RECENT PROGRESS ON SYNTHESIS OF INDOLES THROUGH AMINOPALLADATION ENABLED CASCADE REACTION

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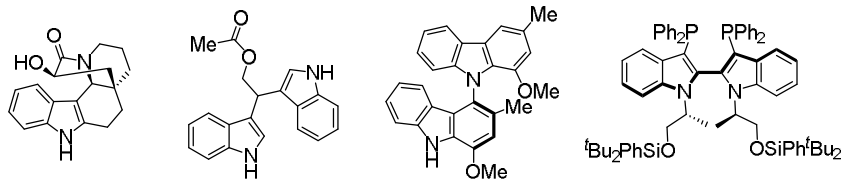
Abstract. *Indoles have emerged as prominent structural fragments in many biologically active molecules, natural products and agrochemicals. Therefore, development of efficient and concise methods for the construction of indoles is of great significance. In this review, the recent representative aminopalladation enabled cascade reactions for the synthesis of indoles from easily accessible 2-alkynylanilines are briefly summarized.*

Contents

1. Introduction

Indoles are not only privileged structural motifs in the natural products, agrochemicals and biologically active molecules, but also used as the ligands in organic synthesis (Scheme 1).[1-8] For example, indole alkaloid Kopsihainanine A was isolated from the leaves and stems of a Chinese medicinal plant, *Kopsia hainanensis*, and dispalys inhibitory activity against acetylcholine esterase (AChE) with IC_{50} values of 38.5 μM.[9] Streptindole, agenotoxic metabolite of human intestinal bacteria Streptococcusfaecium IB 37, exhibited DNA-damaging and genotoxic properties.[10] Murrastifoline F is an indole alkaloid isolated from the plant plant species *Murraya koenigii*.[11] Axially chiral biindole-based diphosphane showed excellent reactivity and enantioselectivity in the hydrogenation of β-ketoesters.[8] Consequently, the development of efficient and straightforward approaches to access indole derivatives from the readily available starting materials is highly desirable.



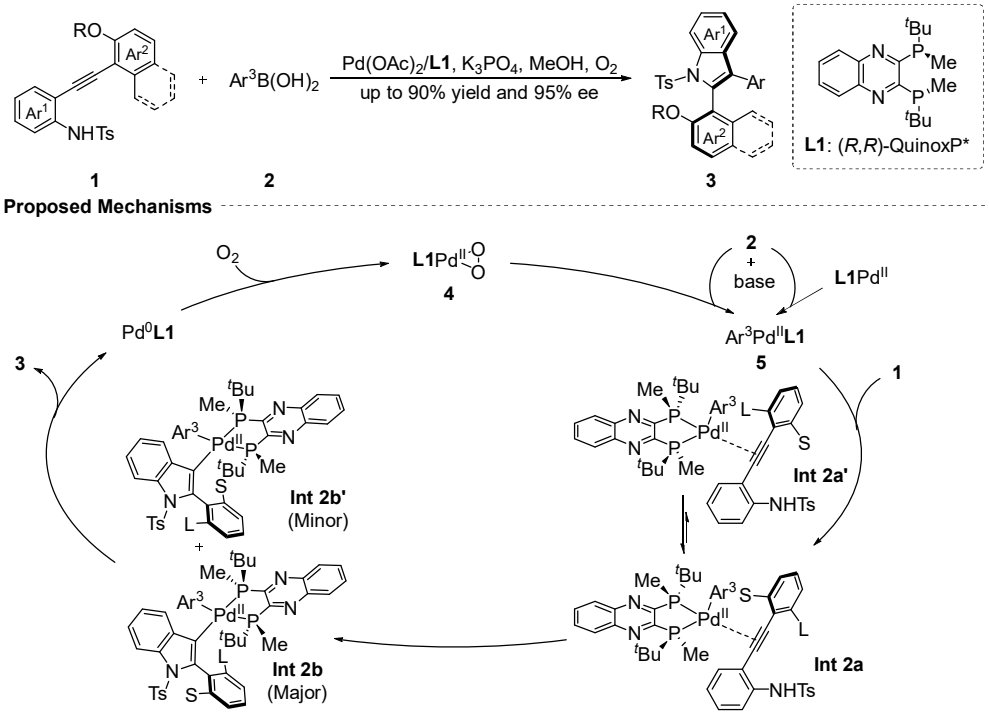
Scheme 1. Indole derivatives in natural products and chiral ligands.

2-Alkynylanilines are easily accessible building blocks *via* Sonogashira reaction of 2-aminoaryl halides and terminal alkynes.[12] The first synthesis of indoles through palladium-catalyzed cyclization of 2-alkynylanilides was described by Taylor and McKillop.[13] In 1992, Cacchi and co-workers documented aminopalladation/cross-coupling cascade reaction of 2-alkynylanilines with vinyl triflates and/or aryl halides.[14] Since then, this field has received considerable attention from the synthetic community, and a

variety of significant works have been reported.[15] Importantly, Kitagawa reported the first enantioselective synthesis of indoles possessing an N1-aryl chiral axis *via* palladium-catalyzed cyclization of 2-alkynylanilides, which was a milestone in the research field of asymmetric synthesis of atropisomeric indoles.[16] In this account, we summarize recent representative progresses made on the synthesis of indoles through aminopalladation enabled cascade reactions of 2-alkynylanilines and provide some insights into future developments.

2. Aminopalladation/arylation cascades

The axially chiral indole-based frameworks are often found in natural products, organic materials and privileged chiral ligands and catalysts. In 2020, Zhu and co-workers reported the first examples of a palladium catalyzed asymmetric Cacchi reaction of *N*-sulfonyl-2-alkynylanilides with aryl boronic acids in the presence of $Pd(OAc)_2$/(*R,R*)-QuinoxP* as the catalyst and oxygen as the oxidant, providing indoles **3** bearing a chiral C2-aryl axis with up to 90% yield and 95% ee (Scheme 2).[17] The control experiments disclosed that the initiation step should be the transmetallation of the palladium complex **4** with aryl boronic acid **2**. Moreover, the authors proposed that the axial chirality is generated by coordination of palladium complex **5** with C≡C bond of 2-alkynylanilides **1** and **Int 2a** should be more favored due to the minimized steric repulsion.

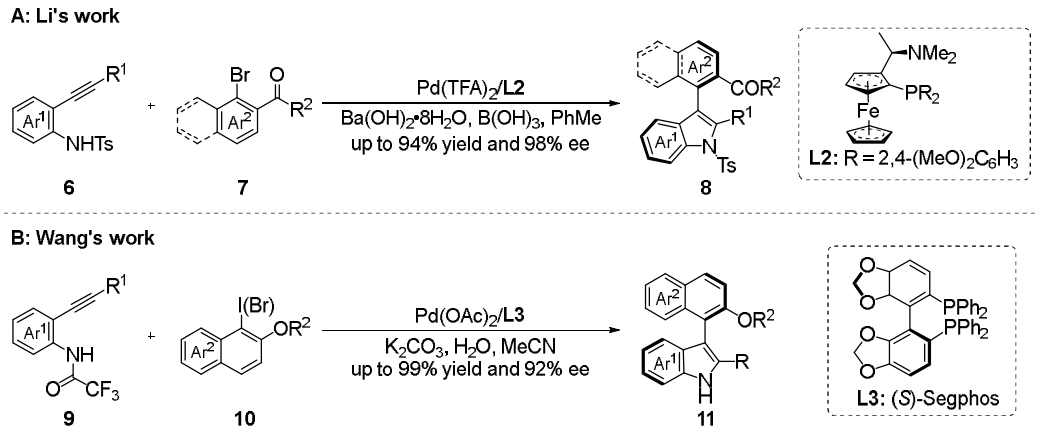


Scheme 2. Synthesis of axially chiral indoles bearing a chiral C2-aryl axis *via* palladium-catalyzed asymmetric Cacchi reaction of *N*-sulfonyl-2-alkynylanilides with aryl boronic acids.

Subsequently, a palladium-catalyzed enantioselective Cacchi reaction between 2-alkynylanilines **6** and aryl bromides **7** was developed by the Li group.[18] A variety of axially chiral 3-arylindoles **8** bearing a chiral C3-aryl axis were obtained in the high yields and excellent enantioselectivities. In this case, $Pd(TFA)_2$ as the palladium precursor, ferrocene-based N,P-ligand **L2** as the chiral ligand, and $Ba(OH)_2 \cdot 8H_2O$ as the base were used. It should be pointed out that the carbonyl group at *ortho*-position of aryl bromides **7** is the key to

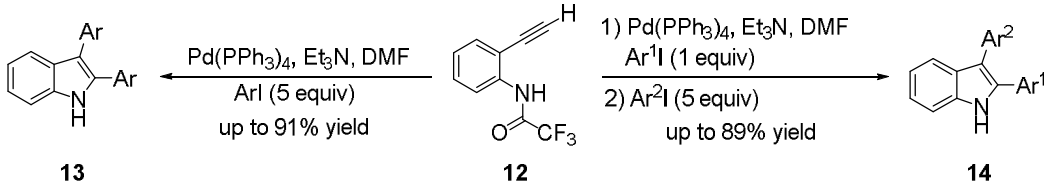
successful reaction because this substituent might be beneficial for the stereoselectivity control of the reaction (Scheme 3A).

At the same time, Wang and co-workers independently achieved an asymmetric Cacchi reaction of *N*-$COCF_3$-2-alkynylanilines **9** with sterically congested naphthyl halides **10** using $Pd(OAc)_2$/(S)-Segphos as the catalyst, affording axially chiral naphthyl-C3-indoles **11** bearing a free NH moiety in high yields and good to excellent enantioselectivities (Scheme 3B).[19] Moreover, this methodology was used for the construction of axially chiral 3-naphthylindole-based monophosphine.



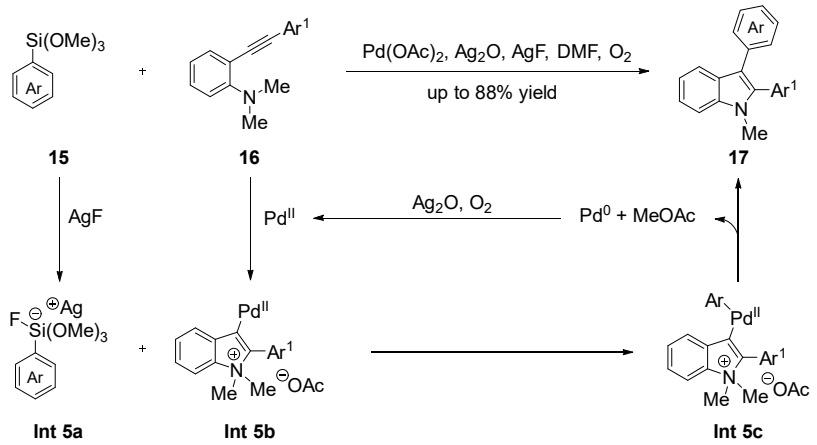
Scheme 3. Synthesis of axially chiral indoles bearing a chiral C3-aryl axis *via* palladium-catalyzed asymmetric Cacchi reaction of 2-alkynylanilides with aryl halides.

2,3-Diarylindoles are often found to exhibit excellent biological activity, including inhibition of tubulin polymerization, anti-inflammatory, bioluminescence properties and so on.[20] The Zhang group accomplished an efficient and concise one-pot protocol for the construction of 2,3-diarylindoles **13** *via* Sonogashira reaction/aminopalladation/arylation cascade reaction of 2-ethynylanilines **12** with aryl iodides (Scheme 4).[21] Interestingly, controlling the amount of aryl iodides in the first step Sonogashira reaction allowed the synthesis of 2,3-diarylindoles **14** with two different aryl groups at 2- and 3-positions.



Scheme 4. Synthesis of 2,3-diarylindoles *via* Sonogashira reaction/aminopalladation/arylation cascade reaction of 2-ethynylanilines with aryl iodides.

Organosilanes are stable and easily prepared compounds with low toxicity and widely employed in cross-coupling reactions.[22] The Lee group reported an elegant approach to 2,3-diaryl-*N*-methylindoles **17** through arylated cyclization of arylsiloxanes **15** and *N,N*-dimethyl-2-alkynylanilines **16** (Scheme 5).[23] This protocol exhibits wide substrate scope and good functional group tolerance. Based on mechanism studies and literature reports, a possible reaction pathway was proposed. Activation of arylsiloxanes **15** with silver fluoride generates intermediate **Int 5a**, and 2-alkynylanilines **16** undergo aminopalladation to form intermediate **Int 5b**. Transmetallation of intermediate **Int 4a** with intermediate **Int 5b** undergoes reductive elimination to afford the desired 2,3-diaryl-*N*-methylindoles **17**.



Scheme 5. Synthesis of 2,3-diaryl-*N*-methylindoles *via* aminopalladation/arylation cascade reaction of 2-alkynylanilides with arylsiloxanes.

Bisindoles are privileged structural units in natural products, biologically active molecules semiconductors and organic light-emitting diodes (OLEDs). Recently, Zheng and co-workers reported an efficient palladium-catalyzed cross-coupling of 2-alkynylanilines **18** and *o*-(2,2-dibromovinyl)anilines **19** for the synthesis of various 2,3'-bisindoles **20** (Scheme 6A).[24] This strategy was further extended to the construction of linked bis-heteroaromatic ring **23** by the Lautens group using phenylacetylenes **21** containing nucleophile at *ortho*-position (Scheme 6B).[25] In this case, the photoluminescence properties of these bis-heteroaromatic ring **23** were investigated, yielding abroad range of emissions from around 400 to 530 nm, with quantum yields up to 0.59. The control experiments revealed that the bromoalkyne **24** is a competent intermediate in this transformation, and density functional theory (DFT) calculation suggested that the pathway involving initial oxidative addition into the cis C−Br bond of the *o*-(2,2-dibromovinyl)aniline **22a** is favored unless *o*-(2,2-dibromovinyl)aniline **22a** irreversibly transforms into the bromoalkyne **24**.

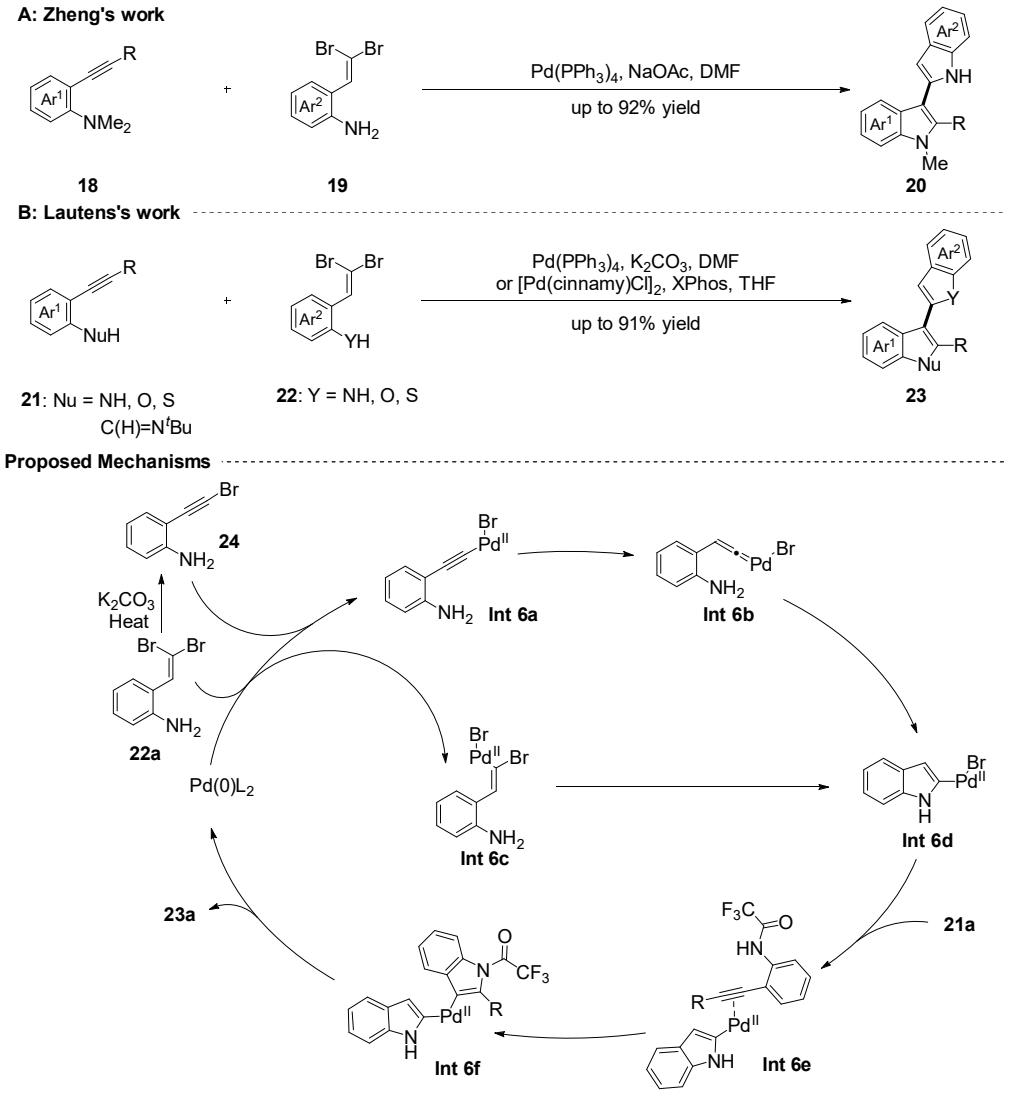
Polycyclic heteroaromatics (PHA) are the core framework of many valuable compounds with a diverse range of applications, including bioactive molecules, organic light-emitting diodes (OLEDs), organic field-effect transistors (OFETs) and organic photovoltaics (OPVs).[26] In 2021, Jin and coworkers realized an intramolecular aminopalladation/*peri*-C−H annulation/*N*-dealkylation cascade reaction of *N,N*-dialkyl- substituted 2-alkynylanilines **25** for the construction of cyclopenta-fused acenaphtho[1,2-*b*]indoles **26** (Scheme 7).[27] The experiment of kinetic isotope effect hinted that the *peri*-C−H bond activation should not be the rate-determining step. Additionally, investigations of the UV-vis absorption and electrochemical properties of these cyclopenta-fused acenaphtho[1,2-*b*]indoles and density functional theory (DFT) calculations implied their potential applications as π-segments in low-band-gap materials.

Recently, an efficient construction of polycyclic heteroaromatics was achieved through a palladium-catalyzed cascade decarboxylative cyclization of 2-alkynylanilines **27** and 2-bromobenzoic acids **28** (Scheme 8).[28] This protocol could be applied to a broad range of 2-alkynylanilines and 2-bromobenzoic acids to furnish dibenzo[*a,c*]carbazole **29** in moderate to good yields. The authors proposed that the key intermediate **Int 8b** was generated *via* aminopalladation, C−H activation and dealkylation. Additionally, the value of kinetic isotope effect of C−H activation is 1.18, suggesting C−H activation is not should not be the rate-determining step. It is worth noting that this protocol is suitable for the 8-bromo-1-naphthoic acid **30**, and multiple arene-fused cyclohepta[1,2-b]indoles **31** were isolated in the moderate yields.

3. Aminopalladation/alkenylation cascades

Indole-*C*-glycosides, as a privileged class of *C*-aryl glycosides, widely exist in various biologically active compounds, natural products and drug candidates.[29] For example, α-*C*-mannosyltryptophan is the first

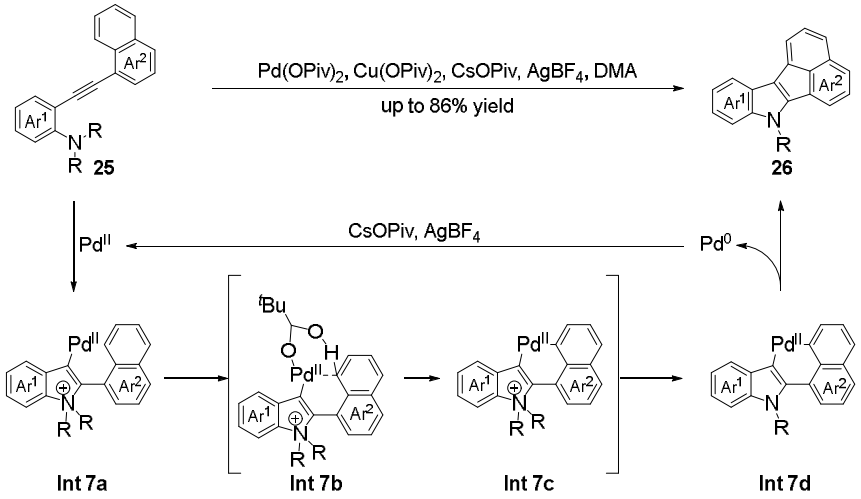
naturally occurring *C*-glycosyl amino acid found in protein.[29a] In 2020, a general and efficient approach for the construction of 3-indolyl-*C*-glycosides **34** *via* an aminopalladation/*C*-glycosylation cascade reaction of 2-alkynylanilines **32** and 1-iodoglycals **33** was developed by the Sun group (Scheme 9).[30] By investigating the reaction conditions, it was found that the R group of alkynylanilines **32** is critical for this transformation. When the R group was H, Bn, Ac or Bz group, the reaction failed to give the desired product. The transformation proceeded smoothly using $C(O)CF_3$ and Ts as R group. This protocol features broad range of substrates good functional group compatibility and scalability.



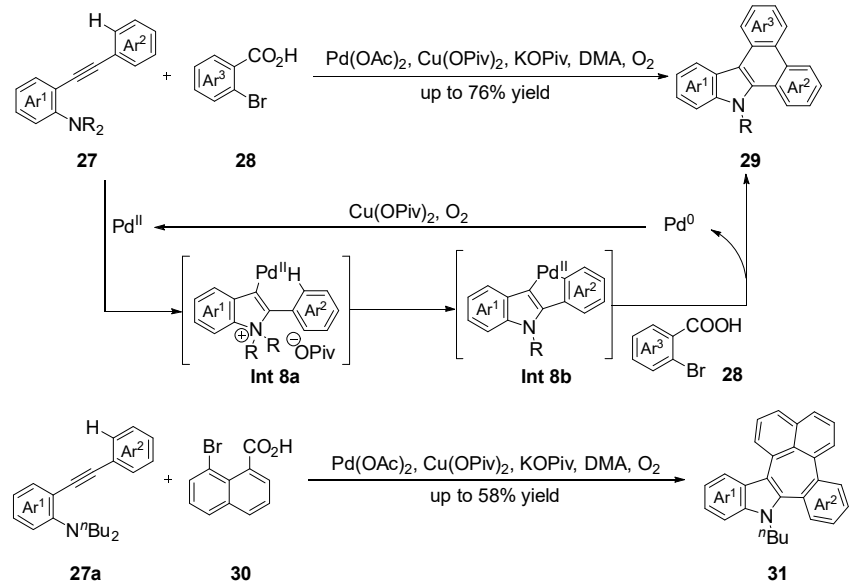
Scheme 6. Synthesis of bisindoles *via* palladium-catalyzed cross-coupling of 2-alkynylanilines and *o*-(2,2-dibromovinyl)anilines.

Apart from oxidative addition of palladium (0) and vinyl (*pseudo*)halides, the *syn*-carbopalladation of alkynes is also an efficient and direct approach for the synthesis of vinyl-Pd^{II} intermediates, which have been

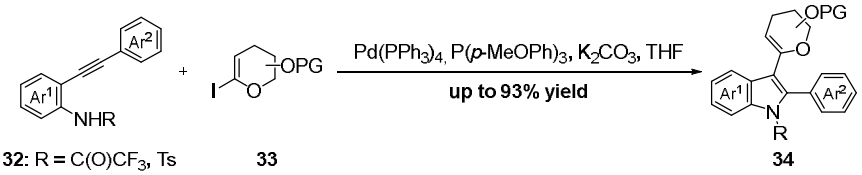
harnessed in various alkenylations.[31] Utilizing this strategy to generate vinyl-Pd^{II} intermediate **Int 10a**, the Lauterns group realized a palladium-catalyzed cascade cyclization of alkyne-tethered carbamoyl chlorides **35** with 2-alkynylanilines **36** (Scheme 10).[32] A series of 3-((1*H*-indol-3-yl)methylene)indolin-2-ones **37** were delivered in up to 96% yield and excellent stereoselectivities (*E*/*Z* >20:1). Notably, the presence of *N*-Ts group for the 2-alkynylanilines was a critical factor to the success of the stereoselectivity control. Transformation afforded the poor stereoselectivity in the absence of an *N*-Ts group. The authors carried out a series of control experiments to further understand the reaction mechanism, and they concluded that the intramolecular *syn*-carbopalladation of alkyne-tethered carbamoyl chlorides followed by palladium(II)-catalyzed cyclization of 2-alkynylanilines.



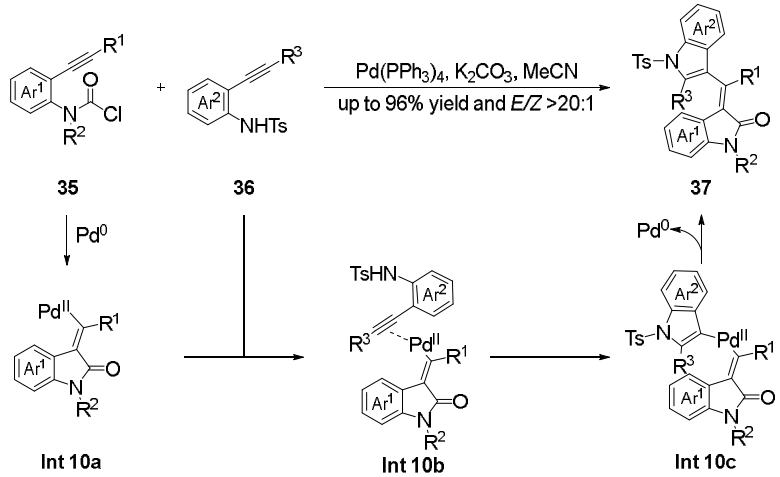
Scheme 7. Synthesis of cyclopenta-fused acenaphtho[1,2-*b*]indoles *via* aminopalladation/*peri*-C−H annulation/*N*-dealkylation cascade reaction of *N,N*-dialkyl-substituted 2-alkynylanilines.



Scheme 8. Synthesis of polycyclic heteroarenes *via* aminopalladation enabled cascade reaction.



Scheme 9. Synthesis of 3-indolyl-*C*-glycosides *via* aminopalladation/*C*-glycosylation cascade reaction. of 2-alkynylanilines and 1-iodoglycals.

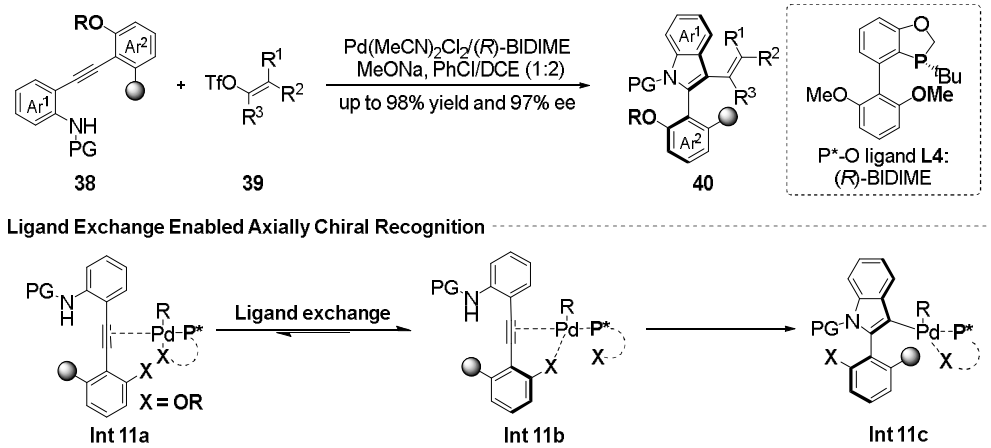


Scheme 10. Synthesis of 3-((1*H*-indol-3-yl)methylene)indolin-2-ones *via* palladium-catalyzed cascade cyclization of alkyne-tethered carbamoyl chlorides with 2-alkynylanilines

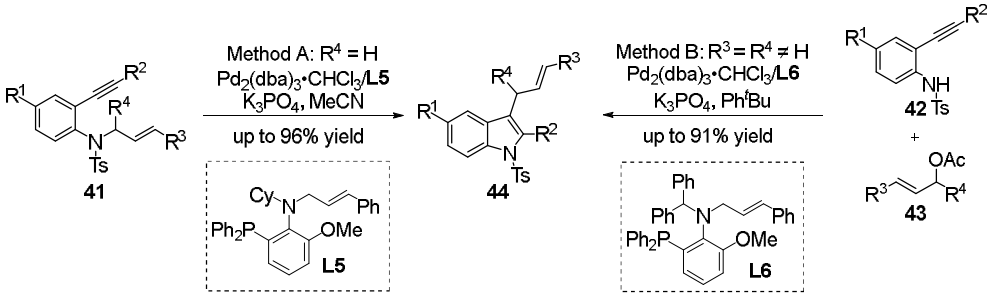
Development of a general and efficient strategy to realize stereoselective recognition for the construction of optically active molecules has been a central topic in asymmetric catalysis. Very recently, our group documented an efficient *O*-ligand exchange between catalyst and substrate enabled axial chiral recognition in asymmetric aminopalladation/olefination of 2-alkynylanilides **38** and vinyl triflate **39** using (*R*)-BIDIME/Pd(MeCN)$_2$Cl$_2$ as the catalyst, affording a series of axially chiral 3-alkenylindoles **40** in good to excellent yields and excellent enantioselectivities (Scheme 11).[33] This protocol features excellent functional group tolerance, late-stage modification of bioactive molecules and scalability. However, 1-arylvinyl triflates were not good reaction partners, and moderate yields and enantioselectivities were observed. Moreover, Experimental and computational studies confirmed that *O*-ligand exchange between (*R*)-BIDIME/Pd complex and alkoxy group of 2-alkynylanilides on the intermediate **Int 11a** was crucial to the success of stereoselectivity control.

4. Aminopalladation/allylation cascades

Palladium-catalyzed allylation is a rapid and practical approach for the construction of Csp^2-Csp^3 bond. In 2022, Mino and co-workers established an efficient assembly of 3-allylindoles **44** through aminopalladation/allylation cascade reaction (Scheme 12).[34] The transformation of *N*-cinnamyl-2-(phenylethynyl)-*N*-tosylanilines **41** proceeded smoothly to furnish the corresponding 3-allylindoles **44** with up to 96% yield when the P,olefin ligand **L5** was employed. To gain insights into the mechanism, the authors performed density functional theory (DFT) calculations, which disclosed that the olefinic moiety in **L5** plays a key role in the promotion of ligand exchange due to its flexible coordination mode. Additionally, an intermolecular one-pot reaction of 2-alkynylanilides **42** and allyl esters **43** was achieved for the synthesis of 3-allylindoles **44** in the presence of P,olefin ligand **L6** and *tert*-butylbenzene as the solvent.



Scheme 11. Synthesis of axially chiral 3-alkenylindoles *via* asymmetric aminopalladation/olefination of 2-alkynylanilides and vinyl triflates.



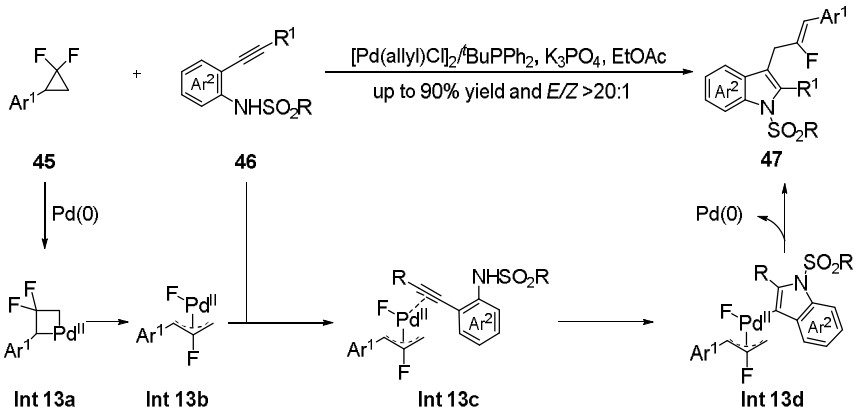
Scheme 12. Synthesis of 3-allylindoles *via* aminopalladation/allylation cascade reaction.

gem-Difluorinated cyclopropanes are ideal and alternative allylic precursors through metal-catalyzed C−C/C−F cleavage.[35] The Li' group developed the construction of 3-allyl indoles by merging ring opening of *gem*-difluorinated cyclopropanes **45** with aminopalladation of 2-alkynylanilines **46** (Scheme 13).[36] Under the conditions of $[Pd(allyl)Cl]_2$/^{t}BuPPh$_2$ as the catalyst, and K_3PO_4 as the base, the reaction provided 3-allyl indoles **47** with up to 90% yield and good to excellent stereoselectivity. On the basis of mechanism studies, a plausible catalytic cycle for this transformation was proposed. Oxidative insertion of Pd(0) with *gem*-difluorinated cyclopropanes **45** generates four-membered cyclopalladium intermediate **Int 13a**, which undergoes β-fluoro elimination to form 2-fluorinated π-allylpalladium **Int 13b**. Coordination of 2-fluorinated π-allylpalladium **Int 13b** with C≡C bond of 2-alkynylanilines **46** undergoes aminopalladation and regioselective reductive elimination to produce the corresponding product 3-allyl indoles **47**.

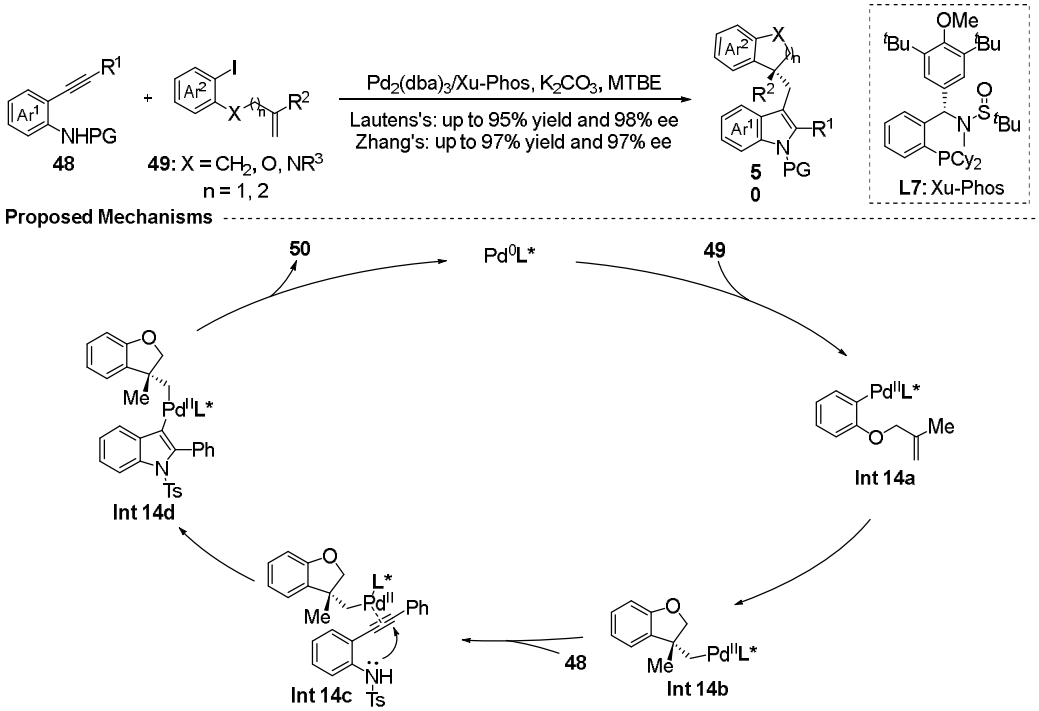
5. Aminopalladation/alkylation cascades

Although the highly active and stabilized arylpalladium vinylpalladium and allylpalladium species, as versatile synthetic intermediates, have been widely utilized in the transformations of 2-alkynylanilides to construct 2,3-disubstituted indoles, alkylpalladium species was rarely involved because their inherent instability could easily lead to β-hydride elimination. In 2018, utilizing *in situ* generation of alkylpalladium species, Yao and Lin documented aminopalladation/alkylation cascade reaction of 2-alkynylanilines and alkene-tethered aryl halogens.[37] Inspired by this work, the Lautens and Zhang groups almost simultaneously accomplished the asymmetric version of the reaction between 2-alkynylanilines **48** and alkene-tethered aryl halogens **49** using $Pd_2(dba)_3$/Xu-Phos as the catalyst, affording 3-alkyl-substituted indoles **50** in moderate to

good yields and excellent enantioselectivities (Scheme 14).[38,39] Mechanistically, oxidative addition and insertion of C=C bond form the alkylpalladium(II) intermediate **Int 14b**, which undergoes C≡C bond coordination, aminopalladation and reductive elimination to deliver the desired product.



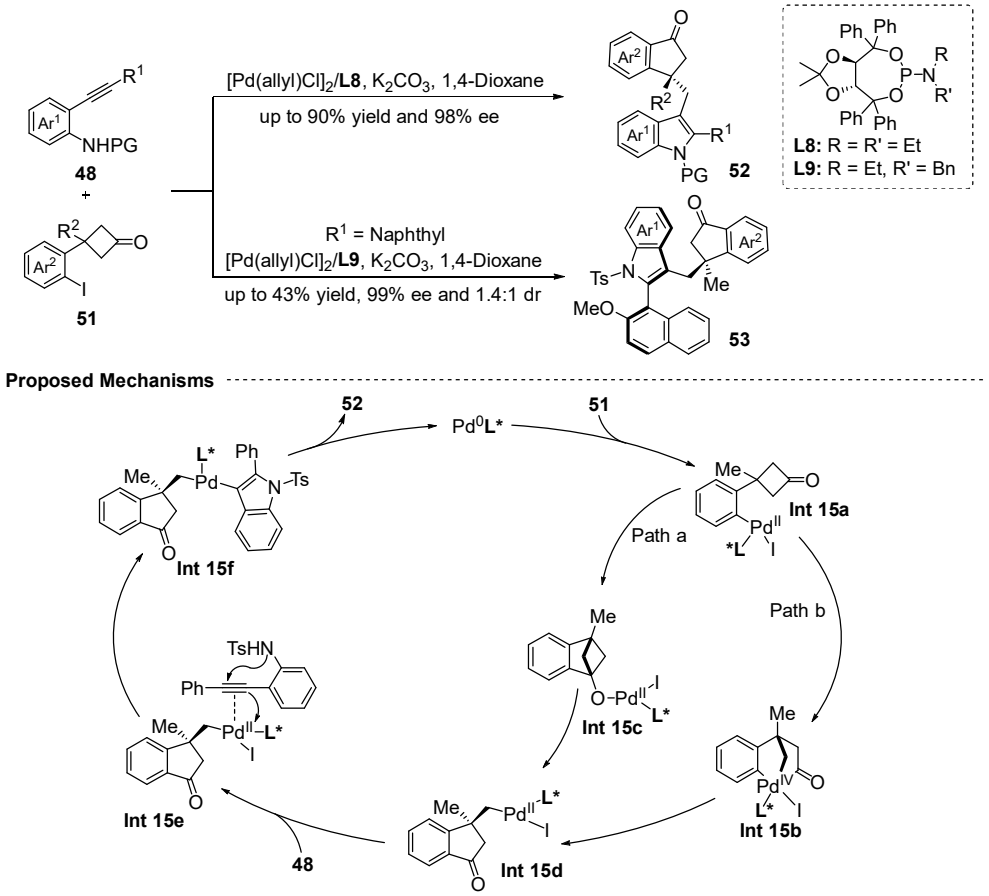
Scheme 13. Synthesis of 3-allyl indoles *via* aminopalladation/allylation cascade reaction of 2-alkynylanilines and *gem*-difluorinated cyclopropanes.



Scheme 14. Enantioselective synthesis of 3-alkylindoles *via* Heck reaction/Cacchi reaction cascade.

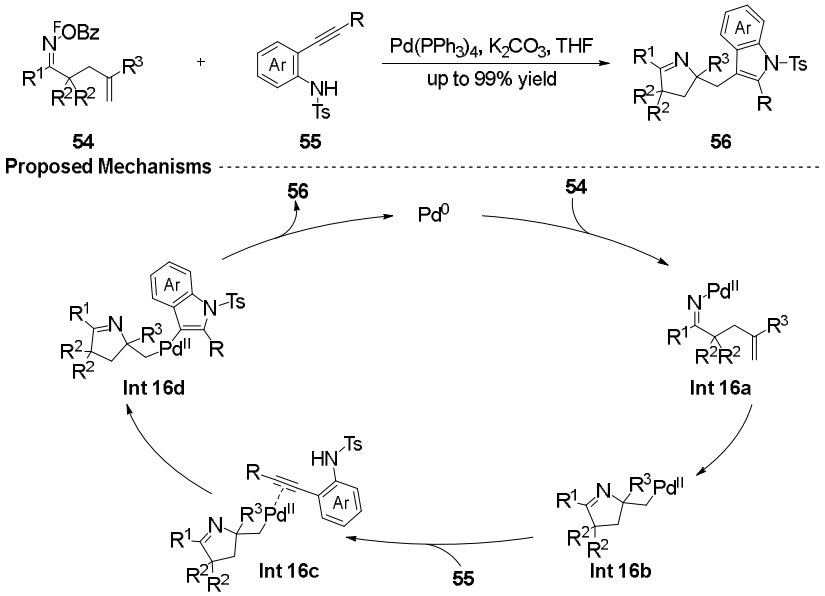
Utilizing the same strategy, the Xu group achieved a palladium-catalyzed asymmetric tandem C−C bond activation/Cacchi reaction of 2-alkynylanilines **48** with cyclobutanone-tethered aryl halogens **51**, affording indanone-substituted indoles **52** bearing an all-carbon quaternary stereocenter in good yields and

excellent enantioselectivities (Scheme 15).[40] Interestingly, this methodology was suitable for the construction of indanone-substituted indoles **53** with both central and axial stereogenic elements albeit with lower dr value. Based on mechanism studies and their previous reports, the authors proposed two possible reaction pathways for the formation of alkylpalladium species **Int 15d**. In pathway a, the intermediate **Int 15a** undergoes insertion of carbonyl group and β-carbon elimination to deliver alkylpalladium species **Int 15d**. Pathway b involves oxidative addition of cyclobutanone and reductive elimination.



Scheme 15. Enantioselective synthesis of 3-alkylindoles *via* tandem C−C bond activation/Cacchi reaction.

Additionally, Narasaka-Heck cyclization is an efficient and alternative approach for the generation of alkylpalladium species. The Lautens group accomplished the construction of 3-alkylindoles by merging Narasaka-Heck cyclization of alkene-tethered oxime esters **54** with cyclization of 2-alkynylanilines **55** (Scheme 16).[41] In the presence of $Pd(PPh_3)_4$ and K_2CO_3, the transformation proceeded smoothly to deliver the 3-alkyl indoles **56** with yields up to 99%. Deuterium labeling study elucidated that the process for the formation of alkylpalladium species is a two-electron migratory insertion. Based on mechanism studies and previous reports, the following mechanistic scenario is proposed. The reaction starts with oxidative addition of the oxime ester **54** with Pd(0) to generate the imino-Pd(II) species **Int 16a**, which undergoes a migratory insertion to form alkylpalladium species **Int 16b**. Coordination of alkylpalladium species **Int 16b** with C≡C bond of 2-alkynylanilines **55** is followed by aminopalladation and reductive elimination to give the desired product **56**.



Scheme 16. Synthesis of 3-alkylindoles *via* Narasaka-Heck cyclization/Cacchi reaction cascade.

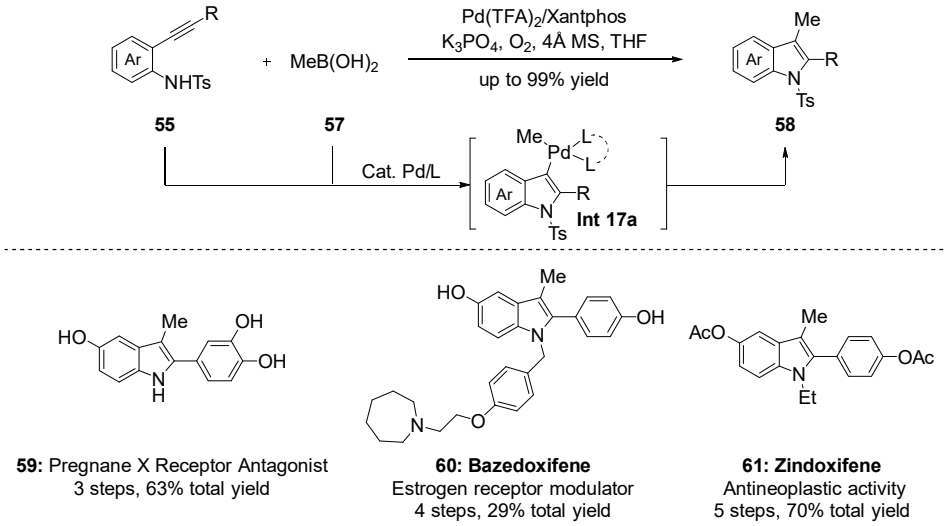
In medicinal chemistry, numerous studies have found that introducing a single methyl group to a drug candidate could significantly improve the biological activity and pharmacokinetic profile, which is described as the "magic methyl" effect.[42] Therefore, developing efficient and general methylations has received considerable attention from the synthetic community. Recently, our group successfully developed an aminopalladation/methylation cascade reaction of 2-alkynylanilines **55** with methylboronic acid **57** using $Pd(TFA)_2$/Xantphos as the catalyst, K_3PO_4 as the base and O_2 as the oxidant, providing 3-methylindoles **58** in moderate to excellent yields (Scheme 17).[43] It is worth noting that this methodology was employed as the key step for synthesis of a pregnane X receptor antagonist **59**, bazedoxifene **60** and zindoxifene **61**. Furthermore, this protocol is also suitable for the synthesis of 3-methylbenzofurans and 4-methylisoquinolines.

6. Aminopalladation/C=X (X=C, O) and C≡N bonds insertion cascades

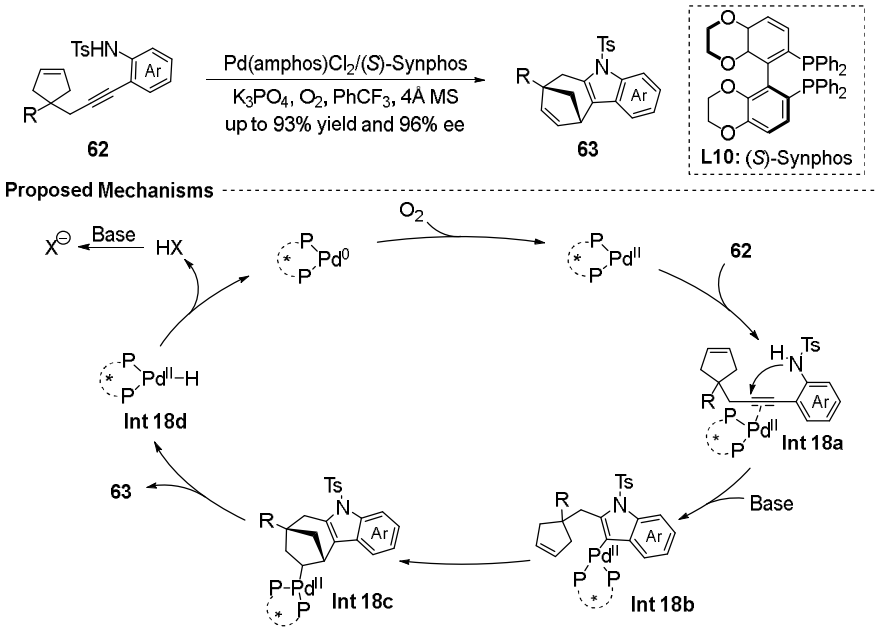
Indole-fused bicyclo[3.2.1]octane as core structure is often found in natural products and biologically active compounds, such as Stryvomicine. Based on retrosynthetic analysis of its structure, our group designed and synthesized cyclopentene-tethered 2-alkynylanilines **62**. With the aid of $Pd(amphos)Cl_2$/(S)-Synphos as the catalyst and oxygen as the oxidant, an asymmetric aminopalladition/Heck cascade reaction of cyclopentene-tethered 2-alkynylanilines **62** was successfully developed, providing indole-fused bicyclo[3.2.1]octanes **63** bearing an all carbon quaternary bridge head stereocenter with up to 96% ee and 93% yield (Scheme 18).[44] The electronic properties of groups on the 2-alkynylanilines **62** had a dramatic influence on the reactivity and enantioselectivity, introducing the electron-withdrawing groups would result in diminished reactivities and enantioselectivities. A catalytic mechanism was proposed. Palladium complex undergoes coordination and aminopalladation to give indol-3-yl palladium species **Int 18b**. Intramolecular insertion of C=C bond is followed by β-H elimination to afford the desired product **63** and Pd-H species **Int 18d**. Regeneration of the palladium(II) complex is achieved through reductive elimination and oxidation with O_2.

Meanwhile, an elegant asymmetric aminopalladation enabled intermolecular Heck reaction of 2-alkynylanilines **64** with prochiral cyclopentenes **65** was disclosed by the Zhu group (Scheme 19).[45] A series of structurally diverse cyclopentene-tethered indoles **66** were obtained with high diastereo- and enantioselectivities in the presence of $Pd(OAc)_2$/Pyrox ligand **L11** as the catalyst and O_2 as the oxidant.

Importantly, the amide group on the cyclopentenes **65** is essential to promote the transformation and stereoselectivity control. In absence of amide group as the directing group, the reaction failed. Based on mechanism studies, a catalytic mechanism was proposed. Aminopalladation of Pd(II) complex with 2-alkynylanilines **64** undergoes coordination with amide group of prochiral cyclopentenes **65** to form intermediate **Int 19b**.

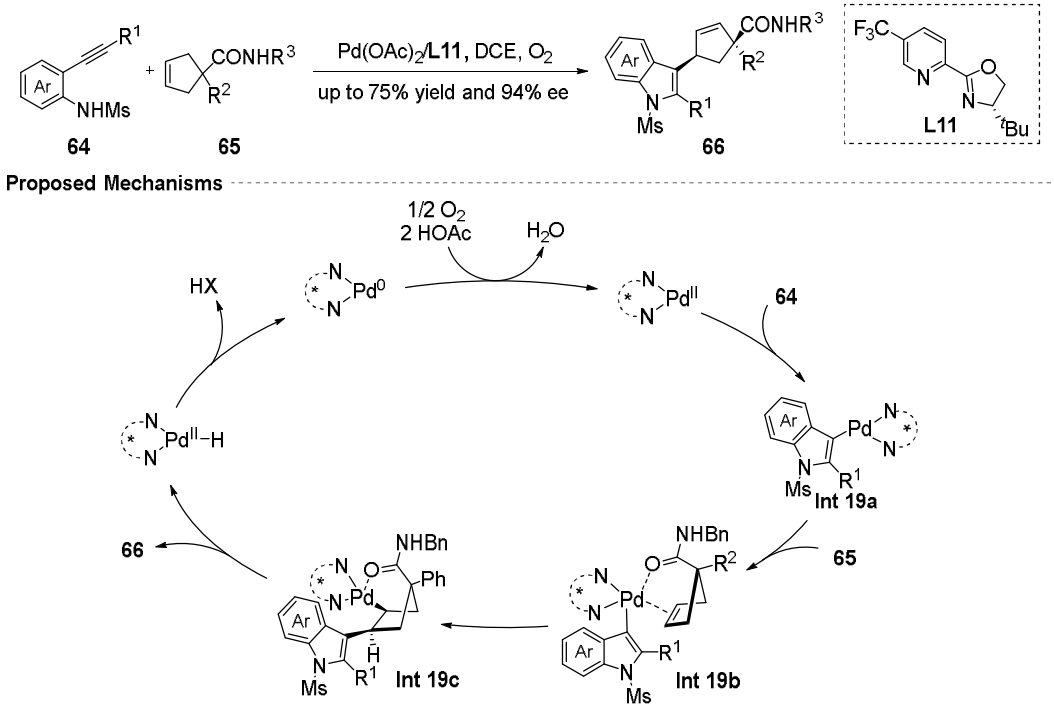


Scheme 17. Synthesis of 3-methylindoles *via* aminopalladation/methylation cascade reaction of 2-alkynylanilines with methylboronic acid.



Scheme 18. Enantioselective synthesis of indole-fused bicyclo[3.2.1]octanes *via* intramolecular tandem aminopalladation/Heck reaction of cyclopentene-tethered 2-alkynylanilines.

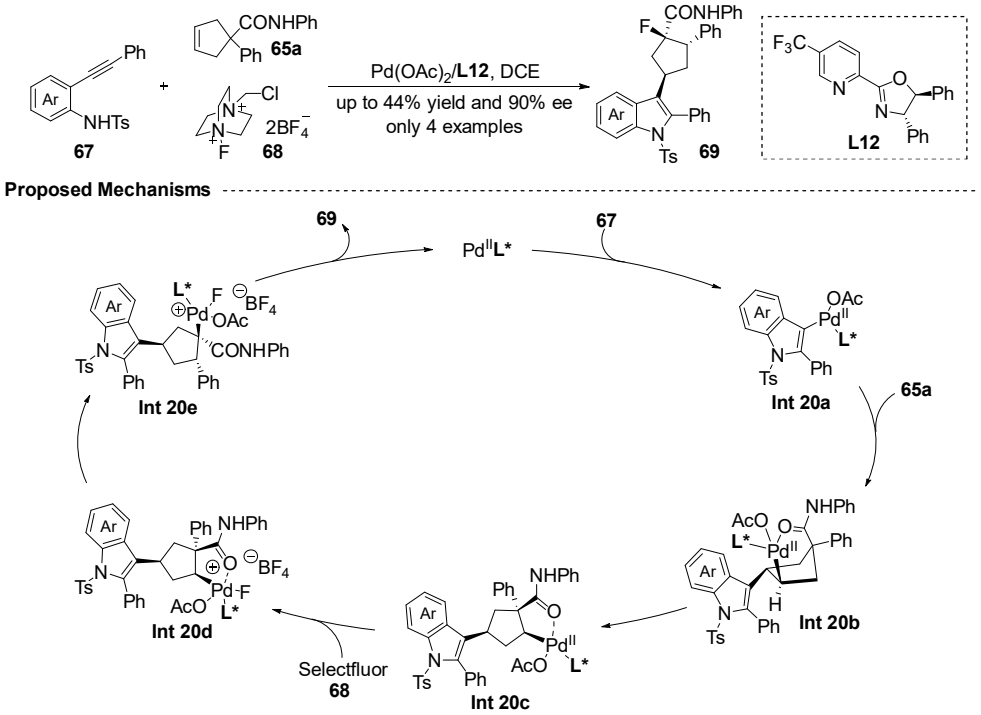
C=C Bond insertion and β-hydride elimination of intermediate **Int 19b** afford desired cyclopentene-tethered indoles **66** and Pd-H complex. The active Pd(II) complex is regenerated by oxidation of Pd-H complex with O_2 (Scheme 19).



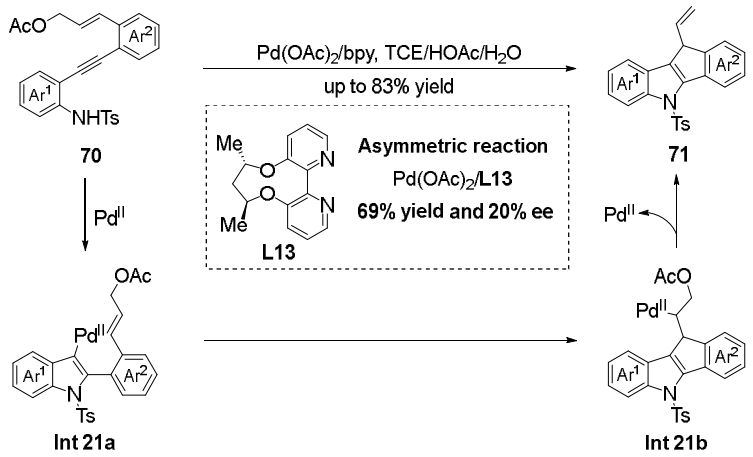
Scheme 19. Enantioselective synthesis of cyclopentene-tethered indoles *via* intermolecular aminopalladation/Heck reaction cascade of 2-alkynylanilines with cyclopentenes.

A novel 1,2-aryl(alkyl)/Pd(V) dyotropic rearrangement was discovered by the Zhu group in the three component reaction of arylboronic acids, cyclopentenes and Selectfluor.[46] However, the indol-3-yl boronic acid is not a good reaction partner. To overcome this limitation, the authors investigated cyclizative cross-coupling of 2-alkynylanilines **67** with cyclopentene **65a** in the presence of Selectfluor **68** (Scheme 20). Under the conditions of $Pd(OAc)_2$/Pyrox ligand **L12** as the catalyst, the transformation proceeded smoothly to deliver the desired product **69** in the acceptable yields and high enantioselectivities. The proposed reaction sequence involves aminopalladation, enantioselective carbopalladation, β-hydride elimination/reinsertion, oxidation of Pd(II) species to Pd(IV) species, 1,2-aryl/Pd(IV) dyotropic rearrangement and reductive C–F bond formation.

Additionally, an intramolecular aminopalladation/alkene insertion/β-acetoxy elimination cascade reaction of cinnamyl acetate-tethered 2-alkynylanilines **70** was established by the Lu group (Scheme 21).[47] The reaction was carried out with $Pd(OAc)_2$/bipyridine as the catalyst and TCE/HOAc/H_2O as the co-solvents, and indenoindoles **71** were furnished in moderate to good yields. Furthermore, preliminary exploration for the asymmetric version of this cascade reaction showed unsatisfactory result with 20% ee. Mechanism studies excluded an alternative pathway involving palladium(0)-catalyzed oxidative addition/aminopalladation/reductive elimination cascade processes, and this transformation is a palladium(II)-catalyzed procedure. Aminopalladation of cinnamyl acetate-tethered 2-alkynylanilines **70** with palladium(II) complex gives intermediate **Int 21a**, which undergoes alkene insertion and β-acetoxy elimination to deliver desired indenoindoles **71** and palladium(II) complex.



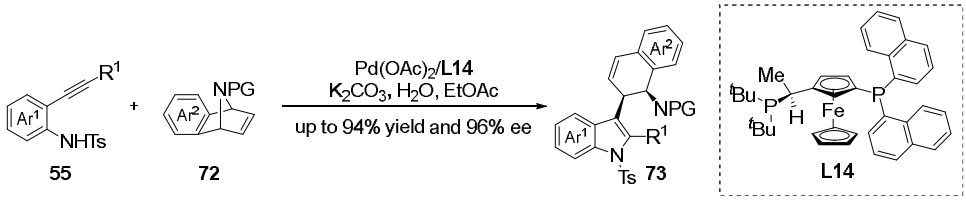
Scheme 20. Enantioselective synthesis of 3-cyclopentyl indoles *via* three component reaction of 2-alkynylanilines, cyclopentenes and Selectfluor.



Scheme 21. Synthesis of indenoindoles *via* intramolecular aminopalladation/alkene insertion/β-acetoxy elimination cascade reaction of cinnamyl acetate-tethered 2-alkynylanilines

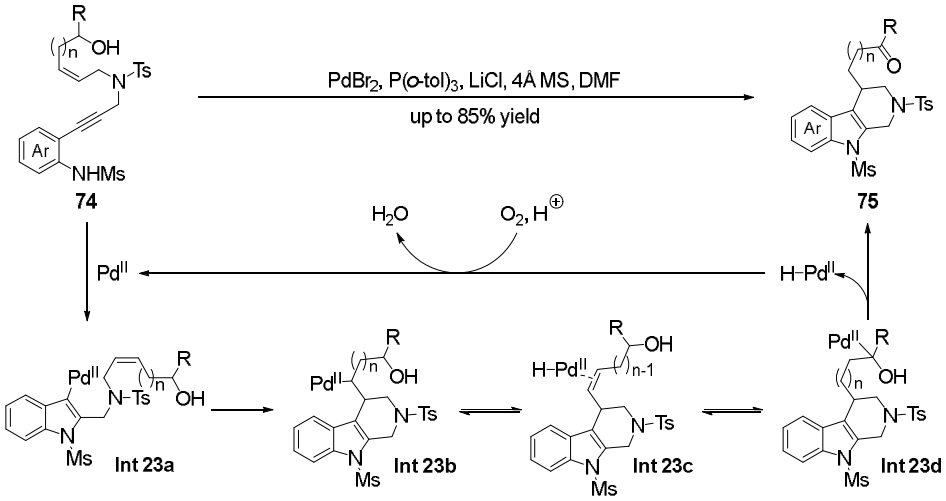
Taking advantage of enantioselective desymmetrization strategy, an intermolecular asymmetric aminopalladation/alkene insertion/β-amino elimination cascade of alkynylanilines **55** with 7-azabenzonorbornadienes **72** was disclosed by the Li group (Scheme 22).[48] The coupling of alkynylanilines **55** with 7-azabenzonorbornadienes **72** occurred smoothly in the presence of $Pd(OAc)_2$/Josiphos ligand **L14**

as the catalyst, K_2CO_3 as the base and H_2O as the additive, and the desired products **73** were isolated with up to 94% yield and 96% ee. To shed light onto the reaction mechanism, the authors carried out the density functional theory (DFT) calculations, revealing that two non-covalent interactions contributed to the observed enantioselectivity.



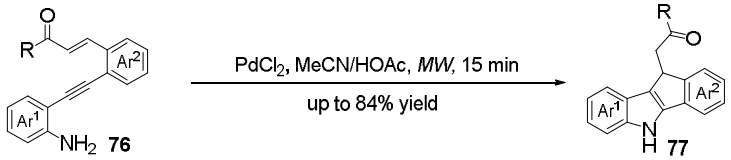
Scheme 22. Enantioselective synthesis of indenoindoles *via* asymmetric aminopalladation/alkene insertion/β-amino elimination of alkynylanilines with 7-azabenzonorbornadienes.

1,2,3,4-Tetrahydro-β-carbolines have been identified as prevalent structural motifs in natural products and pharmaceutical molecules. The Qin group documented a general approach for the assembly of 1,2,3,4-tetrahydro-β-carbolines **75** through aminopalladation enabled intramolecular redox-relay Heck reaction of alkenols **74** (Scheme 23).[49] Reaction condition screening showed that additive LiCl could significantly improve reactivity. Based on the mechanistic studies, a possible mechanism was proposed. The reaction starts with aminopalladation to deliver indol-3-yl palladium species **Int 23a**, followed by C=C bond insertion to give intermediate **Int 23b**. Successive β-hydride elimination and C=C bond insertion afford the desired 1,2,3,4-tetrahydro-β-carbolines **75** and release a Pd(II)–H complex. The Pd(II) complex is reregenerated by oxidation with O_2.



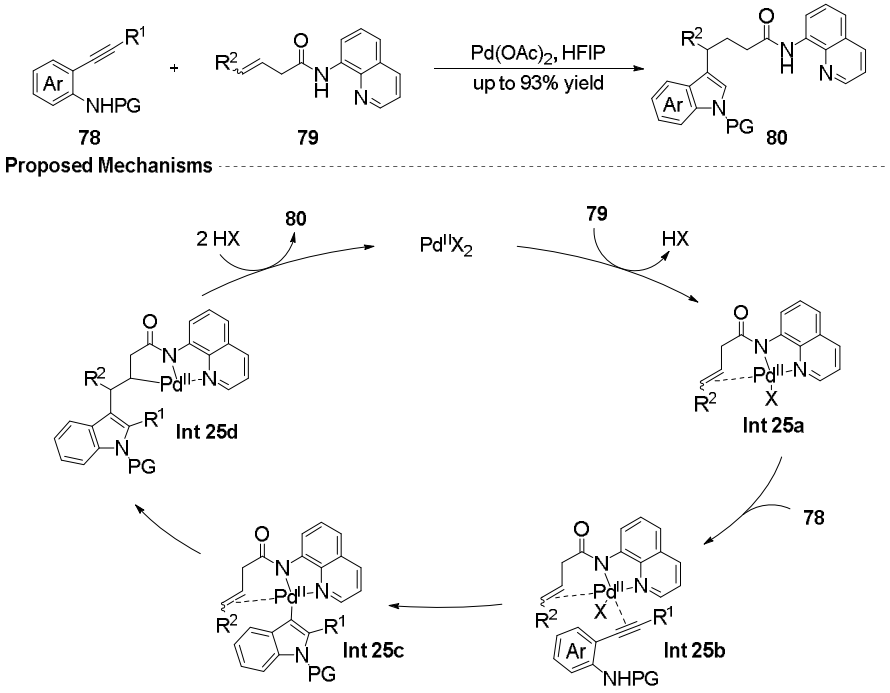
Scheme 23. Synthesis of 1,2,3,4-tetrahydro-β-carbolines *via* aminopalladation enabled intramolecular redox-relay Heck reaction

Microwave irradiation organic synthesis has attracted considerable attention owing to the efficient and relatively friendlier synthesis of a variety of organic compounds. Recently, a microwave-assisted intramolecular aminopalladation enabled 1,4-addition of 2-alkynylaniline-tethered α,β-unsaturated carbonyl compounds **76** was disclosed to access indenoindoles **77** with yields up to 84% in short reaction time (Scheme 24).[50] In this case, authors systematically compared microwave irradiation and conventional heating method for this transformation, revealing the superiority of microwave-assisted approach.



Scheme 24. Synthesis of indenoindoles *via* aminopalladation-enabled 1,4-addition.

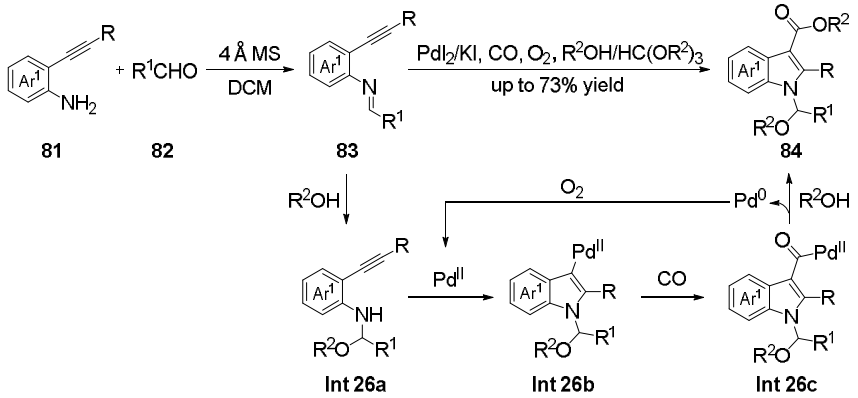
Palladium-catalyzed hydrocarbofunctionalization of unactivated alkenes is a highly challenging topic because alkylpalladium species generated in situ are prone to β-hydride elimination. Using 8-aminoquinoline as a cleavable bidentate directing group to stabilize the alkylpalladium species, the Volla group realized a cascade cyclization and regioselective hydroheteroarylation of unactivated alkenes **79** with 2-alkynylanilines **78**, affording a series of 3-alkylindoles **80** with yields up to 93% (Scheme 25).[51] Control experiments confirmed that alkyl palladium species **Int 25d** coordinated with 8-aminoquinoline prefers protodepalladation rather than β-hydride elimination. On the basis of mechanistic studies and literature precedence, a plausible reaction mechanism was proposed. Firstly, palladium catalyst coordinated with 8-aminoquinoline **79** to form intermediate **Int 25a**, which undergoes C≡C bond coordination of 2-alkynylaniline **78** and aminopalladation to afford intermediate **Int 25c**. Regioselective migratory insertion of intermediate **Int 25c** followed by protodepalladation deliver the desired product **80** and regenerate the active Pd(II) catalyst.



Scheme 25. Synthesis of 3-alkyl indoles *via* aminopalladation/alkene insertion/protodepalladation of unactivated alkenes and 2-alkynylanilines.

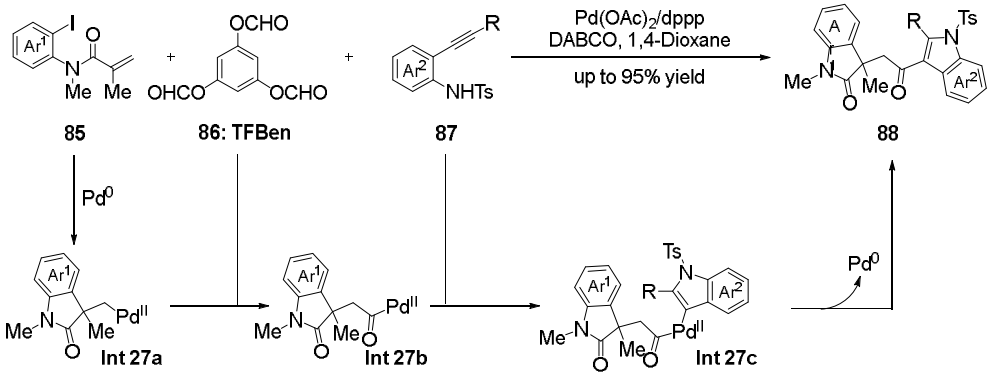
Carbonylative insertion is a powerful and straightforward method for the synthesis of carbonyl compounds, which have been frequently found in numerous bioactive compounds. Gabriele disclosed an elegant palladium-catalyzed multicomponent cascade reaction of 2-alkynylanilines **81**, benzaldehydes **82**, carbon monoxide (CO) and alcohols (R^2OH) for the construction of indole-3-carboxylic esters **84** in the

presence of PdI_2 as catalyst, KI as the additive and $R^2OH/HC(OR^2)_3$ as the co-solvent (Scheme 26). A plausible reaction mechanism was proposed for this multicomponent cascade process by authors.[52] Initially, ROH addition to the imino group of 2-alkynylanilineimines **83** forms intermediate **Int 26a**, which undergoes aminopalladation to give intermediate **Int 26b**. Alkoxycarbonylation of intermediate **Int 26b** affords desired products **84**. Additionally, this catalytic system is suitable for the oxidative carbonylation of 2-alkynylanilines bearing a secondary amino group using MeOH as solvent.[53]



Scheme 26. Synthesis of indole-3-carboxylic esters *via* palladium-catalyzed multicomponent cascade reaction of 2-alkynylanilines, benzaldehydes, carbon monoxide (CO) and alcohols.

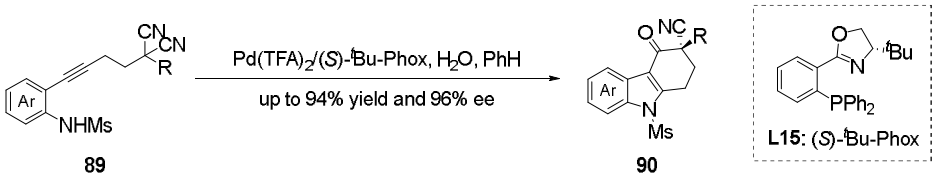
The Wu group described a three component reaction of *N*-(2-iodoaryl)acrylamides **85**, TFBen **86** and 2-alkynylanilines **87** in the presence of $Pd(OAc)_2$/dppp as the catalyst and DABCO as the base, providing 3-carbonyl indoles **88** with yields up to 95% (Scheme 27).[54] This transformation starts with intramolecular Heck reaction of *N*-(2-iodoaryl)acrylamides **85** to form intermediate **Int 27a**, which undergoes carbonylative insertion with TFBen **86** to afford intermediate **Int 27b**. C≡C bond coordination of 2-alkynylaniline **87**, aminopalladation and reductive elimination of intermediate **Int 27b** gives desired 3-carbonyl indoles **88**.



Scheme 27. Synthesis of 3-carbonyl indoles *via* carbopalladation/carbonylative cyclization of *N*-(2-iodoaryl)acrylamides, TFBen and 2-alkynylanilines.

Optically pure carbazolones as prominent structural motifs widely exist in bioactive compounds and nature products. Liu and co-workers documented an elegant enantioselective synthesis of carbazolones **90** bearing all carbon quaternary center through aminopalladation/desymmetrizing nitrile addition cascade reaction of malononitrile-tethered 2-alkynylanilines **89** (Scheme 28).[55] Condition optimization demonstrated

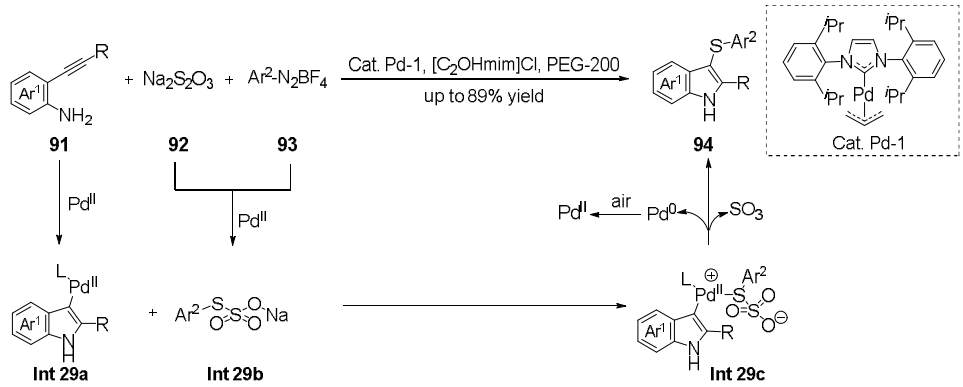
that the *N*-protecting group of 2-alkynylanilines has a dramatic impact on the reactivity and enantioselectivity, and the Ms protecting group gave the best reactivity and enantioselectivity. It is worth noting that this methodology was employed as the key step for synthesis of core structure of *Kopsia* alkaloids, *Aspidosperma* alkaloids and leucomidine A. Furthermore, the density functional theory (DFT) calculation clarified the origin of the experimentally observed enantioselectivity.



Scheme 28. Enantioselective synthesis of carbazolones *via* aminopalladation/desymmetrizing nitrile addition.

7. Miscellaneous reactions

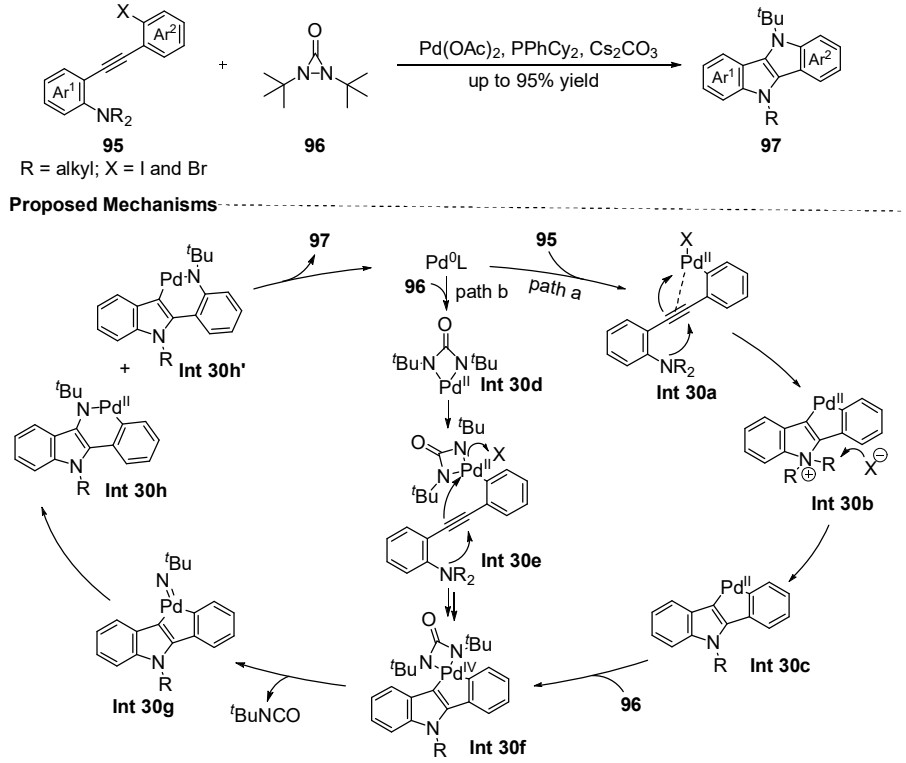
3-Sulfenylindoles are versatile and important structural motifs often found in numerous pharmaceuticals, biologically active molecules, and advanced materials. The Jiang group demonstrated an efficient and direct synthetic approach for the construction of 3-sulfenylindoles **94** through aminopalladation/arylthiolation cascade reaction of 2-alkynylamines **91**, $Na_2S_2O_3$ **92**, and aryldiazonium salts **93** under aerobic conditions with PEG-200 as an environmentally benign medium (Scheme 29).[56] Notably, the ionic liquid [C_2OHmim]Cl as an additive could significantly improve reactivity and make this transformation green. Based on control experiments and previous literature, a plausible reaction mechanism was illustrated. Aminopalladation of Pd(II) complex with 2-alkynylamines **91** gives intermediate **Int 29a**. Meanwhile, the thiosulfate intermediate **Int 29b** is achieved *via* palladium-catalyzed transformation of aryl diazonium salts **93** with $Na_2S_2O_3$ **92**. Next, ligand exchange between intermediate **Int 29a** and thiosulfate intermediate **Int 29b** follows by reductive elimination to deliver the desired 3-sulfenylindoles **94** with release of SO_3.



Scheme 29. Synthesis of 3-sulfenylindoles *via* aminopalladation/arylthiolation of 2-alkynylamines, $Na_2S_2O_3$ and aryldiazonium salts.

Shi's group reported an elegant palladium-catalyzed multiple-C−N bond formation reaction of 2-alkynylamines **95** and di-*tert*-butyldiaziridinone **96** in the presence of $Pd(OAc)_2$/$PhPCy_2$ as the catalyst, affording highly π-conjugated indolo[3,2-*b*]indoles **97** with up to 97% yield (Scheme 30).[57] Notably, the *N*-substituent group of 2-alkynylanilines played a key role in the reactivity, and only *N*-dialkyl 2-alkynylanilines **95** gave the desired products. In this case, the authors proposed two pathways to form the key intermediate pallada(IV)cycle **Int 30f**. Pathway a involves oxidative addition of Pd(0) complex with the

C−X bond, aminopalladation, dealkylation and oxidative addition with di-*tert*-butyldiaziridinone **96**. Pathway b starts with oxidative addition of Pd(0) complex with di-*tert*-butyldiaziridinone **96** to give four-membered Pd species **Int 30d**, which undergoes oxidative addition with the C−X bond and aminopalladation to afford the pallada(IV)cycle **Int 30f**. Conversion of pallada(IV)cycle **Int 30f** to pallada(IV)nitrene species **Int 30g** follows by two consecutive reductive eliminations to deliver indolo[3,2-*b*]indoles **97** with regeneration of the Pd(0) catalyst.



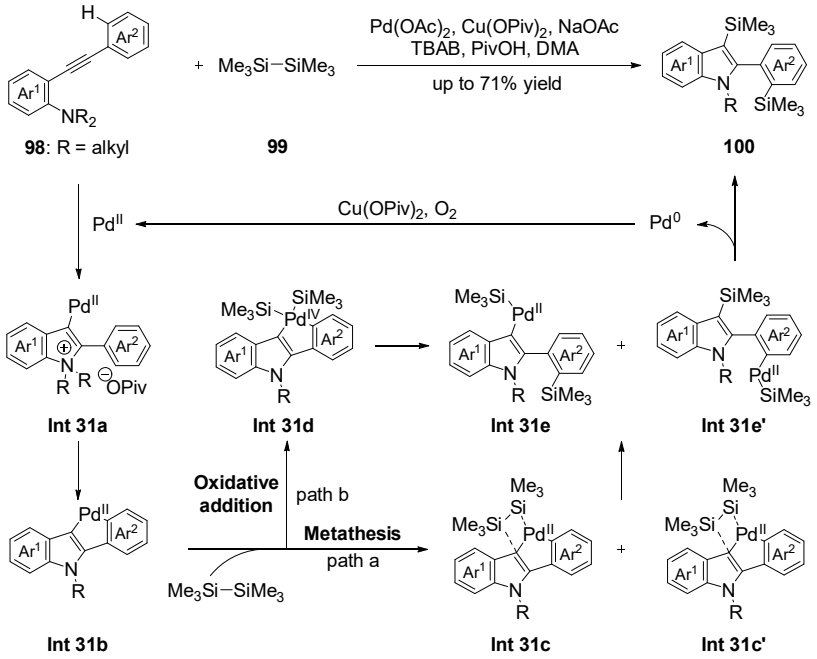
Scheme 30. Synthesis of indolo[3,2-*b*]indoles *via* multiple-C−N bond formation reaction of 2-alkynylamines and di-*tert*-butyldiaziridinone.

Organosilicon compounds are not only useful synthetic intermediates, but also have a wide range of applications in the fields of medicinal chemistry and materials. The Yang group reported an attractive and efficient strategy for the construction of disilylated 2-phenyl-1*H*-indoles **100** through aminopalladation/C−H activation/disilylation of *N*-dialkyl 2-alkynylanilines **98** and hexamethyldisilane **99** (Scheme 31).[58] The experiment of kinetic isotope effect disclosed that the C−H bond activation should not be the rate-determining step and the initial step is aminopalladation. Furthermore, the authors proposed two pathways for the formation of intermediates **Int 31e** and/or **Int 31e'** through oxidative addition and/or metathesis reaction of pallada(IV)cycle **Int 31b** with hexamethyldisilane **99**.

8. Conclusion

In summary, recent representative achievements for the construction of indoles through aminopalladation enabled cross-coupling of 2-alkynylanilines with a variety of nucleophiles and/or electrophiles have been highlighted in this review. Despite these elegant advancements, there are several potential challenges need to be addressed: 1) The catalytic efficiency of the reaction is low, which needs development of novel and potent ligands to improve the catalytic efficiency; 2) Development of

enantioselective synthesis of indoles through asymmetric aminopalladation enabled cross-coupling is slow. We hope this review will arouse intensive research interest in indole chemistry and encourage the chemists to apply these developed methodologies to natural product synthesis and drug design.



Scheme 31. Synthesis of disilylated 2-phenyl-1*H*-indoles *via* aminopalladation/C−H activation/disilylation cascade reaction of *N*-dialkyl 2-alkynylanilines and hexamethyldisilane.

Acknowledgements

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