SYNTHESIS OF FUSED AROMATIC N-HETEROCYCLES BY DOMINO SITE-SELECTIVE PALLADIUM-CATALYZED C-C AND C-N COUPLING REACTIONS

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Tran Quang Hung,[1] Tuan Thanh Dang,[2] Nghia Ngo Pham[2] and Peter Langer[3]

[1]*Institute of Chemistry, Vietnamese Academy of Science and Technology (VAST), 18 Hoang Quoc Viet, Hanoi, Vietnam*

[2]*Faculty of Chemistry, VNU-Hanoi University of Science, 19 Le Thanh Tong, Hanoi, Vietnam*

[3]*Institute of Chemistry, University of Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany*

[3]*Leibniz Institute of Catalysis e.V. at the University of Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany*

(email: peter.langer@uni-rostock.de)

Abstract. *Fused N-Heterocycles are present in many important molecules, such as natural alkaloids, drugs and organic materials. Pd-catalyzed cyclization reactions based on C-C and C-N coupling reactions represent practical and useful methods for regio- as well as stereoselective syntheses of carbo- and heterocyclic compounds. In this review, we have summarized several main approaches to construct fused aromatic five- and six-membered N-heterocycles by Pd-catalyzed intramolecular cyclizations.*

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1. Introduction

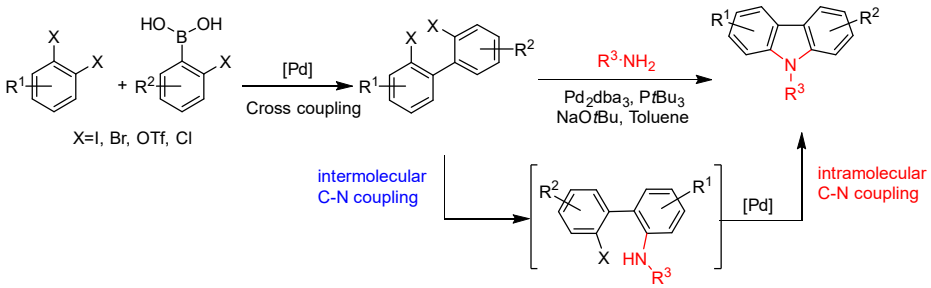
Fused aromatic N-Heterocycles are important motifs appearing in the structures of natural products, drugs and advanced organic materials.[1] Conventional methods for the synthesis of fused aromatic N-heterocycles are often based on the cyclocondensation of a dinucleophilic substrate with a dielectrophilic compound.[2] These reactions are often carried out under harsh conditions and/or long reaction time.[2] On the other hand, the functional group tolerance is often limited in these methods. Recent development of modern synthetic methods relying on transition metal catalysis has opened up new pathways to construct novel fused aromatic N-heterocycles.[3] Especially strategies involving site-selective Pd-catalyzed coupling processes allow an easy access to highly functionalized fused aromatic N-heterocycles with high control of the regio- and stereoselectivity.[4] Furthermore, site-selective Pd-catalyzed domino processes involving C-C/C-N coupling reactions in combination with C-H activation cyclization reactions allow for a practical and efficient formation of large π-conjugated polycyclic fused N-heterocycles in high yields.[4] Due to the recent advances in the field of Pd catalysis, many new applications of fused N-heterocycles have been found and contributed for the development of materials science and medicinal chemistry.[4]

2. Synthesis of fused heterocycles based on domino site-selective Pd-catalyzed C-C and C-N coupling reactions

Carbazoles are present in many important bioactive natural alkaloids as well as in synthetic compounds. They show remarkable bioactivities, such as antibacterial, antimalarial, anticancer, and anti-Alzheimer. They are also used in important optoelectronic materials, due to their high light emitting ability, durability, thermal stability.[5] Therefore, studies related to carbazole as building block gained much attention.[5] A general strategy to form the carbazole framework is based on Pd-catalyzed C-C coupling and sequential double C-N coupling reactions as demonstrated in Scheme 1.[6]

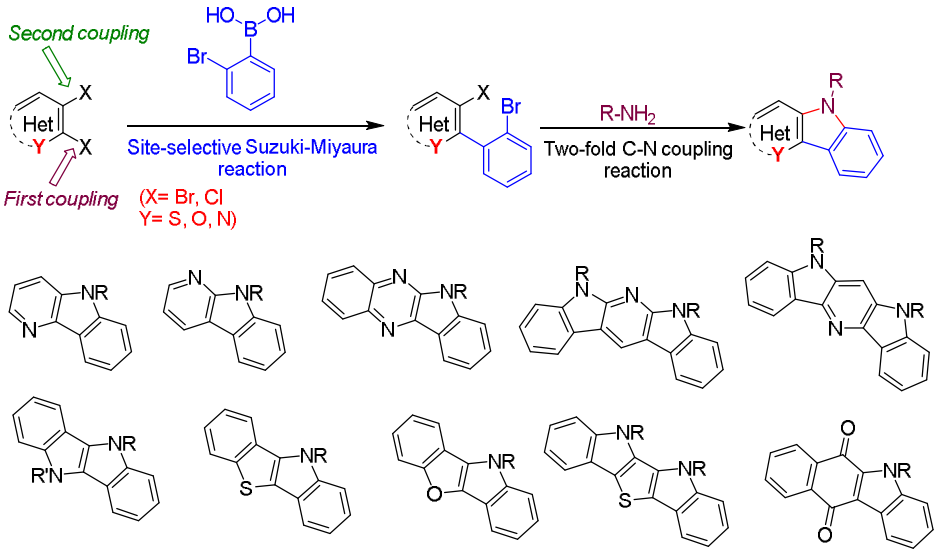
In 2005, Nozaki et. al.[7] developed a strategy to prepare a series of substituted carbazoles. The Suzuki-Miyaura cross-coupling was successfully used for the reaction of *o*-halophenols with *o*-hydroxyphenylboronic acids. In the first step, instead of using coupling reactions of 1,2-dihalobenzenes with organometallic reagents, they used substituted 1-halo-2-hydroxybenzenes in order to avoid selectivity

problems. Then both hydroxyl groups were converted to triflates. Sequential double Pd-catalyzed C-N coupling reactions with primary amines afforded the desired carbazoles. In general, products were obtained in high yields using aromatic amines. Moderate yields were obtained using aliphatic amines and amides. Notably, this protocol was applied to the total synthesis of carbazole alkaloid Mukonine *via* a five step synthesis which proceeded in 40% yield.[5]



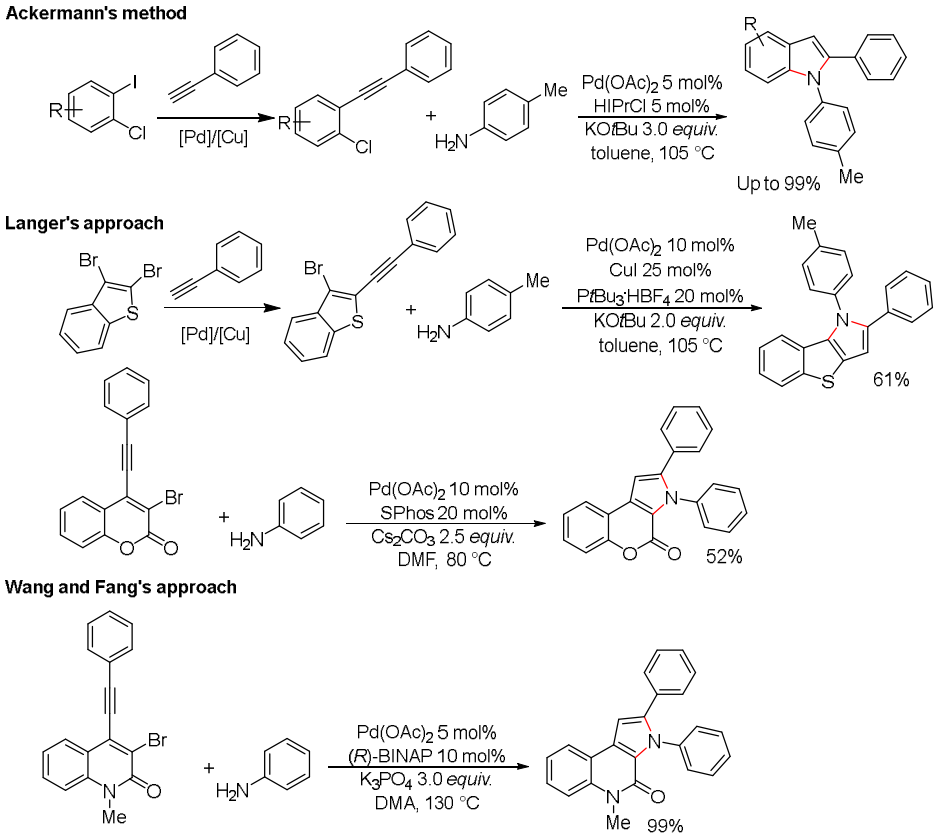
Scheme 1. General synthesis of N-subtituted carbazoles *via* double Pd-catalyzed C-N coupling reactions.

In an attempt to design new optoelectronic materials, Langer's group studied a two step method to prepare fused indoloheterocycles, such as thieno[3,2-b:4,5-b']diindoles, benzothieno[3,2-b]indoles,[8] 5-methyl-5,10-dihydroindolo[3,2-b]indoles,[9] 5,7-dihydropyrido[3,2-b:5,6-b′]diindoles[10] and indolo[2,3-b]quinoxalines[11] (Scheme 2). These processes relied on site-selective Suzuki-Miyaura reactions of 1,2-dihaloheterocycles with *o*-bromophenylboronic acid, sequential double C-N couplings with anilines or aliphatic amines. The optimization of the second step of the reaction for anilines and aliphatic amines revealed that bidentate ligands can provide better yields in most cases. The cyclized products were obtained in high yields. The fluorescence properties are interesting, especially for dihydropyrido[3,2-b:5,6-b′]diindoles. By applying this method, Langer[12] et al. also designed and synthesized a series of α- and δ-carboline derivatives by applying the same strategy.



Scheme 2. N-substituted fused indoloheterocyles prepared by Langer's group.

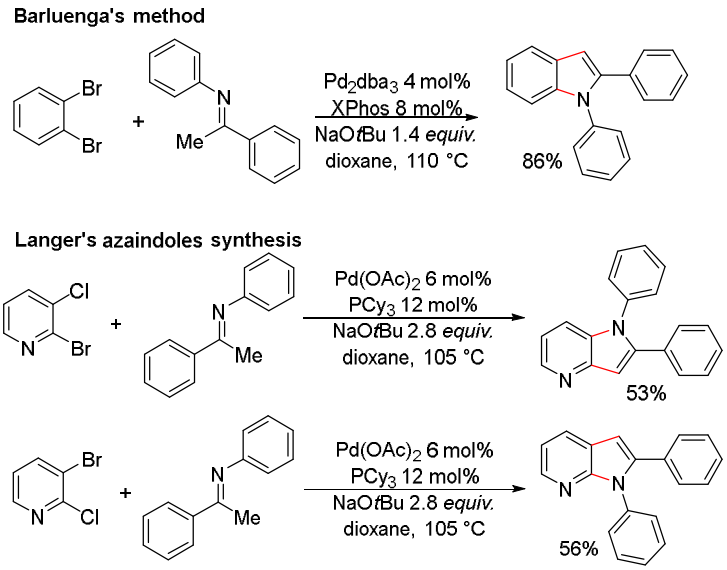
C-N coupling has proven to be efficient when being strategically combined with hydroamination reactions in a domino fashion. A new synthesis of indoles by Pd-catalyzed C-N coupling/hydroamination of *ortho*-halo(arylethynyl)-benzenes with aniline derivatives was reported by Ackermann in 2005 (Scheme 3).[13] This process employed $Pd(OAc)_2$ or CuI catalysts using the imidazolium salt HIPrCl. More detailed investigations related to this reaction revealed other catalyst systems, including $Pd(OAc)_2$/P*t*Bu_3, $Ni(cod)_2$/dppf or $[Pd(cinnamyl)Cl]_2$/Josiphos.[14] On the basis of these findings, Langer's group reported the synthesis of benzothienopyrroles *via* domino C-N coupling/hydroamination (Scheme 3).[15] This method employs the $Pd(OAc)_2$/CuI catalyst system in combination with the P*t*Bu_3·HBF_4 ligand in toluene. Applying the same strategy, Langer's group later developed the synthesis of pyrrolocoumarines employing the $Pd(OAc)_2$/SPhos catalyst system and the base Cs_2CO_3 in DMF (Scheme 3).[16] During this time, Wang and Fang also published a similar preparation of pyrroloquinolinones *via* domino C-N coupling/hydroamination using $Pd(OAc)_2$/(*R*)-BINAP catalyst system and the base K_3PO_4 in DMA (Scheme 3).[17]



Scheme 3. Domino Pd-catalyzed C-N coupling/hydroamination of *ortho*-halo(arylethynyl)-arenes with amines.

A-Methylimines and enamines are considered to be interesting building blocks with two nucleophilic centers in their molecules.[18] In the first Pd-catalyzed cyclization of imines with dihalogenated aromatic compounds, Barluenga et al. developed the cyclization of diphenylmethanimine with aryl dihalides to form the corresponding indoles (Scheme 4).[19] Notably, in the presence of Pd_2dba_3/XPhos as the catalyst, the first C-C coupling took place, followed by an α-arylation type reaction. Then the second coupling between the nitrogen and the second halogenated carbon atom took place, forming the fused pyrrole ring (Scheme 4).[19]

Recently, Langer and coworkers applied successfully a similar method for the site-selective synthesis of azaindole derivatives from *ortho*-dihalopyridines (Scheme 4).[20] In comparison to the reaction conditions reported by Barluenga, this method required the $Pd(OAc)_2/PCy_3$ catalyst system to meet success in the cyclization. The regioisomeric chemistry of products is controlled by the choice of the halogen atom bearing a pyridine ring. Generally, the first C-C coupling occurred at the more reactive carbon center, while the second C-N coupling happened at the other carbon center.[20]



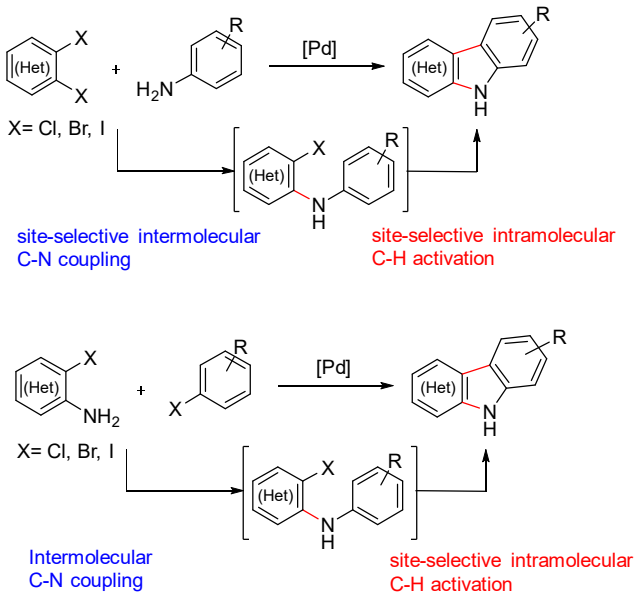
Scheme 4. Domino Pd-catalyzed cyclizations of imines with *ortho*-dihaloarenes**.**

3. Synthesis of fused heterocycles based on domino Pd-catalyzed C-N coupling and C-H activation

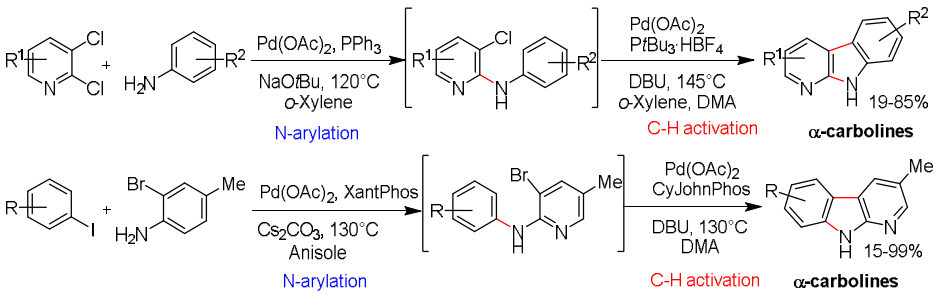
The domino Pd-catalyzed C-N coupling/C-H activation sequence is one of most common and concise strategies to construct carbazole and related structures.[5,6] Possible substrates for the cyclization to construct the carbazole ring can be the reaction of dihalo(hetero)arene with anilines or the reaction of haloarenes with 2-haloanilines.[6] In the presence of a Pd catalyst, the first C-N coupling occurred at the more reactive carbon center. Subsequently, the following intramolecular C-H arylation step happened to form the carbazole ring. In 2007, Ackermann et. al. disclosed the first domino Pd-catalyzed cyclization of *o*-dichlorobenzenes with aniline derivatives which gave up to 81% yield of carbazole (Scheme 5). This method opened up an efficient and concise strategy to access carbazoles without the use of protecting groups.[21]

The initial synthetic strategy to approach α-carbolines was based on the intermolecular Ullmann coupling, followed by intramolecular S_NAr. The products could be obtained in good yields, but only in small scale reactions. The large scale reactions had several limitations, such as the use of expensive starting materials, very high temperature and the formation of homocoupling by-products. In an attempt to access carbolines, Sakamoto et al. reported the first chemo-selective Pd_2dba_3/dppf catalysed C-N coupling reaction of aryl iodides with *o*-bromoanilines with subsequent site-selective C-H activation annulation which was was performed by adding $Pd(OAc)_2$ as a second catalyst.[22] The groups of Maes[23] and Cuny[24] independently applied this method in the synthesis of α-carboline derivatives from aniline and 2,3-dichloropyridines. While Maes et al. had to use two separate reactions (Scheme 6), Cuny used a one-pot, two step reaction with ligands varying from PPh_3 to $PCy_3{\cdot}HBF_4$ (Scheme 6). In fact, in the C-H arylation step, both groups observed that employment of DBU as a base was required for the hydrodehalogenation step under high temperature. Carbolines with different N-substituents were obtained in moderate to good yield. In a similar approach, Mineno and coworkers[25] successfully synthesized α-carbolines from 2-amino-3-bromopyridines and substituted iodobenzenes. The process also went through a two step reaction: N-arylation catalyzed by

$Pd(OAc)_2$/XantPhos and subsequent C-H activation catalyzed by $Pd(OAc)_2$/DCHPB at 130°C. Both protocols had to use different catalysts for each step. A year later, Mineno and Mizufune[26] applied their method to synthesize Aurora B, a potent kinase inhibitor and candidate for cancer therapy. In fact, recent synthetic methods based on domino Pd catalyzed C-N coupling and intramolecular C-H arylation provided high overall yields of carbolines under mild conditions. The $Pd(OAc)_2$ catalyst accompanyed by PCy_3 as ligand was proven to be the most suitable catalyst for this type of reaction.



Scheme 5. Two general methods in the synthesis of carbazoles via domino Pd-catalyzed C-N coupling and C-H activation.

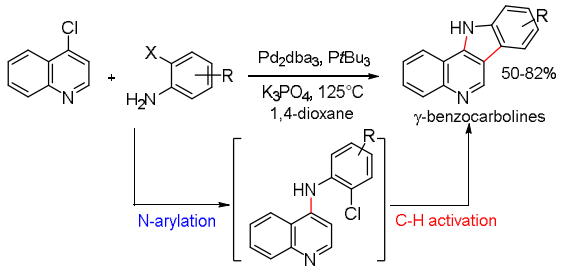


Scheme 6. Two general methods in the synthesis of α-carbolines *via* domino Pd-catalyzed C-N coupling and C-H activation.

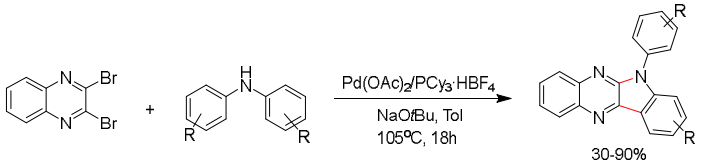
In 2008, Maes disclosed the synthesis of the isocryptolepine (an antiplasmodial natural product) and its derivatives.[27] The one-pot C-N coupling of electron-deficient 4-chloroquinoline with 2-chloroanilines followed by intramolecular C-H activation was catalyzed by Pd_2dba_3/P*t*Bu_3 at carried out at 125 °C and afforded γ-benzocarbolines in 50-82% yield.[27] The desired products were then obtained after methylation reaction (Scheme 7).

More recently, Langer's group[28] attempted to apply Ackermann's procedure in the synthesis of indolo[2,3-b]quinoxalines by one-pot Pd-catalyzed reaction of 2,3-dibromoquinoxaline with secondary

amines. Despite the good yield, the scope was limited and sterically hindered amines could not be used (Scheme 8).

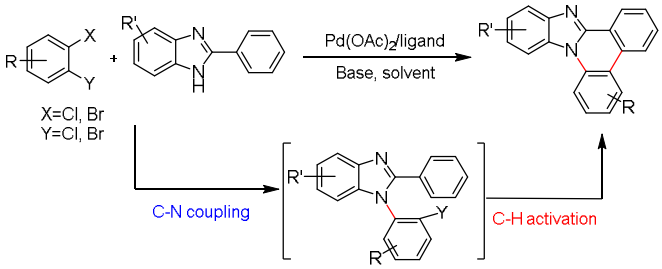


Scheme 7. Synthesis of γ-benzocarbolines *via* domino Pd-catalyzed C-N coupling and C-H activation.



Scheme 8. Synthesis of indolo[2,3-b]quinoxalines *via* domino Pd-catalyzed C-N coupling and C-H activation.

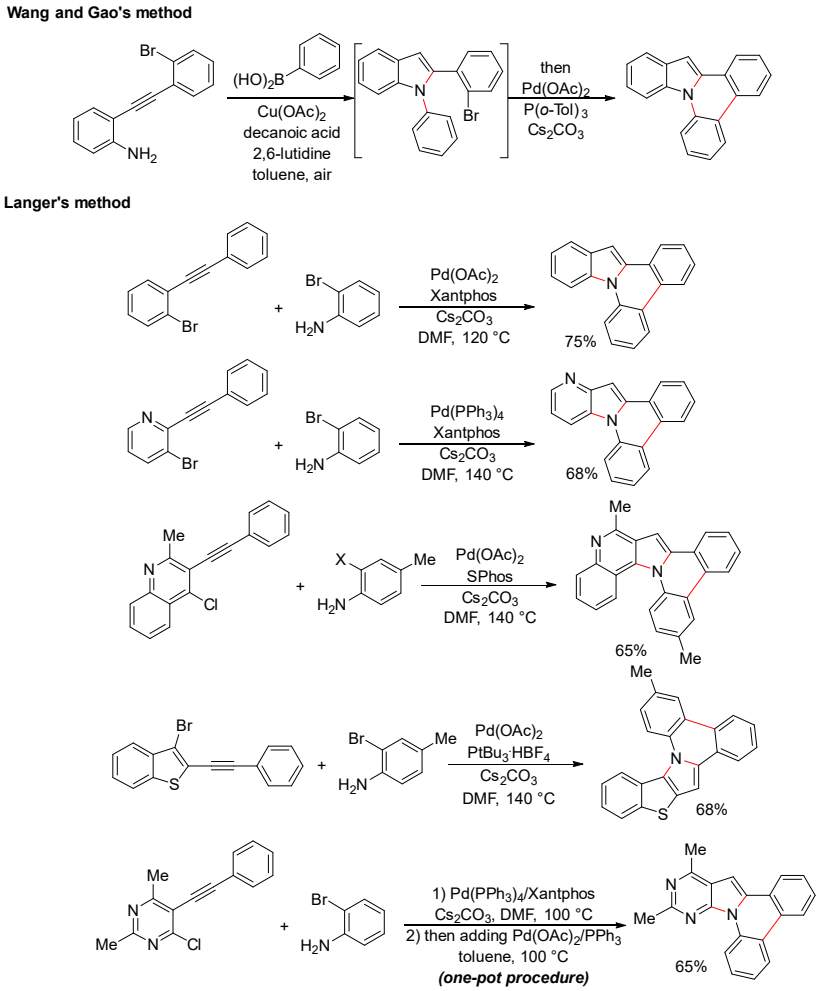
The domino intramolecular N-arylation of benzimidazole with dihaloarenes, followed by cyclization by C-H arylation, was found to be a common method to construct benzimidazole-fused phenanthridines. However, the order of the reaction steps is unclear until now. Such molecules are present in lumiphores in organic ligh-emitting diodes with very interesting physical properties, including blue-emitting performance, high quantum yields, long fluorescence lifetimes and thermal stability.[1] In a similar approach, Liu and Zhou[29] successfully applied this strategy in one-pot, two step reactions under different conditions in each steps: (1) $Pd(OAc)_2$, PPh_3, NaO*t*Bu (for C-N coupling step); (2) $Pd(OAc)_2$, $PCy_3{\cdot}HBF_4$, DBU (for C-H activation step). In the same year, You[30] reported efficient chemo- and site-seletive Pd-catalyzed coupling reactions of (benzo)imidazoles, indoles, and pyrroles with various substituted dihalo(hetero)arenes to form phenantridine derivatives. The products were obtained in good yields *via* one pot reaction in which were employed $Pd(PPh_3)_4$/Xantphos as catalyst and Cs_2CO_3 as base at 140°C. One year later, Chen and Peng[31] also applied this strategy to construct phenantridine derivatives under modified conditions using $Pd(OAc)_2$/XPhos or DPEPhos as catalyst, K_2CO_3 as base at 160 °C (Scheme 9).



Scheme 9. Phenanthridine synthesis *via* domino Pd-catalyzed C-N coupling and C-H activation.

Relying on the success of the domino Pd-catalyzed C-N coupling/hydroamination reaction with different heterocycles, Wang and Xin published the synthesis of indolophenanthridines *via* one-pot domino Chan-Lam C-N coupling/hydroamination, followed by an intramolecular C-H arylation (Scheme 10).[32] One

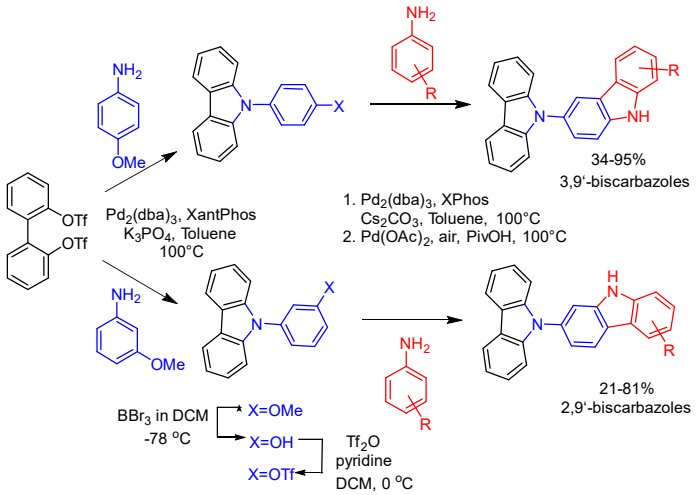
year later, Langer published another improved protocol for the synthesis of indolophenanthridines, in which C-N coupling, hydroamination and C-H arylation steps proceeded in a one-pot domino fashion (Scheme 10).[33] Langer's strategy proved to be highly efficient for the access of highly substituted phenanthridine-fused heterocycles. Applying this method, several fused N-heterocycles, such as azaindolephenanthridines, quinolophenanthridines, benzothienophenanthridines and pyrimidophenanthridines, were successfully prepared (Scheme 10).[34]



Scheme 10. Domino Pd-catalyzed C-N coupling/hydroamination/C-H arylation of *ortho*-halo(arylethynyl)-arenes and ortho-haloaniline derivatives.

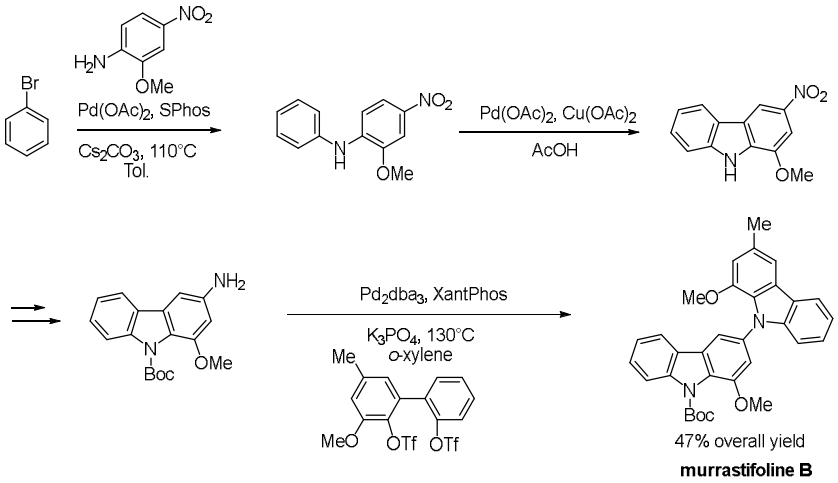
An alternative strategy relies on domino C-N coupling / oxidative C-H activation reactions which have some advantages in comparison with above mentioned strategies.[6] The use of inexpensive, less toxic, more stable starting materials make the processes more practical and environmentally friendly. Oxygen or air are often used as 'green' reagents in the oxidative C-H activation step. The most challenging problems for the oxidative C-H activation were identified to be reactivity and selectivity factors. In 2014, Langer and co-worker successfully applied this strategy as the key step to construct biscarbazoles (Scheme 11).[35] The

synthetic pathway includes several steps: a double Pd-catalyzed C-N coupling of biaryl bistriflates with anisidines forming the carbazole ring, subsequent transformation of the methoxy to a triflate group, and domino Pd-catalyzed N-arylation/oxidative C-H activation of the aryl triflate with aniline derivatives to give the desired 3,9′- and 2,9′- biscarbazoles.[35] As catalysts Pd_2dba_3/XantPhos and $Pd(OAc)_2$/Xphos were employed for each step, respectively. In contrast, $Pd(OAc)_2$ in combination with pivalic acid (an assisting ligand) was employed in the final oxidative C-H activation step. The products were obtained in moderate to good yields and the site selectivity was excellent for all reactions.



Scheme 11. Synthesis of biscarbazoles via the domino Pd-catalyzed C-N coupling/oxidative C-H activation method.

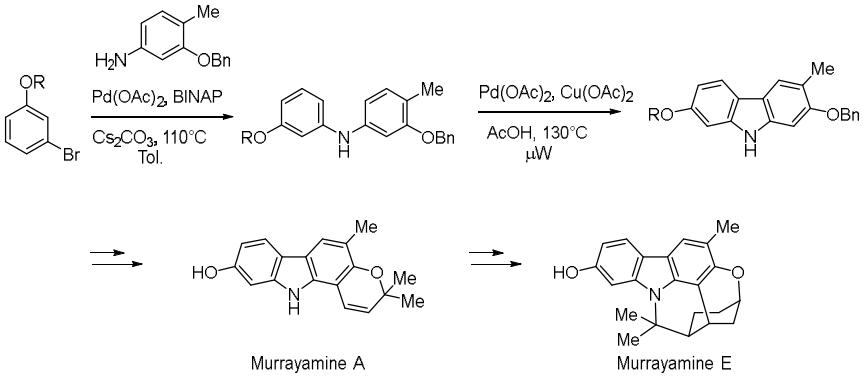
Chida and co-worker[36] reported the total synthesis of Murrastifoline A by parallel synthesis of two units, then combining them by double Pd_2dba_3/CyJohnPhos catalyzed C-N coupling of an aniline derivative with 2,2'-dibromobiaryl. In a similar approach, Knölker[37] et al. disclosed an interesting total synthesis of biscarbazole alkaloid Murrastifoline B (Scheme 12).



Scheme 12. Total synthesis of Murrastifoline B.

The Pd catalyzed oxidative C-H activation cyclization was used to form the carbazole moiety. $Cu(OAc)_2$ was used as the oxidant in this oxidative C-H activation step. Then, the conversion of the nitro group to an amine, subsequent double C-N coupling with a biaryl bistriflate furnished Murrastifoline B in 47% overall yield *via* five steps (Scheme 12).

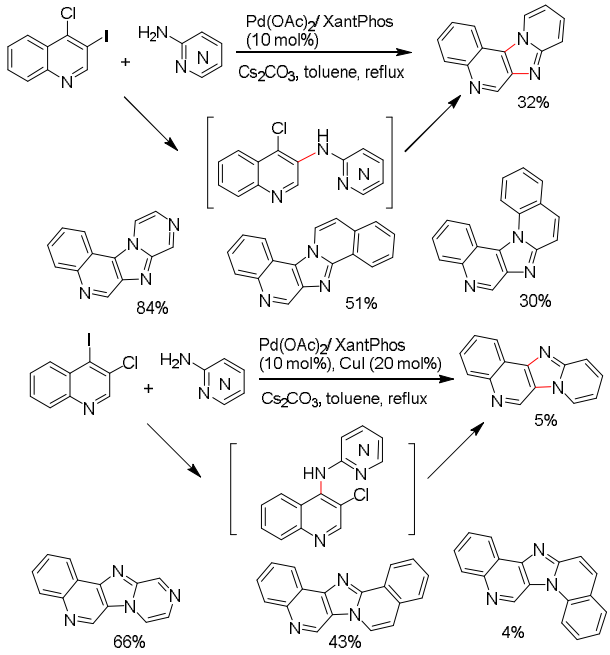
One year later, Knölker and co-worker[38] applied this strategy for the total synthesis of pyranocarbazole alkaloids including Murrayamine E, I, and K which were isolated from *Murraya and Clausena* plants. Murrayamine E, I, K were obtained *via* five to six steps (Scheme 13).



Scheme 13. Total synthesis of Murrayamine A and E.

4. Synthesis of fused N-heterocycles based on domino double Pd-catalyzed C-N coupling reactions

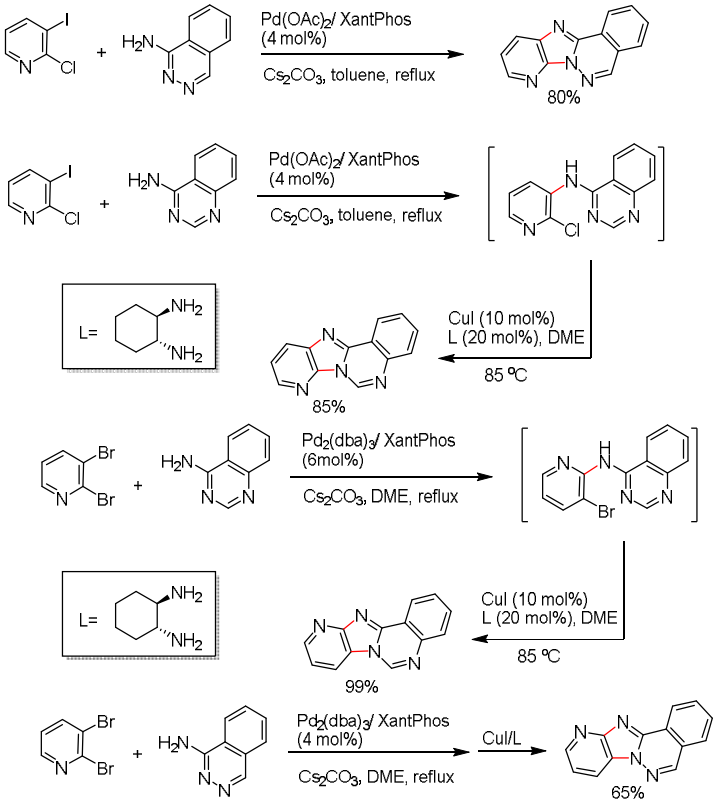
Domino double Pd-catalyzed C-N coupling cyclizations of 2-aminopyridine and its derivatives with 1,2-dihaloarenes provide practical approaches to fused N-heterocycles containing an imidazole moiety.[6] Boganyi et al. reported an interesting method for the synthesis of fused N-heterocycles (Scheme 14).[39]



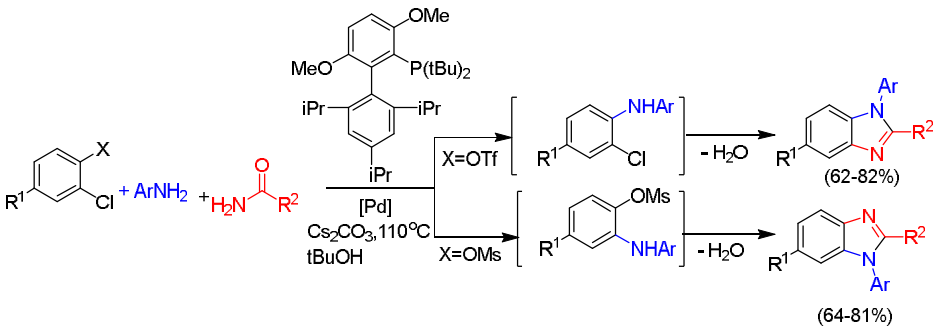
Scheme 14. Pd-catalyzed synthesis of tetra- and pentacyclic fused N-heterocycles.

The one-pot Pd-catalyzed C-N coupling cyclizations of 2-aminopyridines, 2-aminoquinolines, 1-aminoisoquinolines with 4-chloro-3-iodoquinoline gave quinolone-fused N-heterocycles in 30-84% yield. Further development on domino Pd-catalyzed C-N coupling cyclizations of 2-aminopyridines, 2-aminoquinolines, 1-aminoisoquinolines with 3-chloro-4-iodoquinoline also afforded the desired quinolone-fused N-heterocycles, albeit, in lower yield (5-66%) (Scheme 14). In this case, CuI (20 mol%) was used as cocatalyst in combination with $Pd(OAc)_2$/XantPhos as the catalyst to give the corresponding cyclized products.[39]

In a similar approach, Maes et al. disclosed the Pd-catalyzed synthesis of tetracyclic fused N-heterocycles based on the cyclization of 2,3-dihalopyridines with aminobenzodiazines (Scheme 15).[40] Interestingly, fused N-heterocycles were successfully formed with employment of only one $Pd(OAc)_2$/XantPhos catalyst. Under the same conditions, the Pd-catalyzed C-N coupling of 2,3-dihalopyridines with other aminobenzodiazine derivatives gave the corresponding C-N coupling intermediates. The cyclized products were only formed in the presence of a second CuI catalyst. Notably, the site-selectivity of the cyclizations of dihalopyridines with aminobenzodiazines was successfully controlled.[40] Recently, Buchwald et al. reported a regio- and chemoselective Pd-catalyzed synthesis of N-arylbenzimidazoles involving a two-step C-N coupling reaction.[41] According to the preferential oxidative addition of the Pd catalyst to the Ar-X bond (OTf<Cl<OTs), the first C-N coupling reaction of the amine could be easily controlled (Scheme 16). Subsequently, the second C-N coupling of the primary amide occurred at the less reactive halogen atom, followed by cyclization to give the products. Based on site-selective Pd-catalyzed C-N coupling reactions, the two regioisomers of N-arylbenzimidazoles were successfully prepared.[41]



Scheme 15. Pd-catalyzed synthesis of tetracyclic fused N-heterocycles.



Scheme 16. Pd-catalyzed synthesis of highly substituted benzimidazoles.

5. Conclusions and perspectives

Based on recent developments in site-selective Pd-catalyzed coupling processes, many new fused aromatic N-heterocycles have been designed and synthesized. The growth of this field has opened new trends in the development of advanced organic materials, especially, of π-extended fused N-heterocycles. In addition, fused N-heterocycles have also found many important applications in medicinal chemistry. A series of natural alkaloids and bioactive N-heterocycles have been synthesized by site-selective Pd-catalyzed coupling reactions.

With this paper we like to give an updated summary on the synthesis of fused aromatic N-heterocycles by domino site-selective Pd-catalyzed C-C and C-N coupling reactions. In this context, some potential applications of new fused aromatic N-heterocycles in materials science and medicinal chemistry have been highlighted.

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