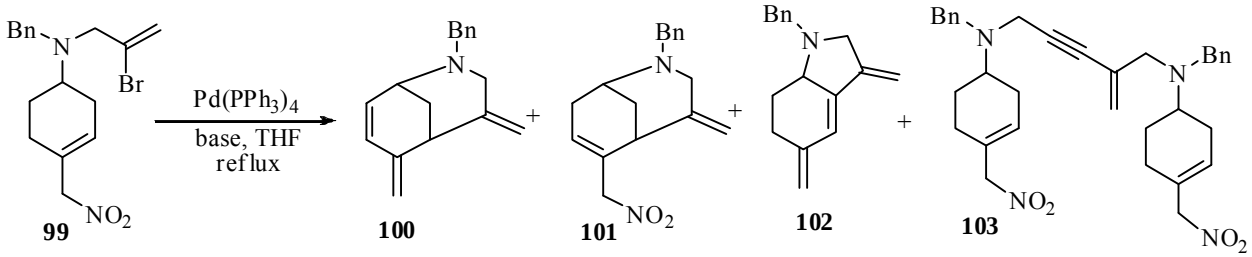


Scheme 30

2.2.2 REACTIONS OF VINYL HALIDES

β,γ-Unsaturated nitro-derivatives[57] as enolate type nucleophile were found to be efficient terminators in the palladium-catalyzed intramolecular coupling with amino-tethered vinyl halide **99**. $Pd(PPh_3)_4$-catalyzed transformation afforded four different products **100-103**. The product formation is dependent on the nature and amount of the base used.[56] Potassium phenoxide (KOPh) is the base of choice in these reactions as it gives exclusively the desired 2-azabicyclo[3.3.1]nonane moiety **101**. Tertiary butoxide (KO*t*-Bu) and Cs_2CO_3 afforded the bridged 1,4-elimination product **100** along with normal Heck product

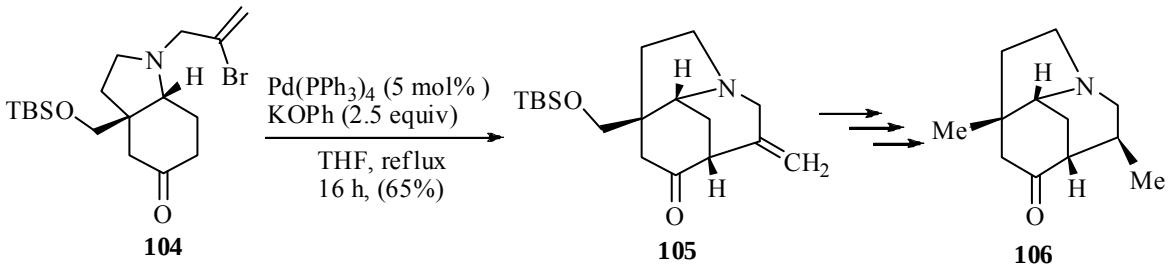
hydroindole **102**. The dimer **103** was obtained when 2.5 equiv of KO*t*-Bu was used as a base (**Scheme 31**).



Scheme 31

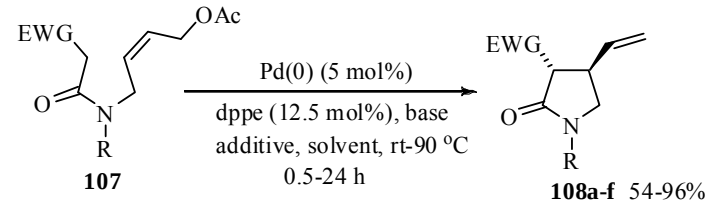
The formation of bridged compounds **101** clearly indicated the involvement of sequential nucleophilic substitution on palladium by the nitronate, reductive elimination and base promoted isomerization. However, in the presence of Pd(0), compound **101** may generate a π-allyl complex by oxidative addition which via 1,4-elimination pathway[58] may give the compound **100**.

Bonjoch *et al*. reported the synthesis of 4-azatricyclo[5.2.2.0^{4,8}]undecan-10-ene core of the natural product calyciphylline **A** where palladium-catalyzed intramolecular enolate alkenylation was utilized as the key step.[59] Thus compound **104** containing an amino-tethered vinyl bromide with a ketone when subjected to $Pd(PPh_3)_4$ and KOPh afforded the tricylic core system **105**. The compound **105** was converted in several steps to the target azatricyclic ketone **106** (**Scheme 32**).

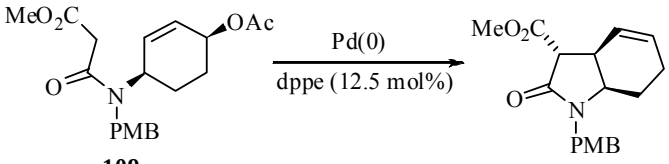


Scheme 32

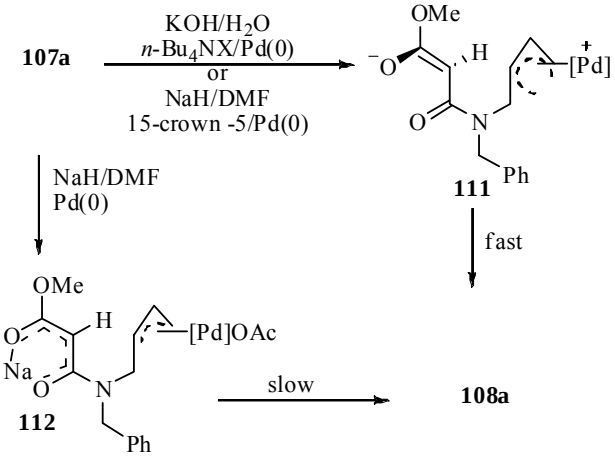
Regio-and stereoselective formation of γ-lactam could be achieved via the intramolecular 5-*exo* reaction between stabilized acetamide enolate anion with properly tethered η^3-allyl-palladium appendage.[60] An investigation on the free enolate alkylation by phase transfer catalysis[61] compatible with the palladium catalysis[62] revealed that the use of *n*-Bu_4NBr as catalyst, $[Pd(C_3H_5)Cl]_2$ as palladium source, dppe as ligand, and KOH as base, in a biphasic CH_2Cl_2/H_2O (1/1; v/v) system, resulted in the formation of hexahydro indole derivatives in high yield.[63] The cyclization of **109** with crown ether 15-C-5 (1.2 equiv) under the same reaction conditions {NaH/DMF/$Pd(OAc)_2$/dppe-based} afforded the hexahydroindole derivatives **110** in moderate-to-good yields (**Scheme 33**). Remarkable efficiency of these new cyclization conditions may be due to the formation of highly reactive zwitterionic[64] enolates/η^3-allyl intermediates **111** under either biphasic PTC conditions or Na-sequestered homogeneous conditions (**Scheme 34**).[65]



107a, EWG = CO_2Me; R = Bn **107b**, EWG = CO_2Me; R = PMB
107c, EWG = CN; R = Bn **107d**, EWG = SO_2Ph; R = Bn
107e, EWG = SPh; R = Bn **107f**, EWG = SO_2Ph; R = Bn



Scheme 33



Scheme 34

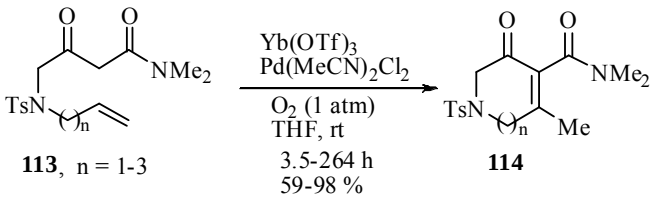
The oxidative cyclization of various *N*-alkenyl *β*-keto amides **113** utilizing Pd(II) catalyst and $Yb(OTf)_3$ as lewis acid has been reported.[66] The reaction underwent through enol formation and intramolecular attack of neucleophilic enol towards Pd(II)-activated olefin[67] (**Scheme 35**).

3. CYCLIZATION VIA C-H BOND FUNCTIONALIZATION REACTIONS

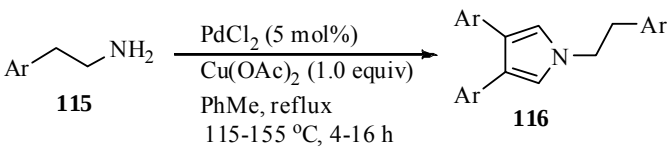
Palladium-catalyzed functionalization of C-H bond[68] has undergone a rapid development over the past decade.[69] The potentiality of this excellent protocol has proven to be extremely useful for the synthesis of a wide variery of N-heterocycles under mild conditions.[70] In general the cyclization via aromatic C-H functionalization proceeds through Pd(IV) intermediate generated by electrophilic palladation on second aromatic or heteroaromatic ring followed by reductive elimination of palladium to afford the heterocycles.[71]

3.1 FUNCTIONALIZATION OF ALKANE C-H BONDS

The development of catalytic system for direct functionalization of alkane sp^3 C-H bond is of considerable interest.[72] The sp^3 C-H bond adjacent to amines are realatively activated and can be functionalized under special condition.[73] Shi *et al*. reported an unusual formation of pyrrole **116** in the multiple deprotonations and deaminations of phenethylamines **115**.[74] The reaction was carried out in the presence of $PdCl_2$, $Cu(OAc)_2$ in refluxing PhMe. The efficiency of the transformation seemed to be highly dependent on the electronic effects of the substituents on the aromatic ring and the trisubstituted pyrrole derivatives were produced (**Scheme 36**).



Scheme 35

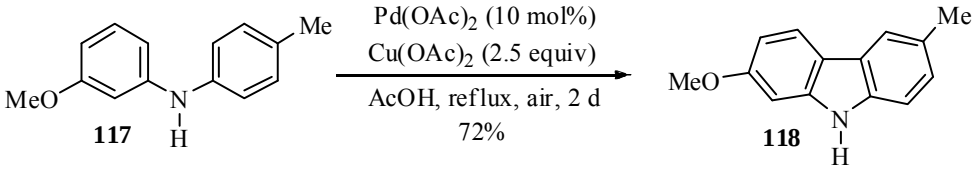


Scheme 36

3.2 FUNCTIONALIZATION OF AROMATIC C-H BONDS

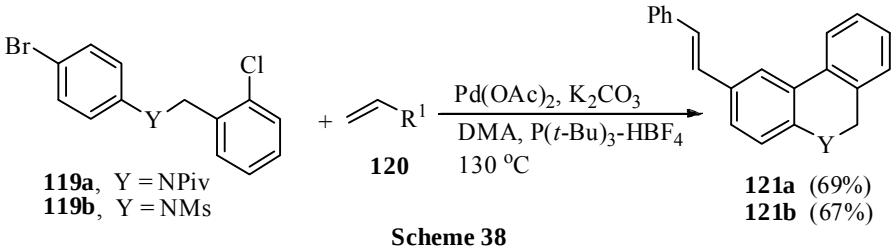
3.2.1 DIRECT FUNCTINALIZATION REACTIONS

The palladium-catalyzed direct functionalization of aromatic or heteroaromatic C-H bond[75] via C-H activation is a versatile way to generate a wide variety of *N*- and *O*-heterocycles under mild conditions.[76] Pd(II)-catalyzed C–H bond activation followed by oxidative cyclization of diaryl amine[77] **117** was utilized for the construction of the 9*H*-carbazole skeleton **118**. The reaction was carried out by utilizing $Pd(OAc)_2$ and an excess of $Cu(OAc)_2$ in AcOH to afford the carbazole derivative (**Scheme 37**).



Scheme 37

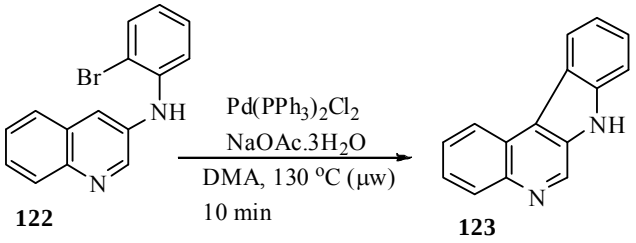
It was observed that by employing a single catalytic system $Pd(OAc)_2/P(t\text{-}Bu)_3\text{-}HBF_4/K_2CO_3$ in the presence of styrene, compound **119a,b** underwent domino intramolecular Heck reaction and direct arylation reaction to give the products **121a**,**b** in one pot[78] (**Scheme 38**).



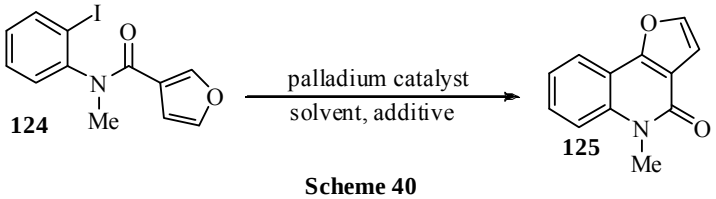
Scheme 38

The intramolecular arylation of 3-(2-bromophenylamino)quinoline **122** employing $Pd(PPh_3)_2Cl_2$ as catalyst and $NaOAc.3H_2O$ as base was tested both under heating and microwave irradiation.[79] Although, in both the cases 7*H*-indolo[2,3-*c*]quinoline **123** was obtained as the major product, microwave irradiation process was found to be superior to normal refluxing condition (**Scheme 39**).

An extensive investigation[80] of the effect of catalyst, base and temperature on the palladium-catalyzed intramolecular arylation to give 5-methylfuro[3,2-*c*]quinolin-4(5*H*)-one has recently been reported. The condition developed by Kuroda and Suzuki[81] was found efficient as the desired compound **125** was obtained in 83% yield from the amide precursor **124** (**Scheme 40**). When the reaction was performed using PdO catalyst and potassium acetate as base in polar solvent DMA at 150 °C the desired tricyclic compound was obtained in 89% yield.

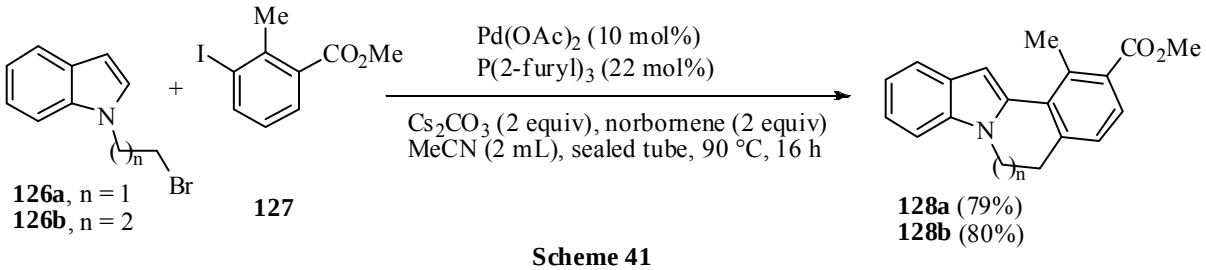


Scheme 39



Scheme 40

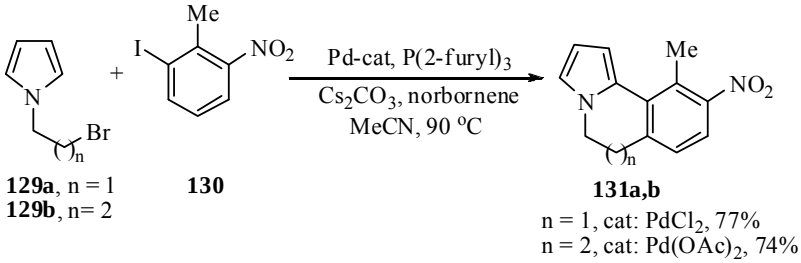
Lautens *et al*. developed a new and straightforward $Pd(OAc)_2$-catalyzed, norbornene-mediated one step approach to highly substituted six- and seven-membered annulated indoles **128a**,**b** using readily available starting materials *N*-brormoalkylindoles **126a**,**b** and aryl iodide **127**.[82] The basic strategy of the synthesis was based on domino aromatic alkylation/aryl-heteroaryl coupling and also involved an aromatic sp^2 C-H activation to generate heterocycles **128** in moderate-to-excellent yields (**Scheme 41**).



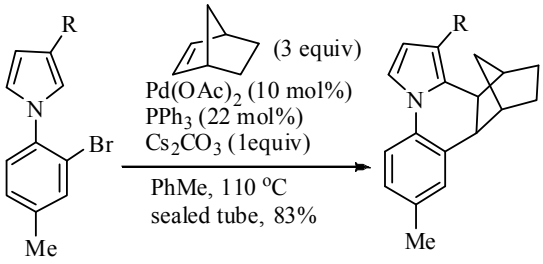
Scheme 41

Similarly, this domino aromatic alkylation/aryl-heteroaryl coupling strategy was also applied to the synthesis of a number of pyrrole-annulated six- and seven-membered heterocycles[83] (**Scheme 42**).

Substituent effect on the regioselectivity of domino annulation of pyrrole with norbornene was also reported.[84] With unsubstituted pyrrole **132**, the annulation in the presence of $Pd(OAc)_2$ as catalyst, PPh_3 and Cs_2CO_3 proceeded efficiently to afford the polycyclic heterocycle **133** (**Scheme 43**).

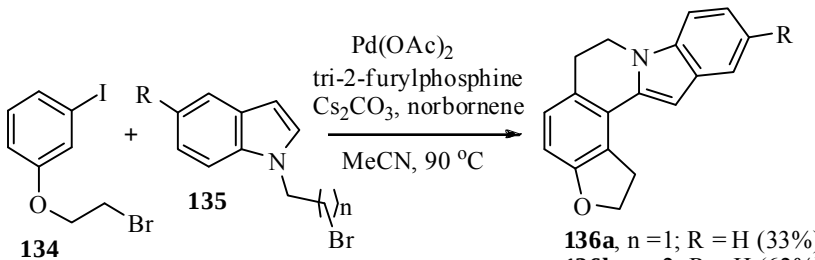


Scheme 42



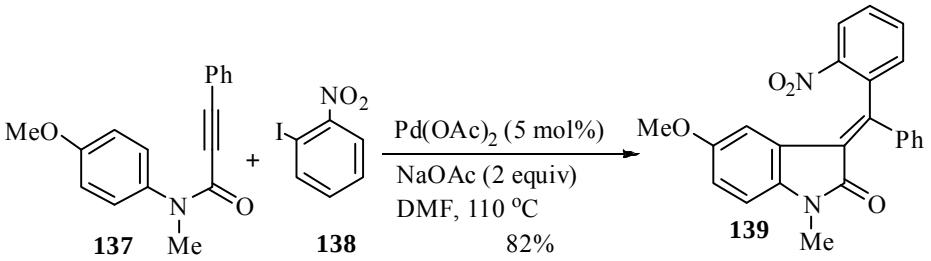
Scheme 43

The norbornene-mediated and $Pd(OAc)_2$-catalyzed reaction of **135** and **134** underwent annulation via three C-H activation in the presence of PPh_3 as ligand to furnish the pentacyclic indole-annulated heterocycles **136** (**Scheme 44**).[85]



Scheme 44

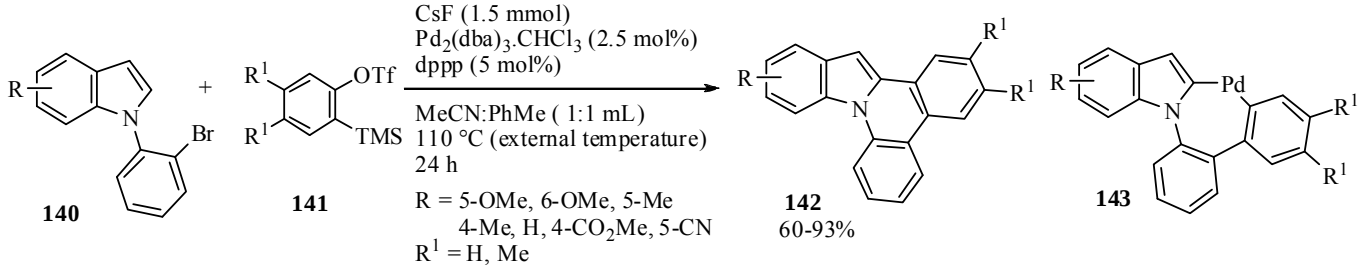
A highly efficient palladium-catalyzed synthesis of unsymmetrically substituted 3-(diarylmethylenyl)indolines **139** has been developed by the reaction between *N*-protected-*N*-aryl-3-phenylpropiolamide **137** and 2-iodonitrobenzenes (**Scheme 45**).[86] Under aforesaid reaction conditions the cyclization of differently substituted diaryl alkynyl amide occurred preferably at the electron poor benzene ring which is incompatible with the S_EAr mechanism for the C-H activation step.[87,88]



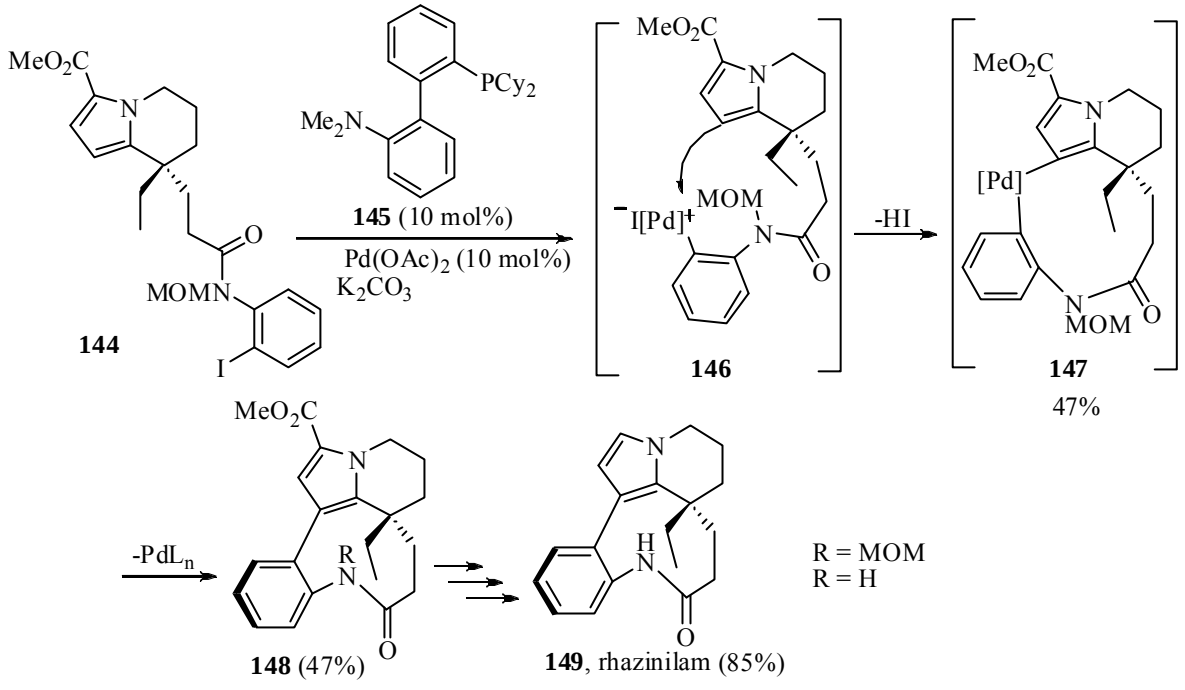
Scheme 45

The intermolecular carboannulation of 1-(2-bromophenyl)-1*H*-indoles **140** with *o*-trimethylsilyl phenyltriflate in the presence of $Pd_2(dba)_3.CHCl_3$ as catalyst and dppp as ligand using mixed solvent MeCN-PhMe (1:1) afforded indolo[1,2-*f*]phenanthridine **142** (**Scheme 46**).[89] The reaction is assumed to proceed via the formation of benzyne intermediate, generated in situ via elimination of *o*-trimethylsilyl phenyltriflate by CsF. The Pd(0) complex may undergo the oxidative addition[90] with 1-(2-bromophenyl)-1*H*-indole to give the arylpalladium intermediate which may then get converted to intermediate **143** via a palladacycle intermediate. Reductive elimination from intermediate **143** may generate the product **142**.

A short synthesis of rhazinilam **149**,[91] a potent anticancer agent, was developed by Trauner *et al.*[92] The key cyclization step for the construction of the nine-membered lactam ring was achieved by heating **144** with $Pd(OAc)_2$ and Buchwald's 'davephos'[93] ligand **145** (**Scheme 47**).



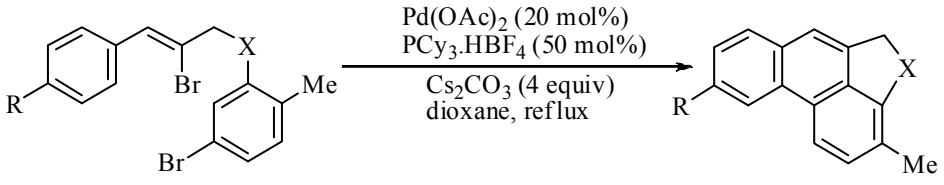
Scheme 46



Scheme 47

The cyclization reaction may proceed through intramolecular nucleophilic attack of the pyrrole moiety onto the Pd(II) center in **146** followed by deprotonation[94] and reductive elimination of Pd(0) from the complex **147** leading to the formation of aryl-heteroaryl bond. Finally, rhazinilam **149** was obtained from **148** in few steps.

Tanaka *et al*. reported direct construction of fused aromatic ring systems by palladium-catalyzed "zipper-mode"[95] double C-H bond activation process. Treatment of **150** with a catalytic amount of $Pd(OAc)_2$ and $PCy_3.HBF_4$ in the presence of Cs_2CO_3 in dioxane afforded[96] 4,5-naphtho[3,2,1-*cd*]indole derivatives **151** (**Scheme 48**).



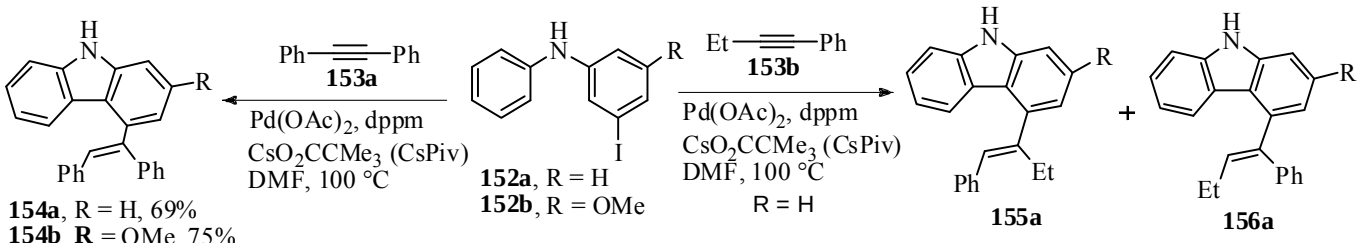
150, X = NTs, NMs, NPiv; R = OMe, Me, CO_2Me

151, 42-63%

Scheme 48

3.2.2 CYCLIZATION VIA 1,4-PALLADIUM MIGRATION

Excellent ability of palladium to insert into unactivated C-H bond is of great interest as it affords wide variety of useful synthetic processes.[69] The through-space palladium rearrangement with simultaneous C-H activation provides a novel way to introduce palladium into a specific location within organic molecules. Recently, Larock *et al*. have applied the nitrogen directed vinylic to aryl palladium migration strategy involving domino C-H activation process for the synthesis of carbazole derivatives.[97] The synthetic studies were carried out in the presence of $Pd(OAc)_2$, bis(diphenylphosphino)methane (dppm) and CsO_2CCMe_3 (CsPiv) in DMF.[98] The reaction with symmetrical alkynes afforded the carbazole **154a** and **154b** exclusively from the starting materials **152a** and **152b** respectively. However, with an asymmetrical alkyne the formation of two regioisomeric compounds **155a**+**156a** in a 10:1 ratio was obtained (**Scheme 49**).



154a, R = H, 69%
154b, **R** = OMe, 75%

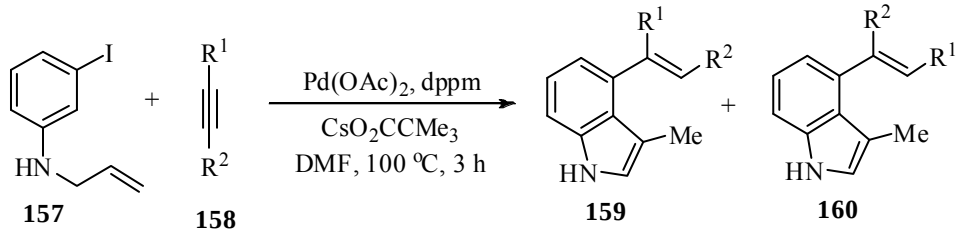
152a, R = H
152b, R = OMe

155a

156a

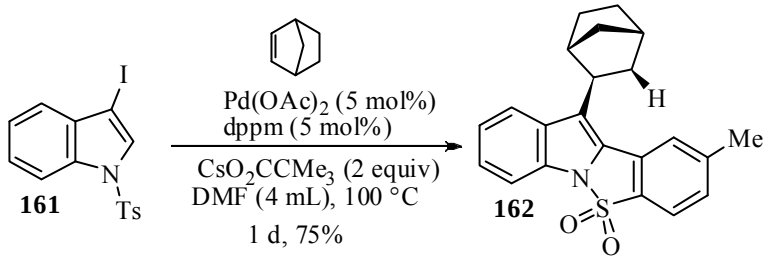
Scheme 49

The same group also showed that the reaction between *N*-allyl-3-iodoaniline **157** under the same reaction conditions furnished the indole **159** as a single diastereoisomer where as the same reaction with unsymmetrical alkyne generated two isomeric indole derivatives **159** and **160** in 10:1 to 15:1 ratios respectively[99] (**Scheme 50**).



Scheme 50

An indole derivative **162** was efficiently synthesized from 3-iodo-1-(4-tosyl)indole **161** in the presence of norbornene as olefin source. The observed stereochemistry of the compound was due to initial *cis*-addition of indol-3-yl palladium iodide to norbornene[100] (**Scheme 51**).

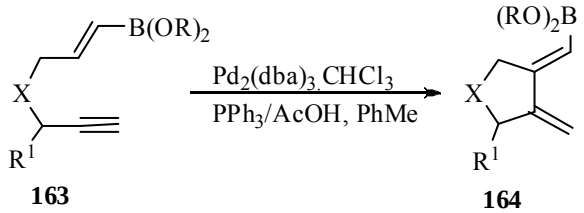


Scheme 51

4. CYCLIZATION OF 1,*n*-UNSATURATED SYSTEMS: CYCLOISOMERIZATION AND CASCADE ADDITION-CYCLIZATION REACTIONS

4.1 CYCLOISOMERIZATION REACTIONS

Palladium-catalyzed cycloisomerization reaction has proven as one of the versatile process to construct cyclic compounds from the acyclic 1,*n*-unsaturated precursors.[101] In general, 1,6-unsaturated system affords five-membered cyclic product. The cycloisomerization of enyne **163** in the presence of palladium source $Pd_2(dba)_3.CHCl_3/PPh_3$/AcOH afforded five-membered heterocycles **164** (**Scheme 52**).[102] By utilizing this protocol, a number of five-membered nitrogen heterocycles were synthesized.



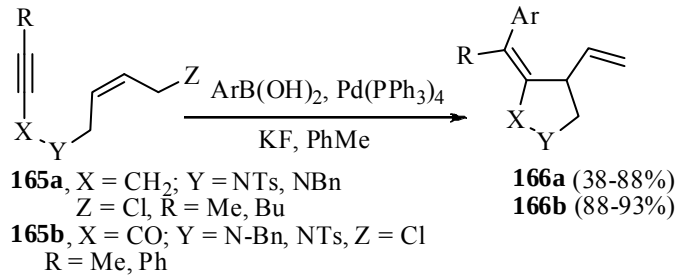
164a, X = NTs, R^1= H, 85%
164b, X = NTs, R^1 = Me, 80%
164c, X = N-Bn, R^1 = H, 73%

Scheme 52

Zhang and collaborators extensively investigated the palladium-catalyzed domino cycloisomerization/Suzuki coupling of 1,6-enynes.[103] By utilizing $Pd(PPh_3)_4$ as catalyst, both electron rich (**165a**) and electron poor (**165b**) enynes underwent this cascade cyclization-coupling reaction to afford five-membered heterocycles **166a** and **166b** with an *exo* double bond (**Scheme 53**).

Ohno et al. reported Pd(0)-catalyzed stereoselective cyclization of allene **167a** for the synthesis of 2,3-*cis*-pyrrolidines **168a**.[104] The cyclization in the presence of iodobenzene was achieved using $Pd(PPh_3)_4$ and

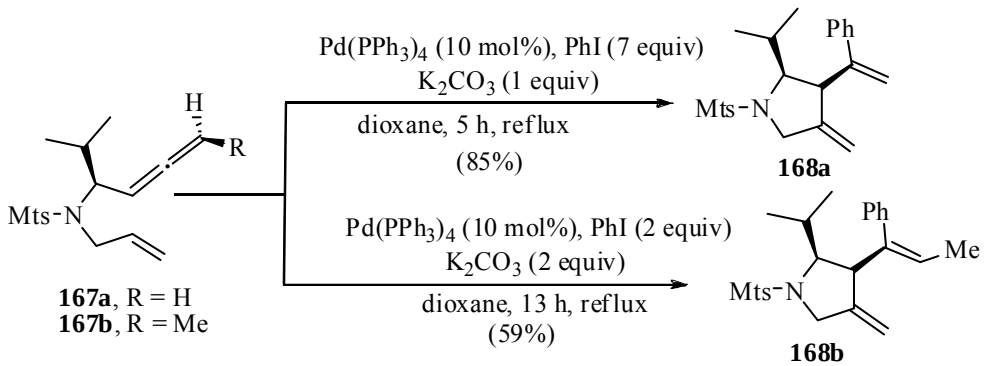
K_2CO_3 in refluxing dioxane to give compound 1**68a**. Internal allene **167b** was also similarly cyclized into five-membered ring **168b**. The observed (*Z*)-geometry of the double bond of **168a** might be a consequence of thermodynamic preference for the *syn*-*π*-allylpalladium(II) intermediate over other isomers (**Scheme 54**).[105]



165a, X = CH_2; Y = NTs, NBn
Z = Cl, R = Me, Bu
165b, X = CO; Y = N-Bn, NTs, Z = Cl
R = Me, Ph

166a (38-88%)
166b (88-93%)

Scheme 53



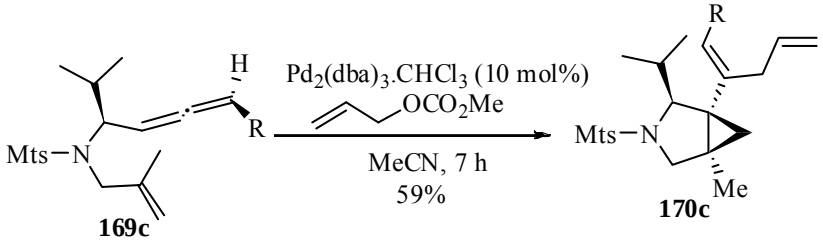
167a, R = H
167b, R = Me

168a

168b

Scheme 54

However, under a different reaction condition [$Pd_2(dba)_3.CHCl_3$ in MeCN at 80 °C] allenenes **169c** underwent steroselective cyclization-cyclopropanation in the presence of allyl carbonate to afford 3-azabicyclo[3.1.0]hexane **170c** (**Scheme 55**).[106] The catalytic cycle for the formation of compound **170c** is suggested to proceed via generation of an unusual palladium carbene intermediate. However, an alternative route via alkyl palladium intermediate may also lead to the cyclopropane derivative.



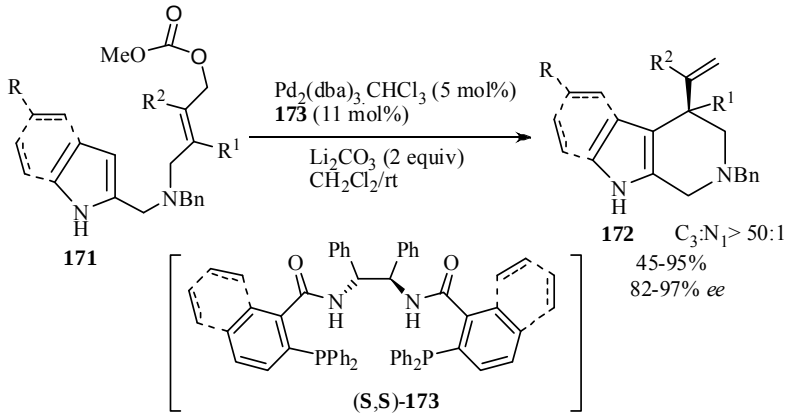
169c

170c
R = H

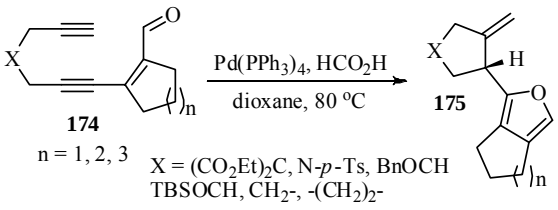
Scheme 55

Indolylcarbonates **171** on treatment with $Pd_2(dba)_3.CHCl_3$ as catalyst and DPPBA-based ligand (**S**,**S**)-**173** commonly known as Trost ligand afforded 4-vinyl-1,2,3,4-tetrahydro-*β*-carbolines **172** in high ee (**Scheme 56**).[107] Pyrrolyl-based polycyclic systems has been synthesized. It is interesting to note that quaternary stereocenter is also accessible through this new approach.

1,6-Diynes **174** bearing a conjugated enone moiety underwent cycloreduction[108] on treatment with $Pd(PPh_3)_4$ and formic acid to afford 2-(2-methylenecycloalkyl)furans **175** in good-to-excellent yields (**Scheme 57**).[109]

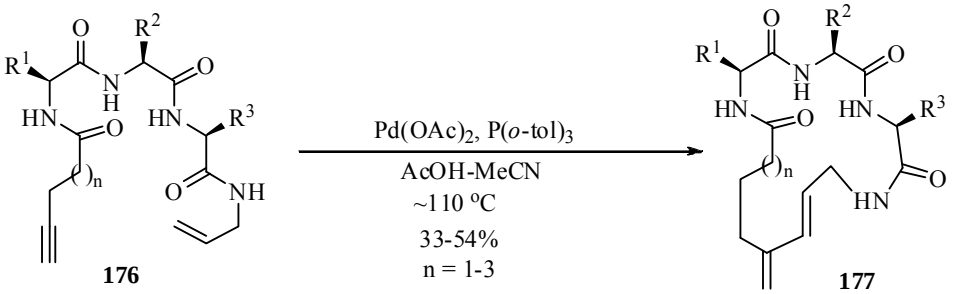


Scheme 56



Scheme 57

The acyclic peptides **176** with varying chain length and amino acid units underwent enyne cycloisomerization to give constrained small cyclic peptides **177** with novel linkers (**Scheme 58**).[110] The reactions were carried out using $Pd(OAc)_2$ as catalyst and P(*o*-tol)$_3$ as ligand. It was anticipated that the linker length might play a role in the *E/Z* selectivity of the endocyclic double bond in products **177**. However, *E*-stereochemistry of the endocyclic double bond and *S-transoid* form of the 1,3-dienes in the cyclic peptide were observed in all the cases.

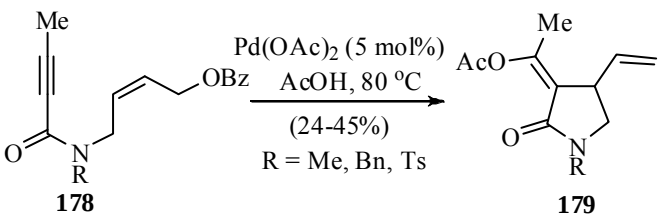


Scheme 58

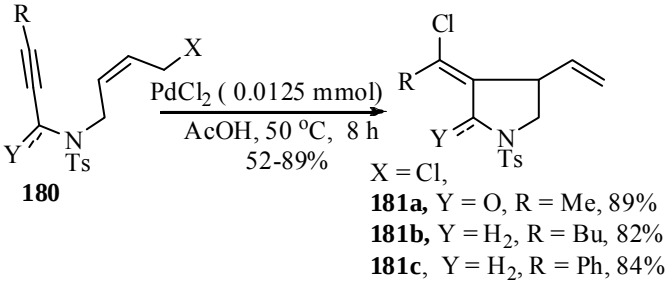
4.2 CASCADE ADDITION-CYCLIZATION REACTIONS

Intramolecular acetoxypalladation-initiated cyclization of *N*-allylic alkylamides **178** for the syntheses of alkylidine-γ-butyrolactams **179** was developed[111] by employing $Pd(OAc)_2$ as catalyst (**Scheme 59**).

An expedient route to the synthesis of stereo-defined α-halomethylene-γ-butyrolactones, lactams and tetrahydrofurans via $PdCl_2$-catalyzed *cis*-chloropalladation-cyclization of 1,6 enynes **180a** in AcOH was developed by Zhang *et al.*[112] The reaction showed excellent stereoselectivity (*E*/*Z* > 99/1) as only five membered (*E*)-**181** were obtained in good yields (**Scheme 60**).

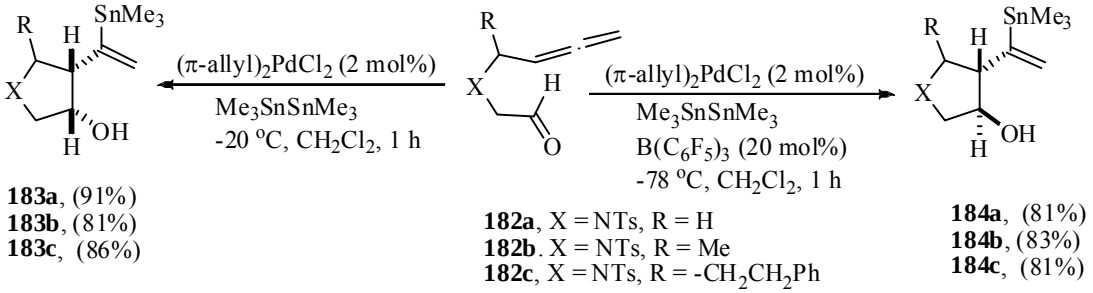


Scheme 59



Scheme 60

Lewis acid additive showed high influence on the diastereoselectivity of the intramolecular allyl transfer reaction of allenic aldehydes **182** with hexamethylditin catalyzed by (π-allyl)$_2$PdCl$_2$ (**Scheme 61**).[113] Moderate-to-good yields of *trans*-products **184** were obtained by using B(C$_6$F$_5$)$_3$ as Lewis acid additive. In the absence of any additive *cis*-products **183** were obtained in good-to-excellent yields.



183a, (91%)
183b, (81%)
183c, (86%)

182a, X = NTs, R = H
182b. X = NTs, R = Me
182c, X = NTs, R = -CH$_2$CH$_2$Ph

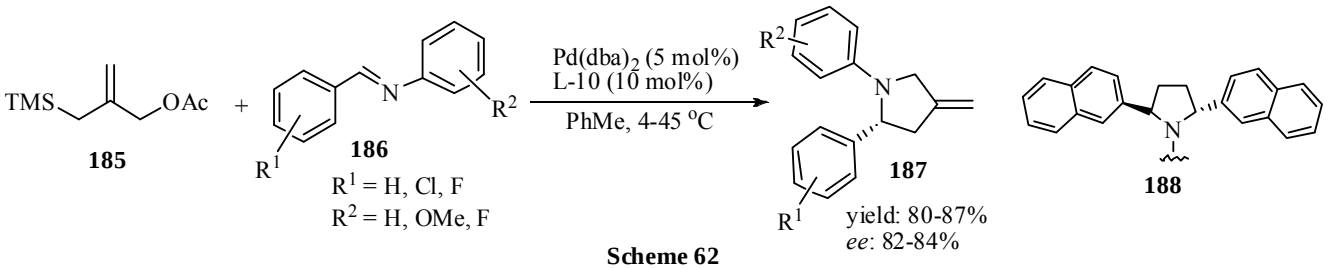
184a, (81%)
184b, (83%)
184c, (81%)

Scheme 61

5. CYCLOADDITION REACTIONS

5.1. [3+2] CYCLOADDITION REACTIONS

Palladium-catalyzed [3+2] cycloaddition[114] reaction is an efficient method to prepare five-membered heterocycles. A number of oxazolidine[115] and imidazolidine[116] derivatives were synthesized by [3+2] cycloaddition between oxiranes and aziridines with heterocumulenes. An extensive investigation on the palladium-catalyzed [3+2] cycloaddition of **185** with different imines **186** was carried out using Pd$_2$(dba)$_3$ as catalyst and phosphoramidite ligand, bis-2-naphthyl ligand **188**, developed by Trost *et al.*[117] The reaction was generally performed at low temperature and both *N*-aryl and *N*-Boc imines underwent cycloaddition to afford substituted pyrrolidines **187** (**Scheme 62**).



185

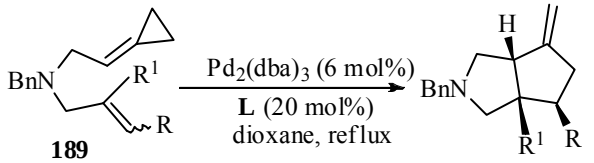
186
R^1 = H, Cl, F
R^2 = H, OMe, F

187
yield: 80-87%
ee: 82-84%

188

Scheme 62

A new mechanistically interesting and challenging [3+2] intramolecular cycloaddition route to bicyclic nitrogen heterocycles,[118] where internal alkenes as two-carbon components in the cycloaddition, has been developed. Thus, alk-5-enylidenecyclopropanes **189** bearing nitrogen atom when refluxed in dioxane (50 mM) using Pd$_2$(dba)$_3$ (6%) and tris(2,4-di-*t*-butylphenyl)phosphine (**L**) (20%) afforded the bicyclic nitrogen heterocycles **190** (**Scheme 63**).



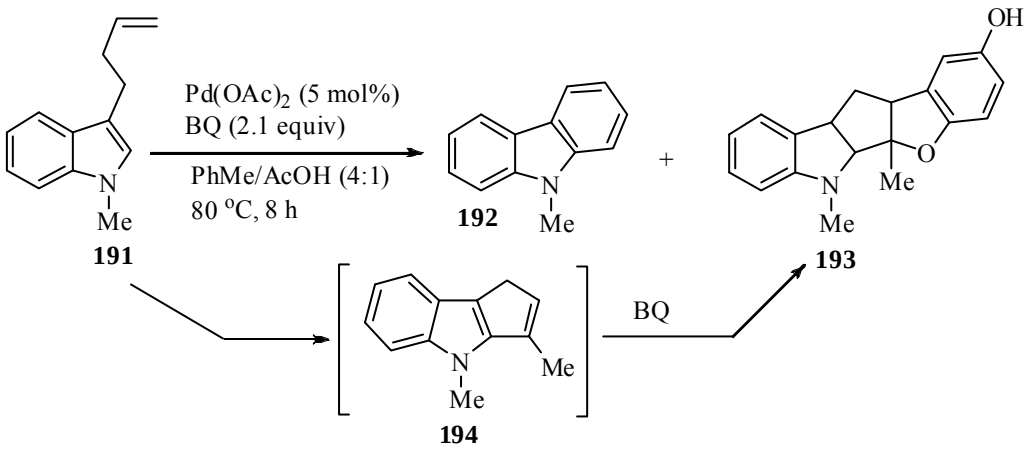
189

L = tris (2,4-di-tert-butylphenyl)phosphine

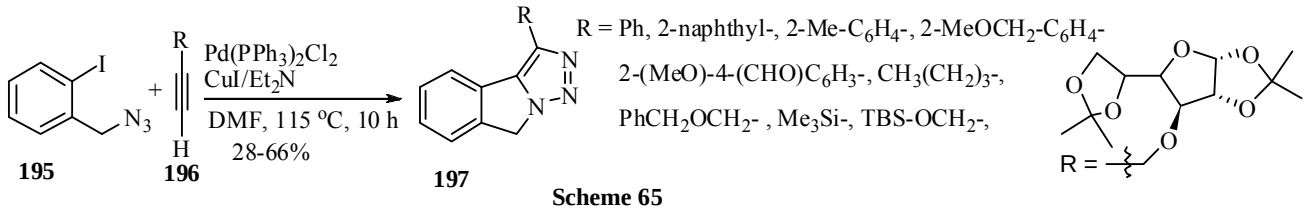
190a, R = R1 = 82%
190b, R = Me, R1 = H, 57%

Scheme 63

An unsusal [3+2] cycloaddition reaction was observed during $Pd(OAc)_2$-catalyzed oxidative cyclization of 3-(3'-alkenyl)-*N*-methyl indole **191** using BQ as oxidant (**Scheme 64**).[119] The reaction afforded an unusual phenolic compound **193** in 27% yield along with the desired *N*-methyl carbazole **192** in 30% yield. The formation of compound **193** presumably proceeded through the intermediate **194**, which underwent formal hetero [3+2] cycloaddition reaction with BQ under the reaction conditions. Isoindoline fused with triazoles was efficiently synthesized by palladium-copper-catalyzed [3+2] cycloaddition reaction.[120] Thus *o*-iodobenzyl azide **195** and terminal alkynes **196** when subjected to $Pd(PPh_3)_2Cl_2$, CuI and Et_3N afforded triazole derivatives **197** (**Scheme 65**).

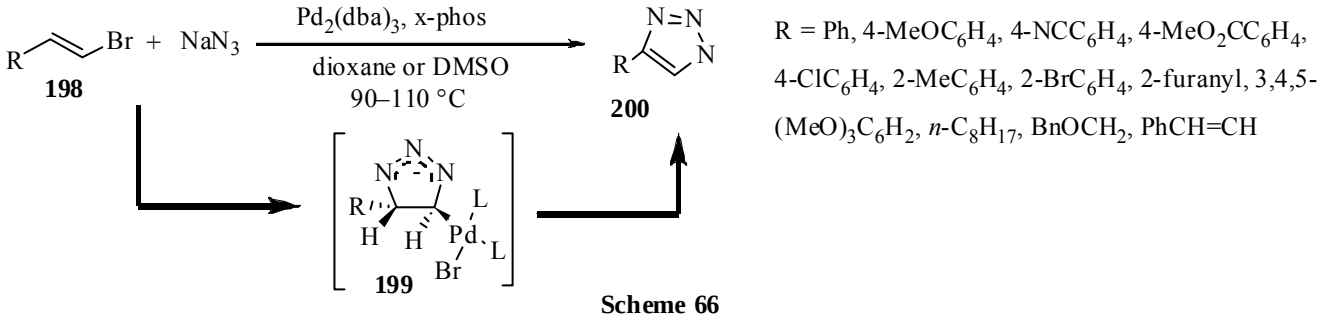


Scheme 64



Scheme 65

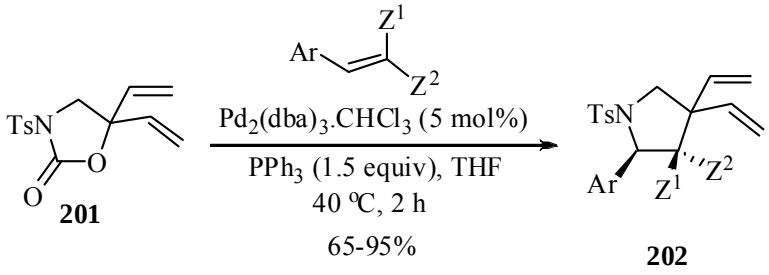
An expedient route to 1*H*-1,2,3-triazole derivatives **200** from sodium azide and alkenyl bromides **198**[121] has been developed by utilizing $Pd_2(dba)_3$ as catalyst and large bite angle ligand x-phos which showed the highest reactivity due to its ability to behave as a *trans*-chelating ligand. The reaction is assumed to proceed via the intermediate **199** generated by a [3+2] cycloaddition of the azide anion with a vinylpalladium species (**Scheme 66**).



Scheme 66

An interesting palladium-catalyzed decarboxylative ring-opening/ [3+2] cycloaddition reaction has been reported.[122] Glycine-derived *N*-tosyl-5,5-divinyloxazolidin-2-one **201** on treatment with $Pd_2(dba)_3.CHCl_3$

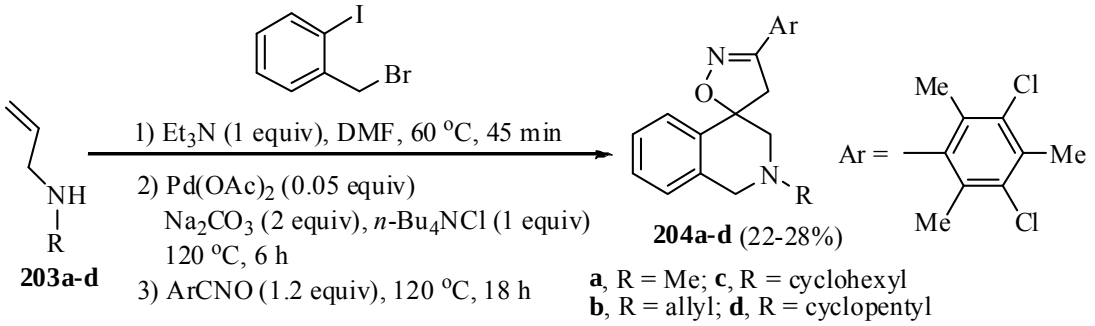
underwent [3+2] cycloaddition with strongly electron-deficient alkylidenemalonate derivatives to give highly substituted pyrrolidines **202** containing two continuous quaternary centers (**Scheme 67**).



201 **202**

Scheme 67

Synthesis of spiro[isoquinolin-4,5'-isoxazole] compounds **204a-d** was achieved by domino intramolecular Heck coupling and 1,3-dipolar cycloaddition.[19] The multicomponent one-pot reaction between 2-iodobenzylbromide, allylamines **203** and 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide was accomplished by using $Pd(OAc)_2$ as catalyst to afford the desired spiro compounds **204** (**Scheme 68**).



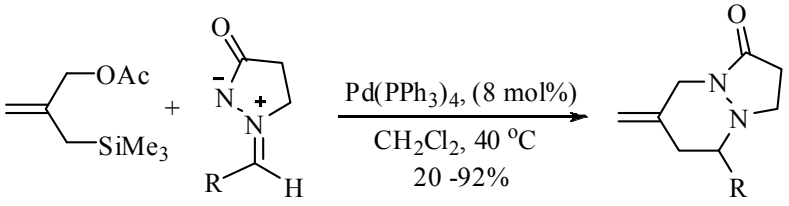
203a-d **204a-d** (22-28%)

a, R = Me; **c**, R = cyclohexyl
b, R = allyl; **d**, R = cyclopentyl

Scheme 68

5.2. [3+3] CYCLOADDITION REACTIONS

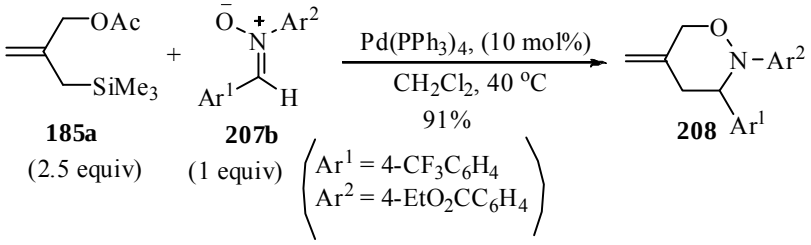
Very few examples of palladium-catalyzed [3+3] cycloaddition have been reported.[123] Hayashi et al. in a recent investigation reported palladium-catalyzed [3+3] cycloaddition of 2-(acetoxymethyl)-3-(trimethylsilyl)propene **185a** with azomethine imine **205a**.[124] The reaction was efficiently carried out in the presence of $Pd(PPh_3)_4$ to give highly functionalized hexahydropyridine derivatives **206** (**Scheme 69**). Similarly, [3+3] cycloaddition reaction of TMM precursors **185a** with **207b** provided the corresponding cycloadduct **208** (**Scheme 70**).



185a **205a** **206**

R = Ph, 4-MeC_6H_4, 4-$CF_3C_6H_4$, 3-ClC_6H_4, 2-FC_6H_4, 2-MeC_6H_4
3-pyridyl, 1-cyclohexenyl, *t*-Bu.

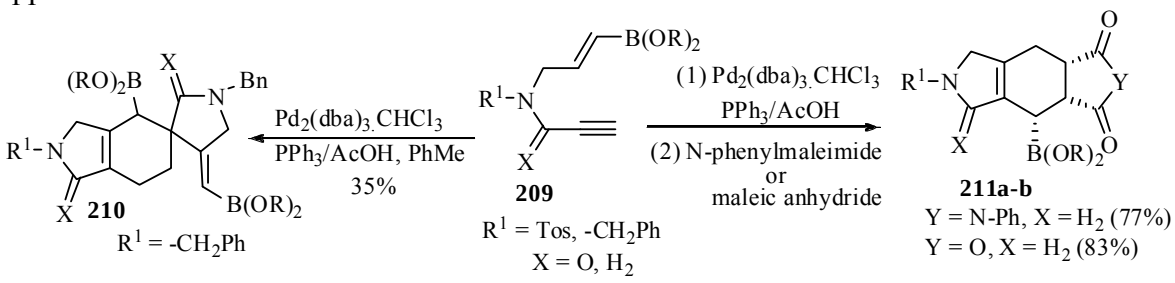
Scheme 69



Scheme 70

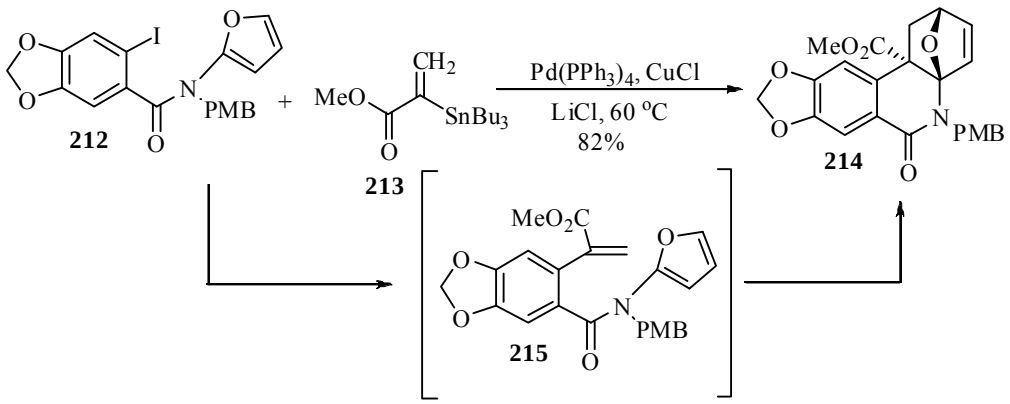
5.3. [4+2] CYCLOADDITION (DIELS-ALDER REACTION)

Catalytic [4+2] cycloaddition reaction between a diene and a dienophile have been extensively applied for the construction of six-membered heterocyclic ring.[125] 1,6-enyne **209a** on treatment with $Pd_2(dba)_3.CHCl_3$ and PPh_3 afforded [4+2] cycloaddition adduct **210** (**Scheme 71**).[102] The reaction proceeds via in situ generation of the diene unit by cycloisomerization. However, trapping of the diene unit with other dienophiles like maleinamide and maleic anhydride gave the tricyclic boronate esters **211a-d** as single diastereomers. The relative configuration of the three stereocenters is in agreement with the expected *endo*-approach.



Scheme 71

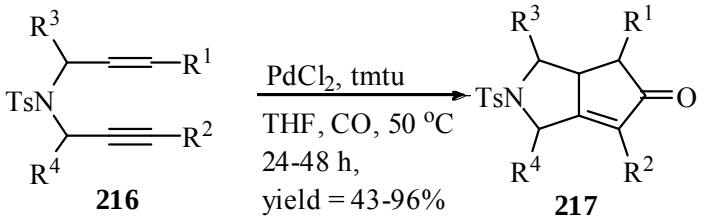
The application of palladium-catalyzed domino Stille coupling and intramolecular [4+2] cycloaddition protocol for the construction of the intermediate oxabicycloadduct **214** was demonstrated during the total synthesis of (±)-lycoridine.[126] The oxabicycloadduct **214** was prepared from amidofuran **212** and methyl-2-tri-*n*-butylstannylacrylate **213** in the presence of $Pd(PPh_3)_4$ (**Scheme 72**). The reaction is suggested to proceed through the expected cross-coupled amidofuran **215** which spontaneously underwent an intramolecular [4+2] cycloaddition to furnish the cycloadduct **214**. It is anticipated that the *exo* orientation of the sidearm of the tethered vinyl group with respect to the oxygen-bridge in the transition state of the cycloaddition step might be responsible for the anti disposition of the carbomethoxy and oxybridge.



Scheme 72

5.4. [2+2+1] CYCLOADDITION REACTIONS

Transition metal-catalyzed [2+2+1] cycloaddition, in particular Pausond-Khand reaction, between two olefin units with carbon monoxide have been well investigated and is considered to be a general method for the construction of five-membered ring compounds containing carbonyl group.[127] Different allylpropargyl amines when subjected to Pausond-Khand reaction utilizing $PdCl_2$ as catalyst and tetramethylthiourea (tmtu)[128] **216** as additive in the presence of CO using THF as solvent at 50 ^oC produced the desired cycloadducts **217** in excellent yields (**Scheme 73**).[129]



Scheme 73

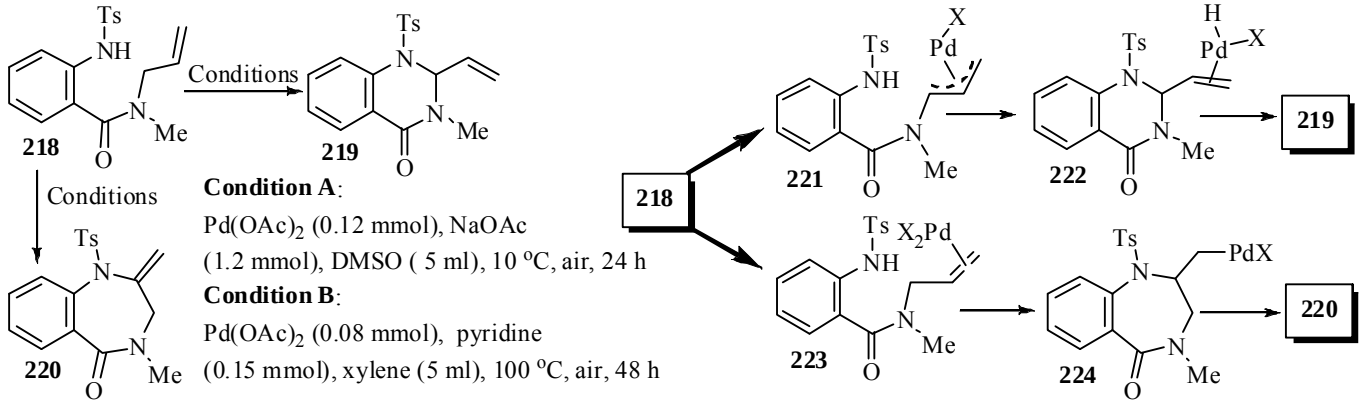
6. HETEROCYCLIZATION REACTIONS: CYCLIZATION VIA CARBON-HETEROATOM BOND FORMATION

6.1. INTRAMOLECULAR ADDITION OF N-H AND C=N BONDS ACROSS ALKENE, ALLENE AND ALKYNE

The applications of Pd catalysis in the formation of carbon-heteroatom bond via intramolecular addition of heteroatom nucleophiles on to carbon-carbon unsaturated bond are the most attractive and important tools in the transition metal-catalyzed synthesis of heterocycles.[1,2]

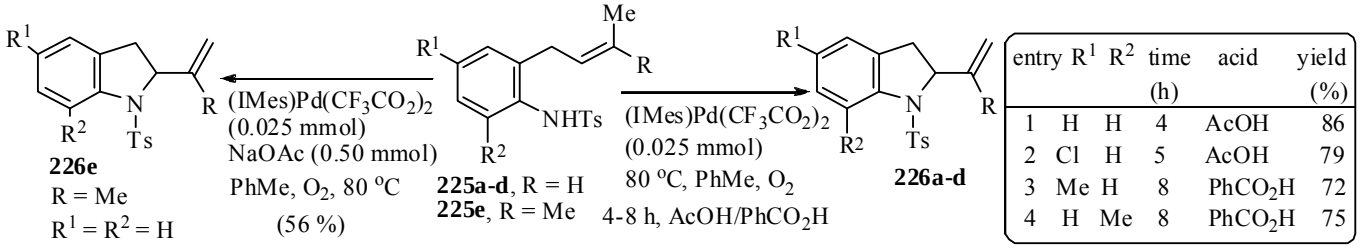
6.1.1. ADDITION TO ALKENE

Alkene appended heteroatom nucleophiles have been found to undergo palladiun(II)-catalyzed heterocyclization to produce a variety of heterocyclic compounds.[130] Both activated and unactivated double bonds can react with the nucleophiles. Pd(II)-catalyzed intramolecular amination of *N*-allyl anthranilamides **218** afforded quinazolin-4-one **219** and 1,4-benzodiazepin-5-one **220** in high yields depending upon the reaction conditions employed (**Scheme 74**).[131] The six-membered quinazoline **219** was obtained when the reaction was performed with $Pd(OAc)_2$ and NaOAc in polar solvent DMSO at 100 ^oC for 24 h. The reaction is suggested to proceed via the initial formation of η^3-allyl-Pd complex **221** and η^2-allyl-Pd-complex **222**.[132] On the other hand, the synthesis of seven-membered benzazepine ring system **220** was achieved by using pyridine as a base in non-polar solvent xylene (**Scheme 74**).



Scheme 74

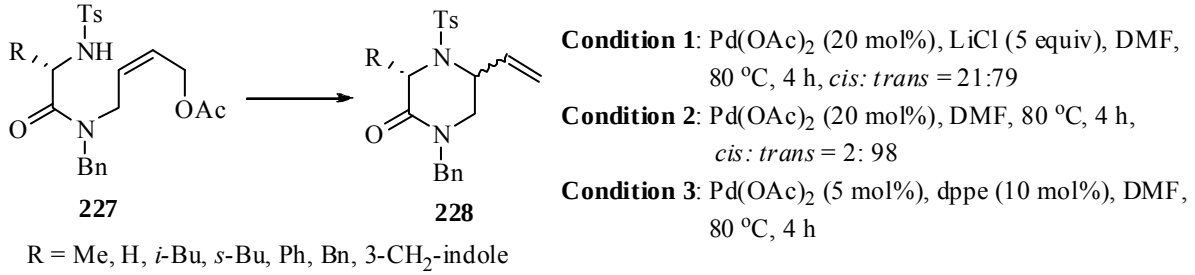
The aerobic intramolecular oxidative amination of olefinic tosyl amines **225a-d** using *N*-heterocyclic carbene[133] (NHC)-coordinated Pd(II) complex (IMes)Pd(CF_3CO_2)$_2$ as catalyst proceeded smoothly with air as well as pure oxygen gas, as the source of oxidant if carboxylic acid like $PhCO_2H$ or AcOH was employed as co-catalyst in the reaction to afford the indole derivatives **226a-d** (**Scheme 75**).[134]



entry	R^1	R^2	time (h)	acid	yield (%)
1	H	H	4	AcOH	86
2	Cl	H	5	AcOH	79
3	Me	H	8	$PhCO_2H$	72
4	H	Me	8	$PhCO_2H$	75

Scheme 75

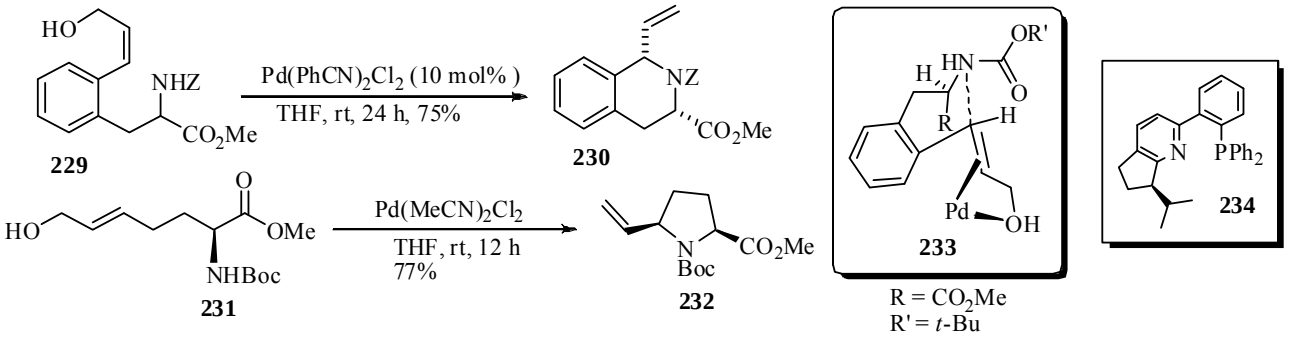
An efficient route to the synthesis of 3,5-disubstituted piperazinones **228** from the corresponding starting material **227** was reported.[135] An extensive study on the diastereoselectivity of the intramolecular amidation reaction during the synthesis of 3,5-disubstutited piperazinones **228** has been reported.[136] The cyclizations were carried out under three different conditions (**Scheme 76**). It is surprising that additive (LiCl) played an important role on the *cis*:*trans* ratios of products. The *cis*:*trans* of the products of Pd(0) catalysis in the presence of LiCl was always higher than those observed using Pd(0) alone. The favoured isomer was always the *cis* as observed. Interestingly, a complete reversal of the diastereoselectivity where *cis*: *trans* ratio spanning 21:79 to 2:98 in favour of the *trans* isomer was observed in the absence of LiCl.



Scheme 76

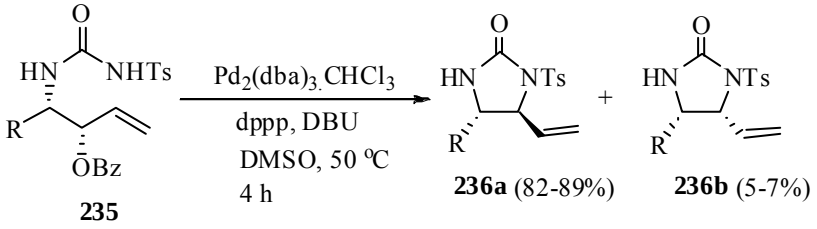
The intramolecular amination of *cis*-allylic alcohol **229** and ester **231** with $Pd(PhCN)_2Cl_2$ in THF at room temperature afforded *cis*-1,3-disubstituted 1,2,3,4-tetrahydroisoquinoline **230** and *cis*-2-carbomethoxy-5-

vinylpyrrolidine **232** respectively (**Scheme 77**).[137] A chair-like trasition state model **233** where axial orientation of allylic alcohol due to the complexation of Pd(II) might be responsible for this *cis*-stereoselectivity in tetrahydroisoquinoline **230**. The asymmetric intramolecular allylic amination was also achieved utilizing $Pd_2(dba)_3.CHCl_3$ in the presence of chiral **P**,**N** ligands-(**234**), 2-phosphinophenyl)pyridine.[138]



Scheme 77

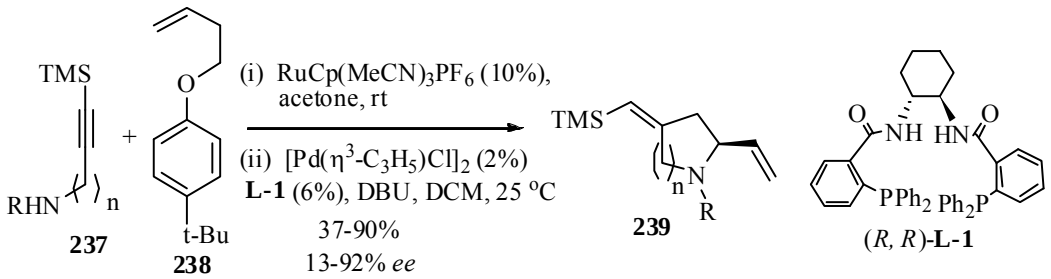
Synthesis of optically active vicinal diamines via palladium-catalyzed C-O to C-N bond transformation involving the intramolecular nucleophilic attack of nitrogen functionality tethered to the C-4 amino group on the C-3 position was achieved.[139] Based on this strategy *trans*- and *cis*-imidazolidin-2-ones (**236a** and **236b**) were synthesized from compound **235** (**Scheme 78**).



R = Bn, CH_2=$CHCH_2$-, $PhSCH_2CH_2$-, Ph-

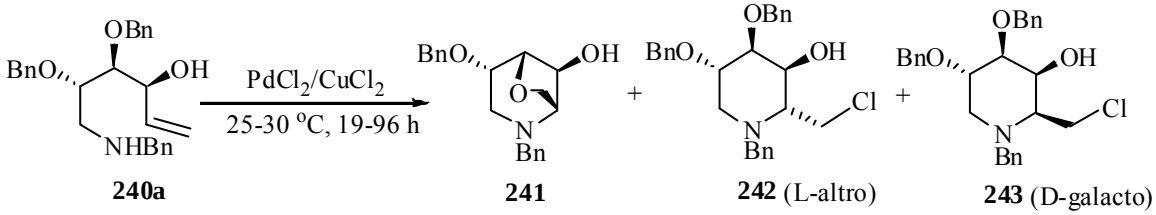
Scheme 78

Trost and collaborators demonstrated a highly efficient and atom economic dual catalytic approach comprised of Ru-catalyzed intermolecular enyne cross-coupling[140] of **237** and **238** followed by intramolecular nucleophilic trapping of π-alkylpalladium species, in a one-pot reaction sequence for the synthesis of enantio- and diastereo pure *N*-heterocycles.[141] The enyne coupling was carried out by sequential addition of $RuCp(MeCN)_3PF_6$ in acetone and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/RR-(**239**) catalytic system followed by intramolecular nucleophile trapping process without isolating the 1,4-diene intermediate. Both pyrrolidines and piperidines are formed with good yield (**Scheme 79**).



Scheme 79

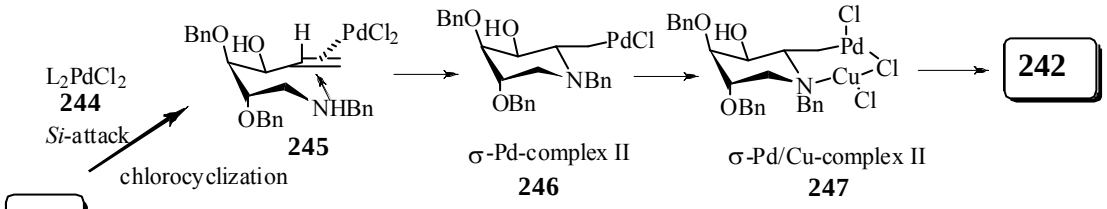
The chemoselectivity and diastereoselectivity of $PdCl_2/CuCl_2$-catalyzed chlorocyclization of aminoalkenitol **240** exhibited a significant dependence on the nature of the solvent used (**Scheme 80**).[142]



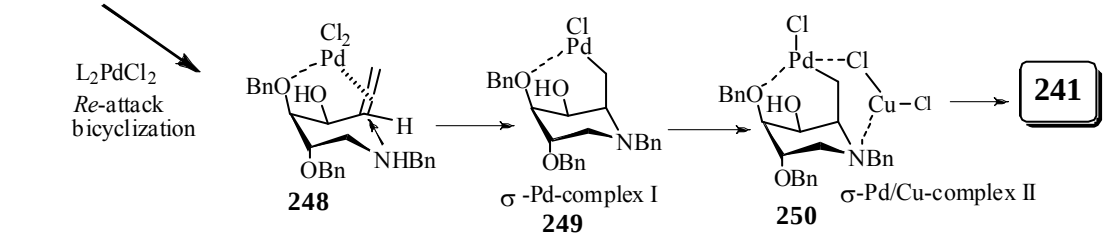
240a **241** **242** (L-altro) **243** (D-galacto)

Scheme 80

Formation of unexpected bicyclic derivative **241** with a lower combined yield of desired C-6 substituted azasugars L-altro **242** and D-galacto **243** was observed when the reaction is conducted in AcOH. A reversal of diastereoselectivity in favour of D-galacto **243** was found in PhMe or methanol albeit in poor des (33% and 50%). DMF as a solvent performed comparatively better (88% de) and it is a solvent of choice for the preparation of L-altro **242**. It is proposed that the initial bis-coordination of $PdCl_2$ with both (C-3) OBn group and C=C moiety of **240** followed by intramolecular *Re*-attack of *N*-nucleophile promotes the formation of a σ-Pd-complex-**I** in a geometrically favorable C_4 chair conformation. Subsequent formation of heterobimetallic[143] σ-Pd/Cu-complex-**249** followed by reductive elimination generates the bicycle **241**, on the other hand nucleophilic addition to Pd(II)-promoted activated double bond from its *Si*-face leading to a σ-Pd-complex-**250**, subsequent formation of σ-Pd/Cu complex-**250** and final reductive elimination furnishes the desired chlorocyclization product **242** (**Schemes 81 and 82**).

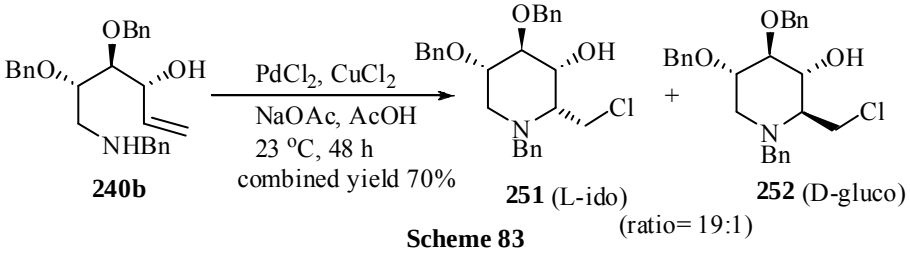


Scheme 81



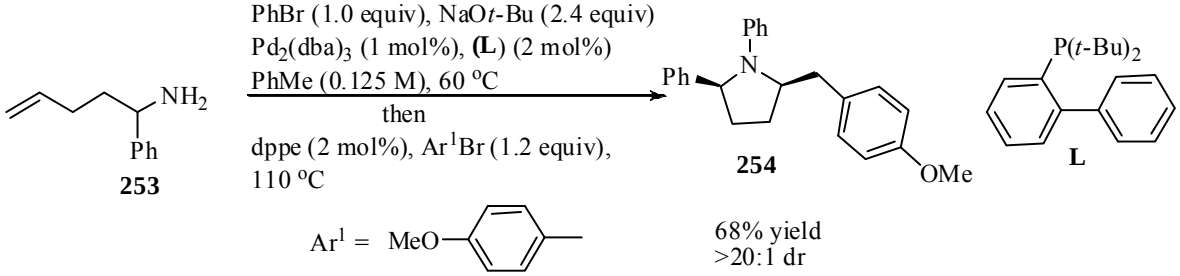
Scheme 82

Similarly, chlorocyclization of sugar-derived aminoalkenitol **240b** when subjected to $PdCl_2/CuCl_2$ catalyst and NaOAc as base in AcOH afforded L-ido configured C-6 chlorinated azasugar **251** as the major product along with its minor D-gluco diasteromer **252** with a good combined yield (70%) and high diastereoselectivity (90% de). The reaction in other solvents like DMF, DCM, THF, MeOH and PhMe were less efficient as poor yield and diastereoselectivity were obtained (**Scheme 83**).



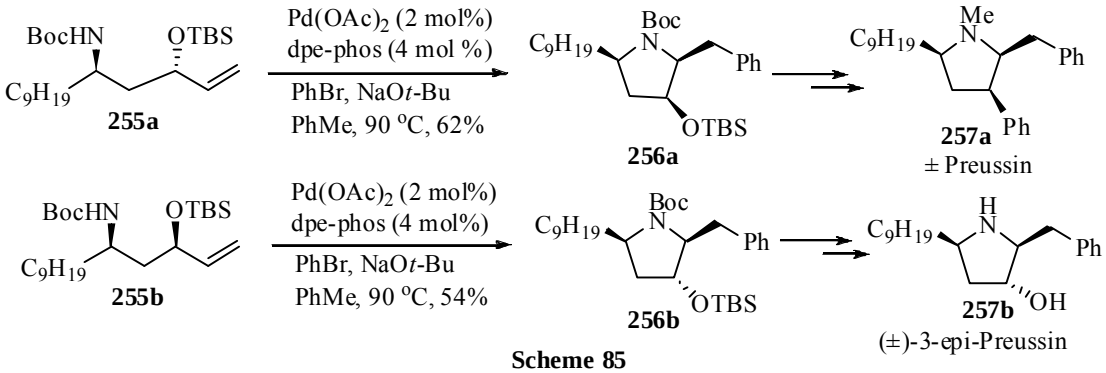
Scheme 83

However, for the palladium-catalyzed domino *N*-arylation/carboamination[144] of *γ*-amino alkenes **253** with two different aryl bromides, an in situ ligand exchange protocol was found to be beneficial as the reaction proceeded through the formation of two C-N bonds and one C-C bond in one-pot.[145] By utilizing $Pd_2(dba)_3$ as catalyst, the first arylation reaction was achieved with monodentate ligand 2-di-*tert*-butylphosphinobiphenyl (**L**) which underwent in situ ligand exchange with the chelating ligand dppe to effect the carboamination-arylation step and providing the *cis*-substituted pyrrolidine **254** (**Scheme 84**).



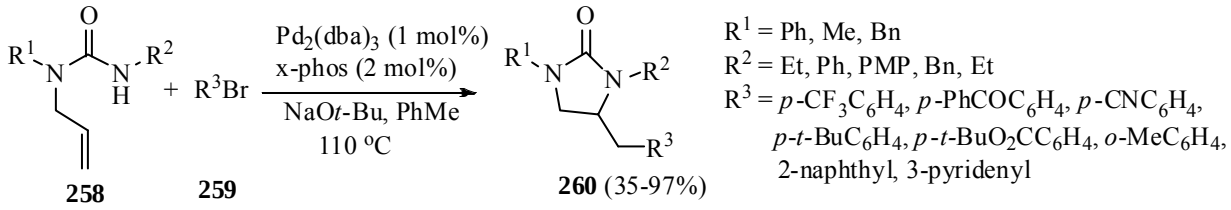
Scheme 84

Another application of palladium-catalyzed carboamination reaction was achieved during the efficient synthesis of (±)-preussin **257a** and (±)-3-*epi*-preussin **257b**,[146] a potent antifungal and antitumer agent. The TBS-protected *anti*- and *syn*-aminoalcohols **255a** and **255b** on treatment with $Pd(OAc)_2$ and dpephos afforded the corresponding pyrrolidine derivatives **256a** and **256b** in 62 and 54% yields respectively (**Scheme 85**)[147] from which (±)-preussin and (±)-3-*epi*-preussin were subsequently synthesized in few steps.



Scheme 85

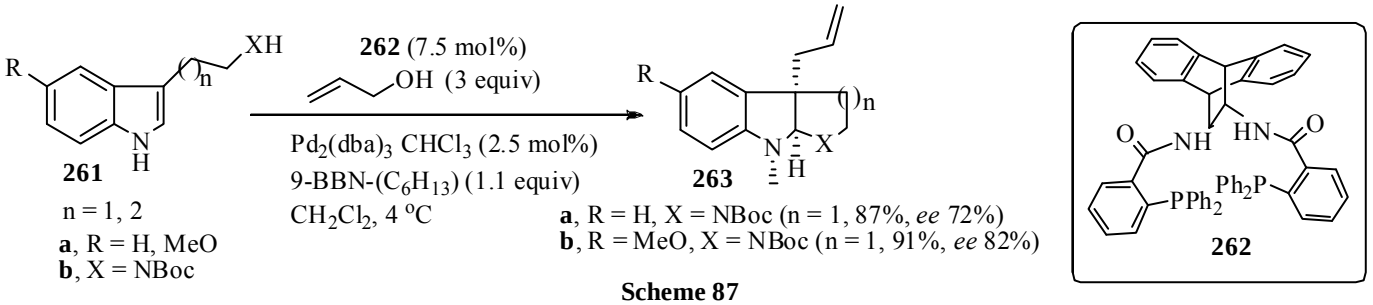
Wolfe *et al*. utilized the palladium-catalyzed cascade C-N and C-C bond formation strategy for the preparation of substituted imidazolidin-2-ones **260**.[148] The acyclic ureas **258** when subjected to intramolecular carbamination reaction in the presence of different aryl and heteroaryl bromides using $Pd_2(dba)_3$ as catalyst, x-phos as cocatalyst afforded the imidazilidin-2-one derivatives **260** (**Scheme 86**).



258 **259** **260** (35-97%)

Scheme 86

Palladium-catalyzed enantioselective C-3 allylation of 3-substituted-1*H*-indoles using trialkylboranes was developed by Trost *et al*.[149] The selectivity is highly dependent on the borane reagent used in the reaction as in addition to promoting the ionization of allyl alcohol[150] (**Scheme 87**).



261
n = 1, 2
a, R = H, MeO
b, X = NBoc

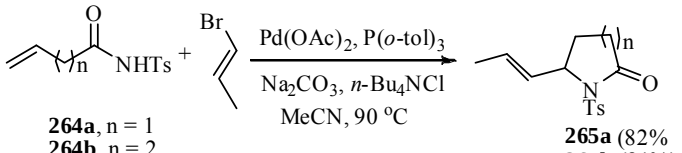
263
a, R = H, X = NBoc (n = 1, 87%, *ee* 72%)
b, R = MeO, X = NBoc (n = 1, 91%, *ee* 82%)

262

Scheme 87

ω-Olefinic-*N*-tosyl amides **264a**,**b** and vinylic bromide underwent domino Heck-allylic substitution[151,152] to furnish substituted pyrrolidone **265a** (n = 1) and piperidone **265b** (n = 2). The reactions were best carried out utilizing $Pd(OAc)_2$, P(*o*-tol)$_3$, Na_2CO_3 and *n*-Bu_4NCl in MeCN at 90 °C to afford compounds **265a** and **265b** (**Scheme 88**).[153]

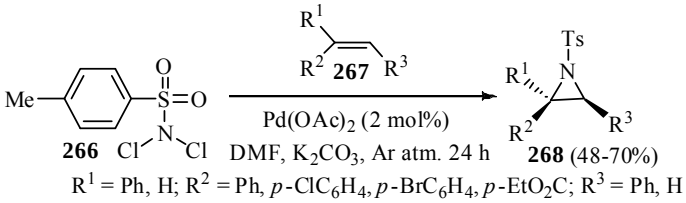
The aziridination of olefin was carried out in a palladium-catalyzed reaction between various alkenes and *N,N*-dichloro-*p*-toluene sulfonamide **266** ($TsNCl_2$) as a nitrogen source.[154] The reaction was carried out at room temperature using $Pd(OAc)_2$ with an alkene/$TsNCl_2$ ratio 1.5:1 (mol/mol) to afford the aziridines **268** (**Scheme 138**). The chemical yields under this condition are higher than those using bromamine-T as a nitrogen source and palladium dichloride as catalyst[155] (**Scheme 89**).



264a, n = 1
264b, n = 2

265a (82%
265b (81%)

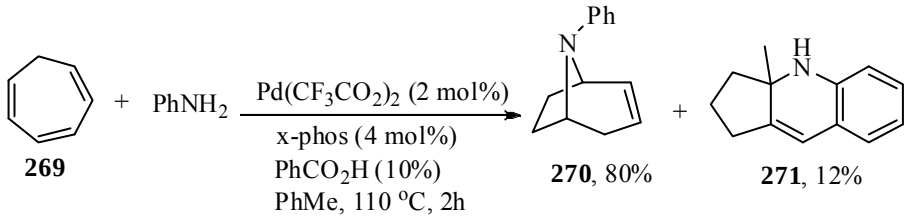
Scheme 88



266 **267** **268** (48-70%)
R^1 = Ph, H; R^2 = Ph, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-EtO_2C; R^3 = Ph, H

Scheme 89

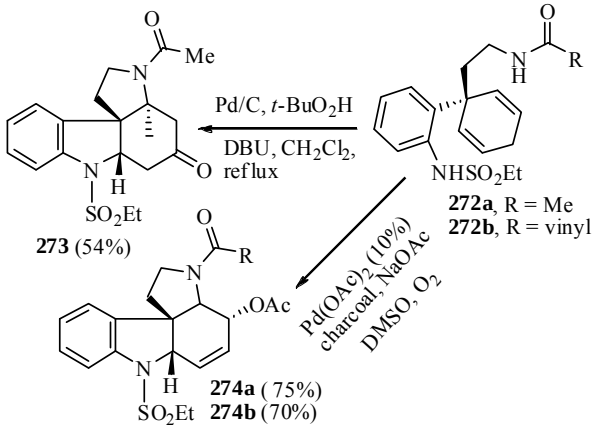
Hartwig *et al*. synthesized tropene derivatives by sequential intermolecular and intramolecular transannular palladium catalyzed hydroamination of cycloheptatrienes.[156] The combination of x-phos, $Pd(CF_3CO_2)_2$ and $PhCO_2H$ showed highest efficiency in this transformation. The product **270** was isolated along with the dihydroquinoline derivative **271** (**Scheme 90**).



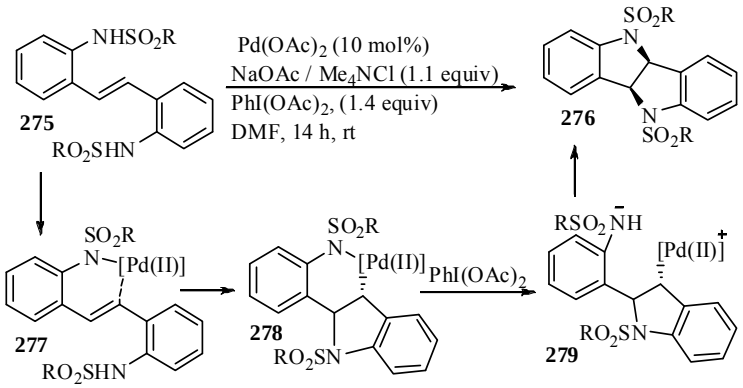
Scheme 90

One-pot double oxidative amination of **272a**,**b** having orthogonally positioned amide and aniline with $Pd(OAc)_2$, charcoal and NaOAc in DMSO and O_2 afforded the tetracyclic compounds **274a**,**b** having three stereogenic centers (**Scheme 91**).[157] The compound **272a** when subjected to dieneoxidation-1,4-cyclization with Pd/C, DBU and *t*-BuO_2H in reflxing CH_2Cl_2 afforded the analogue of Büchi ketone **273**.

Sequential catalytic transfer of two sulfonamides to internal alkenes has been developed as an effective route to construct bisindoline.[158] This domino oxidative diamination of **275** was accomplished utilizing $Pd(OAc)_2$ and NaOAc to give bisindoline derivatives **276** in excellent yields (**Scheme 92**). The characteristic feature of this reaction is the flexibility of palladium catalyst in the sequential formation of C_{sp}^2-N and secondary C_{sp}^3-N bonds,[159] employing a nitrogen source of the same electronic nature. Mechanistically the reaction proceeds through the palladium-tosyl amide precoordination **277** followed by endoselective *anti*-aminopalladation to convert into a chelation-controlled state **278**. The complex-**278** may undergo oxidation to palladium(IV) **279**,[160] amide dissociation followed by selective *anti*-amination/depalladation[161] to afford bisindoles **276**.



Scheme 91



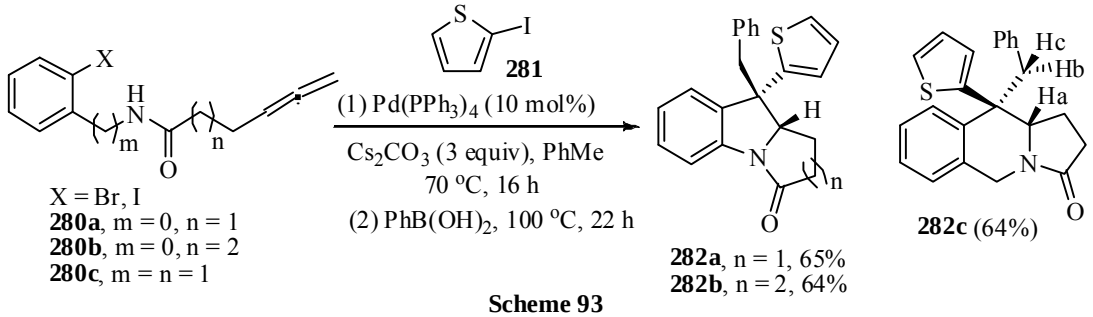
Scheme 92

6.1.2. ADDITION TO ALLENE

The transition metal-catalyzed cyclization of functionalized allenes is important due to its unique reactivity and stereoselectivity.[162] Palladium-catalyzed addition of heteroatom nucleophiles to allenes has found extensive applications in the synthesis of heterocycles.[163]

Grigg *et al*. developed a novel palladium-catalyzed cyclization-anion-capture cascade process involving in situ zipper generation via intramolecular nucleophilic attack on the π-allylpalladium species and their subsequent cyclization-anion-capture using boronic acid as anion capture reagent to access tricyclic

heterocycles **282**.[164] The trifunctional aryl iodide/allene/nucleophile substrates **280a**,**b** were treated with 2-iodothiophene, $Pd(PPh_3)_4$ and Cs_2CO_3 in PhMe at 70 °C for 16 h then phenyl boronic acid was added and the mixture was heated at 100 °C for further 22 h to afford the tricyclic compounds **282a**,**b** as single diastereomers. The interesting feature is that three C-C bond, one C-N bond, two rings, two stereomers, and one tetrasubstituted C-center were formed in this one-pot cascade reaction sequence (**Scheme 93**).



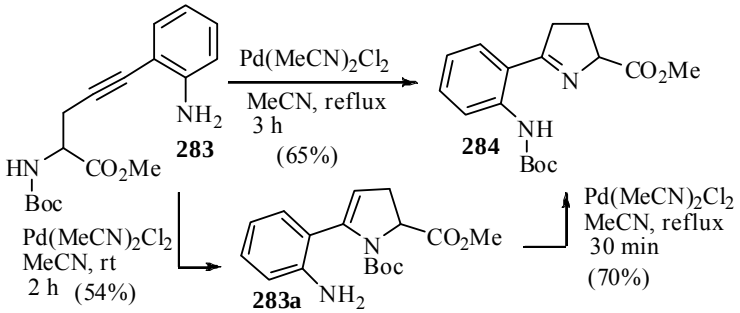
Scheme 93

In the case of compound **280c**, a slightly modified condition was needed to nullify the faster rate of the oxidative addition onto C-Br bond by the more effective coordination of the oxygen atom of the amide due to the difference in electronegativity of the N-atom in position-1 compared to 4. To overcome this difficulty Lyrigg[165] performed the reaction with excess of triphenylphosphine to give the desired cyclized product **282c** as a single diastereomer.

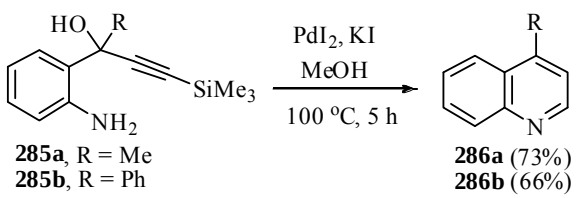
6.1.3. ADDITION TO ALKYNE

Rutjes *et al*. reported an efficient synthesis of unsaturated proline and optically active tryptophan analogues via palladium-catalyzed intramolecular cyclization of aniline containing acetylenic amino acid.[166] The type of product formation depends on the side chain length of the cyclization precursors. Thus, the compound **283** when treated with $Pd(MeCN)_2Cl_2$ afforded the imine **284** (**Scheme 94**). Here the catalyst $Pd(MeCN)_2Cl_2$ acts both as a cyclizing agent as well as a Lewis acid which is evidenced by the formation of cyclic amide **283a** at ambient temperature. Treatment of this enamide with the same Pd catalyst in refluxing acetonitrile led to rapid conversion into the aforementioned imine **284**.

In a recent report it has been observed that 2-(2-aminophenyl)-4-trimethylsilanylbut-3-yn-2-ol **285a** and 1-(2-aminophenyl)-1-phenyl-3-trimethylsilanylprop-2-yn-1-ol **285b** under the same combination of catalyst in MeOH underwent 6-*endo-dig* cyclization-dehydration to afford 4-methylquinoline **286a** and 4-phenylquinoline **286b** (**Scheme 95**).[167]

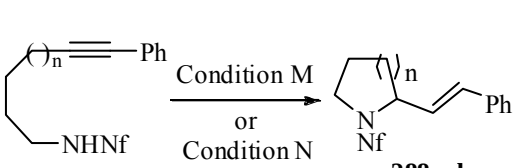


Scheme 94



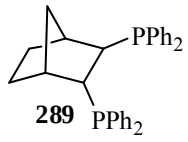
Scheme 95

The asymmetric version of the intramolecular catalytic hydroamination and hydroxylation of alkynes using chiral palladium catalyst in situ generated from $Pd_2(dba)_3.CHCl_3$ and (*R,R*)-renorphos **289** was recently developed by Yamamoto *et al.*[168] The hydroamination reaction of **287** was examined under two different reaction conditions and condition-N was observed to be efficient (**Scheme 96**).



287a, n = 1
287b, n = 2

288a, **b**



289 (*R,R*)-renorphos

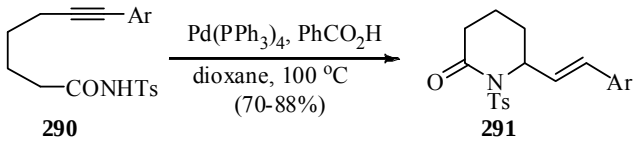
Entry	n	condition	yield (%)	ee (%)
1	1	M	68	83
		N	93	91
2	2	M	63	77
		N	92	90

Condition M: $Pd_2(dba)_3.CHCl_3$ (5 mol%), $PhCO_2H$ (10 mol%)
(*R,R*)-renorphos (25 mol%), PhH, 100 °C, 72 h
Condition N: $Pd_2(dba)_3.CHCl_3$ (20 mol%), $PhCO_2H$ (40 mol%)
(*R,R*)-renorphos (100 mol%), PhH/hexane (2:1), 80 °C, 72 h

Scheme 96

The amidoalkynes **290** underwent intramolecular hydroamination reaction when subjected to $Pd(PPh_3)_4$ in $PhCO_2H$ at 100 °C.[169] The six-membered lactams **291** were obtained with *E*-geometry of the double bond. Tosylamide was formed to give excellent result during this cyclization. The reason behind the cyclization over *β*-hydride elimination might be due to the exchange of ligand at the palladium atom by π-Pd complex generated from **290** (**Scheme 97**), which inhibit the *β*-hydride elimination as well as diminish the basicity of the nitrogen atom of the resulting π-Pd complex due to the presence of two electron-withdrawing groups.

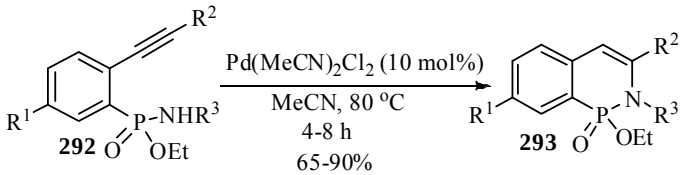
The first example of intramolecular addition of P-NH to substituted alkynes was achieved by the synthesis of novel six-membered phosphorous heterocycles, phosphaisoquinoline-1-ones, **293** with potential bioactivities using the intramolecular regioselective cyclization of *o*-(1-alkynyl)-phenylphosphonamides **292** in presence of $Pd(MeCN)_2Cl_2$ (**Scheme 98**).[170]



290 **291**

Ar = *p*-MeC_6H_4, *p*-$MeOC_6H_4$, 3,4-(-O-CH_2O-)C_6H_3
p-ClC_6H_4, *p*-$CF_3C_6H_4$, *p*-$MeO_2CC_6H_4$, *p*-$NO_2C_6H_4$

Scheme 97

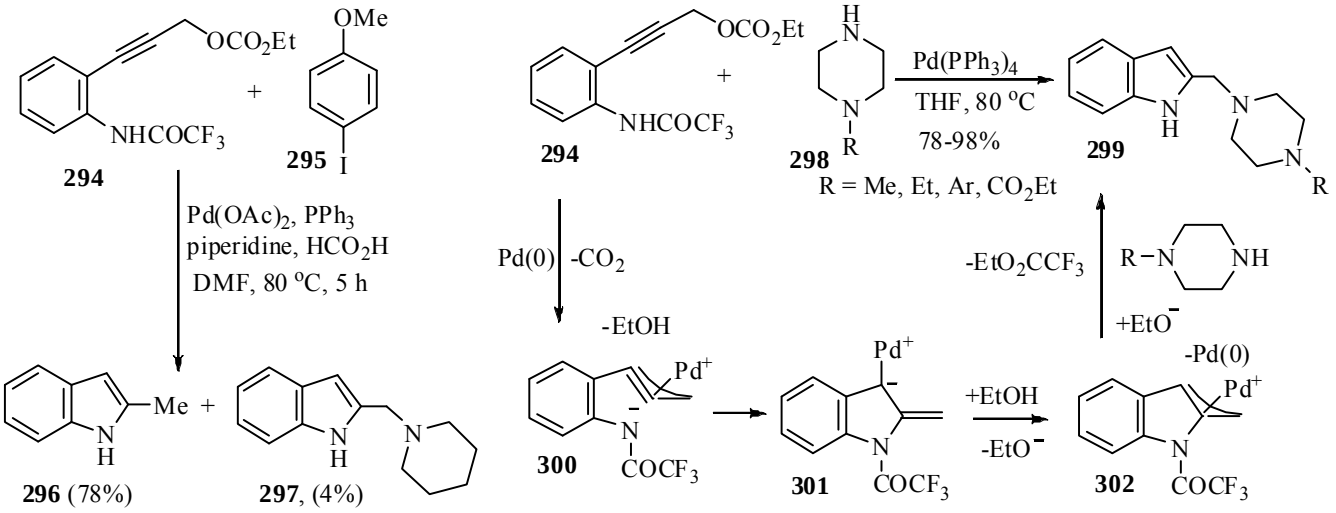


292 **293**

Scheme 98

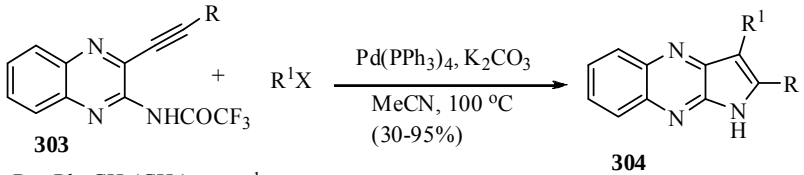
Cacchi *et al*. showed that ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonate **294** reacted with *p*-iodoanisole under the hydroarylation condition $Pd(OAc)_2$, PPh_3, and piperidine to afford 2-methyl indole **296** along with 2-(piperidin-1-ylmethyl)indole **297**.[171] However, in the presence of *N*-substituted piperazine and $Pd(PPh_3)_4$, compound **294** afforded 2-(piperazin-1-ylmethyl)indoles **299**. The mechanistic rationalization for the formation of indole is believed to be initiated with the formation of *σ*-allenylpalladium complex which may be in equilibrium with *π*-propargylpalladium intermediate **300**.[172]

Subsequent intramolecular nucleophilic attack of the nitrogen at the central carbon of the allenyl/propargyl-palladium complex[173] followed by protonation of the resultant carbene **301** may give the σ-allenylpalladium complex **302**. Finally regioselective intermolecular nucleophilic attack of the nitrogen nucleophile at the less hindered allylic terminus of **302** may afford the desired indole derivatives (**Scheme 99**).

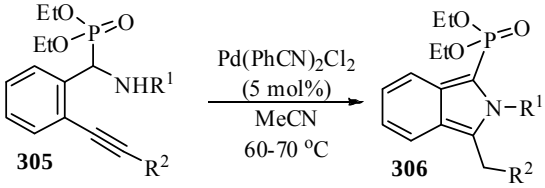


Scheme 99

An aminopalladation-reductive elimination approach[174] was adopted for the synthesis of 2,3-disubstituted pyrrolo[2,3-*b*]quinoxalines **304**. The reaction of 2-alkynyl-3-trifluoroacetamido quinoxalines **303** with aryl and vinyl halides or triflates in the presence of $Pd(PPh_3)_4$ afforded the compounds **304** (**Scheme 100**). α-Amino(2-alkynylphenyl)methylphosphonate **305** underwent *endo*-cyclization when subjected to $Pd(PhCN)_2Cl_2$ in acetonitrile to afford 2,3-disubstituted-2*H*-isoindol-1-ylphosphonates **306** in moderate-to-good yields (**Scheme 101**).[175]

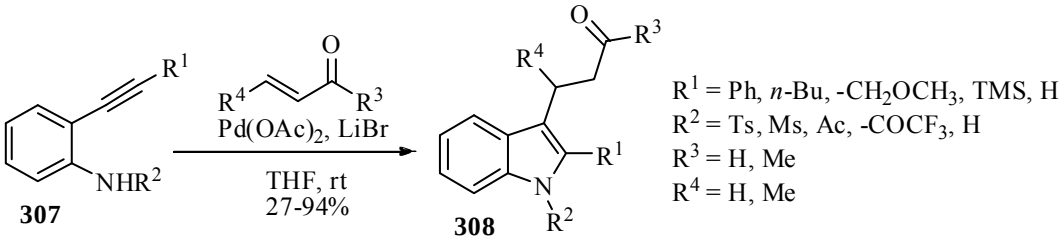


Scheme 100



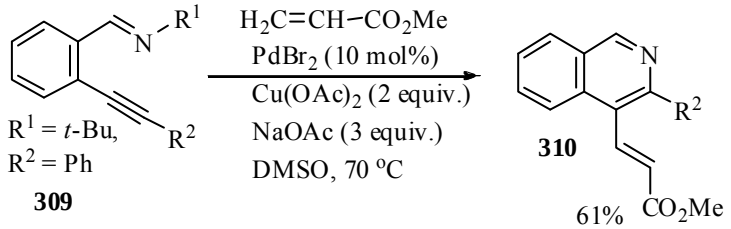
Scheme 101

The domino aminopalladation of 2-alkynylaniline **307** and subsequent conjugate addition to α,β-unsaturated carbonyl compound in the presence of $Pd(OAc)_2$ and LiBr afforded the indole derivatives **308** (**Scheme 102**).[176] The formation of indoles **308** may be rationalized by a domino intramolecular aminopalladation, olefin insertion and protonolysis of carbon-palladium bond. No β-hydride elimination product was formed giving preferentially the protonolysis product in acidic medium.



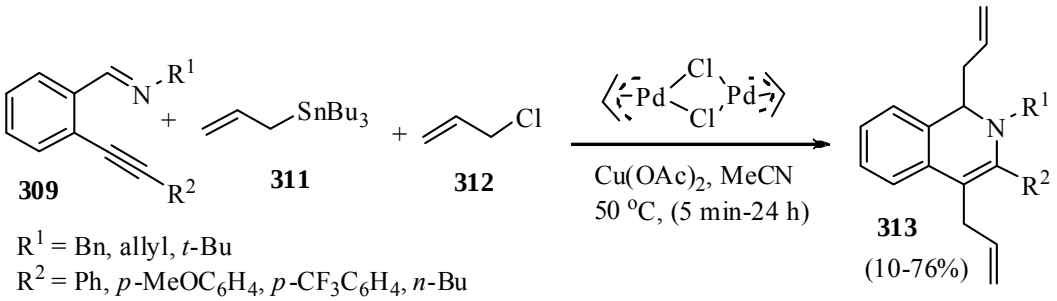
Scheme 102

The synthesis of 4-(1-alkenyl)-3-arylisoquinolines **310** was achieved by the Pd(II)-catalyzed cyclization of 2-(1-alkynyl)arylaldimines **309** in the presence of methyl acrylate (**Scheme 103**).[177] The reaction involved a sequence of Pd(II)-catalyzed intramolecular cyclization of imine onto C-C triple bond followed by intermolecular Heck olefination reaction.



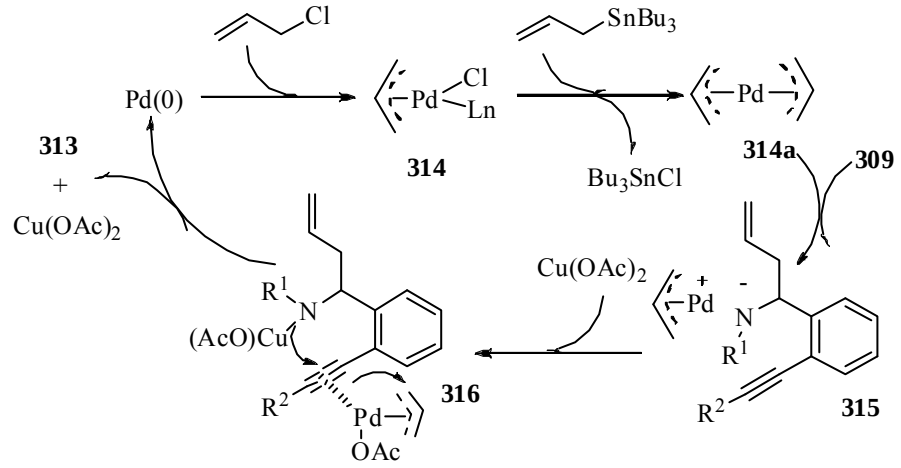
Scheme 103

The *ortho*-alkynylarylimine **309** underwent domino bis allylation[178,179] with allyltributylstannane and allyl chloride in the presence of a catalytic amount of π-allylpalladium chloride dimer and $Cu(OAc)_2$ to afford 1,4-diallyl-1,2-dihydroisoquinolines **313**.[180] The chemical yields of the reaction is highly dependent on the substituent R^2 (**Scheme 104**).



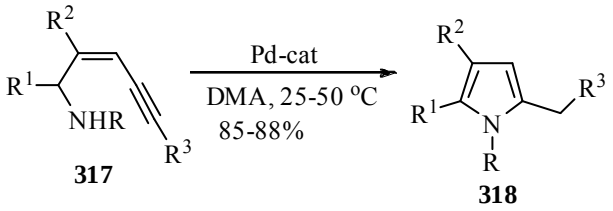
Scheme 104

The reaction proceeds with the generation of the amphiphilic bis-π-allylpalladium complex[181] **314a** by oxidative addition of Pd(0) to allyl chloride followed by transmetallation with allyltributylstannanes. The complex **314a** reacts with **309** to generate π-allylpalladium amides **315** which are subsequently converted to Pd-alkyne complexes **316** by $Cu(OAc)_2$-assisted cleavage of the Pd-N interaction. Finally, attack of the nitrogen atom to the alkyne in a 6-*endo-dig* mode followed by reductive coupling affords the products **313** (**Scheme 105**).



Scheme 105

A general regioselective synthesis of various substituted pyrrole derivatives was reported by Gabriele *et al*.[182] The cycloisomerization reaction was carried out in two ways by employing two different catalytic systems such as Pd(II)-catalyzed and $CuCl_2$-catalyzed cycloisomerization reactions. It is interesting when the triple bond is substituted with an alkyl or alkenyl group. Substrates **317**, underwent cycloisomerization reaction smoothly with Pd(II) to afford the pyrrole derivatives **318** (**Scheme 106**). The pyrrole-2-acetic ester derivatives were also synthesized[183] by the application of the oxidative carbonylation of 3-substituted enynamines.



318a, R = R^3 = Bu, R^1 = H, R^2 = Et, 85%
318b, R = Bn, R^1 = H, R^2 = Et, R^3 = Bu, 85%
318c, R = R^3 = Bn, R^1 = H, R^2 = Ph, 87%
318d, R = Bn, R^1 = R^3 = Bu, R^2 = H, 86%
318e, R = Bn, R^1 = R^2 = H, R^3 = Bu, 88%

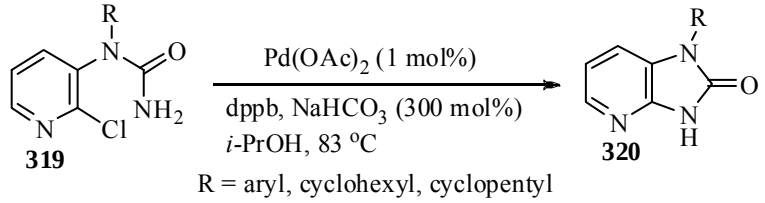
Scheme 106

6.2. INTRA- AND INTERMOLECULAR COUPLING OF NH WITH VINYL AND ARYL HALIDE OR TRIFLATE

Pd-catalyzed cross-coupling between C_{sp}^2-halides or triflates represent some of the most powerful and versatile tools for the construction of C-N and C-O bonds.[1] Methodologies for the construction of this type of bonds intramolecularly have become extraordinarily popular, as they represent a very efficient entry into different types of important nitrogenated and oxygenated heterocyclic compounds.[2]

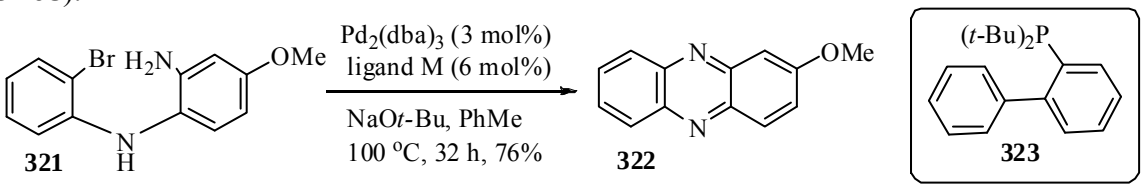
6.2.1. ARYL HALIDES OR TRIFLATES

Both intra- and intermolecular version of the palladium-catalyzed cross coupling reaction between aryl halides and amines[184] have been applied to the synthesis of heterocycles.[185] An efficient regioselective method for the synthesis of structurally diverse imidazopyridones **320** inexcellent yields by Pd-catalyzed reductive cyclization[186] of *N*-substituted *o*-chloroaminopyridines **319** has been reported (**Scheme 107**).



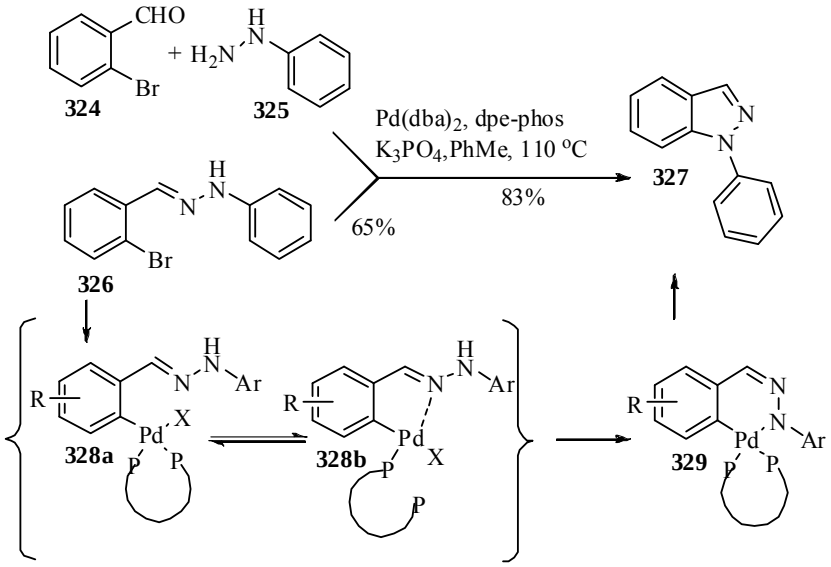
Scheme 107

A facile route based on the Pd(0)-catalyzed *N*-arylation approach for the construction of phenazine **322** has been reported by the cyclization of bromodiphenyl amine **321** using $Pd_2(dba)_3$ and ligand-**323** (**Scheme 108**).[187]



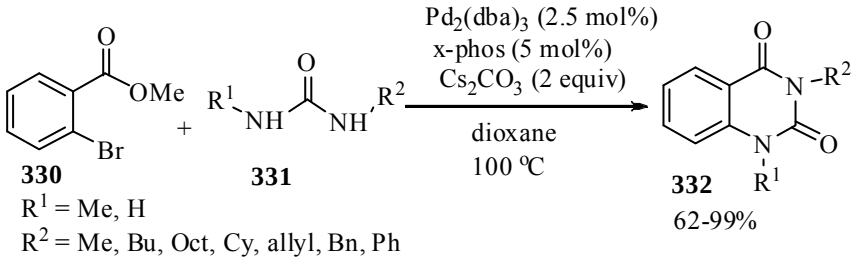
Scheme 108

The intermolecular cross coupling reaction between 2-bromobenzaldehyde with aryl hydrazine was achieved[188] in the presence of $Pd(dba)_2$, dpe-phos and K_3PO_4. The catalyzed reaction is suggested to proceed via the five-membered palladacycle **328b** possibly in equilibrium with open structure **328a** (**Scheme 109**). The cyclization involves a different six-membered palladacycle, which can be formed from **328** by deprotonation of NH by the base and subsequent metallotropic shift of Pd to form palladacycle **329**. Finally dissociation of Pd-N bond produces the indazole compound **327**.



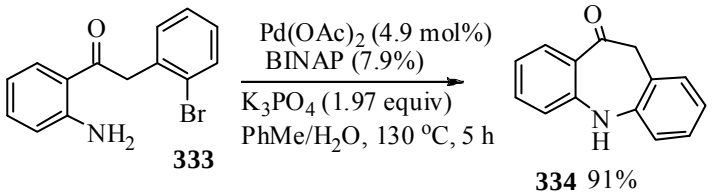
Scheme 109

A versatile route to mono-*N*- and di-*N*-alkylated quinazolinediones **332** via palladium-catalyzed urea arylation-intramolecular ester amidation protocol was achieved[189] in the presence of $Pd_2(dba)_3$, x-phos and Cs_2CO_3 (**Scheme 110**). Between the *o*-chloro and *o*-bromo benzoate, the reaction of the latter one effectively coupled with the urea component **331** and gave both mono-*N*- and di-*N*-substituted compounds **332**.



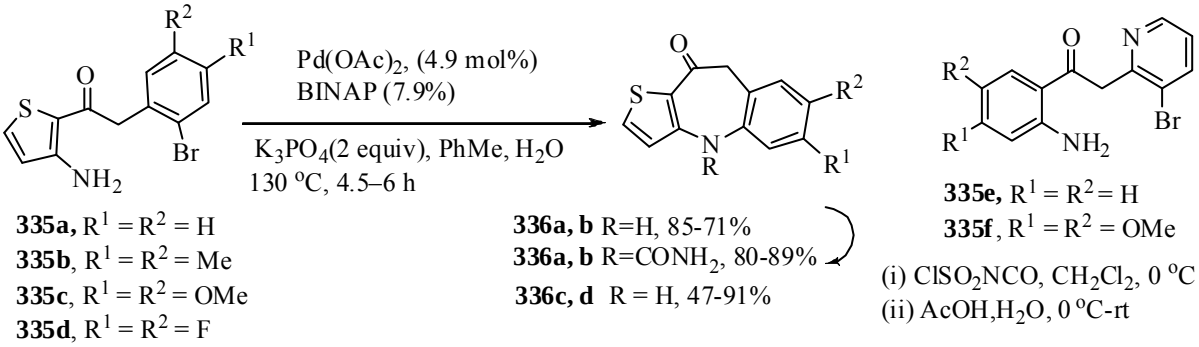
Scheme 110

A new route to oxacarbazepine (trileptal) in which palladium-mediated intramolecular *N*-arylation of the amine **333** was studied.[190] Under the optimized reaction conditions amine **333** afforded the dibenzoazepinone **334**, thus minimizing the amount (<4%) of the dehalogenated byproduct. Moreover, water as a convenient additive or co-solvent produced a beneficial effect on the process in two ways: a) accelerating the rate of the reaction, b) better solvent for K_3PO_4 promoting the target amination (**Scheme 111**).



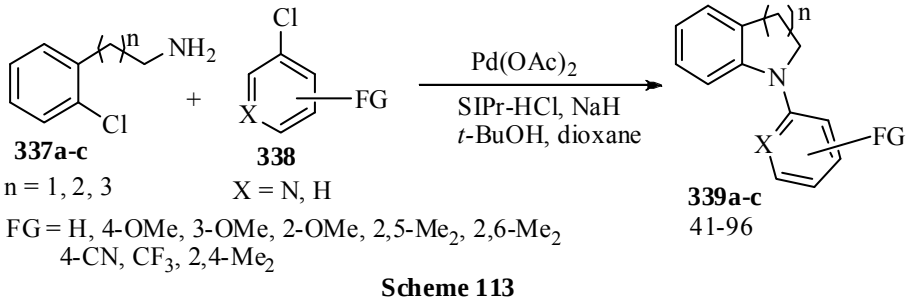
Scheme 111

In case of heteroaromatic substrates **335**, the aforementioned procedure worked well for the thiophene substrates giving the tricyclic compounds **336**.[191] In contrast, for the heteroaromatic substrates like the pyridine derivatives **335e**,**f** failed to give the azepinones (**Scheme 112**).



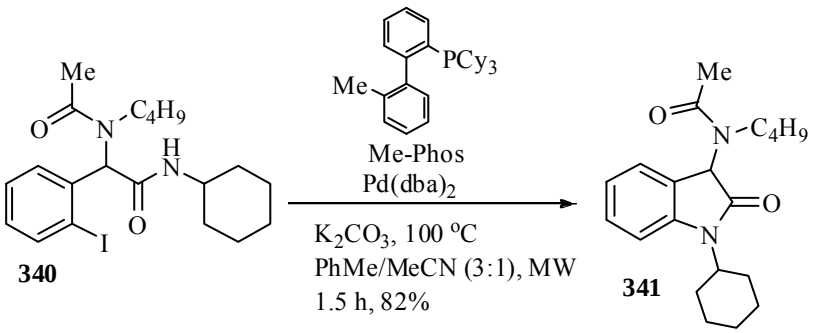
Scheme 112

An efficient synthetic protocol for the synthesis of a wide range of *N*-arylated 5-, 6- and 7-membered heterocycles **339a-c** involving palladium-mediated sequential intramolecular and intermolecular arylamination reactions has been reported.[192] The use of an in situ generated Pd(0) catalyst associated to *N*-heterocyclic carbene, *N*,*N*-bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidine (**SIPr**) as ligand, NaO*t*-Bu and $Pd(OAc)_2$ was found to be effective and various indolines (n = 1), tetrahydroquinolines (n = 2), 2,3,4,5-tetrahydro-1*H*-1-benzazepines (n = 3) **339c** were synthesized by the reactions between compound **337** with aryl chlorides (**Scheme 113**).



Scheme 113

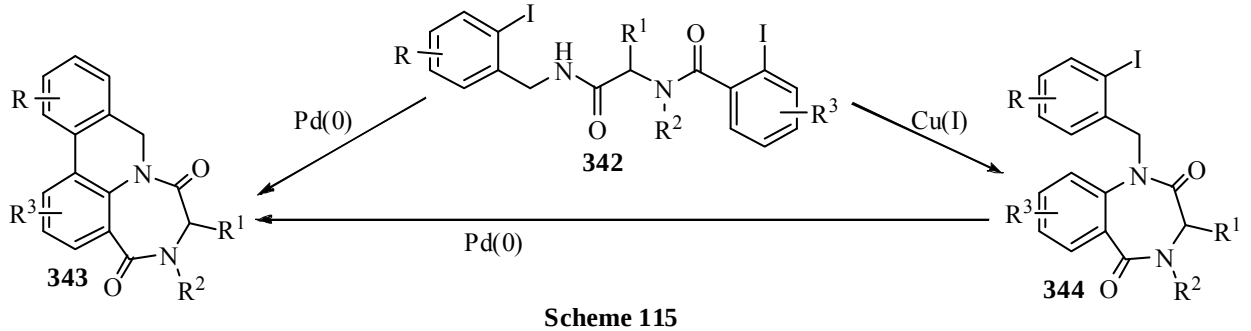
$Pd(dba)_2$-catalyzed intramolecular Buchwald-Hartwig amination of the amide **340** has been found to be highly dependent on the nature of the added ligand and the solvent. $Pd(OAc)_2$ was found to be inefficient and gave poor yield of the desired oxindole.[193] However, oxindole **341** was obtained in 82% yield when the amination was carried out under microwave condition (**Scheme 114**).



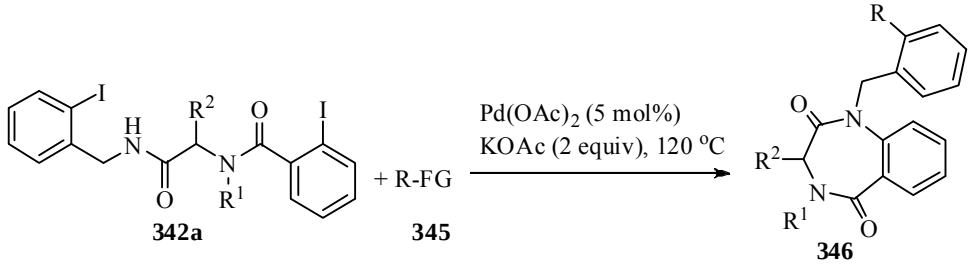
Scheme 114

A novel synthetic strategy for the synthesis of medium ring heterocycles dihydro-8*H*-5,7a-diazacyclohepta[*jk*]phenanthrene-4,7-dione **343** and 1,4-benzodiazepine-2,5-dione **344** from the same starting material **342**, was achieved[194] simply by switching the metal catalyst. Interestingly, $Pd(OAc)_2$ triggered a domino intramolecular *N*-arylation/C-H activation/aryl-aryl bond forming process to provide the compound **343**, while copper iodide promoted only the intramolecular *N*-arylation reaction leading to the formation of the compound **344** (**Scheme 115**). Compound **344** was also converted to the compound **343** simply by a Pd-catalyzed biaryl coupling.

A divergent regiocontrolled palladium-catalyzed domino sequence involving an intramolecular *N*-arylation and an intramolecular cyclization strategy for the synthesis of highly functionalized benzodiazepindiones **346** from the precursors **342a** has been reported[195] (**Scheme 116**).

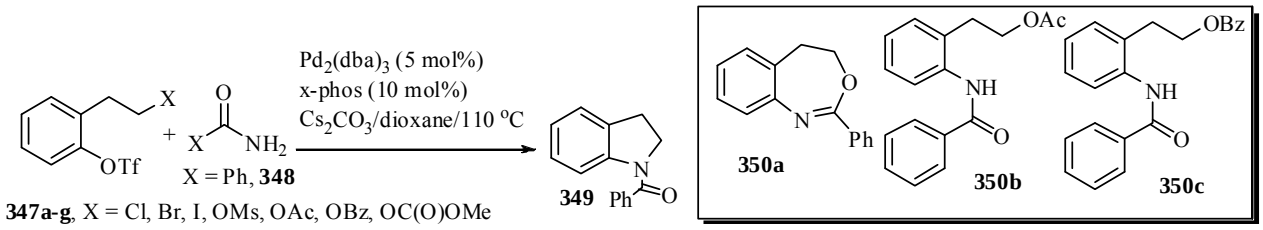


Scheme 115



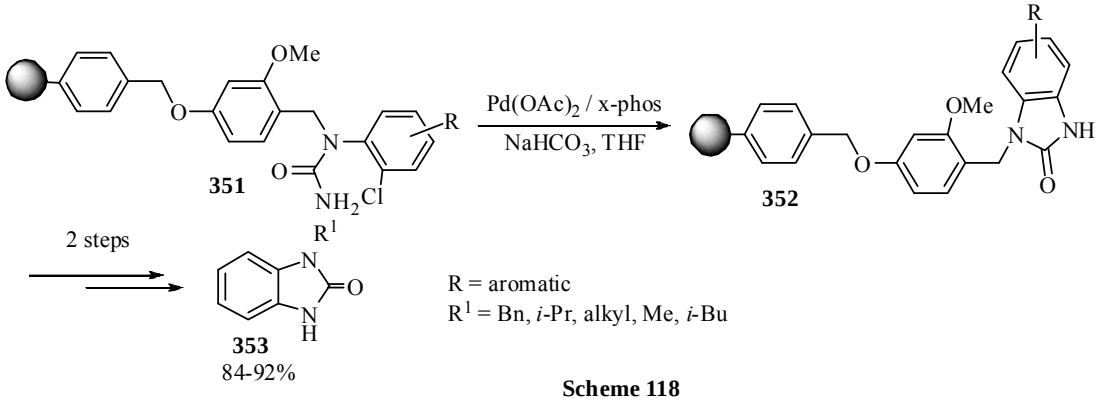
Scheme 116

Amide-NH_2 was employed for the palladium-catalyzed aryl C-N cross-coupling with aryltriflates **347** bearing alkyl chain with a leaving group for the construction of indole derivatives.[196] An optimization study of this domino sp^2-sp^3 amidation reaction revealed that the cyclization is highly dependent on the leaving group (X) of the compound **347**. The formation of seven-membered heterocycle **350a** was achieved when mesylate was used as leaving group. With acetate and carbonate along with the indole **349** uncyclized monoaminated products **350b** and **350c** were obtained. However, 2-triflyloxy phenethyl carbonates **347g** afforded 2,3-dihydroindole **349** in 98% yield when 5 mol% of $Pd_2(dba)_3$ and 10 mol% x-phos as ligand were used (**Scheme 117**).



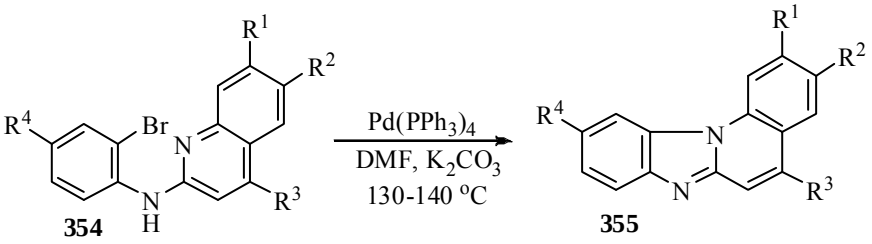
Scheme 117

A combination of microwave techniques and traceless polymer-supported strategies was utilized for the synthesis of benzimidazoles libraries with two point of diversity using ameba resin as a traceless linker.[197] The key intramolecular cyclization of resin bound urea was carried out smoothly, catalyzed by $Pd(OAc)_2$ under microwave irradiation for 15 min. The compounds **352** were converted into polymer free benzimidazolones **353** (**Scheme 118**).



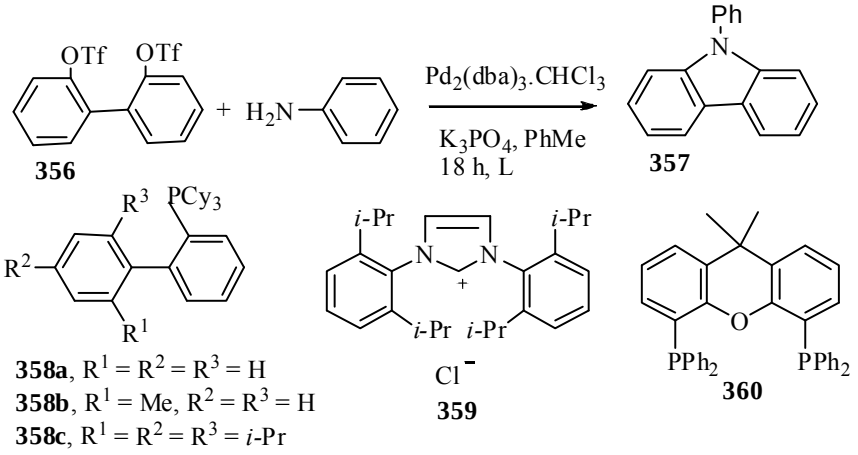
Scheme 118

A new route to benzimidazo[1,2-*a*]quinolines **355** via $Pd(PPh_3)_4$-catalyzed intramolecular heterocyclization of readily accessible 2-(2-bromoanilino)quinolines **354** was reported.[198] The overall process involved Buchwald-Hartwig amination in which the heteroarene ring nitrogen participate in the N-C bond formation (**Scheme 119**).



Scheme 119

Nozaki *et al*. reported double *N*-arylation strategy of primary amines with 2,2′-biphenylene ditriflate for the synthesis of multisubstituted carbazoles **357**.[199] Among the different ligands (**358a-c**, **359**, **360**) employed **358b** and **360** were found to give better results. However ligand **358b** is the ligand of choice as ligand **360** in the presence of Cs_2CO_3 or NaO*t*-Bu instead of K_3PO_4 afforded the carbazole in 50% or 14% yield respectively along with byproduct biphenyldiol (22% or 50%). The hydrolysis of triflate was also reported to occur when nucleophilic strong base was employed (**Scheme 120**).



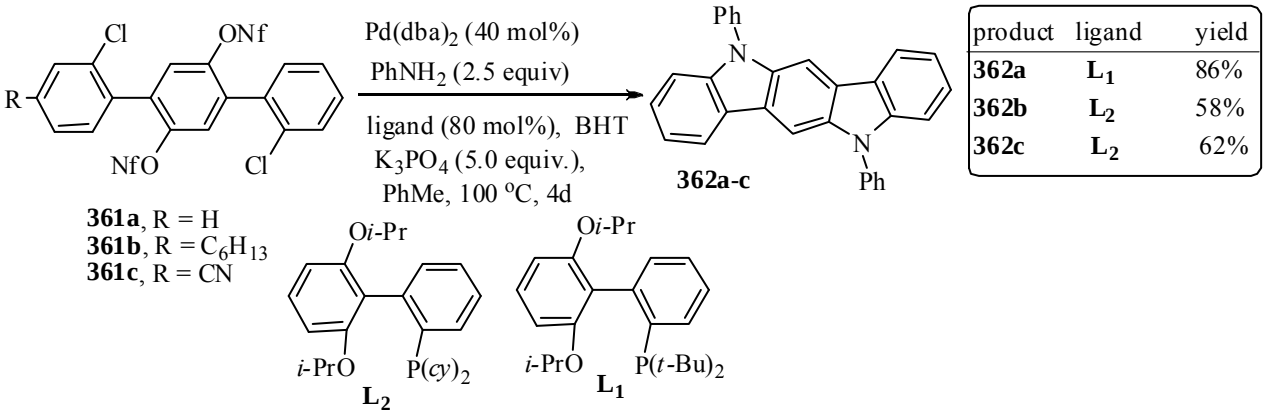
Scheme 120

Synthesis of ladder-type pyrrole rings, indolo[3,2-*b*]carbazoles **362a-c** was achieved[200] by $Pd(OAc)_2$-catalyzed double *N*-arylation of **361a-c** using 2-di-*tert*-butylphosphino-2'-methylbiphenyl (**L_1**) as ligand and 2,6-di-*tert*-butyl-4-methylphenol (BHT) as additive. The diamination reaction with aniline for the formation of compounds **362a-c** was influenced by the ligand employed (**Scheme 121**).

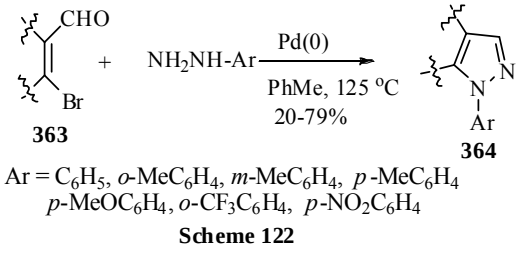
6.2.2. VINYL HALIDES OR TRIFLATES

The cross coupling reaction between vinyl halides or triflates with amine or alcohol are less. This protocol was applied for the synthesis of 1-aryl-1*H*-pyrazoles **364** from cyclic and acyclic *β*-bromovinyl aldehydes **363** and arylhydrazines[201] by using $Pd(OAc)_2$, dppf and NaO^{t}Bu (**Scheme 122**).

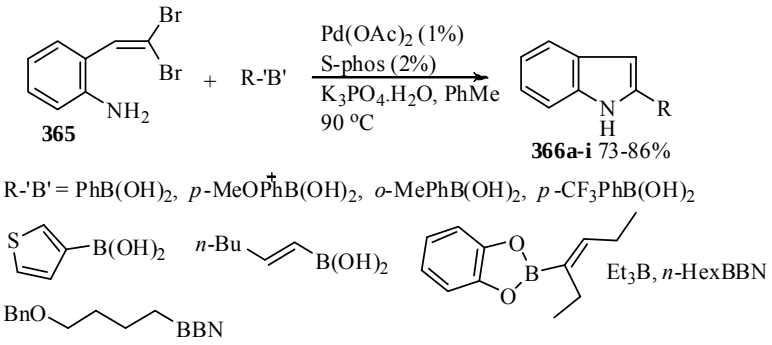
Ortho-gem-dihalovinylaniline **365** underwent domino intramolecular Buchwald-Hartwig amination and intermolecular Suzuki-Miyaura coupling when subjected to aryl boronic acid in the presence of $Pd(OAc)_2$, as catalyst and Buchwald's S-phos ligand. The methodology was examined with a broad variety of boronic acid to give 2-phenyl indoles **366a-i** (**Scheme 123**)[202] with an attractively low catalyst loading (typically 1-3 mol% Pd).



Scheme 121

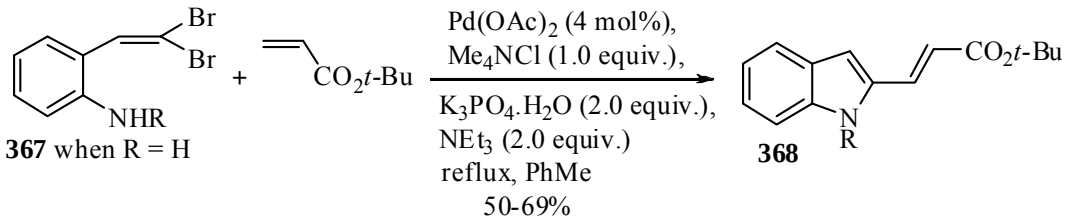


Scheme 122



Scheme 123

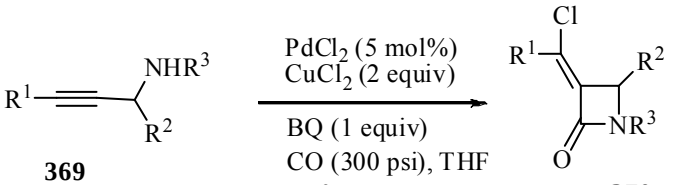
Domino Buchwald-Hartwig amination / Heck reaction was utilized for the synthesis of 2-vinylic indoles **368** from gem-dibromovinylanilines **367**.[203] The reaction was examined under three different catalytic combinations depending upon the nature of the *N*-substituents. The coupling with both electron deficient and electron rich *N*-aryl substrates proceeded smoothly to afford the vinyl indole (**Scheme 124**).



Scheme 124

6.3. CYCLOCARBONYLATION REACTIONS

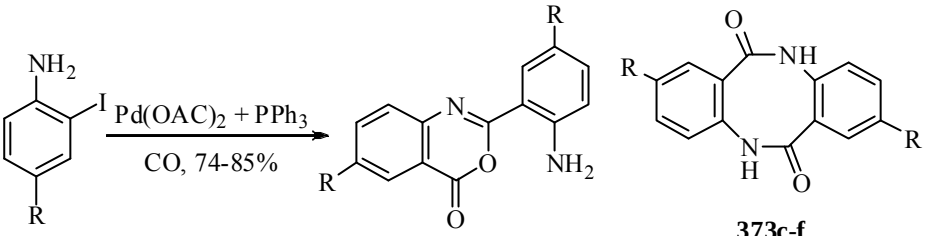
The palladium-mediated carbonylation[204] and carboxylation[205] reactions have been extensively employed in the synthesis of heterocycles. Ma *et al*. reported a mild and efficient Pd-catalyzed carbonylation of propargylic alcohols with various structural patterns for the synthesis of (*Z*)-R-chloroalkylidene-*β*-lactones selectively.[206] The $PdCl_2/CuCl_2$-catalytic system with BQ oxidant and carbon monoxide was highly efficient for the cyclocarbonylation of propargylic amines **369** leading to the synthesis of (*E*)-α-chloroalkylidene-*β*-lactams **370**.[207] No *Z*-isomer or five-membered product was obtained (**Scheme 125**).



R^1 = *n*-C_4H_9, Ph, $PhCH_2CH_2$, *t*-Bu
R^2 = *n*-C_5H_{11}, C_2H_5, *i*-Pr, cyclohexyl, Me, Ph
R^3 = H, Bn, Ts

Scheme 125

In recent report, 2-iodoaniline has been found to behave as a bifunctional substrate during carbonylation with carbon monoxide.[208] When subjected to $Pd(OAc)_2/PPh_3$ catalyst system in the presence of carbon monoxide, the anilines **371a**,**b** afforded 2-aryl-benzo[*d*][1,3]oxazin-4-one derivatives **372a**,**b** via double carbon monoxide insertion keeping one NH_2 intact where as symmetric 5*H*,11*H*-dibenzo[b,*f*][1,5]diazocine-6,12-diones (dianthranilides) **373c-f** were obtained as the major products from the substrates **371c-f**. The reaction is very much chemoselective (>96%) (**Scheme 126**).

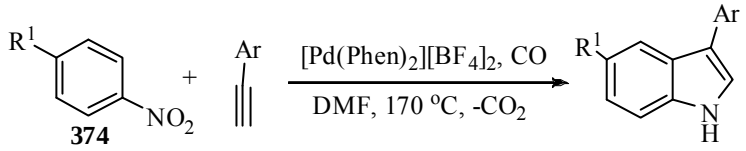


371a-f, R = H, Me, Cl, CN, NO_2

Scheme 126

6.4. REDUCTIVE N-HETEROCYCLIZATION OF NITROARENE

Palladium catalyzed reductive *N*-heterocyclization of nitroarenes is emerging as a versatile method for the preparation of five-membered nitrogenated heterocycles.[209] The carbon monoxide behaves as a reducing agent in the presence of palladium.[210] Ragaini *et al*. carried out a detailed investigation on the scope and efficiency of intermolecular cyclization of unfunctionalized nitroarenes and alkynes catalyzed by palladium-phenanthroline complexes leading to the synthesis of 3-arylindoles **375**.[211] The indole synthesis was achieved in the presence of $[Pd(Phen)_2][BF_4]_2$ as catalyst and carbon monoxide in DMF at 170 °C with excellent selectivity (**Scheme 127**).

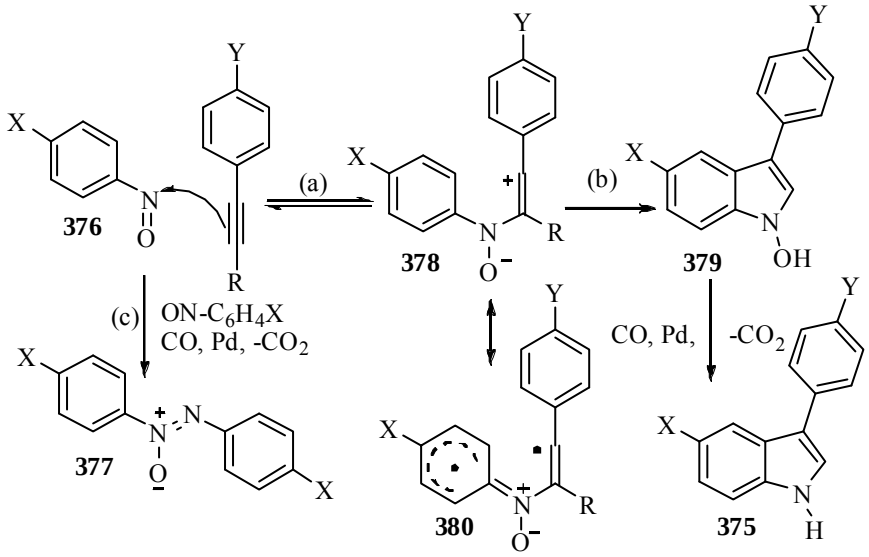


R^1 = H, Cl, Me, CO_2Me, OMe
OC(O)Me, NO_2, CN
Ar = Ph, *p*-$NH_2C_6H_4$, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-$CF_3C_6H_4$

Scheme 127

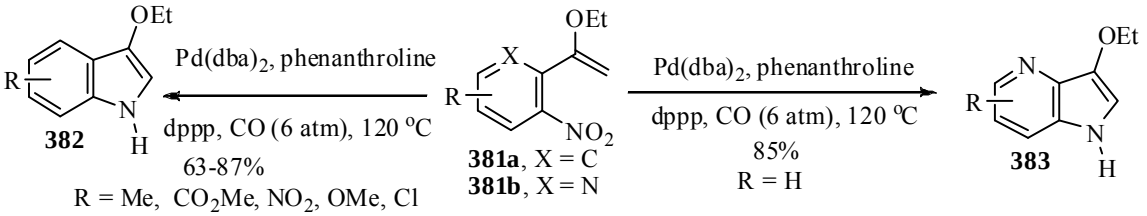
A plausible reaction mechanism for the indole synthesis may involve the formation of nitroarene intermediate **376** which interacts with the alkyne reversibly to give an intermediate **380** having two

possible resonating structures, α-styryl cation[212] and α-styryl radical.[213] Final cyclization would give the hydroxyindole **379** which in the presence of CO and the catalyst is reduced to indole **375** (**Scheme 128**).



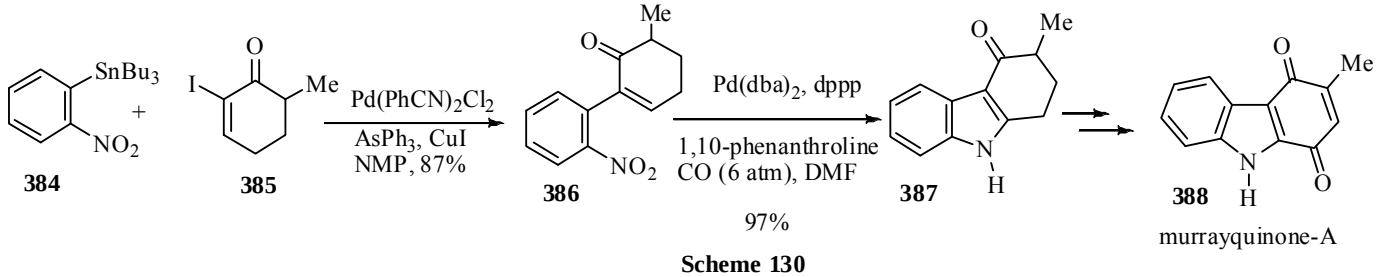
Scheme 128

Another interesting example of *N*-heterocyclization reaction was observed during the synthesis of 3-alkoxy indole derivatives.[214] Relatively lower temperature was required for efficient conversion and in the presence of $Pd(dba)_2$/phenanthroline/dppp catalytic system 1-(2-nitrophenyl)-1-alkoxyalkenes **381a** afforded the indole derivatives. The product **383** was similarly prepared (**Scheme 129**).



Scheme 129

An efficient synthesis of naturally occurring carbazole alkaloid murrayquinone-A **388** has been reported.[215] The carbazolone intermediate **387** was prepared from its nitroarene precursor **386** by $Pd(dba)_2$/dppe/1,10-phenanthroline-catalyzed reductive *N*-heterocyclization in excellent yield. Murrayquinone-A **388** was obtained in few steps from **387** (**Scheme 130**).

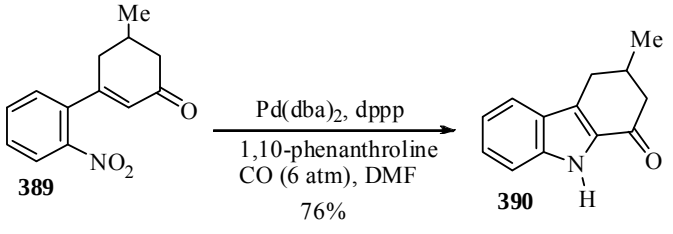


Scheme 130

A range of tetrahydrocarbazolone derivatives **390** was also synthesized as advanced intermediates to carbazole alkaloids utilizing the palladium catalyzed reductive *N*-heterocyclization approach[216] (**Scheme 131**).

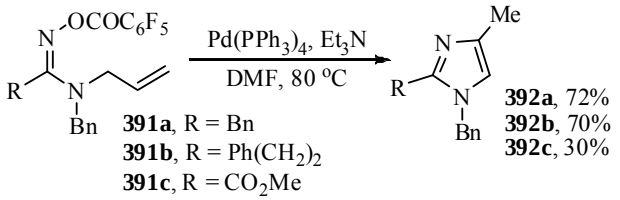
6.5. AMINO HECK REACTION

This reaction has been exploited in the synthesis of various types of pyrrole, isoquinoline and pyridine derivatives.[217] The synthesis of trisubstituted imidazoles with a range of substituents at the 2-position was achieved by amino Heck reaction.[218] This intramolecular C-N bond formation using *N,O*-pentafluorobenzoyl amidoximes **391** as precursors was carried out in the presence of 10 mol% of $Pd(PPh_3)_4$ and 5 equiv of triethylamine in DMF at 80 ^{0}C (**Scheme 132**).



389 **390**

Scheme 131

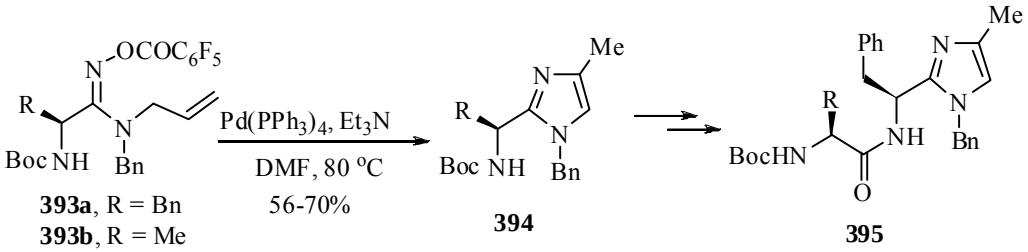


391a, R = Bn
391b, R = $Ph(CH_2)_2$
391c, R = CO_2Me

392a, 72%
392b, 70%
392c, 30%

Scheme 132

This amino-Heck based methodology was also extended to the synthesis of optically active amino acid mimetics with C-terminal imidazole in good yields. The transformation of *S*-Phe and *S*-Leu based amidoximes **393a** and **393b** to the cyclized products **394a** and **394b** underwent smoothly in 1 h where as *S*-ala based cyclization product **394b** was isolated within 30 min. (**Scheme 133**).



393a, R = Bn
393b, R = Me
393c, R = CH_2CHMe_2

394 **395**

Scheme 133

7. CYCLIZATION VIA CASCADE CARBON-CARBON/CARBON-HETEROATOM BOND FORMATION: HETEROCYCLIZATION REACTIONS

7.1 HETEROCYCLIZATION REATIONS WITH ALKYNES

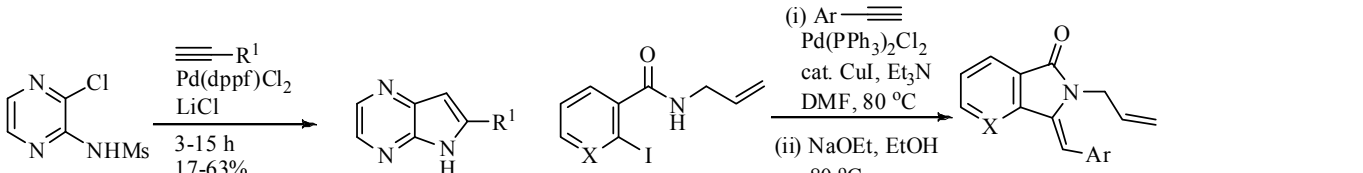
Palladium-catalyzed intermolecular heterocyclization of alkynes has emerged as an accomplished route to the synthesis of large varieties of heterocycles.[219] The annulation occurred via two different mechanistic pathways with the nature of alkyne used.[220]

7.1.1. REACTIONS WITH TERMINAL ALKYNES: SONOGASHIRA COUPLING-CYCLIZATION REACTIONS

Hopkins *et al*. reported the synthesis of 6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazines **397** by the reaction between alkynes and *N*-(3-chloropyrazin-2-yl)methanesulfonamide **396** under different catalytic conditions[221] (**Scheme 134**).

The reaction also proceeded in the presence of $Pd(dppf)Cl_2$-CuI, however, the yield was comparatively low. One-pot Sonogashira coupling-base induced cyclization was applied to the synthesis of 3-

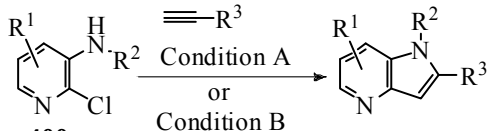
arylmethyleneisoindoline and pyrrolopyridinones **399a,b** starting from their respective amides **398a** and **398b** respectively.[35] The (*Z*)-selectivity may be due to an *anti*-addition across the carbon-carbon triple bond (**Scheme 135**).



396 **397** **398a**, X = CH; **398b**, X = N **399a**, X = CH, Ar = 2-MeOC$_6$H$_4$CH$_2$, 70%; **399b**, X = N, Ar = Ph, 52%

Scheme 134 **Scheme 135**

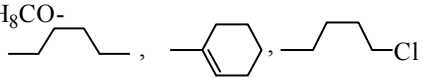
An expedient synthesis of biologically active azaindole and indole comprises of Sonogashira coupling and base promoted cyclization starting from less commonly used 2-chloro-3-aminopyridines **400**.[222] 2-Chloro-3-aminopyridines **400** were successfully converted to azaindoles **401** in excellent yields when subjected to $Pd(OAc)_2$-dppb catalytic system (**Scheme 136**, condition A). Alternatively $Pd(MeCN)_2Cl_2$-x-phos catalytic system (**Scheme 136**, condition B) was found to have the same catalytic efficiency for the conversion.



400 **401** (83-91 %)

R^1 = F, NO_2, Me

R^2 = *p*-MeOC$_6$H$_4$CO-, *p*-FC$_6$H$_4$CO-, PhCO-, C$_6$H$_{11}$CO-, C$_5$H$_8$CO-

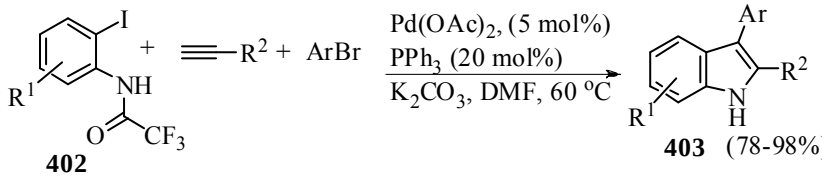
R^3 = Ph, 

Condition A: $Pd(OAc)_2$ (2 mol%), dppb (4 mol%), K_2CO_3 (300 mol%), MeCN (10 mL/g), 80 °C, 16 h, then 1 M KO*t*-Bu in THF (50 mol%), rt

Condition B: $Pd(MeCN)_2Cl_2$ (1 mol%), x-phos (3 mol%), K_2CO_3 (300 mol%), MeCN (10 mL/g), 60 °C, 16 h, then 1 M KO*t*-Bu in THF (50 mol %), rt

Scheme 136

Lu *et al*. reported a Pd-catalyzed practical one-pot three-component process for the preparation of 2,3-disubstituted indoles **403**. Sonogashira coupling and aminopalladation were carried out under the same reaction conditions (**Scheme 137**).[223] An examination of the base, solvent, temperature and ligand effect on the reaction revealed that a combination of 5 mol% of $Pd(OAc)_2$, 20 mol% of PPh_3 and K_2CO_3 in DMF at 60 °C was effective enough for this one-pot process to give the 2,3-disubstituted indole derivatives **403** in excellent yields.



402 **403** (78-98%)

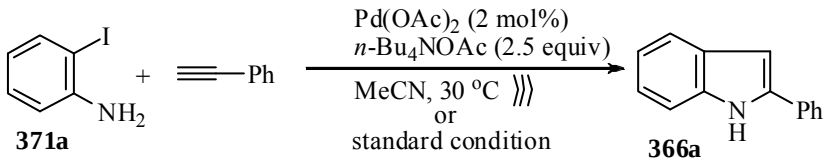
R^1 = H, CO_2Me, CN Ar = Ph, *p*-MeOC$_6$H$_4$, *o*-NO$_2$C$_6$H$_4$, *p*-NO$_2$C$_6$H$_4$, *p*-CO$_2$MeC$_6$H$_4$

R^2 = Ph, *p*-tol

Scheme 137

A ligand-, copper- and amine-free synthesis of 2-substituted indole **366a** in good yield via Sonogashira coupling-5-*endo-dig* cyclization has been reported.[224] The reaction between *N*-tosyl 2-iodoaniline and phenyl acetylene was conducted under both ultrasonic irradiation and standard stirred condition utilizing

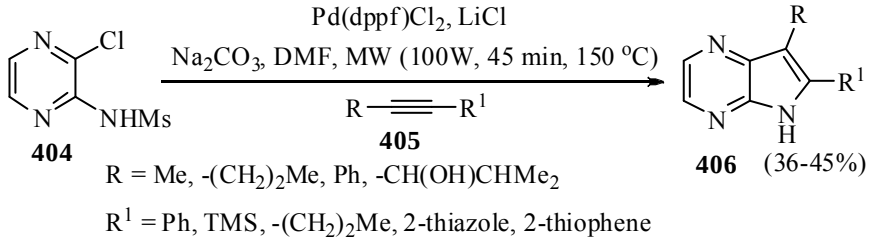
$Pd(OAc)_2$. A significant enhancement of rate was observed under ultrasonic irradiation (**Scheme 138**).



Scheme 138

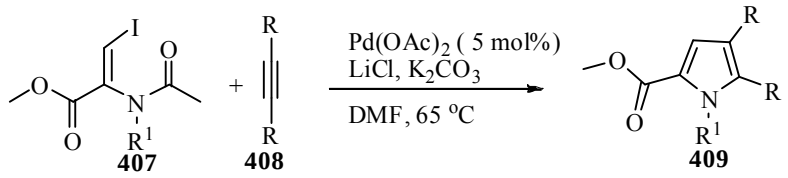
7.1.2. REACTIONS WITH INTERNAL ALKYNES

The heterocyclization reaction between *N*-(3-chloropyrazin-2-yl)-methanesulfonamide **404** and internal alkynes in the presence of $Pd(dppf)Cl_2$ as catalyst and LiCl as additive under microwave irradiation furnished 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines **406** (**Scheme 139**).[225]



Scheme 139

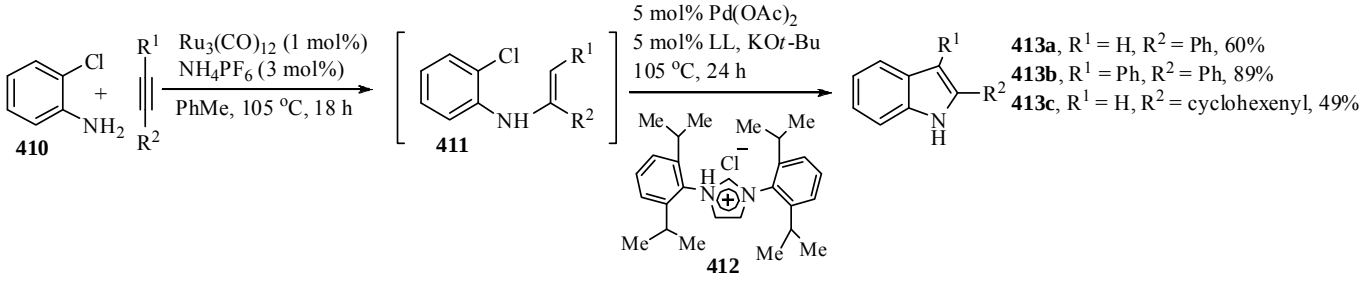
A palladium-catalyzed synthetic strategy for the regioselective synthesis of highly substituted pyrroles **409** was developed[226] by coupling-cyclization between stabilized iodoenamines and symmetrical alkynes utilizing $Pd(OAc)_2$ as catalyst to afford the pyrroles in good yields. With unsymmetrical alkynes two methods were attempted to accomplish the reaction which showed poor regioselectivity affording two regioisomeric pyrroles in the ratio spanned from 1.5:1 to >25:1 (**Scheme 140**).



409a, R = *n*-Pr; R^1= Ac (78%)
409b, R = Me; R^1= Ac (58%)
409c, R = $SiMe_3$; R^1= Ac (60%)
409d, R = *n*-Pr; R^1= H (94%)
409e, R = Me_2COH; R^1= H (62%)
409f, R = Ph; R^1= H (77%)

Scheme 140

A one-pot synthesis of 2-aryl- and 2-vinyl indoles based on a ruthenium-catalyzed hydroxyamination[227] and a palladium-catalyzed intramolecualr Heck reaction using 2-chloroaniline **410** as precursor[352, 228] has recently been reported (**Scheme 141**).

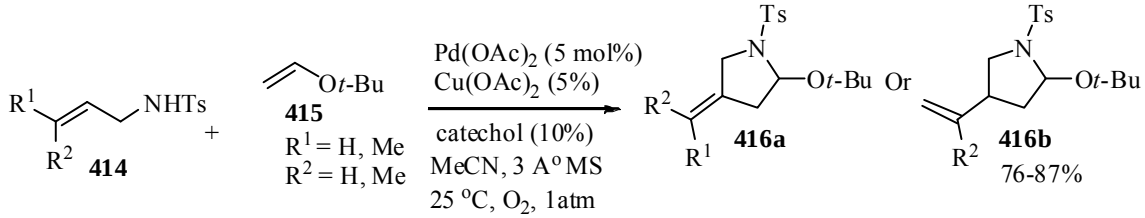


413a, R^1 = H, R^2 = Ph, 60%
413b, R^1 = Ph, R^2 = Ph, 89%
413c, R^1 = H, R^2 = cyclohexenyl, 49%

Scheme 141

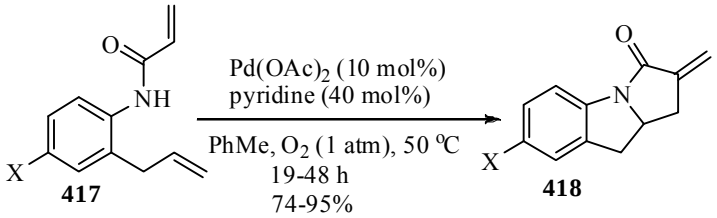
7.2 HETEROCYCLIZATION REACTIONS WITH ALKENES

The allyl tosylamides were found to undergo intermolecular oxidative coupling reaction with *t*-butyl vinyl ether in the presence of $Pd(OAc)_2$ as catalyst and $Cu(OAc)_2$ as additive.[229] Catechol and MS (3Å) were found to be beneficial co-catalyst in this reaction and in the presence of molecular oxygen as oxidant pyrrolidine derivatives **416** were synthesized (**Scheme 142**).



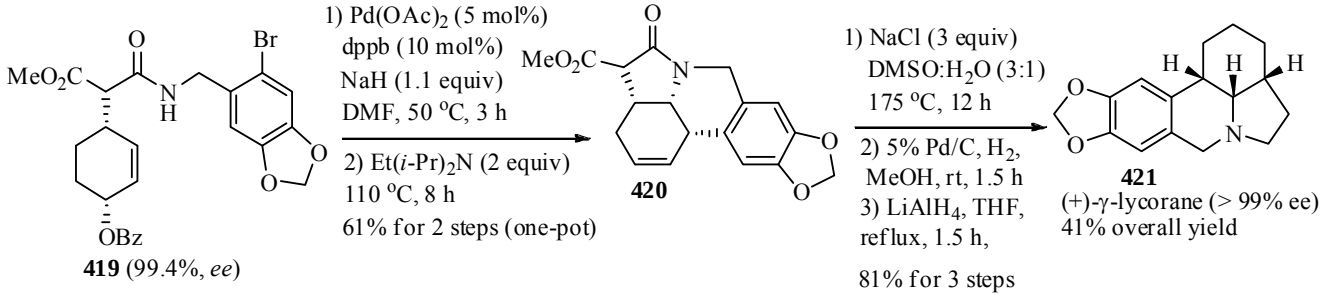
Scheme 142

In a recent development, Pd(II)/pyridine catalyst system has been employed for the tandem oxidative cyclization of **417** to afford indoline derivatives[230] **418**. The reaction was successfully accomplished utilizing $Pd(OAc)_2$ as catalyst and molecular oxygen as sole oxidant (**Scheme 143**).



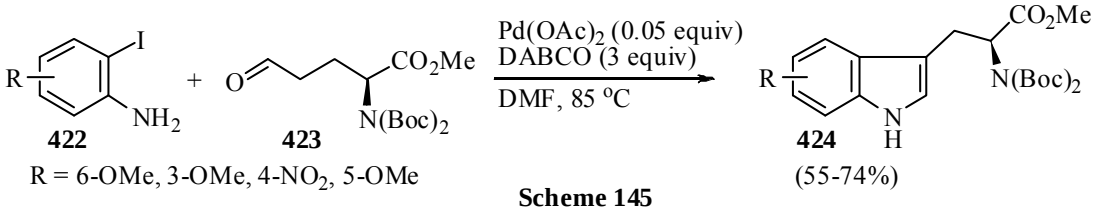
Scheme 143

The total synthesis of enantiopure (+)-γ-lycorane was achieved[231] from the intermediate pentacyclic oxylycorane **420** which was in turn synthesized through $Pd(OAc)_2$-dppb catalyzed one-pot domino allylic amination-intramolecular Heck reaction (**Scheme 144**).



Scheme 144

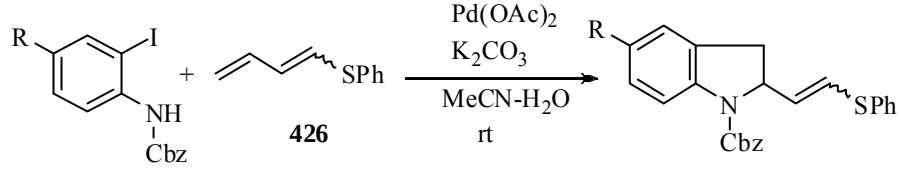
A domino-heterocyclization reaction between *o*-iodoaniline and 2-*N*,*N*-di-*t*-butoxycarbonylamino-5-oxopentanoate **423** was adopted for the synthesis of ring-A substituted tryptophan derivatives **424**[232] (**Scheme 145**).



Scheme 145

7.3. HETEROCYCLIZATION REACTIONS WITH DIENES

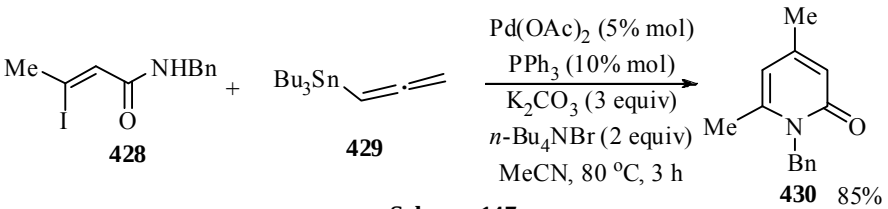
The heterocyclization of *N*-carbobenzyloxy-*o*-iodoanilines **425** with 1-phenylthio-1,3-butadiene **426** was carried out in aqueous MeCN containing K_2CO_3 in the presence of a catalytic amount of $Pd(OAc)_2$[233] to afford vinylogous 2-(phenylthio)indole derivatives **427a-c** in 49-75% yields (**Scheme 146**).



425a-c, R = H, Me, CO_2Me **427a-c**

Scheme 146

The regio- and stereoselective annulation[234] of tributylstannylallenes **429** with (*Z*)-3-substituted-3-iodoprop-2-enamides **428** catalyzed by $Pd(OAc)_2$ afforded 4,6-disubstituted-2-pyridone **430** in 85% yield. This annulation probably occurred via Stille reaction followed by intramolecular cyclization (**Scheme 147**).

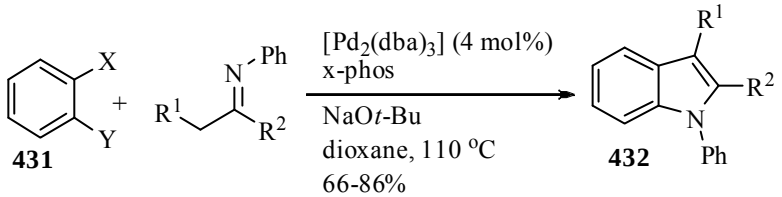


Scheme 147

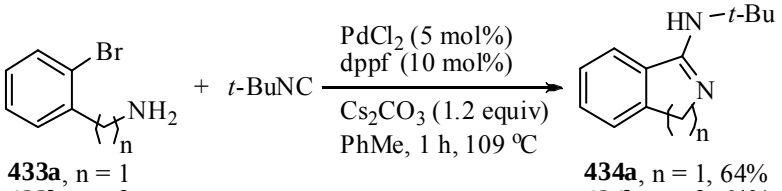
7.4. HETEROCYCLIZATION REACTIONS WITH CARBON-HETEROATOM UNSATURATED BOND

The participation of the aza-allylic anions generated from imines in sequential Pd-catalyzed C-C and C-N bond-forming reactions has lead to the development of a new and efficient method for the synthesis of indole derivatives.[235] Aza-allylic anions have been extensively employed as three atom synthons in Classical heterocyclic chemistry.[236] The two component cascade sequence involving C- and N-arylations between *o*-dihalobenzenes and imine **431** was carried out in the presence of $[Pd_2(dba)_3]$ as catalyst, x-phos as ligand and sodium tertiary butoxide as base in to give indoles **432** (**Scheme 148**).

The reaction of 2-bromobenzylamine **433a** and 2-(2-bromophenyl)ethanamine **433b** with *tert*-butylisonitrile in the presence of $PdCl_2$, dppf and Cs_2CO_3 gave cyclic amidines **434a,b**[237] (**Scheme 149**).



Scheme 148

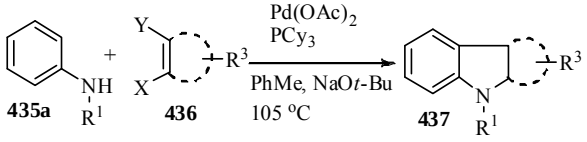


Scheme 149

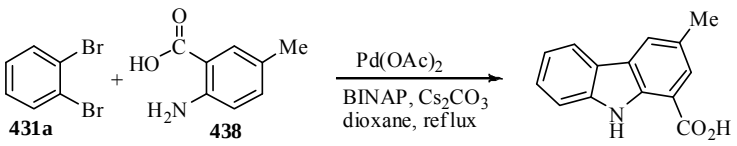
7.5. HETEROCYCLIZATION REACTIONS WITH ARENES

Direct synthesis of carbazole by palladium-catalyzed domino reaction has been reported.[238] The reaction involves an amination and direct arylation using readily available *N*-phenyl anilines and 1,2-halo(hetero)arenes **436** in the presence of $Pd(OAc)_2$ as catalyst, PCy_3 as ligand and sodium tertiary butoxide as base. PPh_3 and *N*,*N*'-bis(diisopropylphenyl)imidazolium chloride gave good yields of carbazole derivatives **437** (**Scheme 150**).

A one-pot synthesis of carbazole derivative was achieved by palladium-catalyzed intermolecular coupling between *o*-dibromobenzene and 5-methylanthranillic acid.[239] It is interesting to note that instead of second nucleophilic attack leading to the formation of *o*-diarylaminobenzene, the intramolecular reductive elimination occurred affording the carbazole derivative **439** (**Scheme 151**).

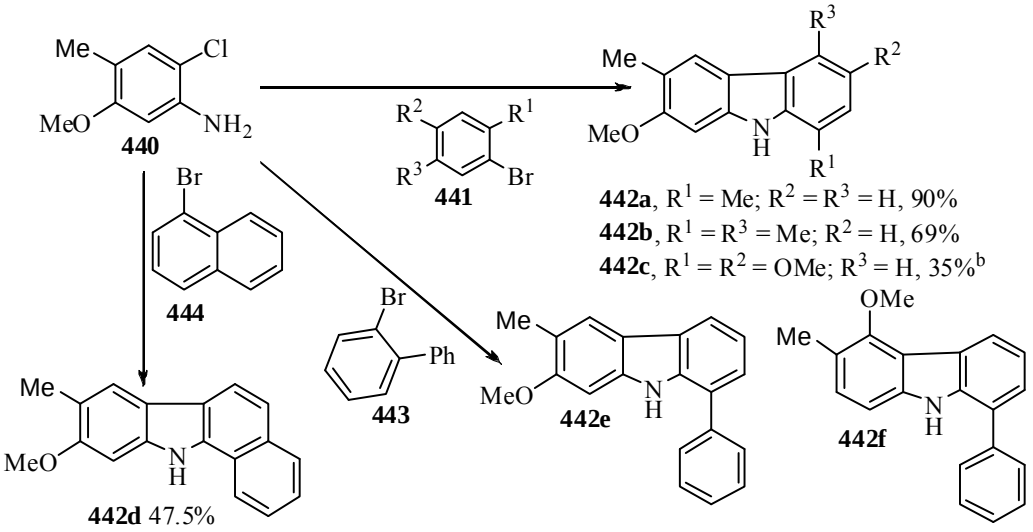


Scheme 150



Scheme 151

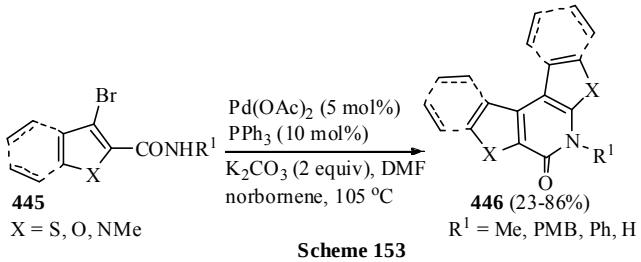
An efficient methodology for the construction of N-H carbazoles from 2-chloroanilines has recently been reported.[240] The microwave assisted intermolecular reaction between 2-chloroaniline with different arylbromides using $Pd(OAc)_2$ as catalyst and $P(t\text{-}Bu)_3$ as ligand afforded the carbazole derivatives **442a-d**. However, the reaction between 2-chloroaniline and 2-bromobiphenyl yielded an inseparable mixture of **442e** and **442f**. The domino reaction may proceed via Buchwald-Hartwig amination followed by intramolecular ring closure by C-H activation (**Scheme 152**).



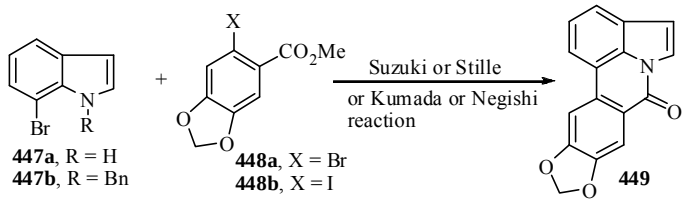
Scheme 152

A simple catalytic synthesis of condensed pyridones involving *ipso* substitution via palladacycles was reported by Catallani *et al*.[241] Symmetrically condensed pyridones **446** were obtained starting from *o*-bromocarboxamides **445** in the presence of norbornene, $Pd(OAc)_2/PPh_3$ as the catalyst, K_2CO_3 as base in DMF (**Scheme 153**).

Total synthesis of hippadine **449** by a one-pot domino metallation-cross coupling-lactonization was achieved from 7-bromo indole **447** and 6-halogenated piperonoate **448** (**Scheme 154**).[242]



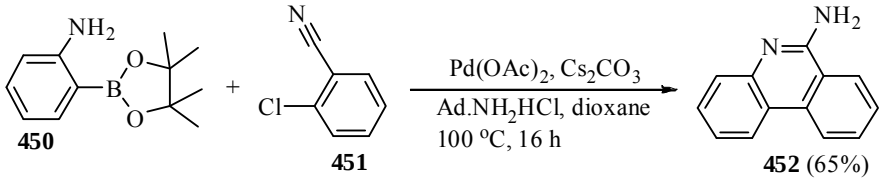
Scheme 153



Scheme 154

Suzuki reaction of 6-bromo indole afforded the hippadine derivatives in 21-74% yields where as comparatively lower yield of hippadine was obtained under Suzuki and Stille condition from electron-deficient methyl-6-iodo- and 6-bromopiperonoate.

A simple synthesis of bioactive 6-aminophenanthridines by Suzuki-Miyaura coupling reaction has recently been described.[243] The condensation between 2-(4,4,5,5-tetramethyl-1,3-dioxaborolan-2-yl)aniline **450** and 2-chlorobenzonitrile **451** in the presence of $Pd(OAc)_2$ (0.05 molequiv), Cs_2CO_3, $AdNH_2.HCl$ (adamantanamine hydrochloride), in dioxane afforded 6-aminophenanthridine **452** (**Scheme 155**).



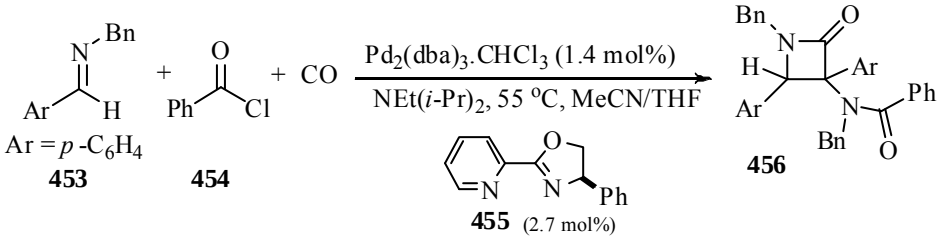
Scheme 155

8. PALLADIUM-CATALYZED MULTI-COMPONENT REACTION

Recently there is flurry of activities in the development of efficient synthetic procedure that can affect multiple chemical reactions in a one-pot event.[244,245] Palladium-catalysts help to synthesize the libraries of heterocyclic compounds[1] by multicomponent reaction.

8.1. PALLADIUM-CATALYZED THREE-COMPONENT REACTION

A one-pot coupling of imines, carbon monoxide and acid chloride employing $Pd_2(dba)_3.CHCl_3$ as catalyst and diimine ligand **455** afforded 3-amido-substituted-β-lactams in low-to-good yields (**Scheme 156**).[246]

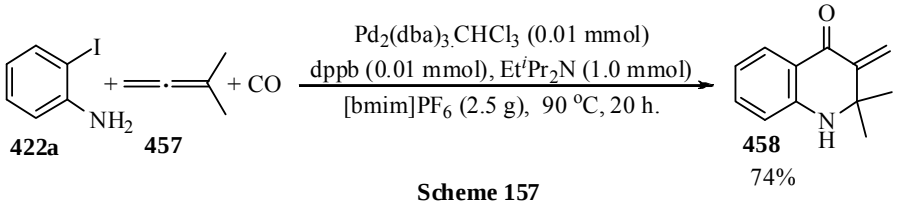


Scheme 156

The use of ionic liquid [bmim]PF_6 for the cyclocarbonylation of phenols and anilines has been reported by Alper *et al*.[247] Recently, the same group also demonstrated the efficiency of the ionic liquid [bmim]PF_6

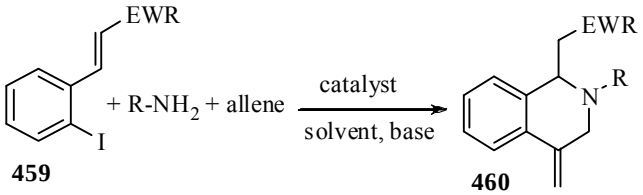
and $Pd_2(dba)_3.CHCl_3$ for the multicomponent cyclocarbonylation of *o*-iodo aniline with substituted allenes under low pressure (5 atm) of carbon monoxide[248] to give 3-methylene quinolone derivative **458** (**Scheme 157**). The ionic liquid functioned as solvent and promoter, enhanced the efficiency of the cyclocarbonylation.

Grigg *et al*.[249] recently reported a novel three-component palladium-catalyzed allene insertion-nucleophile incorporation-Michael addition cascade reaction for the synthesis of novel tetrahydroisoquinolines **460**. When aryl iodide, nucleophile, palladium catalyst and allene were reacted in the presence of K_2CO_3 in PhMe at 100 °C, the corresponding tetrahydroisoquinoline derivatives **460** were obtained in moderate-to-good yields (**Scheme 158**).



422a **457** **458** 74%

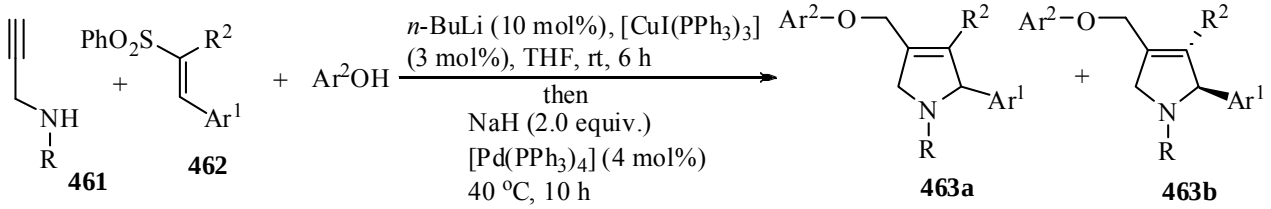
Scheme 157



459 **460**

Scheme 158

A new one-pot, three-component coupling strategy based on two consecutive metal-catalyzed reactions, providing a straightforward route to elaborate five-membered nitrogen heterocycles was developed.[250] The coupling of three flexible and readily available starting materials: propargylamines **461**, vinyl sulfones (or nitroalkenes) **462** and phenolic derivative is suggested to involve a copper-catalyzed cycloaddition combined with palladium-catalyzed allylic substitution to give polysubstituted pyrrolines **463a**,**b** in two isomeric forms in 34-69% yields in a ratio ranging from 54:46 to 100:0 (**Scheme 159**).



461 **462** **463a** **463b**

R = Me, Bn, R^2 = CO_2Me, CN Ar^2 = Ph, *p*-ClC_6H_4-, *p*-$MeO_2CC_6H_4$

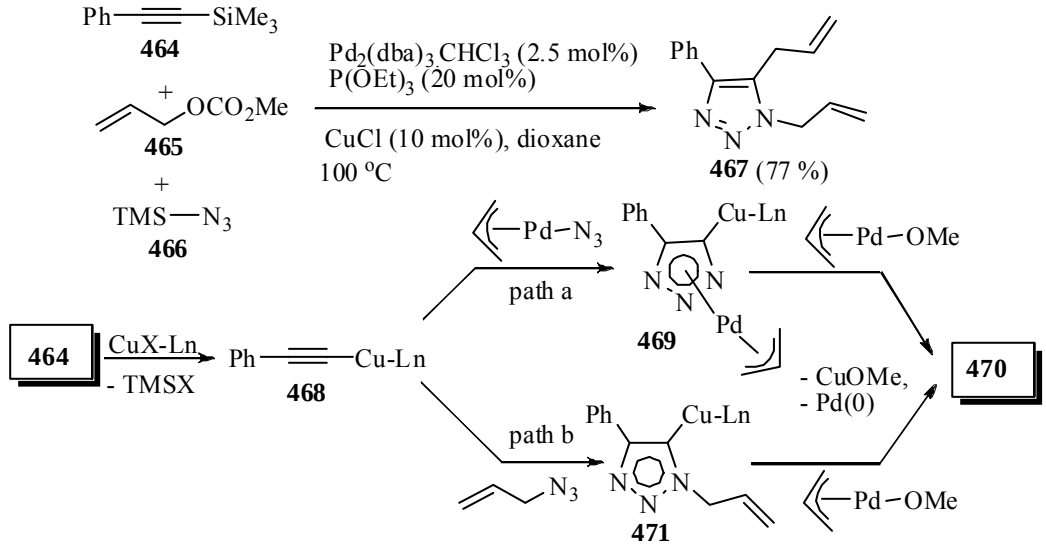
Ar^1 = Ph, $C_{10}H_7$ *p*-$MeOC_6H_4$, 3,4-(-OCH_2O-)C_6H_3, $C_{10}H_7$

Scheme 159

8.2 PALLADIUM-CATALYZED FOUR-COMPONENT REACTION

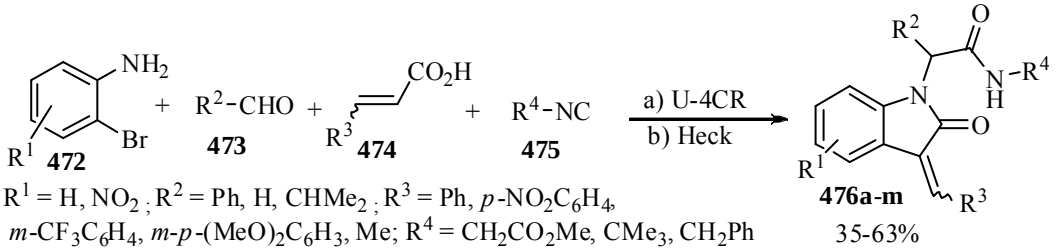
Four component reaction of unactivated silylacetylenes, allyl carbonate and trimethylsilyl azide in the presence of bimetallic catalyst $Pd_2(dba)_3.CHCl_3$-CuCl and phosphine ligand $P(OEt)_3$ afforded the triazole derivative **467**.[251] In both the cases, a [3+2] cycloaddition reaction between initially generated copper

acetylide and π-allyl palladium azide[252] (Path a) or between allyl azide and π-allyl palladium methoxide (Path b) may occur to afford the triazole skeleton (**Scheme 160**).



Scheme 160

A novel one-pot solution phase Ugi-Heck reaction (Ugi-4CR-Heck) for the preparation of indol-2-ones has been reported.[253] The reaction is suggested to proceed via the intermediate Ugi product, which subsequently undergoes intramolecular Heck reaction to afford the indol-2-one derivatives **476** (**Scheme 161**).



R^1 = H, NO_2 ; R^2 = Ph, H, $CHMe_2$; R^3 = Ph, *p*-$NO_2C_6H_4$, *m*-$CF_3C_6H_4$, *m*-*p*-$(MeO)_2C_6H_3$, Me; R^4 = CH_2CO_2Me, CMe_3, CH_2Ph

a) trifluoreethanol; 24 h, 50 °C; b) MeCN; 24 h, 80 °C; PPh_3

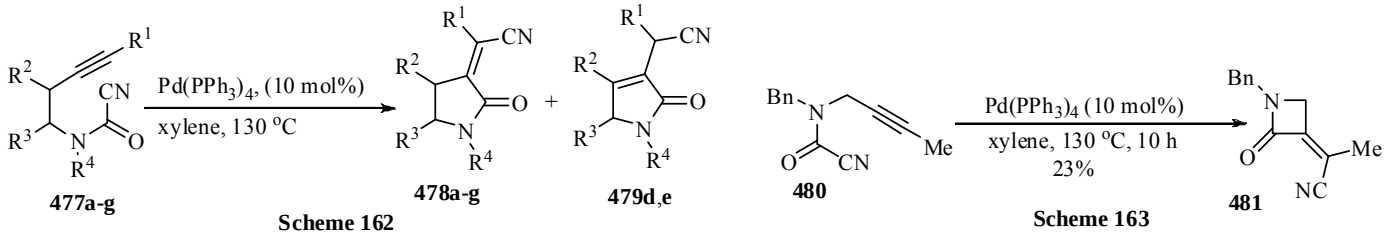
Scheme 161

9. MISCELLANEOUS REACTIONS

9.1. CYANOAMIDATION REACTION

The synthesis of α-alkylidene derivatives by the palladium-catalyzed intramolecular cyanoamidation of alkynyl cyanoformamides has recently been described.[254] Different alkynyl cyanoformamides **477** underwent cyclization in the presence of $Pd(PPh_3)_4$ to afford the α-alkylidene derivatives **478** in 45-99% yields. The reaction proceeds exclusively in a 5-*exo*-manner. The other product **479** was formed probably via 1,3-migration of the C-4 proton (**Scheme 162**).

The same synthetic strategy has been applied to the synthesis of 4-membered lactam ring.[255] The cyanoformamide **480** in the presence of $Pd(PPh_3)_4$ affoirded the lactam **481** (**Scheme 163**).

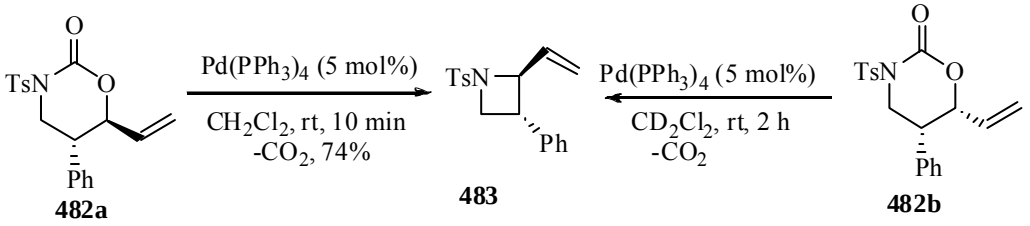


477a-g **478a-g** **479d,e** **480** **481**

Scheme 162 **Scheme 163**

9.2. RING-OPENING CYCLIZATION REACTION

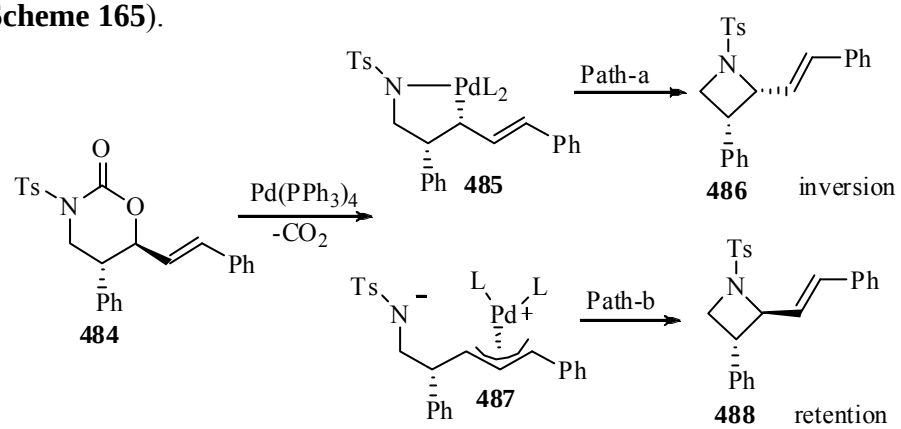
6-Vinyl-1,3-oxazinanone **482a** underwent decarboxylative ring formation in the presence of $Pd(PPh_3)_4$ to afford 2-vinylazitidine **483**.[256] Notably, the ratio of the diastereomers in the product azitidine (16:1) was slightly lower than that of the starting material perhaps due to interconversion of the diastereomers on the time scale of the cyclization. The faster than cyclization, epimerization through π-σ-π allyl interconversation was further ascertained by the formation of **483** from *cis*-**482b** (**Scheme 164**).



482a **483** **482b**

Scheme 164

Two separate mechanistic pathways, involving five-membered metallacycle **485** (Path a) or π-allyl complex **487** (Path b) are suggested to operate for the rapid formation of azitidine moiety. Reductive elimination from the five-membered metallacycle should give overall inversion of stereo-chemistry where as over all retention of stereo chemistry is observed due to the back side attack of the free nitrogen anion. Interestingly, it was observed that vinyl azitidine formed from **484** was shown to be anti isomer which clearly indicated a back side attack of the amide anion on the π-allyl ligand with over all retention of stereochemistry (**Scheme 165**).

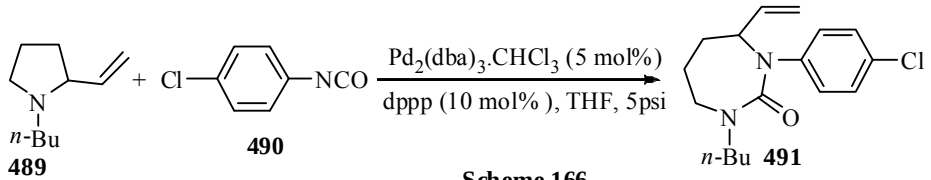


484 **485** **486** **487** **488**

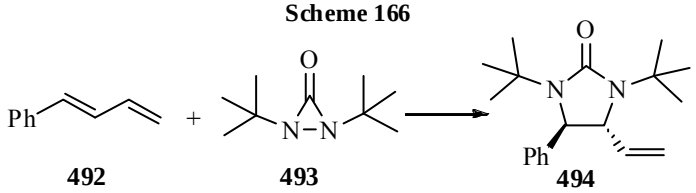
Scheme 165

Highly regioselective palladium-catalyzed ring opening and cyclization reaction of 2-vinylpyrrolidines **489** with aryl isocyanates **490** was carried out in the presence of $Pd_2(dba)_3.CHCl_3$ and dppp at 40-60 °C in THF to furnish 1,3-diazepin-2-ones **491** in good isolated yield[257] (**Scheme 166**).

The feasibility of NHC-Pd(0) complexes as viable catalysts for the diamination of conjugated diene was recently investigated.[258] The reaction between di-*t*-butyldiaziridinone **493** as nitrogen source and 1-phenylbutadiene **492** was tested with several commercially available NHC-Pd complexes. The reaction is highly regio- and stereoselective with catalysts, (NHC)Pd(allyl)Cl complexes to produce the diaminated product **494** in moderate-to-excellent yields. The steric hindrance of NHC ligand played an important role in the reductive elimination step of the catalytic cycle as is evident in the higher conversion with more sterically hindered (IPr)Pd(allyl)Cl than IMesPd(allyl)Cl. Due to good solubility in organic solvent sodium *t*-pentoxide was found to be most effective for this diamination reaction (**Scheme 167**).



Scheme 166



Scheme 167

10. CONCLUSION

Hetrocyclic compounds are in high demand in chemical, pharmaceutical and agrochemical industries. The application of Pd-based catalysts in the synthesis of heterocycles is highly essential now because they are air-stable versatile in catalyzing a wide varity of chemical transformations and functionalities. In this review we have presented a portion of exiciting palladium chemistry which is now a powerful tool for the synthesis of nitrogen heterocycles.

Significant contributions have already been made in the synthesis of nitrogen heterocycles by Pd-catalyzed reactions. Unfortunately or fortunately new challenges are continuously forthcoming. Proper tuning of the reaction conditions and development of improved Pd-catalysts will lead to the development of new protocols that may allow synthesis of much more complex biologically active materials. We sincerely hope that this review will be useful not only for organic synthetic and organometallic chemists but also for heterocyclic natural product, pharmaceutical and agrochemical synthetic chemistry.

11. ACKNOWLEDGEMENTS

We thank the DST (New Delhi) for financial assistance. Both of us (B. C. and S. S.) is grateful to the CSIR (New Delhi) for a senior research fellowship.

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