Heterocycle Synthesis Based on Palladium-Catalyzed C−H Bond Functionalization Methods

Raffaella Ferraccioli*

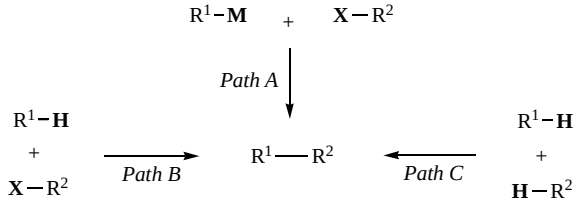
CNR-Istituto di Scienze e Tecnologie Molecolari (ISTM), Via C. Golgi 19, 20133 Milano, Italy

Abstract: This Review reports recent developments in the synthesis of benzo-fused heterocycles through Pd-catalyzed carbon−carbon and carbon−heteroatom bond forming reactions *via* direct C−H activation. Nitrogen-, oxygen- and sulfur-containing heterocyclic rings can be rapidly assembled starting from precursors with minimal preactivation. Compared to classical coupling reactions (i.e. Suzuki, Stille, Buchwald-Hartwig), these methods provide a more straightforward and economical route to various heterocyclic scaffolds, which is of practical importance considering their role in biology and pharmaceutical industry.

Keywords: Palladium, homogeneous catalysis, C−H activation, organic halides, oxidation, heterocycles, cyclization.

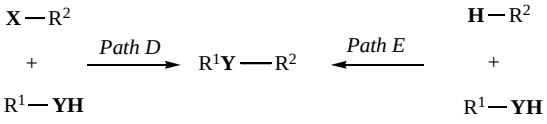
1. INTRODUCTION

Important palladium-catalyzed transformations such as cross-coupling (i.e. Suzuki, Stille), and Buchwald-Hartwig reactions allow to generate carbon−carbon (C−C) and carbon−heteroatom (C−Y) bonds with high selectivity [1]. These reactions require the use of substrates containing a carbon−X bond (X = halide, triflate or tosylate) which can be easily transformed into a C−Pd(II)X bond. The subsequent reaction with a proper nucleophile R^1M (M = group containing a non transition metal) or R^1YH, leads to the formation of new C−C or C−Y bonds (*Path A*, Scheme **1**) (*Path D*, Scheme **2**).



Scheme 1. C−H bond activation in the C−C cross-coupling reaction.

Direct and selective functionalization by palladium-catalyzed cleavage of a C−H bond is an atom economical alternative to traditional cross-coupling reactions (Scheme **1**, *Path B*, *C*; Scheme **2**, *Path E*) [2, 3]. The use of less functionalized starting materials shortens reaction sequence and reduces the formation of toxic by-products.



Scheme 2. C−H bond activation in the C−Y cross-coupling reaction.

The development of these methodologies prompted organic chemists to re-design simpler synthetic routes to complex molecules which attract interest as bio-active compounds or potential pharmaceuticals. Interestingly, most of them contains heterocyclic rings [4]. This Review describes recent progress in the synthesis of *benzo-fused heterocycles* through Pd-catalyzed C−C and C−Y coupling *via* C−H activation methodologies.

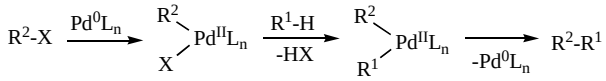
*Address correspondence to this author at the CNR-Istituto di Scienze e Tecnologie Molecolari (ISTM), Via C. Golgi 19, 20133 Milano, Italy; Tel: +39-(0)2-50314141; Fax: +39-(0)2-50314139; E-mail: Raffaella.Ferraccioli@istm.cnr.it

2. C−H BOND ACTIVATION/C−C COUPLING REACTIONS

The articles accompanying the review regard two types of pathways involved in the synthesis of the heterocyclic rings: direct substitutive coupling with aryl, alkenyl, alkyl halides (*Path B)* and oxidative coupling (*Path C*). In each case the examples reported have been grouped considering the two molecular fragments taking part in the C−C bond formation process.

2.1. Direct Substitutive Coupling *(Path B)*

Inter- and intramolecular cross-coupling reactions involving C−H activation with organic halides R^2X (R^2 = aryl, alkenyl, alkyl; X = halides) as coupling partners are initiated by the oxidative addition of organic halides to Pd(0) species followed by the electrophilic attack of the generated Pd(II) species to R^1H. Then, deprotonation and reductive elimination occur leading to the coupling product and Pd(0) species, which can begin a new catalytic cycle (Scheme **3**).



Scheme 3. General mechanism of cross-couplings of C–H bonds with organic halides.

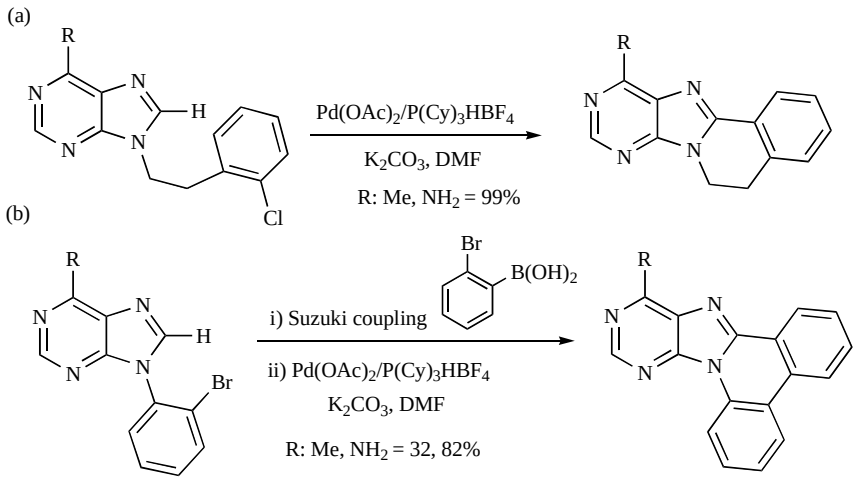
The selective functionalization of a specific C−H bond in a molecule containing similar C−H bonds is a crucial point. High regioselectivity could be achieved when C−H bond functionalization was assisted by (a) a heteroatom (b) a directing-group (c) a palladacycle [2, 3].

2.1.1. Aryl–Aryl Coupling

The early examples of direct arylation of heteroarenes, furan [5] and indole [6], were reported in the mid 1980s. Over the following two decades the intramolecular version of this methodology has become a standard procedure to achieve a variety of poly-heterocycles [2].

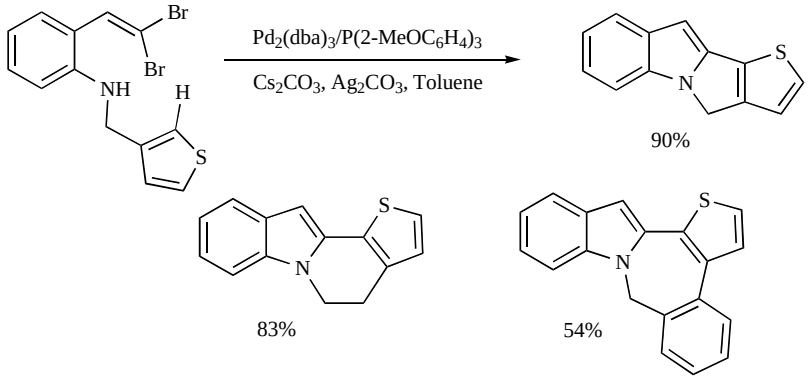
Recently, purino[8,9-a]isoquinolines were synthesized by cyclization of 9-(2-chlorophenethyl)purine (Scheme **4a**) [7]. Of particular interest are those processes where direct *heteroatom-assisted* arylation is combined with a second catalytic reaction. An example is the synthesis of fused purines (Scheme **4b**) [7]. They were assembled from 9-(2-bromophenyl)purines and 2-bromobenzeneboronic acid, under palladium(0) catalysis. The reaction sequence started with a Suzuki coupling affording a bromo-biphenyl derivative which subsequently underwent cyclization through purine C–H arylation, in a one-pot process.

1570-1794/12 $58.00+.00 © 2012 Bentham Science Publishers



Scheme 4. Synthesis of purino[8,9-a]isoquinolines and purino[8,9-f]phenanthridines [7].

Fused indoles were synthesized from *ortho-gem*-dihalovinyl anilines by tandem amination/arylation (Scheme **5**) [8]. Intramolecular amination occurred first, leading to the indole ring formation. Palladium(0) added oxidatively to the C−Br bond of the indole ring affording the C−Pd(II)Br complex. Subsequent intramolecular thiophene arylation in the α position of the sulfur atom generated the second ring. Modifying the linker between the nitrogen atom and the thiophene ring led to six- and seven-membered ring formation. Interestingly, the addition of cationic silver, in the form of Ag_2CO_3, had a beneficial effect on reaction selectivity. In the absence of it, lower conversion and less clean reactions were obtained.



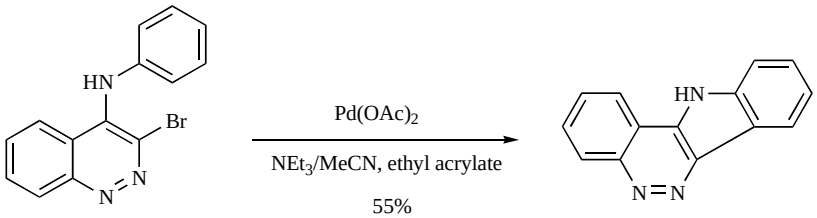
Scheme 5. Synthesis of fused indole derivatives [8].

In these reactions the heteroatom is supposed to coordinate the palladium catalyst, contributing to stabilize the formation of a carbon−Pd bond at a proximal site.

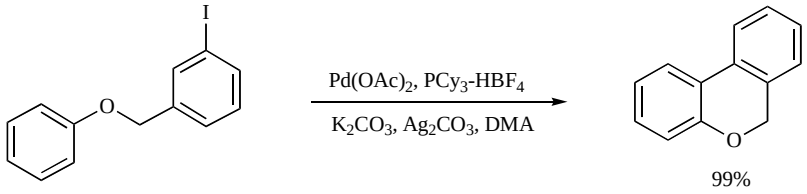
In 1982, Ames reported that 2-bromo-4-phenylaminocinnoline underwent cyclization leading to indolo[3,2-c]cinnoline (Scheme **6**) [9]. The reaction occurred in the presence of $Pd(OAc)_2$ as a catalyst and ethyl acrylate as an additive. Its use was determining to realize selective transformations. Later, dibenzofuran derivatives could be obtained from diphenyl ethers, in the absence of the alkene additive [10].

Since these seminal papers a significant progress has been made in the C−H arylation of *unactivated* arenes.

A number of benzo-condensed heterocycles could be synthesized using reactive iodo and bromoarenes(heteroarenes), as starting halides [2]. Interestingly, coupling direct intramolecular arylation and C–N bond forming reactions (Buchwald-Hartwig) allowed to generate significant molecular complexity from simple precursors. In 2002, Bedford developed a sequential synthesis of carbazoles from 2-chloroanilines and arylbromides [$(Pd(OAc)_2/P\textit{t}Bu_3$ and NaO*t*Bu, toluene] [11]. Later, Zhu reported the synthesis of dihydroazaphenanthrenes fused with a benzodiazepine ring by double cyclization of a substrate bearing two diiodide functions, using [$PdCl_2$(dppf)], as catalyst, KOAc, as base, in DMSO [12].

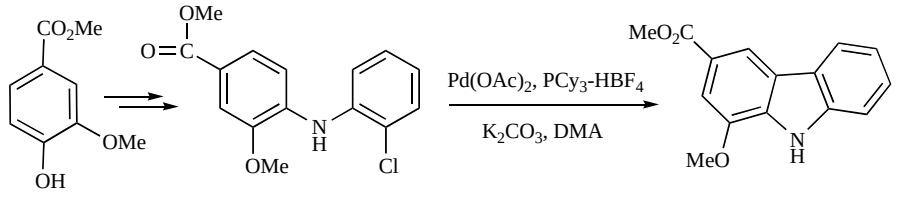


Scheme 6. Synthesis of indolo[3,2-c]cinnoline [9].



Scheme 7. Synthesis of dibenzopyrane [13].

Recently, some trialkylphosphines such as tricyclohexylphosphine (PCy_3) and di-*tert*-butylmethylphosphine [$PMe(t\text{-}Bu)_2$] turned out to be highly efficient and robust catalysts in the synthesis of a variety of tricyclic heterocycles from aromatic halides [13]. With aryl iodides the addition of silver salts as additives (AgOTf and Ag_2CO_3) allowed to obtain complete conversion, accumulation of iodide anion being responsible for catalyst poisoning (Scheme **7)**.

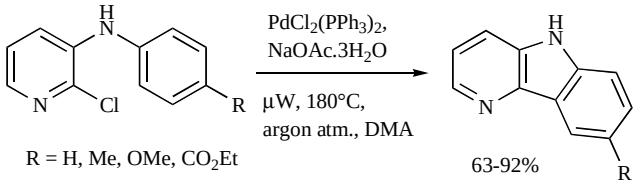


Scheme 8. Synthesis of Mukonine [13].

In the presence of such catalytic systems, also less reactive aryl chlorides could be successfully used [14]. An example is the synthesis of the alkaloid Mukonine, achieved through a sequence where the key-step was the cyclization of a properly substituted chlorodiarylamine (Scheme **8**) [13].

Likewise, naturally occurring Murrayafoline A (72%) was assembled through a domino process by reacting 2-methoxy-4-methylaniline and inexpensive 1,2-dichlorobenzene, using $Pd(OAc)_2/PCy_3$ as a catalytic system, K_3PO_4 as base in *N*-methylpyrrolidinone [15].

Interestingly, Maes and coworkers reported that Pd-catalyzed intramolecular direct arylation reaction leading to 5*H*-δ-carbolines from the corresponding 2-chloropyridin-3-amine derivatives occurred faster when it was carried out at high temperature (180−200 °C) (Scheme **9**). A low catalyst loading (0.2 mol%) was necessary to achieve complete conversion. The developed high temperature protocol proved to be general for the synthesis of a variety of azaheteroaromatic ring systems such as indolo-fused quinoline and pyridazino-fused benzo[b]furane [16].

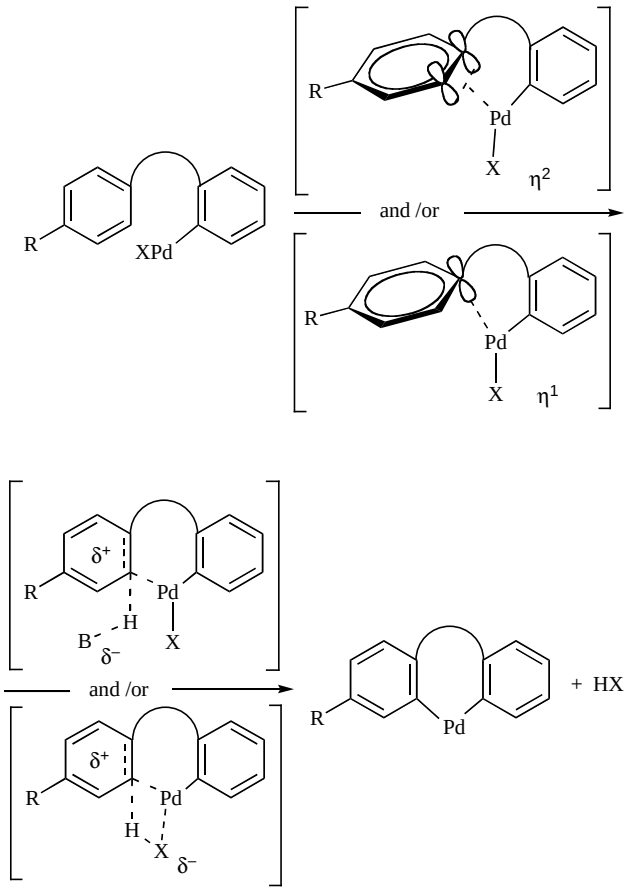


Scheme 9. Synthesis of 5*H*-δ-carbolines [16].

It is well known that the nature of the substrates, palladium catalysts, solvents and additives can strongly affect the mechanism of a reaction. However, recent experimental and theoretical studies suggested that C−H arylation proceeded through a concerted metallation/deprotonation process (Scheme **10**) [13, 17].

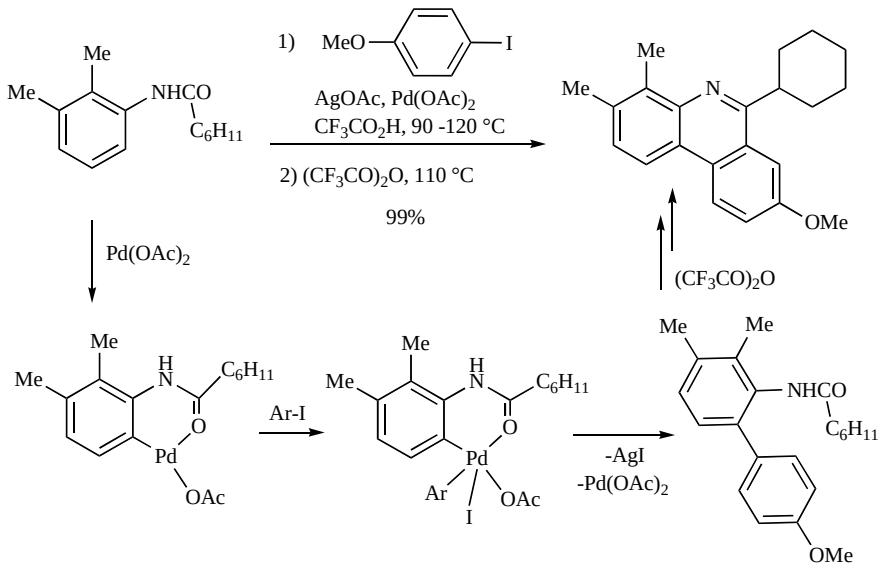
Accordingly, the initially formed oxidative addition complex coordinated to the arene to be arylated through a π,η^2− or π,η^1−bond. Subsequently, intramolecular electrophilic palladation occurred where an external base (S_E3) or a ligand (σ-bond metathesis) bonded to the metal deprotonated the arene as the Pd−C bond was forming. Significant kinetic isotope effect (KIE) as well as the finding that substrate electronic properties (R = electron-withdrawing and electron-donating groups) did not affect reaction rate were consistent with the mechanism proposed [17].

In 1984, Tremont described the palladium-catalyzed *ortho* alkylation of anilides by reaction with alkyl iodides in the presence of a Pd(II) salt which conserved its oxidation state during the catalytic cycle [18]. This reaction proved that C−H activation could be directed by *chelation through heteroatom-containing groups*.



Scheme 10. Proposed pathway for direct intramolecular arylation [13].

Recently, Daugulis discovered that also anilides, pyridines, benzylamines, benzamides and benzoic acids could be functionalized in the *ortho*-position using aryl iodides, a catalytic



Scheme 11. Synthesis of phenanthridines [20].

amount of $Pd(OAc)_2$, Ag^+ salts, in trifluoroacetic acid as a solvent [19].

An interesting application was the one-pot synthesis of phenanthridines combining Pd−catalyzed *ortho*-arylation of *N*-substituted anilides and successive cyclization upon addition of $(CF_3CO)_2O$ and heating (Scheme **11**) [20]. Anilide underwent cyclometalation, favoured by the initial coordination of palladium to the chelating heteroatom. In this case the formation of a five-membered palladacycle [21] represented the driving-force which directed the reactivity in the *ortho* position. Oxidative addition of aryl iodide to Pd(II) species afforded a high-energy Pd(IV) intermediate [22]. Fast reductive elimination and anion exchange (Ag^+ salt) provided the product and regenerated the catalyst. Electron-rich as well as electron-poor anilides were equally reactive. While aryl iodides of all electronic properties could be used, *ortho*-substitution was not tolerated.

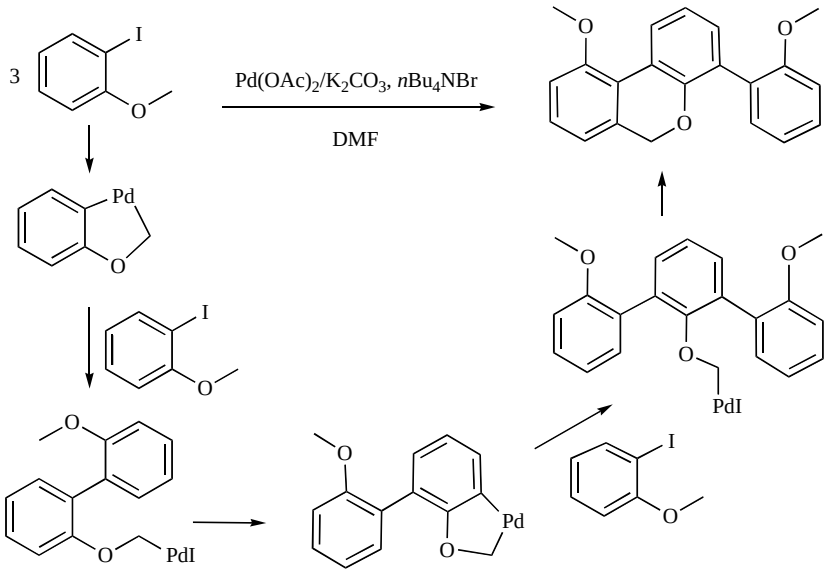
In 1992, Dyker described the unusual synthesis of a dibenzopyran derivative starting from three molecules of *o*-iodoanisole (Scheme **12**) [23]. According to the proposed mechanism, the initial aryl-Pd(II) iodide species transformed into the five-membered ring palladacycle by C−H activation of the MeO group [21 b]. This type of palladacycle promoted successive C−H arylation with two molecules of 2-iodoanisole, according to a Pd(II)/Pd(IV) mechanism. The resulting *o-o'*-disubstituted arylpalladium(II) iodide complex underwent six-membered ring cyclization leading to the pyran ring.

Pd(0)/Norbornene-catalyzed synthesis of 6-phenanthridinones is a further example of *metallacycle-directed* C−H arylation (Scheme **13**) [24, 25]. Aryl−aryl cross-coupling occurred at the stage of a palladacycle generated by the insertion of *o*-substituted aryl-Pd(II) iodide to norbornene and subsequent ring closure by C−H activation. The reaction with the bromoamide probably occurred through a Pd(II)/Pd(IV) mechanism. Subsequently, norbornene deinsertion led to a biphenylylpalladium bromide complex. Intramolecular amidation completed the catalytic cycle.

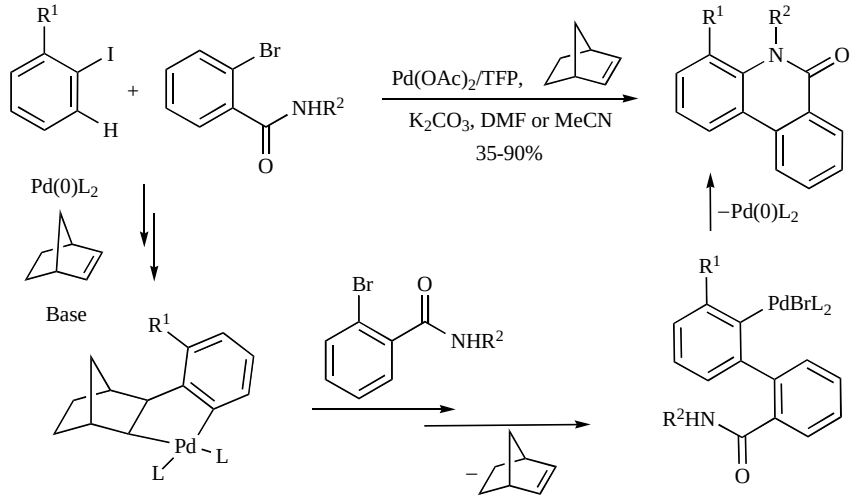
6*H*-Dibenzopyrans [26] and phenanthridines [27] were also synthesized through Pd(0)/norbornene catalyzed unsymmetrical arylation of *o*-substituted iodoarenes. A recent example is the synthesis of the antibiotic Carbazomicin A (Scheme **14**) [28].

2.1.2. Aryl−Alkenyl Coupling

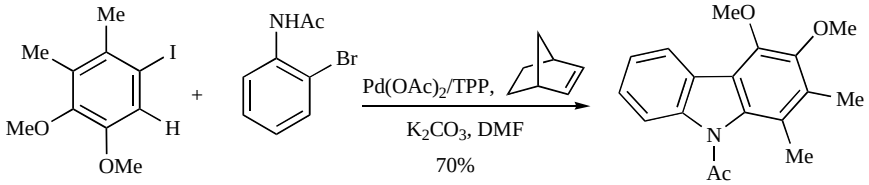
In 1997, Rawal reported the synthesis of indole and benzofuran derivatives through intramolecular coupling of vinyl halides with phenols in the presence of Hermann's palladacycle catalyst



Scheme 12. Synthesis of dibenzopyran derivative through catalytic domino arylation [23].



Scheme 13. Synthesis of 6-phenanthridinones [25].



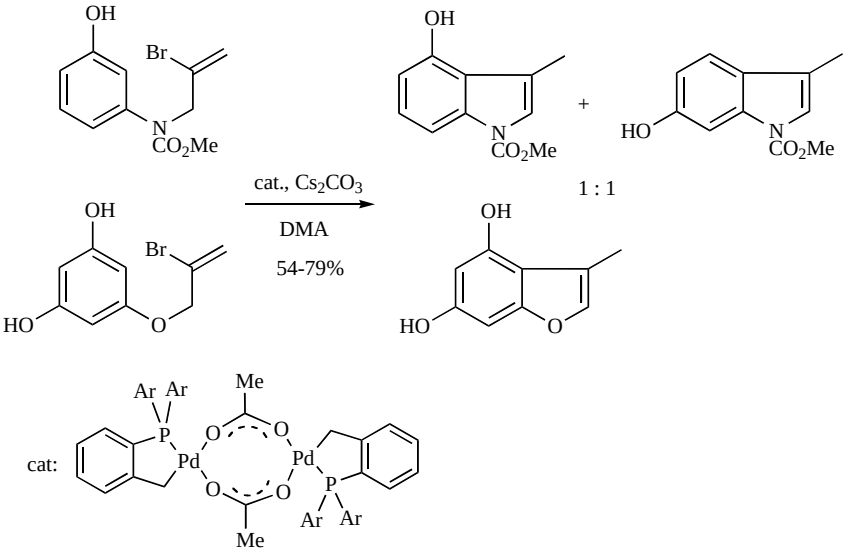
Scheme 14. Synthesis of Carbazomycin A [28].

(Scheme **15**) [29]. An excess of base was necessary to promote the attack of the aromatic ring on to the metal centre of the vinyl-Pd(II) bromide complex.

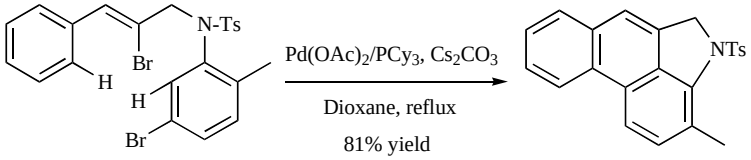
More recently, aryl−alkenyl coupling was used in combination with other catalytic transformations to develop domino and tandem synthesis of highly-fused heterocyclic systems.

4,5-Naphtho[3,2,1-*cd*]indole was built up through sequential activation of the vinyl and aryl bromides present in the substrate (Scheme **16**) [30]. The most reactive vinyl-Pd(II) bromide complex initially underwent C−H activation leading to the five-membered aza-heterocyclic ring. The aromatic bromide took part in the second cyclization leading to the product.

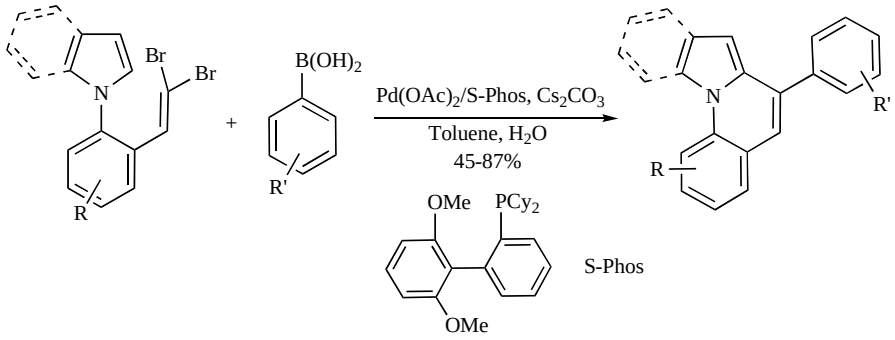
Pyrrolo[1,2-a]quinolines were synthesized through a tandem Suzuki reaction/direct alkenylation sequence using *gem*-dibromoolefins and boronic acids, as precursors (Scheme **17**) [31]. *Trans* vinylbromide was initially involved in a Suzuki coupling with arylboronic acids. The subsequent oxidative addition of the *cis*



Scheme 15. Synthesis of indole and benzofuran derivatives [29].



Scheme 16. Zipper-mode synthesis of 4,5-naphtho[3,2,1-*cd*]indole [30].



Scheme 17. Synthesis of pyrrolo[1,2-a]quinolines [31].

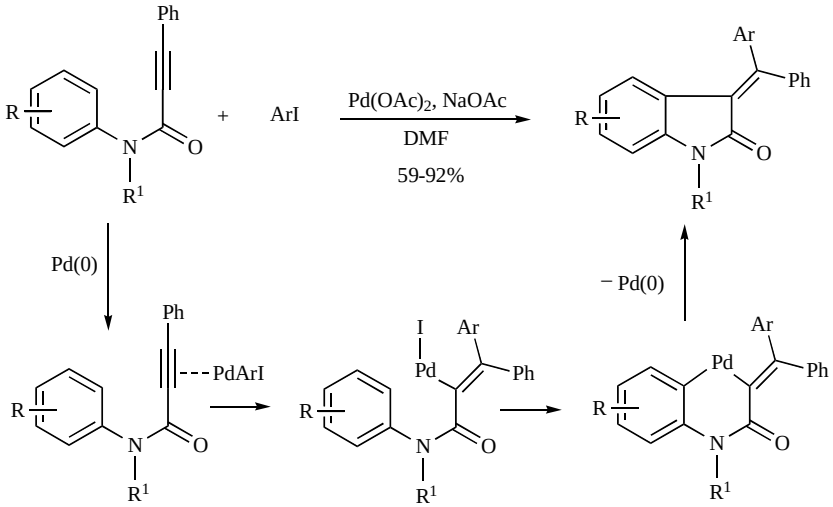
vinylbromide to Pd(0) triggered the cyclization leading to the final compound.

A further, interesting example is the synthesis of oxindoles from *N*-(aryl)-*N*-alkyl-3-phenylpropiolamides and aryl iodides (Scheme **18**) [32]. Carbopalladation of an electrophilic Ar−Pd(II) iodide complex to the triple bond generated *in situ* a vinyl−Pd(II) iodide complex which underwent electrophilic palladation. Palladacycle reductively eliminated the desired product. The regioselective *syn* insertion of the arylpalladium species to the triple bond of the propiolamide accounted for the observed double bond geometry.

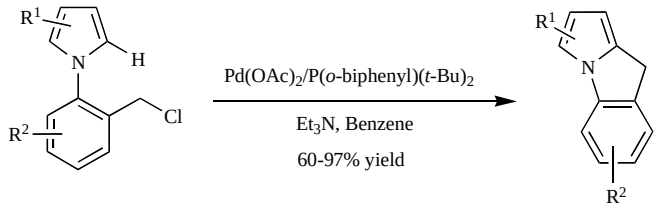
2.1.3. Aryl−Alkyl Coupling

In 2003, Buchwald reported that α-chloroacetanilides underwent cyclization affording oxindoles, under mild conditions (Scheme **19**) [33]. The reaction is a valuable alternative to the Friedel-Crafts reaction. Both anilides bearing electron–rich and electron–poor substituents (i.e. OMe, CF_3, TMS) reacted smoothly. The reaction was believed to proceed by the initial oxidative addition of the alkyl halide to Pd(0), leading to the alkyl-Pd(II)Cl complex. Three alternative pathways (electrophilic substitution, carbopalladation, σ-bond-methatesis) were then proposed to rationalize the formation of the six-membered palladacycle, which reductively eliminated the product.

Analogously, pyrrolo[1,2-a]indoles were synthesized from *N*-(2-halobenzyl)pyrroles through intramolecular pyrrole C–H alkylation (Scheme **20**) [34]. The use of $Pd(OAc)_2$/2-(di-*tert*-bythylphosphino)biphenyl as a catalyst gave the best results in terms of selectivity, with a broad range of *N*-(2-chlorobenzyl) pyrroles, included those bearing electron-withdrawing substituents on the pyrrole ring.

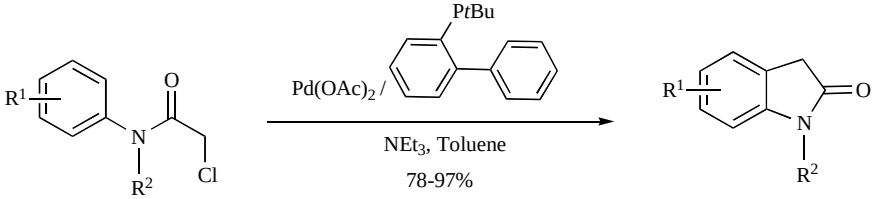


Scheme 18. Synthesis of 3-(diarylmethylenyl) oxindoles [32].

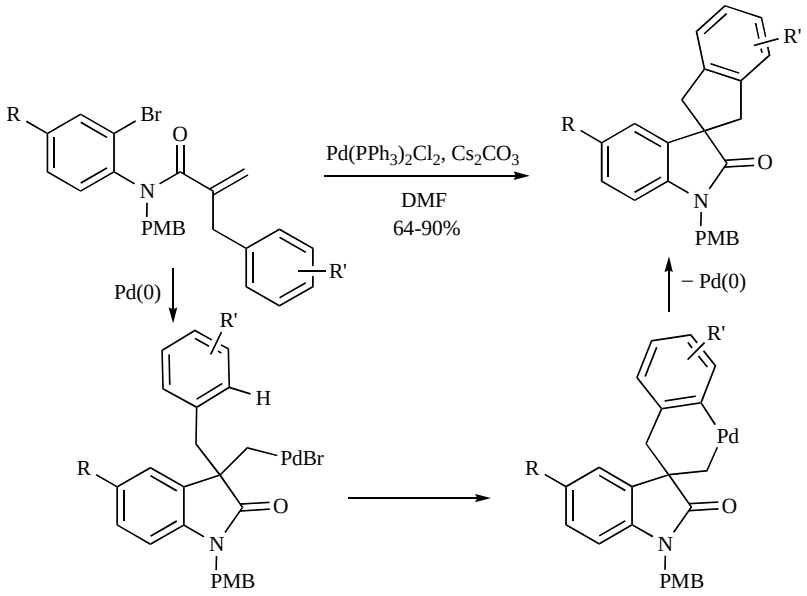


Scheme 20. Synthesis of 9H-pyrrolo[1,2-*a*]indoles [34].

An alternative route to heterocycle synthesis based on aromatic C−H bond alkylation is to employ a Heck coupling of an aryl halide with an alkene in a domino sequence with a direct arylation step



Scheme 19. Synthesis of indolin-2-ones [33].

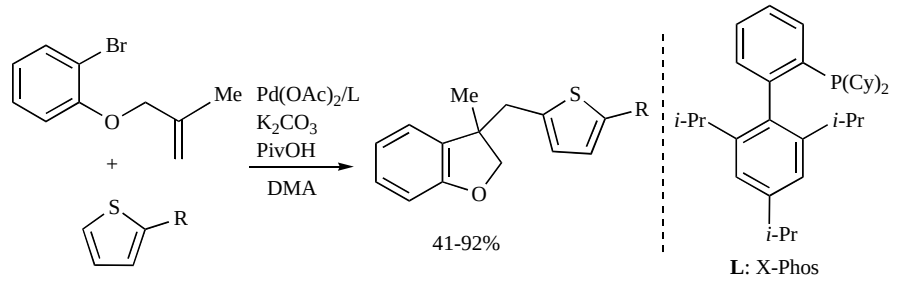


Scheme 21. Synthesis of spiro-fused indane-oxindoles [36].

[35]. Such a strategy has been recently applied to synthesize spiro-fused indane-oxindoles (Scheme **21**) [36]. Intramolecular carbopalladation of the Ar-Pd(II) bromide complex to the alkene led to the formation of a reactive alkyl-Pd(II)Br complex. Intramolecular alkylation of the unactivated, aromatic C−H bond generated the second ring, thus completing the catalytic cycle. The transformation was effective over a range of electronic properties on the phenyl ring to be C−H functionalized, from electron-donating to electron-deficient.

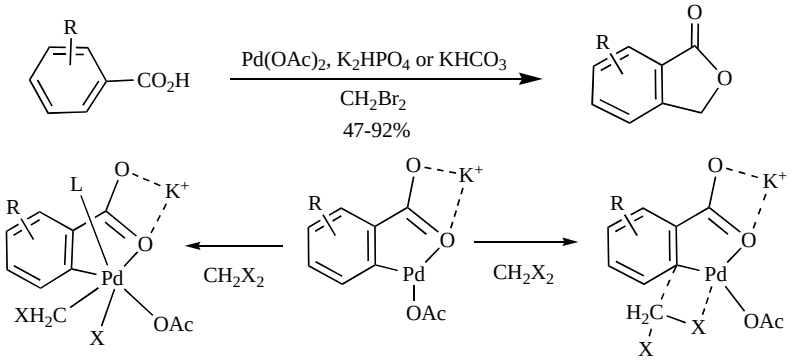
Highly functionalized indolines and dihydrobenzofurans (Scheme **22**) were synthesized through a domino Heck/*intermolecular* direct arylation at an alkyl-Pd(II) intermediate [37]. The reaction of the bromoarene derivative and thiophene occurred selectively using X-Phos as a ligand, K_2CO_3 as the base, and PivOH as an additive [38].

The pioneering paper of Tremont (1984) [18] inspired recent advances in the field of directing-group assisted intermolecular aromatic alkylation. In 2009, Yu reported that benzolactones were synthesized by reacting benzoic acids in dichloromethane or dibromomethane as the solvent, in the presence of a catalytic amount of $Pd(OAc)_2$ and a stoichiometric amount of base (Scheme **23**) [39]. Coordination of palladium with a carboxylate group forced the Pd(II) center to chelate in the proximity of the *ortho* C−H bond and to cleave it. The reaction with alkyl halides probably occurred through a Pd(II)/Pd(IV) or a σ-bond metathesis path. Final cyclization through an intramolecular nucleophilic substitution led to the product.

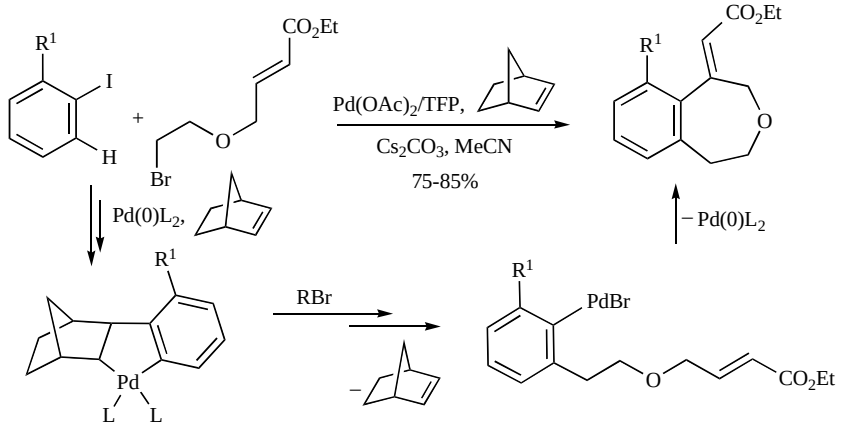


Scheme 22. Synthesis of dihydrobenzofurans [37].

In the last decade Pd(0)/norbornene−catalyzed C−H alkylation [24] turned out to be a useful tool for the synthesis of a variety of benzo-fused heterocycles. 4-Benzoxepine was the first heterocyclic



Scheme 23. Synthesis of benzolactones [39].

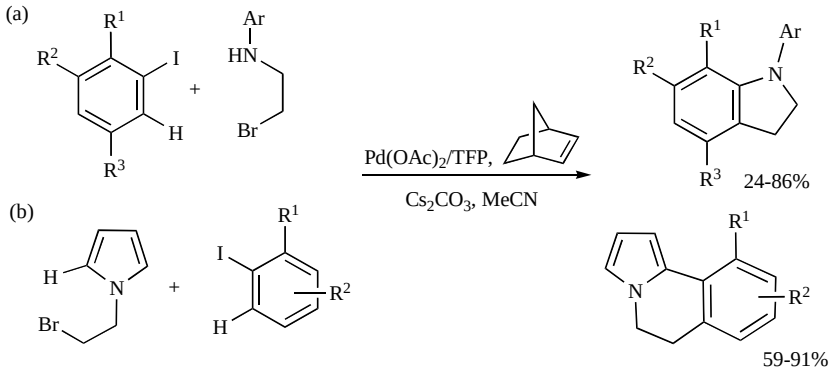


Scheme 24. Synthesis of 4-benzoxepines [40].

scaffold built up taking advantage of this methodology (Scheme **24**, L = TFP) [40]. According to the mechanism proposed, the *o*-substituted aryl iodide was involved in the formation of the palladacyle, promoting aromatic alkylation through a Pd(II)/Pd(IV) mechanism. Norbornene de-insertion afforded *o,o*-substituted aryl-Pd(II) bromide complex which underwent intramolecular Heck reaction, as a terminating step. Noteworthy, the use of monophosphines as ligands was crucial to develop selective transformations [41].

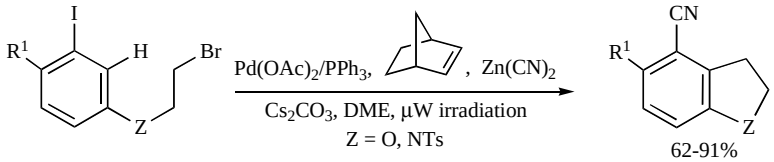
Despite the complexity of the catalytic cycle, a variety of heterocyclic molecules could be synthesized starting from simple precursors. Indolines and pyrrolo[2,1-a]isoquinolines were achieved using alkyl halides bearing a NH-Ar substituent or a pyrrole ring (Scheme **25**) [42, 43]. In the first case the catalytic cycle was completed by a C−N bond forming reaction. In the second one, heteroatom-directed C−H arylation was the terminating step.

A further, original application was the synthesis of polycyclic benzonitriles (Scheme **26**) [44]. Iodoarenes *meta*-substituted by an alkyl chain bearing a primary halide, and $Zn(CN)_2$ were reacted under Pd/norbornene catalysis. Intramolecular C−H alkylation occurred first, generating a new heterocyclic ring and an aryl-Pd(II) bromide complex. Transmetallation and subsequent reductive elimination delivered cyano-heterocycles.

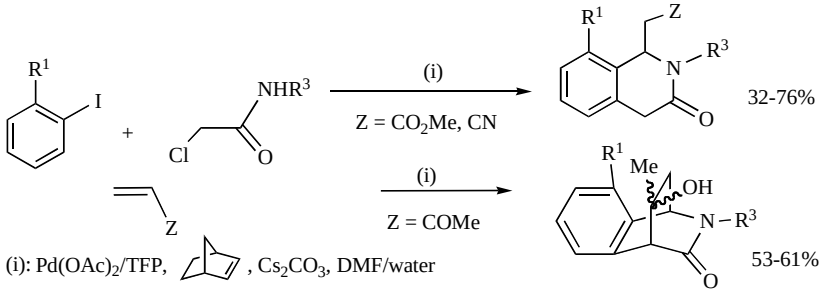


Scheme 25. Synthesis of: (a) indolines [42], (b) 5,6-dihydro-pyrrolo[2,1-a]isoquinoline [43].

Three-component synthesis of tetrahydroisoquinoline derivatives was developed combining aromatic alkylation/vinylation and addition reactions (Scheme **27**) [45].



Scheme 26. Synthesis of polycyclic benzonitriles [44].

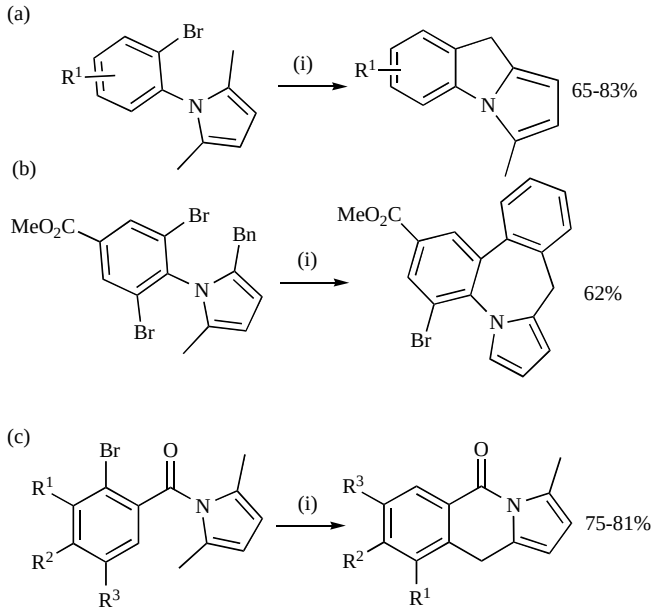


Scheme 27. Synthesis of tetrahydroisoquinolin-2-ones [45].

Aryl−*alkyl* coupling could be accomplished using aryl halides and *alkanes*, as coupling partners. The domino coupling reactions of *o*-iodoanisole (Scheme **12**) [23] or *o*-*tert*-butyliodobenzene [46] discovered by Dyker, are the first examples where C(sp^3)−H bond activation has been evidenced.

In 2006, Knochel reported that *N*-(2-haloaryl)pyrroles underwent ring closure providing 9*H*-pyrrolo[1,2-*a*]indoles (Scheme **28a**) [47]. The reaction was further extended to *N*-acyl-2,5-pyrrole substrates which were successfully converted into pyrrolo[1,2-b]isoquinolines (Scheme **28c**).

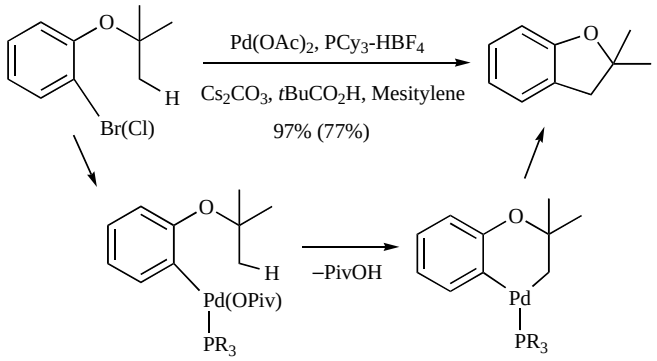
Intramolecular arylations occurring at unactivated C(sp^3)−H bonds are less easy than those at C(sp^2)−H bonds, described in previous sections. Interestingly, when one of the two substituents in the 2,5-position of the pyrrole ring was a benzyl group, C−H activation preferentially occurred on the phenyl ring of the benzyl substituent, leading to a seven-membered ring formation (Scheme **28b**).



(i): $Pd(OAc)_2$/*p*-Tol_3P, Cs_2CO_3, Toluene, 110°C, 12h

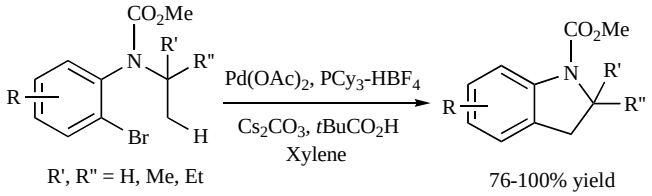
Scheme 28. Synthesis of 9*H*-pyrrolo[1,2-*a*]indoles and pyrrolo[1,2-b]isoquinolines [47].

Direct, intramolecular alkane arylation was also involved in the synthesis of 2,2-dialkyldihydrobenzofurans from haloaryl alkyl ethers, developed by Fagnou in 2007 (Scheme **29**) [48]. The reaction has been carried out in mesitylene using pivalic acid as an additive. The presence of both an inorganic base and a catalytic amount of an organic, soluble carboxylate allowed complete conversion. Mechanistic studies pointed to the involvement of a concerted palladation-deprotonation pathway.



Scheme 29. Synthesis of dihydrobenzofurans [48].

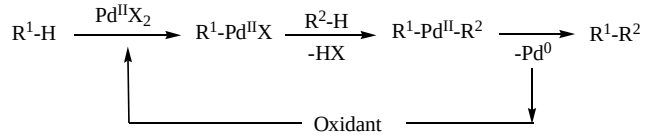
Later, Fujii and Ohno reported that indolines could be synthesized from *N*-alkyl-2-bromoanilines, under similar conditions (Scheme **30**) [49]. Interestingly, they showed that C−H activation of a methyl group occurred selectively even without the assistance of an α-quaternary carbon atom (R' = H).



Scheme 30. Synthesis of indolines [49].

2.2. Oxidative Coupling *(Path C)*

R^1H substrates bearing a C(sp^2)−H bond can react with $Pd(II)X_2$ species via C−H bond cleavage, generating R^1−Pd(II)X complex (Scheme **31**). The reaction with a carbon-nucleophile (R^2H) followed by reductive elimination leads to the coupling product and Pd(0) species. Reoxidation to Pd(II) complex is necessary to close the catalytic cycle.



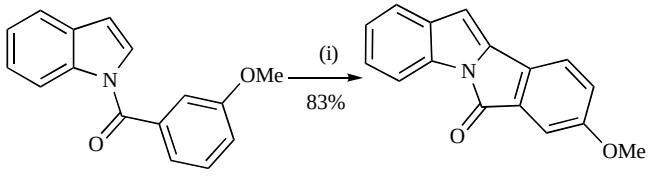
Scheme 31. Cross-coupling mechanism of C–H bonds with carbon–nucleophiles.

In this type of reactions the advantage is that halogenation of the substrates is not required. However, an oxidant reagent has to be added to make the reaction catalytic [50].

2.2.1. Arene−Arene Coupling

Oxidative intermolecular coupling of diphenyl ethers, diphenylamines and benzanilides in acetic acid, using a stoichiometric amount of $Pd(OAc)_2$, was reported in the mid-seventies [51]. A key problem in developing catalytic transformations was the reoxidation of the catalyst. Only recently, such reactions were made catalytic by using appropriate co-oxidants [52].

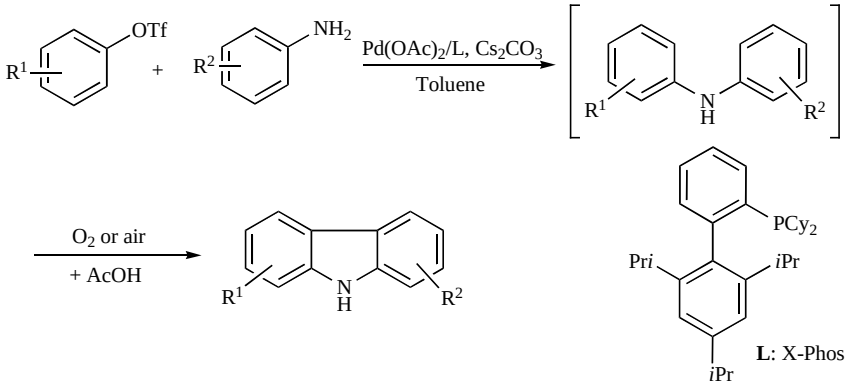
In 2007, DeBoef reported that indole-based polyheterocycles were synthesized through an aerobic, intramolecular oxidative cyclization of *N*-benzoyl and *N*-(3-methoxy)benzoyl indole. In the last case, ring closure occurred at the less hindered aromatic carbon atom (Scheme **32**) [53].



(i): $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1 equiv), AcOH, O_2, 120°C.

Scheme 32. Synthesis of indole derivatives [53].

Contemporarily, Fujii and Ohno described a selective one-pot synthesis of carbazoles starting from aryl triflates and anilines (Scheme **33**) [54]. Intermolecular Pd-catalyzed *N*−arylation quantitatively led to substituted diarylamines. Subsequent oxidative aryl−aryl coupling occurred intramolecularly after the addition of acetic acid, under oxygen or air atmosphere. The best results in terms of selectivity, were obtained by reacting diarylamines deriving from electron-rich aryl triflates and electron-poor anilines.

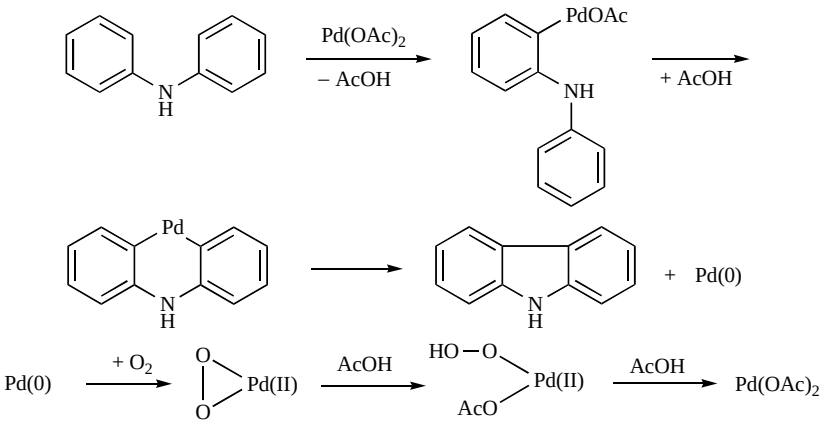


Scheme 33. One-pot synthesis of carbazoles [54].

Intramolecular C−C coupling proceeded through a double C−H bond activation process (Scheme **34**). The reaction of diarylamine with $Pd(OAc)_2$ led to the aryl−Pd complex which underwent the second C−H bond activation. The palladacycle reductively eliminated carbazole and Pd(0).

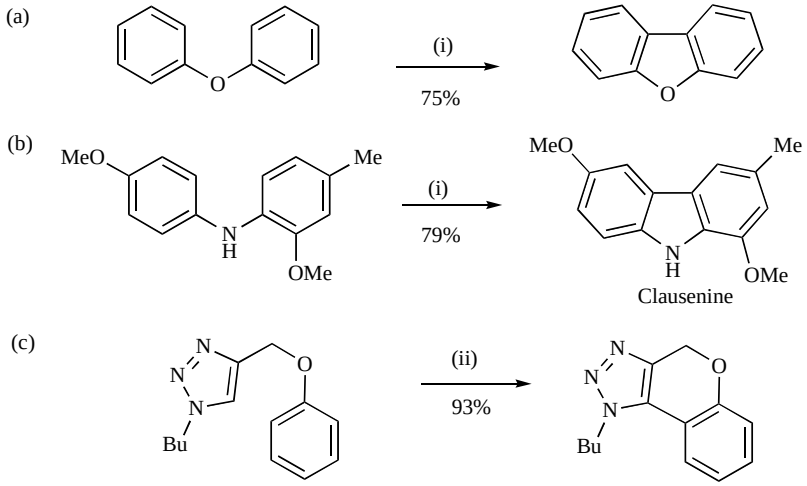
Aerobic reoxidation of Pd(0) occurred through an η^2-peroxido Pd(II) species, protonolysis with acetic acid to afford Pd(II) hydroperoxide. Ligand exchange with acetate led to H_2O_2 and Pd(II) species.

Unfunctionalized arene coupling was further developed and successfully extended to obtain diphenyl ether and electron-rich diarylamines, such as Clausenine (Scheme **35a,b**) [55]. The reactions were performed using a catalytic amount of K_2CO_3 and pivalic acid as a solvent. The pivalate ligand probably played a key role in the C−H bond cleavage favoring aryl−Pd complex formation [56].



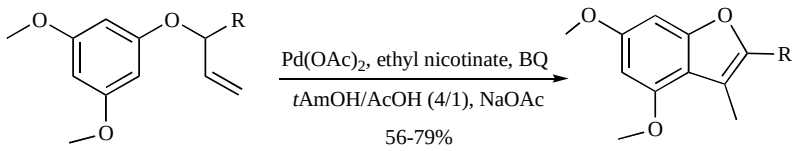
Scheme 34. Proposed mechanism of biaryl oxidative coupling [54].

Recently, intramolecular dehydrogenative direct arylation of 1,2,3-triazole derivatives was developed (Scheme **35c**) [57]. The



(i): $Pd(OAc)_2$ (3-10 mol%), K_2CO_3 (10 mol%), PivOH, air, 110-120°C
(ii): $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (1 equiv), Toluene/PivOH, air, 140°C

Scheme 35. Heterocycle syntheses by dehydrogenative aryl-aryl coupling: (a) and (b) [55], (c) [57].



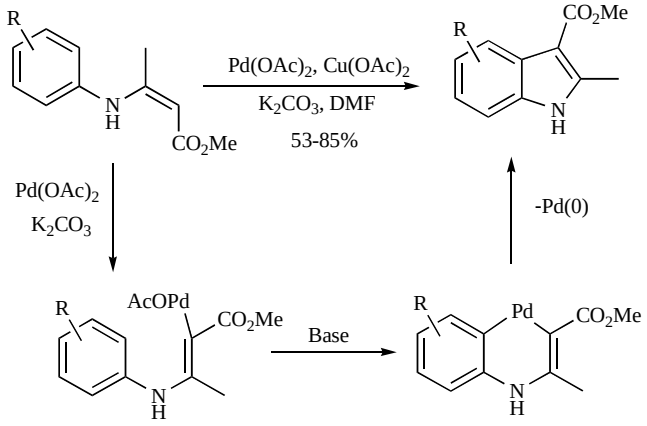
Scheme 36. Synthesis of benzofuran derivatives [59].

use of $Cu(OAc)_2$ as a terminal oxidant at ambient pressure of air allowed to achieve more effective cyclizations.

2.2.2. Arene−Alkene(Alkyne) Coupling

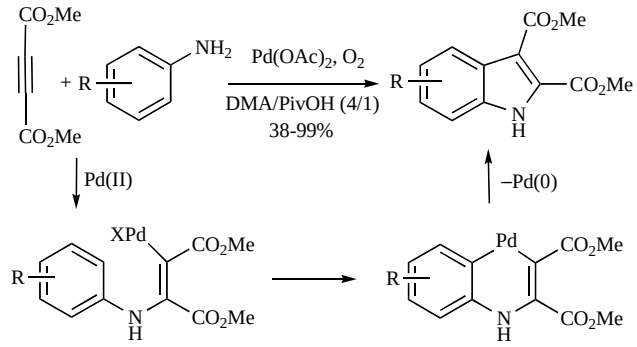
Intermolecular oxidative coupling of unfunctionalized arenes with olefins in the presence of a *stoichiometric* amount of highly electrophilic palladium cationic species, generated in situ in an acid medium [$Pd(OAc)_2$, in refluxing AcOH] was discovered by Fujiwara and Moritani, in 1967 [58]. A few years later, Stoltz reported that allyl phenyl ethers underwent catalytic, oxidative cyclization leading to electron-rich benzofurans (oxidative Heck reaction) (Scheme **36**) [59]. The reaction took place in the presence of $Pd(OAc)_2$ as a catalyst and 1,4-benzoquinone (BQ) as an oxidant. The scope is limited to the use of electron-rich arenes, which easily underwent C−H bond activation. Subsequent olefin insertion, followed by β−hydride elimination provided the heteroaromatic product, after double bond isomerization.

In 2008, Glorius reported that *N*-aryl enamine carboxylates were directly converted into indoles (Scheme **37**) [60]. As the reaction was conducted under basic conditions which lowered the electrophilicity of the cationic $[PdX]^+$ species, initial palladation of the nucleophilic enamine and deprotonation took place. The resulting Pd(II) complex underwent a second aromatic activation through σ-bond metathesis or base-assisted deprotonation, as suggested by significant KIE. A variety of electron-poor and electron-rich anilines could be used in the reaction.



Scheme 37. Synthesis of indoles [60].

Very recently, Nagasawa described the synthesis of 3-alkylidenoxindoles from *N*-cinnamoylaniline bearing alkyl, alkoxy and halogen substituents, by intramolecular oxidative coupling, in chlorobenzene using $PdCl_2MeCN_2$ as a catalyst and $AgOCOCF_3$ as an oxidant [61].

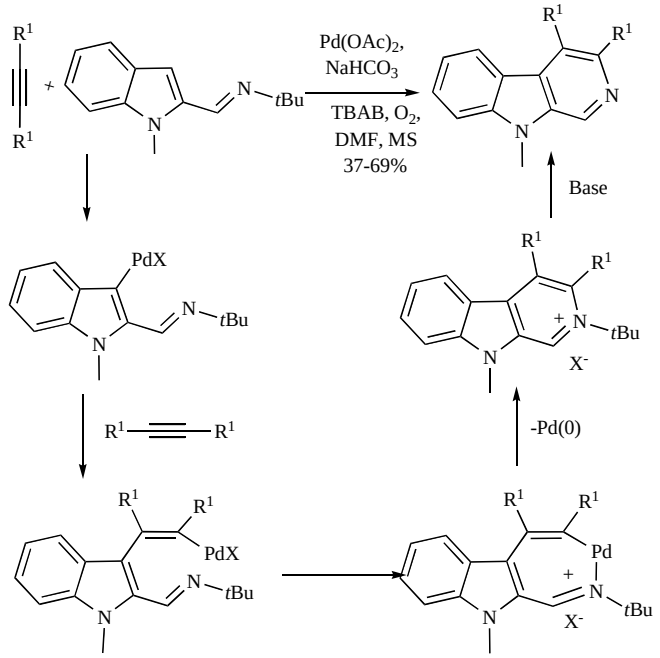


Scheme 38. Synthesis of indoles [62].

Indole derivatives were also synthesized by oxidative coupling of anilines or *N*-alkyl monosubstituted anilines and internal alkynes using $Pd(OAc)_2$ as a catalyst and O_2 as the oxidant, in acidic media (Scheme **38**) [62]. An enamido−Pd(II)X complex has been proposed as the key intermediate, which could be generated through: (a) aminopalladation of the alkyne or (b) electrophilic palladation of the enamide.

Anilines having electron-withdrawing or electron-donating groups could be efficiently coupled with electron-deficient alkynes.

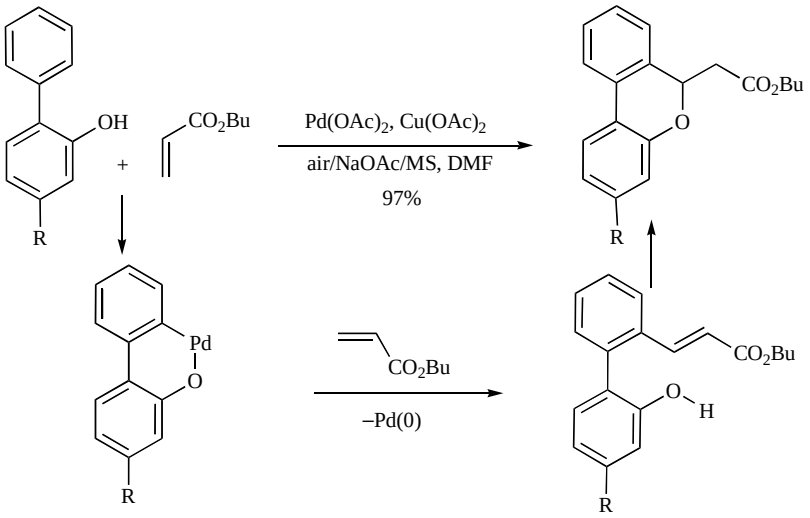
Very recently, β– and γ–carbolines were synthesized through a catalytic oxidative iminoannulation of internal alkynes and *tert*-butylimines of *N*-substituted 2- or 3-indolecarboxaldehydes (Scheme **39**) [63]. Notably, *ortho* aromatic palladation leading to the key heteroarylPd(II) complex was assisted by chelation of the imino group. Alkyne insertion afforded the seven-membered palladacyclic immonium salt which reductively eliminated *tert*-butylcarbolinium salt. Pd(0) was reoxidized using dioxygen, as a clean oxidant. Final *tert-butyl* group fragmentation produced carbolines.



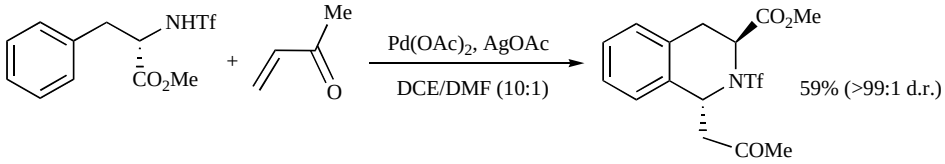
Scheme 39. Synthesis of carbolines [63].

Aromatic compounds bearing heteroatom containing substituents with acidic hydrogen atoms (phenolic, hydroxyl, sulfonylamino, carboxyl groups) easy coupled with alkenes *via* direct palladation on their *ortho* positions [64]. Five- or six-membered ring palladacycle formation represents the driving force enabling C−H activation.

In the late 1990s, Miura reported that 2-phenylphenols and 2-sulfonylaminobiphenyls underwent intermolecular coupling with acrylate esters giving 6*H*-dibenzo[*b*,*d*]pyrans and dihydrophenanthridines, respectively. In both cases final cyclization occurred through a nucleophilic addition (Scheme **40**) [65, 66].



Scheme 40. Synthesis of 6*H*-dibenzo[*b*,*d*]pyran [66].

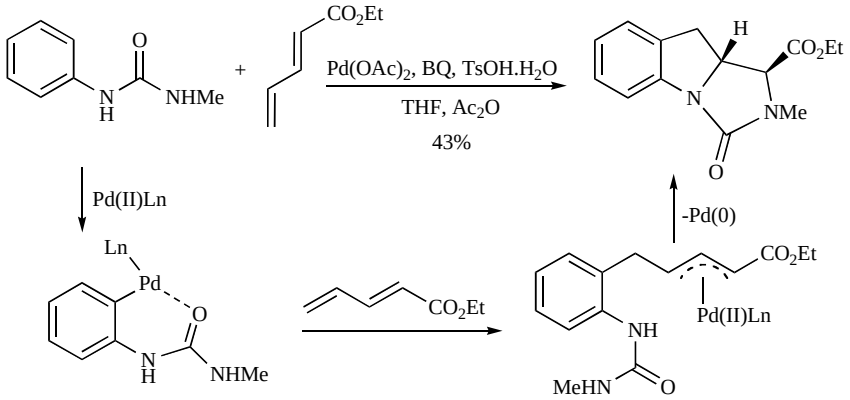


Scheme 41. Synthesis of tetrahydroisoquinolines [67].

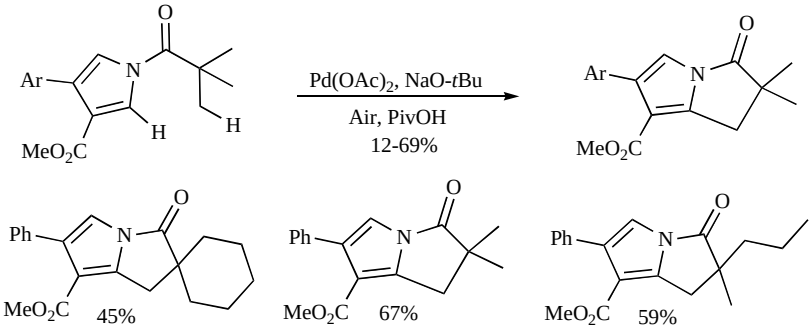
These reactions proceeded in the presence of $Cu(OAc)_2$/air as reoxidizing system.

Interestingly, the triflamide of phenylalanine turned out to be a chiral building block for the diastereoselective synthesis of tetrahydroisoquinoline, obtained by tandem oxidative C–H alkenylation and Michael addition (Scheme **41**) [67]. The acidity of the TfN−H bond was crucial to initially promote the N−Pd bond.

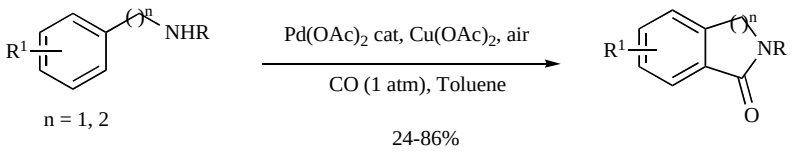
An efficient route to indolines from *N*-aryl ureas and electron-deficient dienes, was developed by Lloyd-Jones and Booker-Milburn, in 2008 (Scheme **42**) [68]. *N*-aryl ureas underwent aromatic C−H activation in the *ortho* position, under relatively acidic conditions. Highly electrophilic $Pd(OTs)_2$ or the monotosylated species, generated in *situ* using $Pd(OAc)_2$ as a pre-catalyst, were the active catalysts promoting aromatic activation. The resulting aryl-Pd(II) complex inserted the diene leading to an η^3–allyl Pd(II) complex, as an intermediate. Intramolecular carbon diamination led to the tricyclic product, as a single diastereomer. The generated Pd(0) species was reoxidized in the presence of benzoquinone.



Scheme 42. Synthesis of indoline derivatives [68].



Scheme 43. Synthesis of azoles [69].



Scheme 44. Benzolactam synthesis [70].

2.2.3. Arene−Alkane Coupling

In 2008, Fagnou and Liègault reported that *N*-pivalylpyrrole derivatives underwent an intramolecular oxidative coupling leading to azoles (Scheme **43**) [69]. This is a rare example of an arene−alkane coupling. Air was employed as the terminal oxidant. KIE studies pointed out that the reaction proceeded by a reversible pyrrole palladation followed by an irreversible and slower alkane C–H activation. Apparently, the presence of both an aromatic and a resonance electron-withdrawing group on the pyrrole ring favored the reaction, which was extended to various substituted amides.

2.2.4. Arene–CO Coupling

Heterocyclic scaffolds of biologically and medicinally useful molecules are characterized by the presence of the Ar–CO–Y moiety (Y = heteroatom), as a common motif [4]. The finding that an arene could undergo selective palladation in the *ortho* position of a directing group disclosed the possibility of developing C–H activation/CO insertion sequences leading to interesting heterocycles.

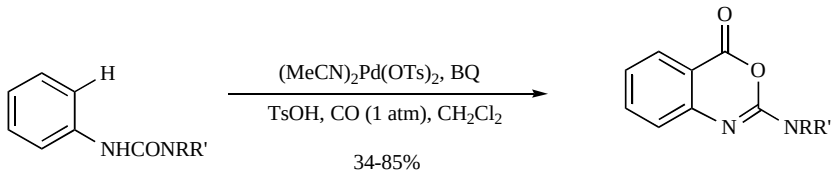
3. C–H BOND ACTIVATION/C–Y COUPLING REACTION *(Path E)*

The construction of heterocycles through direct intramolecular C–heteroaromatic (C–Y) bond forming reactions represents an important objective. This type of coupling has been less studied, so far. The examples reported regard heterocycle synthesis based on direct C–N and C–S bond forming reactions.

3.1. C–N Coupling Reaction

Simple arenes bearing a nitrogen-containing group capable of directing Pd(II)-catalyzed C–H bond activation in the *ortho*-position are used as precursors in most of the examples reported [3].

In 2005, Buchwald described the synthesis of carbazoles from 2-acetamidobiphenyls in toluene, using $Pd(OAc)_2$ as a catalyst and $Cu(OAc)_2$ as a terminal oxidant under an atmosphere of air or oxygen (Scheme **47**) [73]. Coordination of $Pd(OAc)_2$ to the



Scheme 45. Synthesis of cyclic imidates [71].

In 2004, Orito described the synthesis of five- and six-membered ring benzolactams through Pd(II)-catalyzed carbonylation/amidation starting from *N*-alkyl-*ω*-arylalkylamines (Scheme **44**) [70]. Reaction selectivity was not substantially affected by the electronic properties of the substituents on the phenyl ring (R^1). Noteworthy, bromo-, and chloro-arylbenzyl-amines were converted to lactams without compromission of the halide substituent.

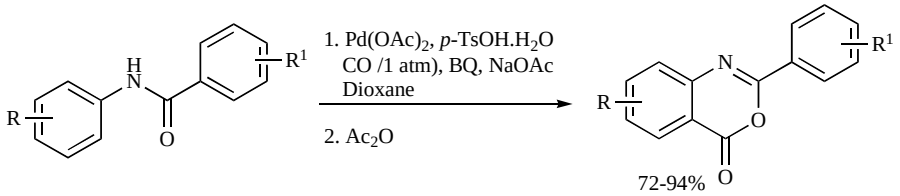
N-Aryl ureas have been reported to undergo *ortho* C−H palladation under relatively acidic conditions [68]. Carbonylation of the aryl−Pd complex was immediately followed by cyclization to cyclic imidates, at ambient temperature (Scheme **45**) [71]. The process has been made catalytic by using benzoquinone as an oxidant.

Benzoxazinones were synthesized through a one-pot procedure from *N*-benzoylanthranilic acids by cyclization in the presence of Ac_2O (Scheme **46**) [72]. Anthranilic acid derivatives were generated by selective *ortho* carbonylation of benzanilides, under mild acidic conditions. *p*-TsOH exerted a crucial effect in the C−H bond cleavage of the substrate.

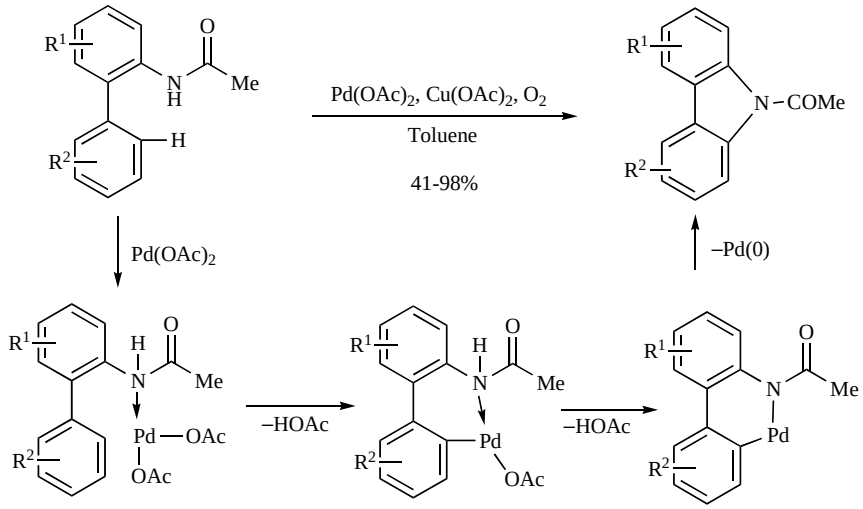
nitrogen atom promoted *ortho*-palladation with the release of acetic acid. The resulting six-membered palladacycle reductively eliminated the product. The reaction was tolerant for a variety of electron-withdrawing and electron-donating substituents on both the aromatic rings.

In 2008, Shi and coworkers reported that 4-Deoxycarbazomycin B could be synthesized simply starting from a proper aniline derivative and benzene through multiple oxidative C–H functionalization (Scheme **48**) [74]. Remarkably, halogenated and organometallic reagents were completely avoided. The initially formed aryl-Pd complex probably underwent Ph–H activation through proton abstraction assisted by the carboxylate of the $EtCO_2H$ [56]. Reductive elimination led to the *ortho*-phenylated acetanilide, which was subsequently transformed into the desidered product under Buchwald C−N bond-forming conditions.

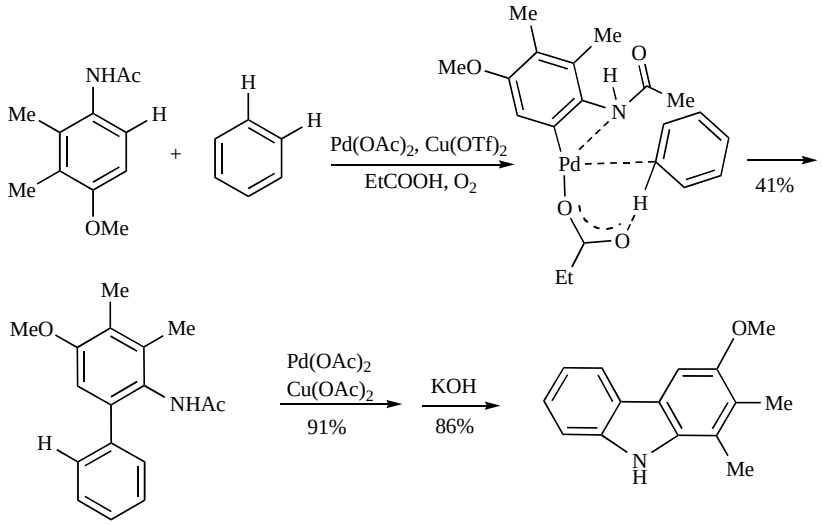
In 2008, Gaunt developed an interesting, alternative approach to carbazole synthesis (Scheme **49**) [75]. *Ortho*-phenylarylamines, *N*-substituted with an electron-donating group were converted into the products, using $Pd(OAc)_2$ as a catalyst, and $PhI(OAc)_2$, in toluene. Nitrogen–directed C–H activation led to the cyclopalladium(II) complex, which underwent oxidation with $PhI(OAc)_2$, an



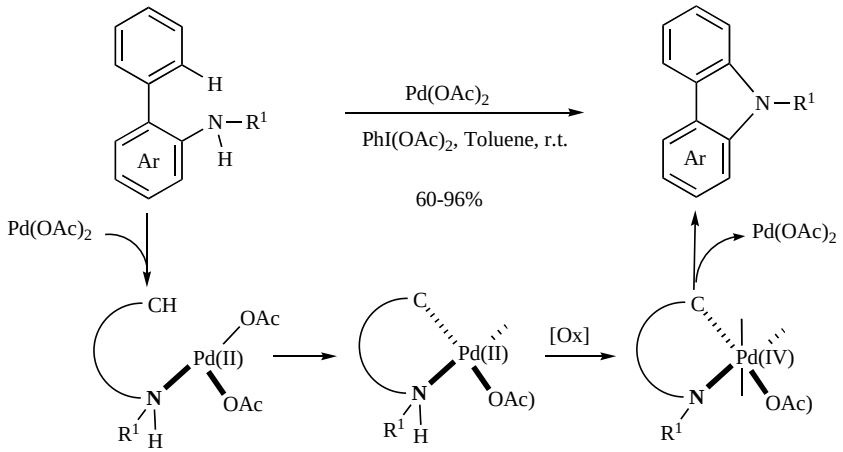
Scheme 46. One-pot synthesis of benzoxazinones [72].



Scheme 47. Buckwald synthesis of carbazoles [73].



Scheme 48. Synthesis of 4-Deoxycarbazomicin through multiple C–H activation steps [74].

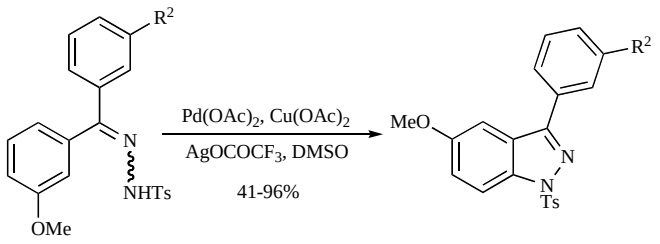


Scheme 49. Gaunt synthesis of carbazoles [75].

established oxidant for Pd(II)/Pd(IV) redox chemistry [3b]. The resulting Pd(IV) species reductively eliminated carbazole derivative and $Pd(OAc)_2$. The reaction was tolerant for a wide range of substituents on the aniline ring.

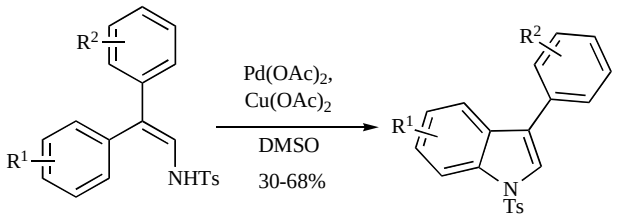
In 2007, Inamoto and Hiroya described the synthesis of indazole derivatives from benzophenone hydrazones (Scheme **50**) [76]. Cyclization was controlled by both steric and electronic factors. The presence of an electron-donating group at the *meta* position accelerated cyclization at the less hindered C-6 atom. With substrates bearing two different *meta*-substituents, ring formation took place on the more electron-rich arene. Apparently, regioselectivity observed was independent on the *E/Z* isomer ratio of the substrate.

Both $Cu(OAc)_2$ and $AgOCOCF_3$ are believed to be involved in the Pd(0) re-oxidation, although the mechanism of this step needs to be further elucidated.



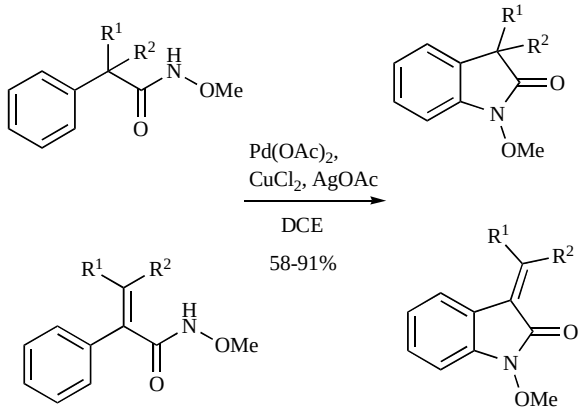
Scheme 50. Synthesis of indazoles [76].

The corresponding tosyl enamides were also converted into indoles (Scheme **51**) [77]. When R^1 and R^2 were different a mixture of isomers was obtained, suggesting that *E*/*Z* enamine isomerization occurred rapidly in the course of the reaction.



Scheme 51. Synthesis of indoles [77].

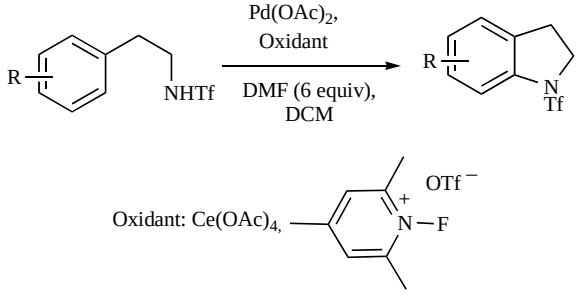
In 2008, Yu discovered that *N*-methoxyhydroxamic acids were converted into benzo-lactams. The reaction presumably involved a Pd(II)/Pd(IV) catalysis using $CuCl_2$/AgOAc as the oxidants (Scheme **52**) [78]. The presence of two alkyl groups adiacent to the directing group turned out to be necessary to favor initial arene *o*-palladation (Thorpe−Ingold effect).



Scheme 52. Synthesis of lactams [78].

Later, Murakami reported that also *N*-tosyl-2-methyl-2-phenylpropanamides underwent oxidative cyclization leading to 3,3-disubstituted oxindoles. The reaction occurred under Pd(II)/Pd(0) catalysis [79].

Triflamide protected phenylethylamines were transformed into indolines (Scheme **53**) [80]. The reaction proceeded through a P(II)/Pd(IV) mechanism using a one-electron oxidant [$Ce(OAc)_4$],

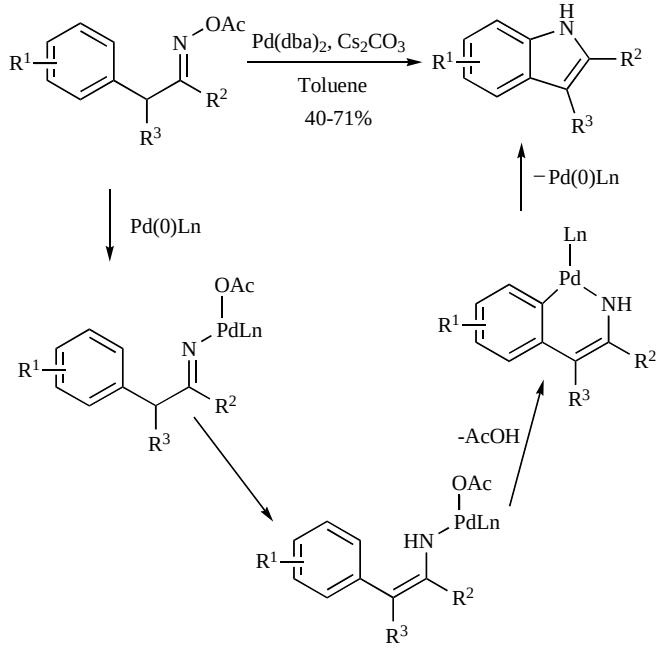


Scheme 53. Synthesis of substituted indolines [80].

or a two-electron oxidant (*N*-fluoro-2,4,6-trimethylpyridinium triflate) [3b]. The presence of DMF as an additive was crucial, probably acting as a labile ligand. The best results in terms of selectivity were obtained with *N*-fluoro-2,4,6-trimethylpyridinium triflate. In this case the reaction tolerated a wide range of functional groups, strong electron-withdrawing substituents included.

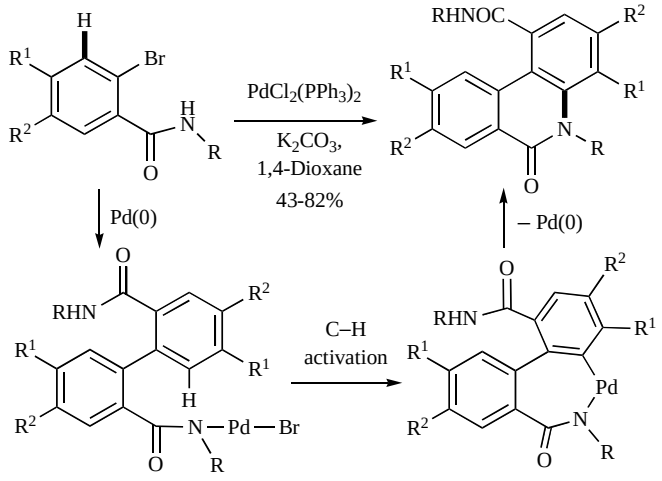
Very recently, Hartwig described the synthesis of indoles involving oxime acetates, in the presence of a low loading of Pd(0) species (Scheme **54**) [81]. Interestingly, this approach did not require the use of an external oxidant, as the reaction occurred under redox conditions.

Oxidative addition of an oxime ester to Pd(0) followed by tautomerization led to the formation of a palladacycle and acetic acid. Subsequent C−N bond forming reductive elimination afforded the product.



Scheme 54. Synthesis of indoles [81].

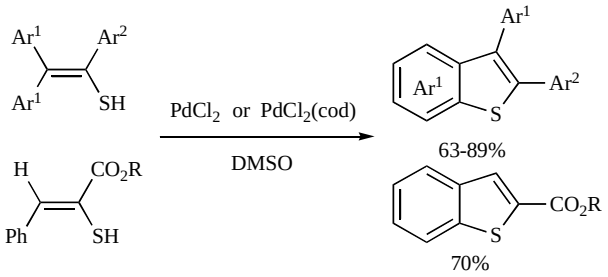
An unusual synthesis of phenanthridinones were achieved from two molecules of *o*-bromobenzamide in the presence of a catalytic amount of palladium(0) complex, in dioxane (Scheme **55**) [82]. Pd(II)/Pd(IV)-catalyzed coupling of two molecules of the substrate gave the amido-Pd(II) bromide complex [83]. This species underwent C−H bond activation leading to a seven-membered palladacycle, which reductively eliminated the product.



Scheme 55. Synthesis of phenanthridinones [82].

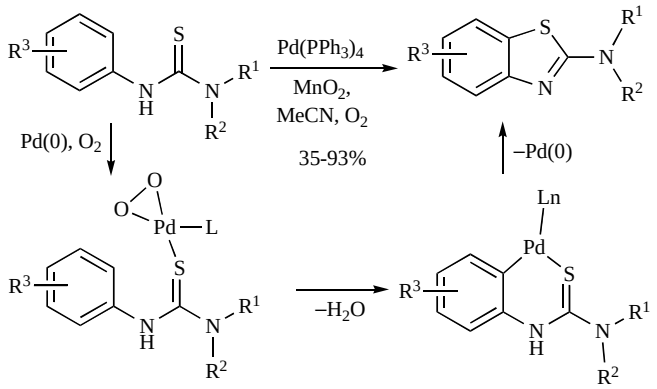
3.2. C–S Coupling Reaction

The synthesis of substituted benzothiophenes is a rare example of heterocycle synthesis based on palladium-catalyzed C−H activation/C−S bond forming strategy (Scheme **56**) [84]. The regioselective cyclization of thioenols took pace in DMSO using $PdCl_2$, as a catalyst. Interestingly, the reaction occurred efficiently in the absence of re-oxidants. The authors proposed that the key-intermediate was a disulfide which formed by oxidation of the starting thioenol in the presence of DMSO. Apparently, the disulfide oxidatively added to Pd(0). Subsequent, electrophilic attack of the aryl ring on to the metal led to a palladacycle which reductively eliminated the expected product.



Scheme 56. Synthesis of benzothiophenes [84].

2-Aminobenzothiazoles were synthesized through the direct cyclization of *N*-arylthioureas (Scheme **57**) [85]. The use of palladium(0) and activated MnO_2 as a co-oxidant under an oxygen atmosphere was crucial to achieve successful transformations. The reaction worked well with a variety of *meta*, *para* and *ortho*-substituted *N*-arylthiourea precursors. Electron-withdrawing substituents favored cyclization. These findings and KIE studies indicated that cyclization proceeded through a σ-bond methatesis mechanism where an anionic peroxo/peroxide-Pd-bound ligand aided in proton abstraction. MnO_2 might serve as a catalyst to decompose hydrogen peroxide.



Scheme 57. Synthesis of 2-aminobenzothiazoles [85].

CONCLUSION AND OUTLOOK

Synthetic application is the true test of the usefulness of a method. In the last decade the number of benzo-fused heterocycle syntheses accomplished by direct Pd-catalyzed functionalization enhanced significantly.

Oxidative coupling reactions promoting C−C and C−heteroatom bonds are particularly attractive, as substrate pre-activation with halides is completely omitted. Intermolecular, selective functionalization can be achieved using arenes bearing groups (in most cases nitrogen containing groups) capable of directing C−H bond cleavage. An extension to oxygen containing groups should expand applicability.

The fact that an external oxidant is required to realize catalytic transformations is usually considered a critical point, as preparative synthetic application can be hampered. However, the increasing number of the examples where only dioxygen or air are successfully used should prompt a greater evaluation of oxidative coupling application in organic synthesis.

C−C Bond forming reactions based on direct substitutive coupling with organic halides, unexpensive chlorides included, have become versatile tools. The possibility of performing regioselective C−H functionalization through several approaches (by heteroatoms, by chelation, or by metallacycle) expanded substrate scope, making possible the synthesis of a large variety of heterocycles. Moreover, practicality of these reactions allowed their use in combination with other parallel, catalytic transformations in order to synthesize complex heterocyclic molecules in a single operation.

ACKNOWLEDGEMENT

Cited reports of my lab were founded by Consiglio Nazionale delle Ricerche (CNR).

LIST OF ABBREVIATIONS

Ac	=	Acetyl
*t*AmylOH	=	2-Methylbutan-2-ol
Ar	=	Aryl
atm	=	Atmosphere
Bn	=	Benzyl
BQ	=	1,4-Benzoquinone
Bu	=	Butyl
Cy	=	Cyclohexyl
cod	=	Cyclooctadiene
dba	=	Dibenzylideneacetone
DCE	=	Dichloroethane
DCM	=	Dichloromethane
DMA	=	Dimethylacetamide
DME	=	Dimethoxyethane
DMF	=	Dimethylformamide
DMSO	=	Dimethyl sulfoxide
dppf	=	l,l'-bis(Diphenylphosphino)ferrocene
d.r.	=	Diastereomeric ratio
Et	=	Ethyl
L	=	Ligand
Me	=	Methyl
μW	=	Microwave
MS	=	Molecular sieves
Ph	=	Phenyl
Piv	=	Pivaloyl
PMB	=	*p*-Methoxybenzyl
r.t.	=	Room temperature
S_E3	=	Trimolecular electrophilic substitution
TBAB	=	Tetrabutylammonium bromide
*t*Bu	=	*tert*-Butyl
Tf	=	Trifluoromethanesulfonyl
TFP:	=	Tri(2-furyl)phosphine
THF	=	Tetrahydrofuran

TMS	=	Trimethylsilyl
TPP	=	Triphenylphosphine
Ts	=	4-Toluenesulfonyl, tosyl

REFERENCES

[1] Tsuji, J. "*Palladium Reagents and Catalysts: new perspectives for the 21st century*, Wiley & Sons: New York, **2004**.

[2] *For recent reviews on transition-metal catalyzed C−H/C−C functionalization*, see: (a) Campeau, L. C.; Fagnou, K. Palladium-catalyzed direct arylation of simple arenes in synthesis of biaryl molecules. *Chem. Commun.*, **2006**, *12*, 1253-1264. (b) Alberico, D.; Scott, M. E.; Lautens, M. Aryl-aryl bond formation by transition-metal-catalyzed direct arylation. *Chem. Rev.*, **2007**, *107*, 174-238. (c) Seregin, I. V.; Gevorgyan, V. Direct transition metal-catalyzed functionalization of heteroaromatic compounds. *Chem. Soc. Rev.*, **2007**, *36*, 1173-1193. (d) Catellani, M.; Motti, E.; Della Cà, N.; Ferraccioli, R. Recent developments in catalytic aryl coupling reactions. *Eur. J. Org. Chem.*, **2007**, *25*, 4153-4165. (e) McGlacken, G. P.; Bateman, L. M. Recent advances in aryl-aryl bond formation by direct arylation. *Chem. Soc. Rev.*, **2009**, *38*, 2447–2464. (f) Ackermann, L.; Vicente, R.; Kapdi, A. R. Transition-metal-catalyzed direct arylation of (hetero)arenes by C−H bond cleavage. *Angew. Chem. Int. Ed.*, **2009**, *48*, 9792-9826. (g) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Palladium(II)-catalyzed C−H activation/C−C cross-coupling reactions: versatility and practicality. *Angew. Chem. Int. Ed.*, **2009**, *48*, 5094-5115.

[3] *For recent reviews on transition-metal catalyzed C−H/C−Y functionalization, see:* (a) Zhang, M. Construction of heterocycle scaffolds via transition metal-catalyzed sp^2 C−H functionalization. *Adv. Synth. Catal.*, **2009**, *351*, 2243-2270. (b) Lyons, T. W.; Sanford, M. S. Palladium-catalyzed ligand-directed C−H functionalization reactions. *Chem. Rev.*, **2010**, *110*, 1147-1169 and references therein.

[4] (a) Michael, J. P. Quinoline, quinazoline and acridone alkaloids. *Nat. Prod. Rep.*, **2008**, *25*, 166-187. (b) Smythe, M. L. The combinatorial synthesis of bicyclic privileged structures or privileged substructures. *Chem. Rev.*, **2003**, *103*, 893-930. (c) Knoelker, H.-J.; Reddy, K. R. Isolation and synthesis of biologically active carbazole alkaloids. *Chem. Rev.*, **2002**, *102*, 4303-4428.

[5] Chiusoli, G. P.; Catellani, M.; Ricotti, S. A new palladium-catalyzed synthesis of 1,2,3,4,4*a*,8*b*-hexahydro-1,4-methanobiphenylenes and 2-phenylbicyclo[2.2.1]hept-2-enes. *J. Organomet. Chem*., **1985**, *296*, C11-C15.

[6] Akita, Y.; Itagaki, Y.; Takizawa, S.; Ohta, A. Cross-coupling reactions of chloropyrazines with 1-substituted indoles. *Chem. Pharm. Bull.*, **1989**, *37*, 1477-1480.

[7] Cerna, I.; Pohl, R.; Klepetàrovà, B.; Hocek, M. Intramolecular direct C−H arylation approach to fused purines. Synthesis of purino[8,9-*f*]phenanthridines and 5,6-dihydropurino[8,9-*a*]isoquinolines. *J. Org. Chem.*, **2010**, *75*, 2302-2308.

[8] Bryan, C.; Lautens, M. Silver-promoted domino Pd-catalyzed amination/direct arylation: access to polycyclic heteroaromatics. *Org. Lett.*, **2008**, *10*, 4633-4636.

[9] Ames, D. E.; Bull, D. Some reactions of 3-halogenocinnolines catalysed by palladium compounds. *Tetrahedron*, **1982**, *38*, 383-387.

[10] Ames, D. E.; Opalko, A. Synthesis of dibenzofurans by palladium-catalysed intramolecular dehydrobromination of 2-bromophenyl phenyl ethers. *Synthesis*, **1983**, 234-235. Ames, D. E.; Opalko, A. Palladium-catalysed cyclisation of 2-substituted halogenoarenes by dehydrohalogenation. *Tetrahedron*, **1984**, *40*, 1919-1925.

[11] Bedford, R. B.; Cazin, S. J. A novel catalytic one-pot synthesis of carbazoles *via* consecutive amination and C–H activation. *Chem. Commun.*, **2002**, *20*, 2310-2311.

[12] Cuny, G.; Bois-Choussy, M.; Zhu, J. One-pot synthesis of polyheterocycles by a palladium-catalyzed intramolecular N-arylation/C–H activation/aryl–aryl bond-forming domino process. *Angew. Chem. Int. Ed.*, **2003**, *42*, 4774-4777.

[13] Campeau, L-C.; Parisien, M.; Jean, A.; Fagnou, K. Catalytic direct arylation with aryl chlorides, bromides, and iodides: intramolecular studies leading to new intermolecular reactions. *J. Am. Chem. Soc.*, **2006**, *128*, 581-590.

[14] *For an early example of carbocycle synthesis based-on intramolecular aromatic arylation using aryl chlorides, see:* Smet, M.; Van Dijk, J.; Dehaen, W. An improved synthesis of substituted rubicenes providing access to heterocyclic rubicene analogues. *Synlett*, **1999**, 495-497.

[15] Ackermann, L.; Althammer, A. Domino N−H/C−H bond activation: palladium-catalyzed synthesis of annulated heterocycles using dichloro(hetero)arenes. *Angew. Chem. Int. Ed.*, **2007**, *46*, 1627-1629.

[16] (a) Franck,P.; Hostyn, S.; Daika-Halàsz, B.; Polonka-Bàlint, A; Monsieurs, K.; Màtyus, P.; Maes, B. U.W. Pd-catalyzed intramolecular direct arylations at high temperature. *Tetrahedron*, **2008**, *64*, 6030-6037. (b) Hostyn, S.; Van Baelen, G.; Lemière, G. L. F.; Maes, B. U. W. Synthesis of α-carbolines starting from 2,3-dichloropyridines and substituted anilines. *Adv. Synth. Catal.*, **2008**, *350*, 2653-2660.

[17] (a) Garcìa-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. Proton abstraction mechanism for the palladium-catalyzed intramolecular arylation. *J. Am. Chem. Soc.*, **2006**, *128*, 1066-1067. (b) Garcìa-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. Proton-abstraction mechanism in the palladium-catalyzed intramolecular arylation: substituent effects. *J. Am. Chem. Soc.*, **2007**, *129*, 6880-6886.

[18] Tremont, S. J.; Rahman, H. U. Ortho-alkylation of acetanilides using alkyl halides and palladium acetate. *J. Am. Chem. Soc.*, **1984**, *106*, 5759–5760.

[l9] Daugulis, O.; Do, H.-Q.; Shabashov, D. Palladium- and copper-catalyzed arylation of carbon-hydrogen bonds. *Acc. Chem. Res*., **2009**, *42*, 1074-1086.

[20] Shabashov, D.; Daugulis, O. Palladium-catalyzed anilide *ortho*-arylation and subsequent one-pot cyclization to phenanthridines. *J. Org. Chem.*, **2007**, *72*, 7720-7725.

[21] *For reviews on palladacycles, see:* (a) Riabov, A. D. Mechanisms of intramolecular activation of C-H bonds in transition-metal complexes. *Chem. Rev.*, **1990**, *90*, 403-424. (b) Dyker, G. Palladacycles as reactive intermediates. *Chem. Berichte*, **1997**, *130*, 1567-1578. (c) Dupont, M.; Consorti, J.; Spencer, J. The potential of palladacycles: more than just precatalysts. *Chem. Rev.*, **2005**, *105*, 2527-2571.

[22] *For recent reviews on Pd(IV) chemistry, see*: (a) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. Pd-catalyzed oxidative coupling with organometallic reagents via C–H activation. *Chem. Soc. Rev.*, **2010**, *39*, 712-733. (b) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. Emergence of palladium(IV) chemistry in synthesis and catalysis. *Chem. Rev.*, **2010**, *110*, 824-889.

[23] Diker, G. Transition metal catalyzed coupling reactions under C−H activation. *Angew. Chem. Int. Ed.*, **1992**, *31*, 1023-1025.

[24] Catellani, M. In: *Topics in Organometallic Chemistry: Palladium in Organic Synthesis*, Jiro Tsuji, Ed.; Springer: Berlin, **2005**; Vol. *14*, pp 21-53.

[25] Ferraccioli, R.; Carenzi, D.; Rombolà, O.; Catellani, M. Synthesis of 6-phenanthridinones and their heterocyclic analogues through palladium-catalyzed sequential aryl-aryl and *N*-aryl coupling. *Org. Lett*., **2004**, *6*, 4759-4762.

[26] Motti, E.; Faccini, F.; Ferrari, I.; Catellani, M.; Ferraccioli, R. Sequential unsymmetrical aryl coupling of *o*-substituted aryl iodides with o-bromophenols and reaction with olefins: palladium-catalyzed synthesis of 6H-dibenzopyran derivatives. *Org. Lett.*, **2006**, *8*, 3967-3970.

[27] Della Ca', N.; Motti, E.; Catellani, M. Palladium-catalyzed synthesis of selectively substituted phenanthridine derivatives. *Adv. Synth. Catal*., **2008**, *350*, 2513-2516.

[28] Della Ca', N.; Sassi, G.; Catellani, M. A direct palladium-catalyzed route to selectively substituted carbazoles through sequential C−C and C−N bond formation: synthesis of carbazomycin A. *Adv. Synth. Catal*., **2008**, *350*, 2179-2182.

[29] Hennings, D. D.; Iwasa, S.; Rawal, V. H. Anion-accelerated palladium-mediated intramolecular cyclizations: synthesis of benzofurans, indoles, and a benzopyran. *Tetrahedron Lett*., **1997**, *38*, 6379-6382.

[30] Ohno, H.; Iuchi, M.; Fujii, N.; Tanaka, T. Zipper-mode double C−H activation: palladium-catalyzed direct construction of highly-fused heterocyclic systems. *Org. Lett*., **2007**, *9*, 4813-4815.

[31] Chai, D. I.; Lautens, M. Tandem Pd-catalyzed double C−C formation: effect of water. *J. Org. Chem.*, **2009**, *74*, 3054-3061.

[32] Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. Synthesis of 3-(diarylmethylenyl)oxindole by a palladium-catalyzed domino carbopalladation/C−H activation/C−C bond-forming process. *Org. Lett.*, **2006**, *8*, 4927-4930.

[33] Hennessy, E. J.; Buchwald, S. L. Synthesis of substituted oxindoles from α-chloroacetanilides via palladium-catalyzed C−H functionalization. *J. Am. Chem. Soc*., **2003**, *125*, 12084-12085.

[34] Huang, S. J.; Cho, S. H.; Chang, S. Synthesis of condensed pyrroloindoles via Pd-catalyzed intramolecular C−H bond functionalization of pyrroles. *J. Am. Chem. Soc*., **2008**, *130*, 16158-16159.

[35] Grigg, R.; Fretwell, P.; Meerholtz, C.; Sridharan, V. Palladium catalysed synthesis of spiroindolines. *Tetrahedron*, **1994**, *50*, 359-370.

[36] Ruck, R. T.; Huffman, M. A.; Kim, M. M.; Shevlin, M.; Wynne V. Kandur, W. V.; Davies, I. W. Palladium-catalyzed tandem Heck reaction/C−H functionalization-preparation of spiro-indane-oxindoles. *Angew. Chem. Int. Ed.*, **2008**, *47*, 4711-4714.

[37] Renè, O.; Lapointe, D.; Fagnou, K. Domino palladium-catalyzed Heck-intermolecular direct arylation reactions. *Org. Lett.*, **2009**, *11*, 4560-4563.

[38] *This methodology was further applied to develop regio- and stereoselective syntheses of fused polycycles:* (a) Hu, Y.; Ouyang, Y.; Qu, Y.; Hu, Q.; Yao, H. Rapid construction of five contiguous stereocenters in a multi-cascade reaction. *Chem. Commun*., **2009**, *30*, 4575-4577. (b) Hu,Y.; Yu, C.; Ren, D.; Hu, Q.; Zhang, L.; Cheng, D. One-step synthesis of the benzocyclo[penta- to octa-]isoindole core. *Angew. Chem. Int. Ed*., **2009**, *48*, 5448-5451.

[39] Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. Palladium(II)-catalyzed ortho alkylation of benzoic acids with alkyl halides. *Angew. Chem. Int. Ed.*, **2009**, *48*, 6097-6100.

[40] Lautens, M.; Paquin, J.-F.; Piguel, S. Palladium-catalyzed sequential alkylation–alkenylation reactions. Application to the synthesis of 2-substituted-4-benzoxepines and 2,5-disubstituted-4-benzoxepines. *J. Org. Chem.*, **2002**, *67*, 3972-3974.

[41] Lautens, M.; Piguel, S. A new route to fused aromatic compounds by using a palladium-catalyzed alkylation-alkenylation sequence. *Angew. Chem. Int. Ed.*, **2000**, *39*, 1045-1046.

[42] Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. Synthesis of benzannulated N-heterocycles by a palladium-catalyzed C−C/C−N coupling of bromoalkylamines. *Org. Lett.*, **2007**, *9*, 5255-5258.

[43] Blaszykowski, C.; Aktoudianakis, E.; Bressy, C.; Alberico, D.; Lautens, M. Preparation of annulated nitrogen-containing heterocycles via a one-pot palladium-catalyzed alkylation/direct arylation sequence. *Org. Lett.*, **2006**, *10*, 2043-2045.

[44] Mariampillai, B.; Alberico, D.; Bidau, V.; Lautens, M. Synthesis of polycyclic benzonitriles via a one-pot aryl alkylation/cyanation reaction. *J. Am. Chem. Soc.*, **2006**, *128*, 14436-14437.

[45] Ferraccioli, R.; Forni, A. Selective synthesis of isoquinolin-3-one derivatives combining Pd-catalysed aromatic alkylation/vinylation with addition reactions: The beneficial effect of water. *Eur. J. Org. Chem.*, **2009**, 3161-3166.

[46] Dyker, G. Palladium-catalyzed C−H activation of tert-butyl groups: a simple synthesis of 1,2-dihydrocyclobutabenzene derivatives. *Angew. Chem. Int. Ed.*, **1994**, *33*, 103-105.

[47] (a) Ren, H.; Knochel, P. Chemoselective benzylic C−H activations for the preparation of condensed N-heterocycles. *Angew. Chem. Int. Ed.*, **2006**, *45*, 3462-3465. (b) Ren, H.; Li, Z.; Knochel, P. Chemoselective C(sp^3)−H bond activation for the preparation of condensed N-heterocycles. *Chem. Asian J.*, **2007**, *2*, 416-433.

[48] Lafrance, M.; Gorelsky, S. L.; Fagnou, K. High-yielding palladium-catalyzed intramolecular alkane arylation: reaction development and mechanistic studies. *J. Am. Chem. Soc.*, **2007**, *129*, 14570-14571.

[49] Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. Palladium-catalyzed sp^3 C−H activation of simple alkyl groups: direct preparation of indoline derivatives from N-alky-2-bromoanilines. *Org. Lett.*, **2008**, *10*, 1759-1762.

[50] *For a recent review on Pd(II)-catalyzed oxidative rections, see:* Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. C−C, C−O, C−N bond formation on sp^2 carbon by Pd(II)-catalyzed reactions involving oxidant agents. *Chem. Rev.*, **2007**, *107*, 5318-5365.

[51] Åkermark, B.; Eberson, L.; Jonsson, E.; Pettersson, E. Palladium-promoted cyclization of diphenyl ether, diphenylamine, and related compounds. *J. Org. Chem.*, **1975**, *40*, 1365-1366.

[52] Hagelin, H.; Oslob, J. D.; Åkermark, B. Oxygen as oxidant in palladium-catalyzed inter- and intramolecular coupling reactions. *Chem. Eur. J.*, **1999**, *5*, 2413-2416.

[53] Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. C−C bond formation via double C−H functionalization: aerobic oxidative coupling as a method for synthesizing heterocoupled biaryls. *Org. Lett.*, **2007**, *9*, 3137-3139.

[54] Watanabe, T.; Ueda, S.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. One-pot synthesis of carbazoles by palladium-catalyzed N-arylation and oxidative coupling. *Chem. Commun.*, **2007**, *43*, 4516-4518; Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. Palladium-catalyzed direct synthesis of carbazoles via one-pot N-arylation and oxidative biaryl coupling: synthesis and mechanistic study. *J. Org. Chem.*, **2009**, *74*, 4720-4726.

[55] Liegault, B.; Lee, D.; P. Huestis, M. P.; Stuart, D. R.; Fagnou, K. Intramolecular Pd(II)-catalyzed oxidative biaryl synthesis under air: reaction development and scope. *J. Org. Chem.*, **2008**, *73*, 5022-5028.

[56] Lafrance, M.; Fagnou, K. Palladium-catalyzed benzene arylation: incorporation of catalytic pivalic acid as a proton shuttle and a key element in catalyst design. *J. Am. Chem. Soc.*, **2006**, *128*, 16496-16497. Lafrance, M.; Lapointe, D.; Fagnou, K. Mild and efficient palladium-catalyzed intramolecular direct arylation reactions. *Tetrahedron*, **2008**, *64*, 6015-6020, and references cited therein.

[57] Ackermann, L.; Jeyachandran, R.; Potukuci, H. K.; Nvàk, P.; Buettner, L. Palladium-catalyzed dehydrogenative direct arylations of 1,2,3-triazoles. *Org. Lett.*, **2010**, *12*, 2056-2059.

[58] Jia, C.; Kitamura, T.; Fujiwara, Y. Catalytic functionalization of arenes and alkanes via C−H bond activation. *Acc. Chem. Res.*, **2001**, *34*, 633-639.

[59] Zhang. H.; Ferreira, E. M.; Stoltz, B. M. Direct oxidative Heck cyclizations: intramolecular Fujiwara-Moritani arylations for the synthesis of functionalized benzofurans and dihydrobenzofurans. *Angew. Chem. Int. Ed.*, **2004**, *43*, 6144-6148.

[60] Wuertz, S.; Rakshit, S.; Neumann, J. J.; Droege, T.; Glorius, F. Palladium-catalyzed oxidative cyclization of N-aryl enamines: from anilines to indoles. *Angew. Chem. Int. Ed.*, **2008**, *47*, 7230-7233.

[61] Ueda, S.; Okada, T.; Nagasawa, H. Oxindole synthesis by palladium-catalysed aromatic C−H alkenylation. *Chem. Commun*., **2010**, *46*, 2462-2464.

[62] Ding, S.; Shi, Z.; Jiao, N. Indoles from simple anilines and alkynes: palladium-catalyzed C−H activation using dioxygen as the oxidant. *Angew. Chem. Int. Ed.*, **2009**, *48*, 4572-4576.

[63] Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. Pd(II)-catalyzed synthesis of carbolines by iminoannulation of internal alkynes via direct C−H bond cleavage using dioxygen as oxidant. *Org. Lett.*, **2010**, *12*, 1540-1543.

[64] Miura, M.; Satoh, T. In: *Topics in Organometallic Chemistry: Palladium in Organic Synthesis*; Jiro Tsuji, Ed.; Springer: Berlin, **2005**; Vol. *14*, pp 55-83.

[65] Miura, M.; Tsuda, T.; Satoh, T.; Sommai Pivsa-Art, S.; Nomura, M. Oxidative cross-coupling of N-(2'-phenylphenyl)benzenesulfonamides or benzoic and naphthoic acids with alkenes using a palladium-copper catalyst system under air. *J. Org. Chem*., **1998**, *63*, 5211-5215.

[66] Miura, M.; Tsuda, T.; Satoh, T.; Miura, M. Palladium-catalyzed oxidative cross-coupling of 2-phenylphenols with alkenes. *Chem. Lett.*, **1997**, *26*, 1103-1104.

[67] Li, J.-J.; Mei, T.-S.; Yu, J.-Q. Synthesis of indolines and tetrahydroisoquinolines from arylethylamines by Pd^{II}-catalyzed C–H activation reactions. *Angew. Chem. Int. Ed.*, **2008**, *47*, 6452-6455.

[68] Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagne, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. Distinct reactivity of $Pd(OTs)_2$: the intermolecular Pd(II)-catalyzed 1,2-carboamination of dienes. *J. Am. Chem. Soc.*, **2008**, *130*, 10066-10067.

[69] Liegault, B.; Fagnou, K. Palladium-catalyzed intramolecular coupling of arenes and unactivated alkanes in air. *Organometallics*, **2008**, *27*, 4841-4843.

[70] Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. Preparation of benzolactams by $Pd(OAc)_2$-catalyzed direct aromatic carbonylation. *J. Am. Chem. Soc.*, **2004**, *126*, 14342-14343.

[71] Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. T.; Gagnè, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. Room-temperature palladium-catalyzed C–H activation: ortho-carbonylation of aniline derivatives. *Angew. Chem. Int. Ed*., **2009**, *48*, 1830-1833.

[72] Giri, R.; Lam, J. K.; Yu, J.-Q. Synthetic applications of Pd(II)-catalyzed C−H carboxylation and mechanistic insights: expedient routes to anthranilic acids, oxazolinones, and quinazolinones. *J. Am. Chem. Soc.*, **2010**, *132*, 686-693.

[73] Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. Combined C−H functionalization/C−N bond formation route to carbazoles. *J. Am. Chem. Soc.*, **2005**, *127*, 14560-14561.

[74] Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-S. Multiple C–H activations to construct biologically active molecules in a process completely free of organohalogen and organometallic components. *Angew. Chem. Int. Ed.*, **2008**, *47*, 1115-1118.

[75] Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. Oxidative Pd(II)-catalyzed C−H bond amination to carbazole at ambient temperature. *J. Am. Chem. Soc*., **2008**, *130*, 16184-16186.

[76] Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. Palladium-catalyzed C−H activation/intramolecular amination reaction: a new route to 3-aryl/alkylindazoles. *Org. Lett.*, **2007**, *9*, 2931-2934.

[77] Inamoto, K.; Saito, T.; Hiroya, K.; Doi, T. A new approach to 3-substituted indoles through palladium-catalyzed C–H activation followed by intramolecular amination reaction of enamines. *Synlett*, **2008**, *20*, 3157-3162.

[78] Wasa, M.; Yu, J.-Q. Synthesis of β-, γ-, and δ-lactams via Pd(II)-catalyzed C-H activation reactions. *J. Am. Chem. Soc.*, **2008**, *130*, 14058-14059.

[79] Miura, T.; Ito, Y.; Murakami, M. Synthesis of oxindoles by palladium-catalyzed C-H bond amidation. *Chem. Lett.*, **2009**, *38*, 328-329.

[80] Mei, T.-S.; Wang, X.; Yu, J.-Q. Pd(II)-catalyzed amination of C−H bonds using single-electron or two-electron oxidants. *J. Am. Chem. Soc.*, **2009**, *131*, 10806-10807.

[81] Tan, Y.; Hartwig, J. F. Palladium-catalyzed amination of aromatic C−H bonds with oxime esters. *J. Am. Chem. Soc*., **2010**, *132*, 3676-3677.

[82] Donati, L.; Michel, S.; Tillequin, F.; Porèe, F.-H. Selective unusual Pd-mediated biaryl coupling reactions: solvent effects with carbonate bases. *Org. Lett.*, **2010**, *12*, 156-158.

[83] Ferraccioli, R.; Carenzi, D.; Motti, E.; Catellani, M. A simple catalytic synthesis of condensed pyridones from o-bromoarylcarboxamides involving *ipso* substitution via palladacycles. *J. Am. Chem. Soc.*, **2006**, *128*, 722-723.

[84] Inamoto, K.; Arai, Y.; Hiroya, K. Doi, T. Palladium-catalysed direct synthesis of benzo[b]thiophenes from thioenols. *Chem. Commun.*, **2008**, *43*, 5529-5531.

[85] Joyce, L. L.; Batey, R. A. Heterocycle formation via palladium-catalyzed intramolecular oxidative C−H bond functionalization: an efficient strategy for the synthesis of 2-aminobenzothiazoles. *Org. Lett.*, **2009**, *13*, 2792-2795.

Received: July 02, 2010 Revised: July 31, 2010 Accepted: December 02, 2010