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Synthesis of Chiral Heterocycles from Asymmetric Cascade Palladium Catalysis

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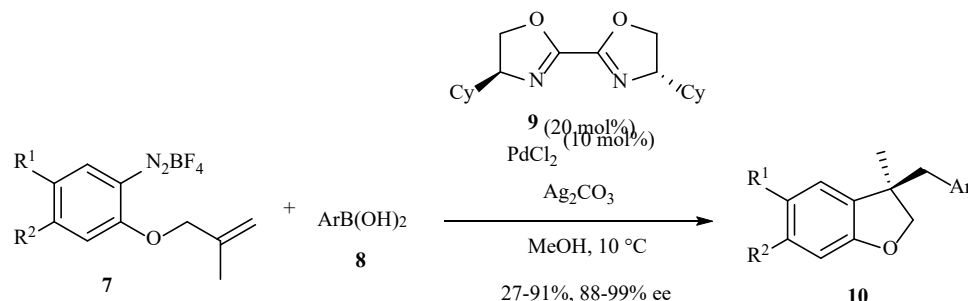
Abstract: This review updates the field of asymmetric cascade palladium catalysis applied to the synthesis of chiral heterocycles since 2019. It illustrates how much a diversity of chiral palladium catalysts promote unprecedented asymmetric domino reactions of many types, allowing a direct access to a wide variety of complex and densely functionalized chiral heterocyclic molecules.

Keywords: Palladium; heterocycles; cascade reactions; domino reactions; asymmetric metal catalysis; chirality

1. INTRODUCTION

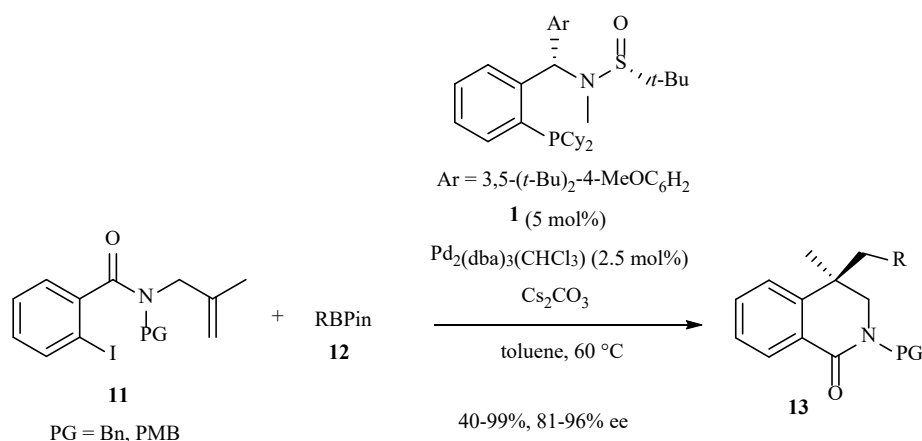
Chiral heterocycles are widely distributed in nature and constitute the skeletons of important molecules, spanning from drugs, agrochemicals to materials [1]. Among the numerous synthetic methodologies to prepare chiral heterocycles are asymmetric catalyzed one-pot reactions. Especially, asymmetric metal catalysis [2] combined with the concept of domino reactions [3] has allowed the efficient elaboration of a wide diversity of complex chiral heterocyclic molecules including many bioactive ones [3n,t,w]. Among metals, palladium [4] is especially accommodated to induce cascade reactions with many initiated by a Heck reaction [5]. The sequence begins with an oxidative addition of palladium to a C=C bond (or C≡C triple bond), a C–H activation, or a nucleopalladation. Subsequently, a relay system (alkene, alkyne, allene, carbon monoxide, carbene, etc.) allows the intra- or intermolecular elongation of the structure. Finally, a nucleophilic attack or a C–H activation [6], followed by the regeneration of the active catalyst completes the cascade. Other types of bond activations are involved in palladium-catalyzed domino reactions [7]. In the last three decades, a number of highly enantioselective versions of palladium-catalyzed cascade reactions have been developed, allowing the one-pot construction of many complex chiral architectures [8]. The goal of this review is to update the field of asymmetric palladium catalysis applied to the synthesis of chiral heterocycles through enantioselective domino reactions since the beginning of 2019, since this area was most recently reviewed in 2019 by Sansano and Döndas, covering general (including racemic) palladium-catalyzed domino reactions up to 2018 [9]. Moreover, the special field of palladium-catalyzed domino annulations was the subject of a review in 2020 albeit including no reference of asymmetric domino reactions \geq 2019 [10]. It must also be noted that a report, dealing with the construction of quaternary stereocenters through palladium-catalyzed carbopalladation-initiated cascade reactions, was published in 2019 but did not include references \geq 2019 [11]. The present review is divided into four sections dealing successively with enantioselective two-component Heck-initiated domino reactions; three-component domino reactions; one- and two-component domino multicyclization reactions; and miscellaneous one- and two-component domino reactions. In most sections, subdivisions are organized according to the atoms participating in the new bonds formed and size of polycycles synthesized. It is interesting to note that more than half of the review deals with asymmetric Heck-initiated domino reactions, demonstrating that the Heck reaction still ranks among the most versatile and useful tools in organic synthesis. This field is far from being exhausted as the asymmetric formation of carbon–carbon bonds is fundamental for the synthesis of chiral complex products that are useful in medicinal, biological, agrochemical, as well as material/nanoscience-related domains. It must be noted that some

In the same area, Chen and Kong reported the use of another type of chiral palladium catalyst which was generated from 20 mol% of chiral bisoxazoline ligand **9** and 10 mol% of PdCl₂ in related reactions [14]. As illustrated in Scheme 2, the domino Heck-type/Suzuki reaction of arenediazonium salts **7** with arylboronic acids **8** occurring in methanol at 10 °C afforded the corresponding chiral dihydrobenzofurans **10** with 27-91% yields and 88-99% ee. A variety of substituents on the phenyl ring of the arylboronic esters were tolerated as well as heteroarylboronic acids.



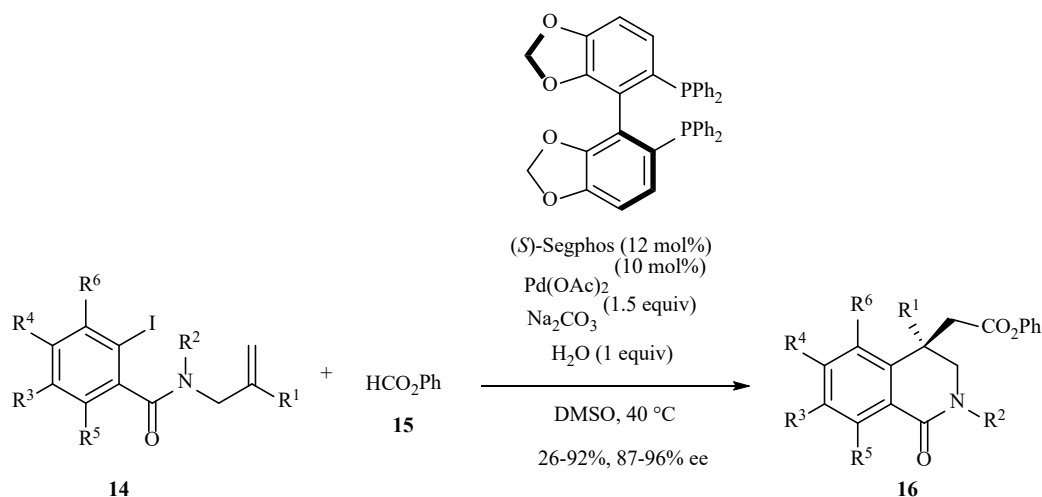
Scheme 2. Domino Heck-type/Suzuki reaction of arenediazonium salts with arylboronic acids.

Later in 2021, the asymmetric domino Heck/Suzuki reaction between 2-iodobenzamides **11** and borates **12** was developed by Guo, Yang and Zhang in the presence of 5 mol% of chiral phosphine ligand **1** combined with 2.5 mol% of Pd₂(dba)₃·CHCl₃ (Scheme 3) [15]. Performed at 60 °C in toluene, it led to the corresponding biologically interesting chiral dihydroisoquinolinones **13** with 40-99% yields and 81-96% ee.

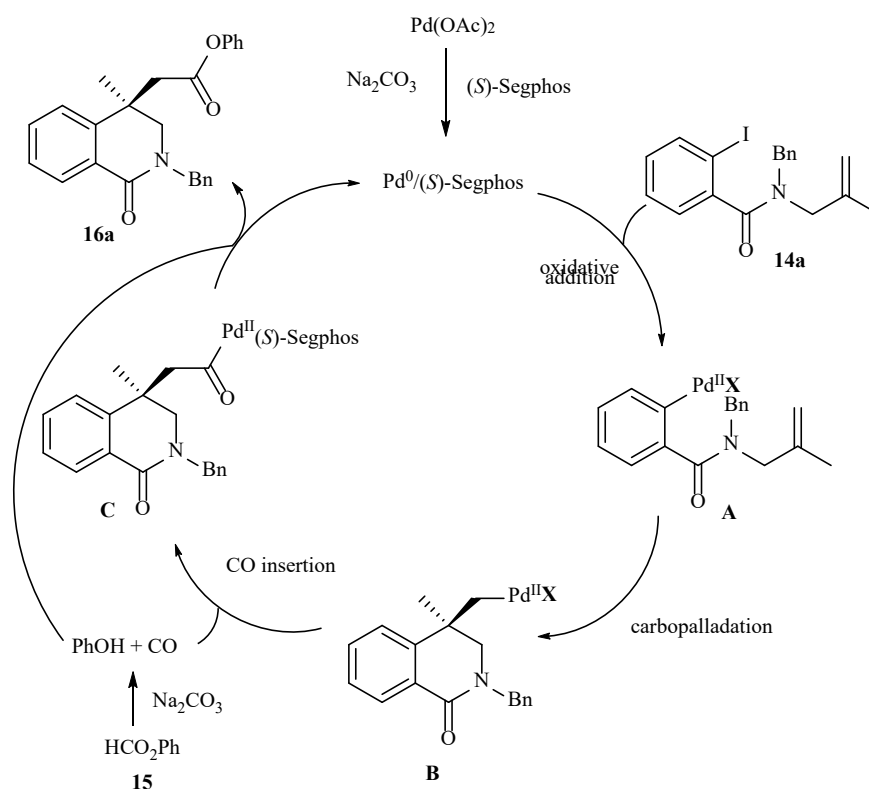


Scheme 3. Domino Heck/Suzuki reaction of 2-iodobenzamides with borates (Bn= benzyl, PG = protecting group, Pin = pinacolato, PMB = *para*-methoxybenzyl).

Another type of enantioselective Heck-initiated domino reactions was reported in 2019 by Zhang et al. [16]. It dealt with asymmetric domino Heck/carboxyphenylation reaction between *N*-allyl benzamides **14** and phenyl formate **15** as source of CO which allowed the synthesis of chiral carbonylated 3,4-dihydroisoquinolines **16** exhibiting a quaternary stereogenic center to be achieved with 26-92% yields and 87-96% ee, as illustrated in Scheme 4. The process, employing a combination of 10 mol% of Pd(OAc)₂ and 12 mol% of (*S*)-Segphos (5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole) as catalyst system, was carried out in DMSO (dimethylsulfoxide) at 40 °C in the presence of Na₂CO₃. The mechanism proposed in Scheme 4 involves the oxidative addition of aryl iodide **14a** (R¹ = Me, R² = Bn, R³ = R⁴ = R⁵ = R⁶ = H) to an in situ generated Pd(0) species, leading to Pd(II) intermediate **A**. Then, **A** underwent an intramolecular carbopalladation to afford σ-alkyl Pd(II) complex **B**. In the presence of Na₂CO₃, phenyl formate **15** produced CO and phenol. The insertion of CO into the σ-alkyl–Pd bond provided acylpalladium complex **C**. Subsequently, the attack of phenol followed by reductive elimination delivered the product along with regenerated Pd(0) catalyst.



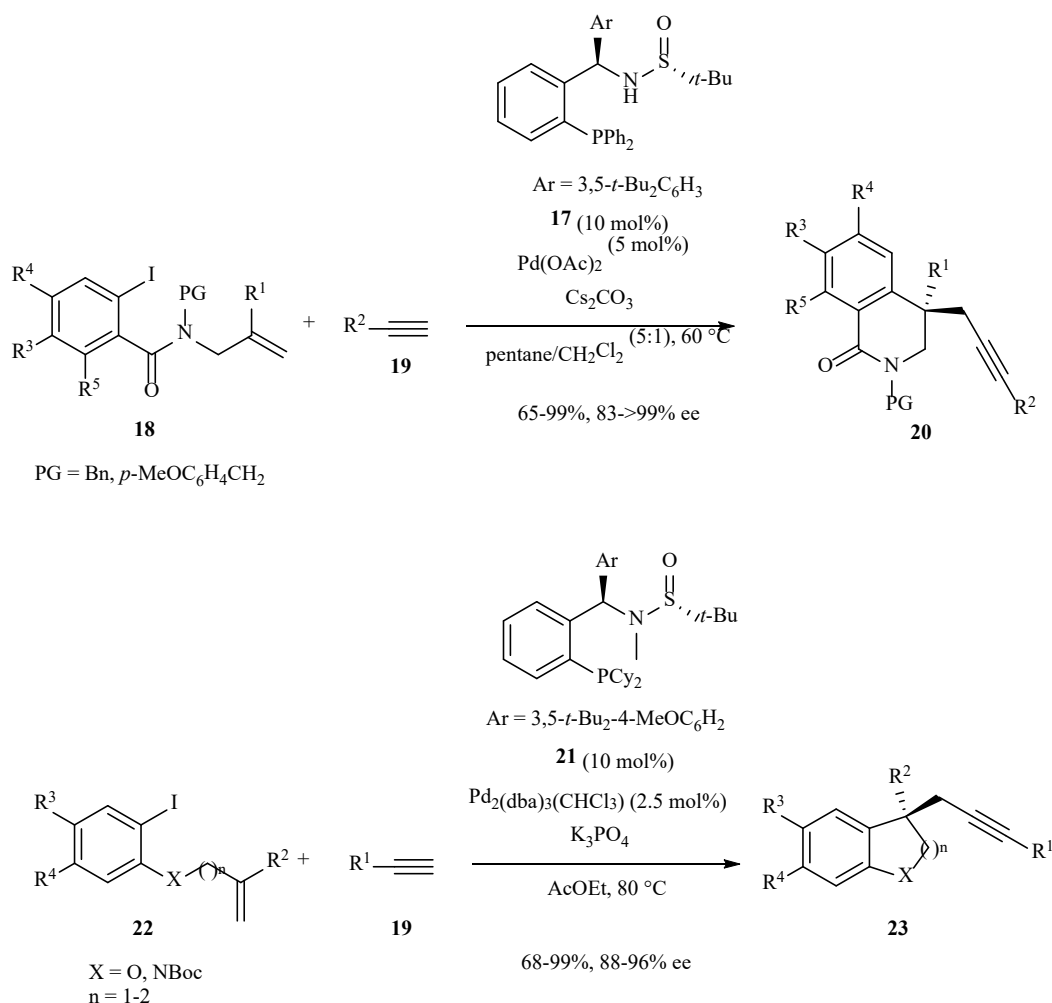
mechanism (with $\text{R}^1 = \text{Me}$, $\text{R}_2 = \text{Bn}$, $\text{R}_3 = \text{R}_4 = \text{R}_5 = \text{R}_6 = \text{H}$):



Scheme 4. Domino Heck/carboxyphenylation reaction of *N*-allyl benzamides with phenyl formate.

In 2020, Zhang and Zhang described a rare example of enantioselective palladium-catalyzed aryl-alkynylations of alkenes which evolved through an asymmetric palladium-catalyzed domino Heck/Sonogashira reaction [17]. It was achieved by using a combination of 10 mol% of chiral P,N-ligand **17** with 5 mol% of Pd(OAc)_2 as catalyst system. As presented in Scheme 5, the cascade reaction between *N*-allyl carboxamides **18** and terminal alkynes **19** performed at 60 °C in a mixture of dichloromethane and pentane as solvent and in the presence of a base such as Cs_2CO_3 resulted in the formation of the corresponding chiral bicyclic products **20** bearing a quaternary stereogenic center with 65-99% yields and 83->99% ee. A wide range of arylacetylenes bearing various substituents on the

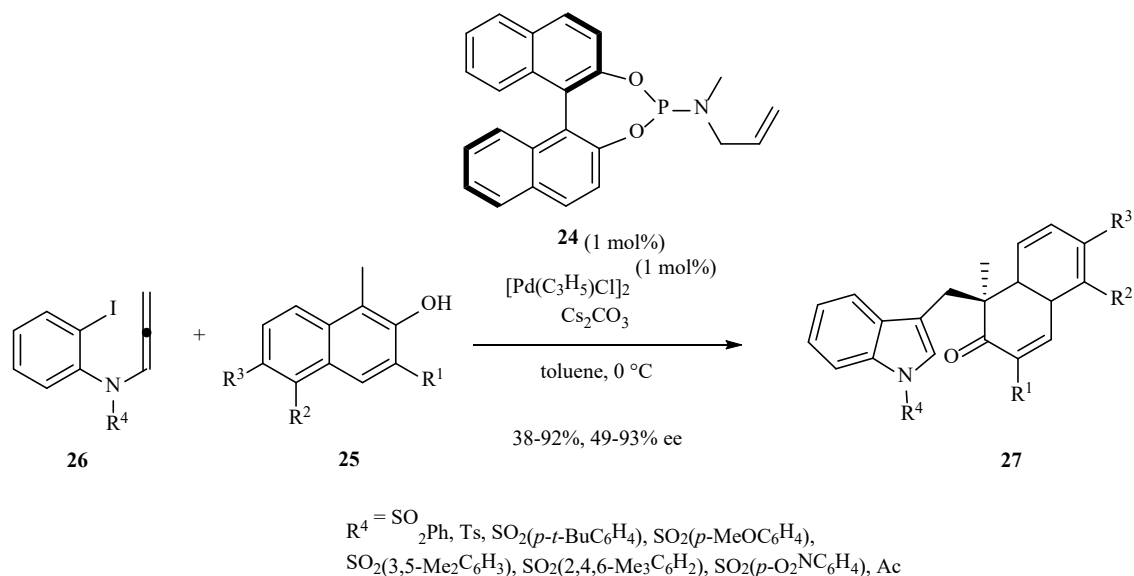
phenyl ring were compatible as well as heteroarenes. Alkenyl alkynes ($R^2 = \text{CH}_2=\text{C}(\text{Me})$, 1-cyclohexenyl) reacted smoothly with 90-94% ee while aliphatic alkynes ($R^2 = n\text{-Hex}$ (hexyl), $n\text{-decyl}$, $\text{Cl}(\text{CH}_2)_3$) provided slightly lower ee values (88-94% ee). Moreover, *N*-allyl carboxamides bearing electron-donating or electron-withdrawing substituents on the phenyl ring were compatible. Various alkyl substituents (R^1) attached to the alkene moiety were also compatible. In a second time, the authors showed that the scope of this methodology could be extended to the synthesis of other bicyclic chiral heterocycles potentially bioactive, such as indoline, 3,3-disubstituted dihydrobenzofuran, and chromane derivatives. To reach this goal, 10 mol% of closely related chiral ligand **21** was combined with 2.5 mol% of $\text{Pd}_2(\text{dba})_3$ to in situ generate the active catalyst which promoted at 80 °C in ethyl acetate as solvent in the presence of K_3PO_4 as base, the domino Heck/Sonogashira reaction between *N*- or *O*-tethered alkenes **22** with a wide variety of alkynes **19**, leading to chiral 3,3-disubstituted dihydrobenzofurans ($X = \text{O}$, $n = 1$), chromanes ($X = \text{O}$, $n = 2$) or indolines ($X = \text{NBoc}$, $n = 1$) **23** with 68-99% yields and 88-96% ee. The catalyst system tolerated the presence of different substituents on the alkene moiety (R^2) of the *N*/*O*-tethered alkenes as well as (hetero)aryl, alkyl and alkenyl alkynes.



Scheme 5. Domino Heck/Sonogashira reactions of *N*-allyl carboxamides/*N*- or *O*-tethered alkenes with terminal alkynes.

Only 1 mol% of a chiral palladium catalyst in situ generated from $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$ and chiral phosphoramidite ligand **24** was applied by Wang and Guo to promote enantioselective domino Heck/dearomatization reaction between β -naphthols **25** and *N*-(2-iodophenyl)allenamides **26** (Scheme 6) [18]. When the reaction was carried out in toluene at 0 °C in the presence of Cs_2CO_3 as base, chiral indole-functionalized β -naphthalenone products **27** were obtained with 38-92% yields and 49-93% ee. The nature of the *N*-protecting group (R^4) of the allenamide

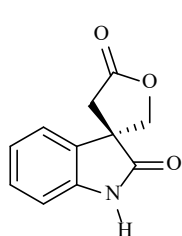
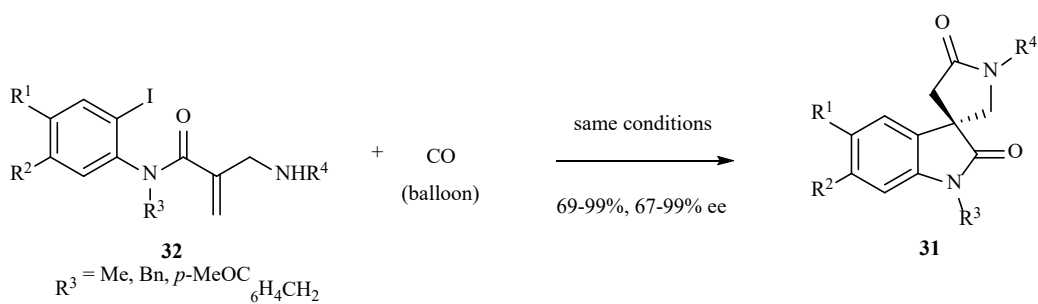
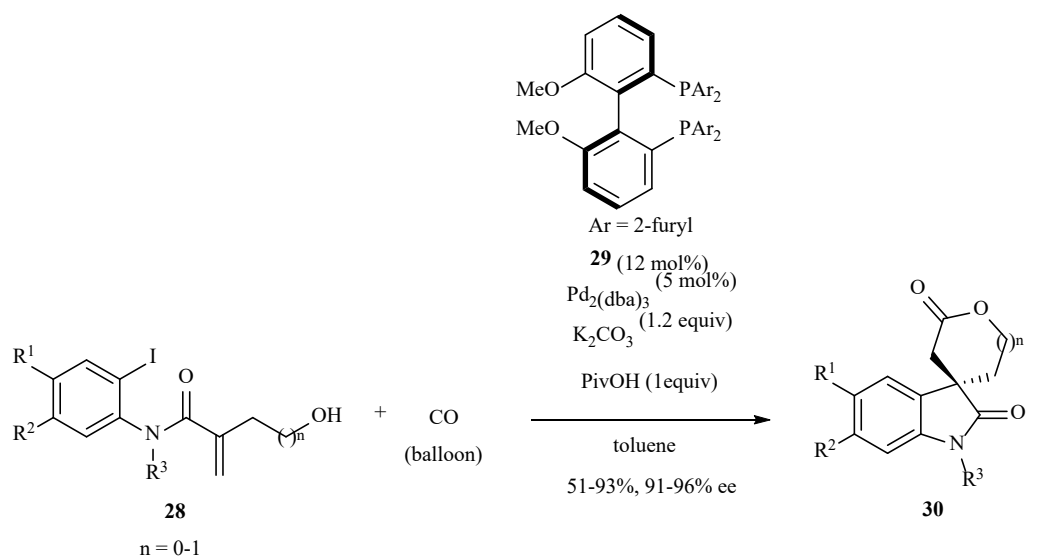
was found to have a great influence on the enantioselectivity of the reaction, since sulfonamides ($R^4 = \text{SO}_2\text{NR}$) provided 69-93% ee while lower ee values (49-70% ee) were obtained in the reaction of acetamides ($R^4 = \text{Ac}$).



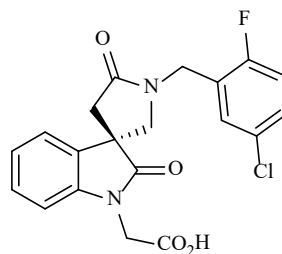
Scheme 6. Domino Heck/dearomatization reaction of β -naphthols with N -(2-iodophenyl)allenamides (Ts = tosyl).

2.1.2. Tricyclic Molecules

Chiral oxindoles constitute the skeleton of many natural and biologically active products, thus making their synthesis especially challenging [19]. In 2019, Zhu and Luo developed an asymmetric domino Heck/carbonylative lactonization reaction of N -(2-iodophenyl)- N -alkyl-acrylamides **28** exhibiting a branched homoallylic alcohol under CO pressure using as catalyst system a combination of 5 mol% of $\text{Pd}_2(\text{dba})_3$ with 12 mol% of chiral bisphosphine **29** (Scheme 7) [20]. Performed in the presence of a base (K_2CO_3), the reaction afforded chiral spirooxindole δ - or γ -lactones **30** with 51-93% yields and 91-96% ee. The synthetic utility of this novel cascade reaction was demonstrated in the total syntheses of natural product coixspirolactam and receptor antagonist CRTH2. Furthermore, the scope of this methodology was extended to the synthesis of chiral spirooxindole γ - and δ -lactams **31** through domino Heck/carbonylative lactamization reaction of the corresponding substrates **32** bearing an intramolecular nitrogen nucleophile instead of an alcohol group. As shown in Scheme 7, a range of products **31** were produced with 69-99% yields and 67-99% ee. The formation of spirooxindole γ - and δ -lactones/lactams **30/31** can be explained by the mechanism depicted in Scheme 7, beginning with oxidative addition followed by the chelation of the terminal alkene to the Pd(II) coordinated to the bidentate bisphosphine ligand in **D**. Subsequently, insertion of the alkenyl moiety to Ar-Pd(II) generated the quaternary carbon center, and then an alkyl Pd(II) species **E** underwent CO insertion and cyclization to deliver the final product **30/31**.

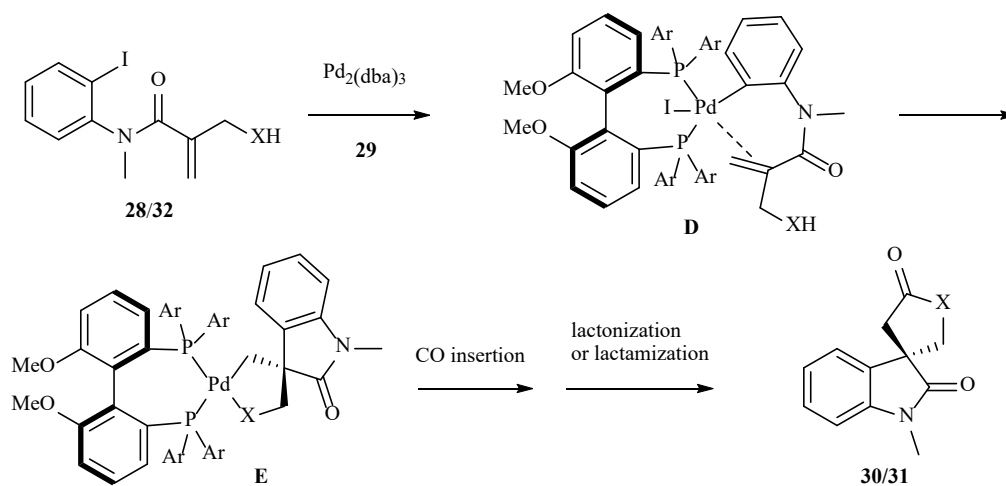


coxspirolactam



receptor antagonist CRTHZ

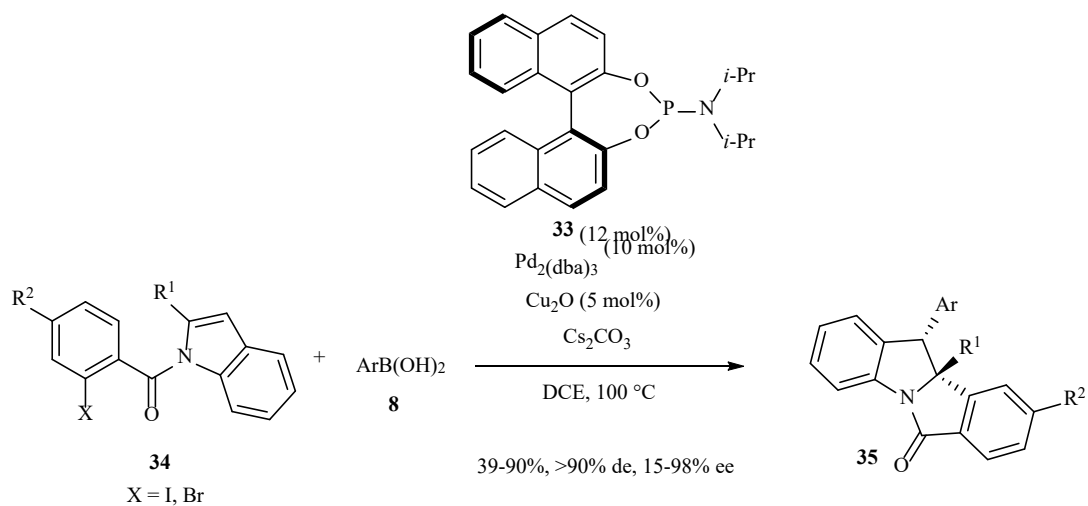
mechanism (with $\text{XH} = \text{OH}$, NHR^4 , $n = 0$, $\text{R}^1 = \text{R}_2 = \text{H}$, $\text{R}_3 = \text{Me}$):



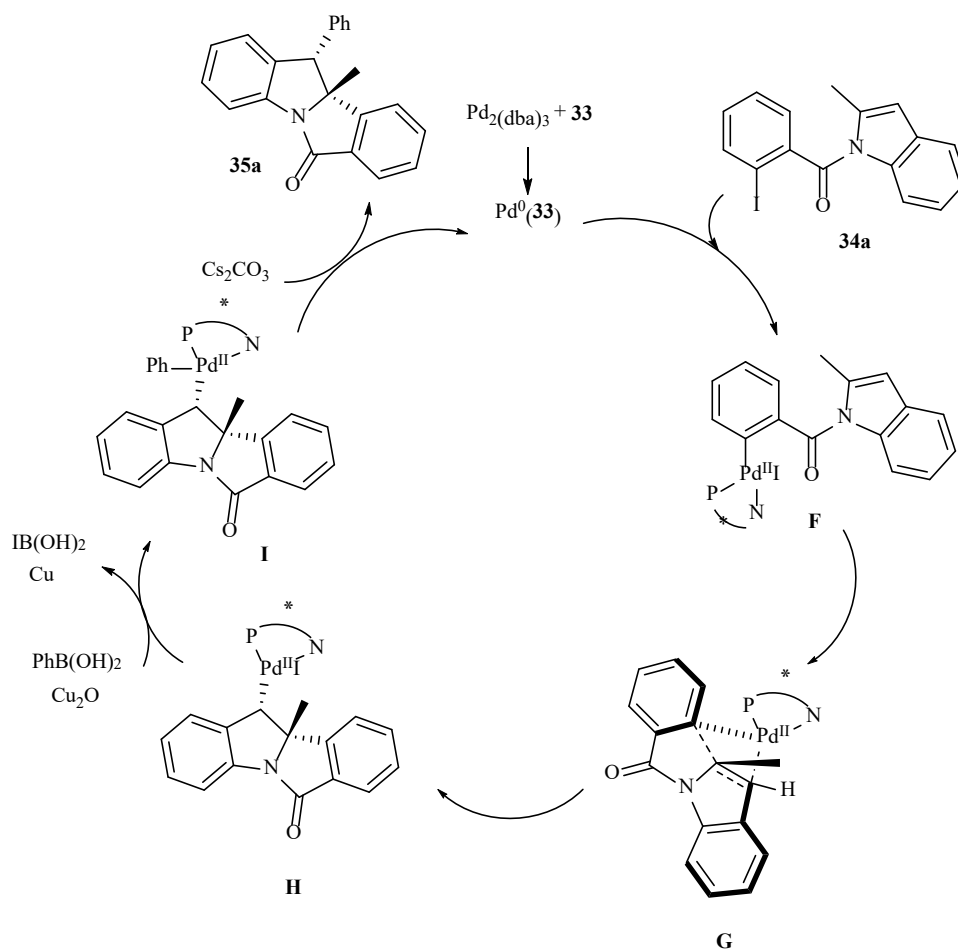
Scheme 7. Domino Heck/carbonylative lactonization/lactamization reactions of *N*-(2-iodophenyl)-*N*-alkyl-acrylamides (Piv = pivaloyl).

2.1.3. Tetracyclic Molecules

Another type of cascade initiated by a Heck reaction was disclosed in 2021 by Zhao and Han, dealing with a domino Heck/Suzuki reaction of indoles **34** with arylboronic acids **8** (Scheme 8) [21]. It involved a chiral palladium catalyst in situ generated from 12 mol% of chiral BINOL-based phosphoramidite ligand **33** and 10 mol% of Pd₂(dba)₃. This unprecedented asymmetric intramolecular cascade cyclization was performed at 100 °C in DCE (dichloroethane) as solvent in the presence of 5 mol% of Cu₂O as an additive and Cs₂CO₃ as base, yielding chiral indolines **35** bearing an all-carbon quaternary stereogenic center as almost single diastereomers (>90% de) with 39-90% yields and 15-98% ee. Comparable enantioselectivities were obtained for aryl bromides (X = Br, 26-98% ee) and aryl iodides (X = I, 15-98% ee) while the latter generally reacted with better yields (53-90% vs 39-66%). In the mechanism shown in Scheme 8, the chiral active catalyst undergoes oxidative addition to the C–I bond of aryl iodide **34a** (R¹ = Me, R² = H, X = I) to generate intermediate **F**, which is further submitted to intramolecular *syn*-insertion into the C=C bond of the indole, leading to intermediate **G**. Then, insertion in intermediate **G** affords intermediate **H**, followed by intermolecular coordination and insertion of a phenyl copper species, in situ generated from the reaction between phenylboronic acid and Cu₂O, which furnishes intermediate **I**. Final reductive elimination of intermediate **I** yields product **35a** along with regenerated catalyst.



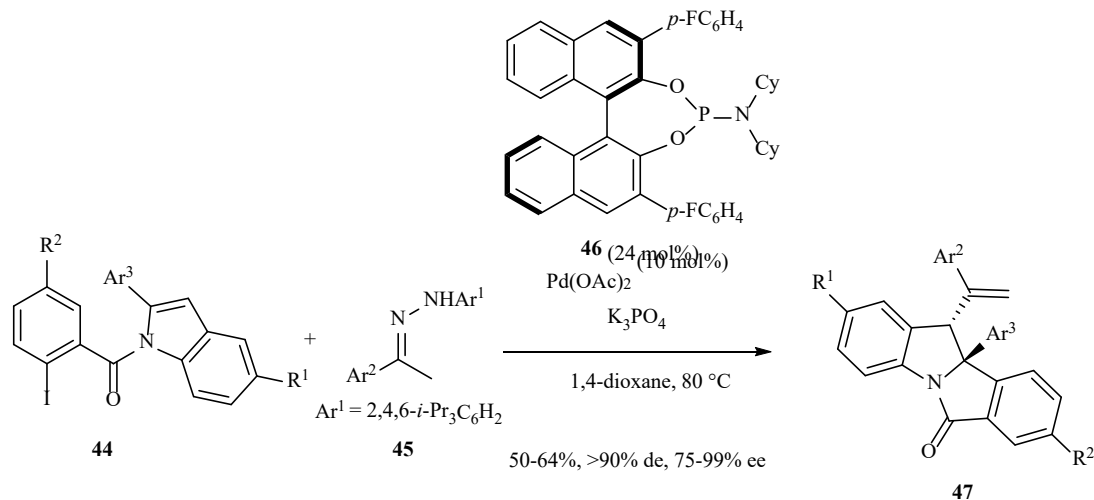
mechanism (with $\text{R}^1 = \text{Me}$, $\text{R}_2 = \text{H}$, X = I , Ar = Ph):



Scheme 8. Domino Heck/Suzuki reaction of indoles with arylboronic acids.

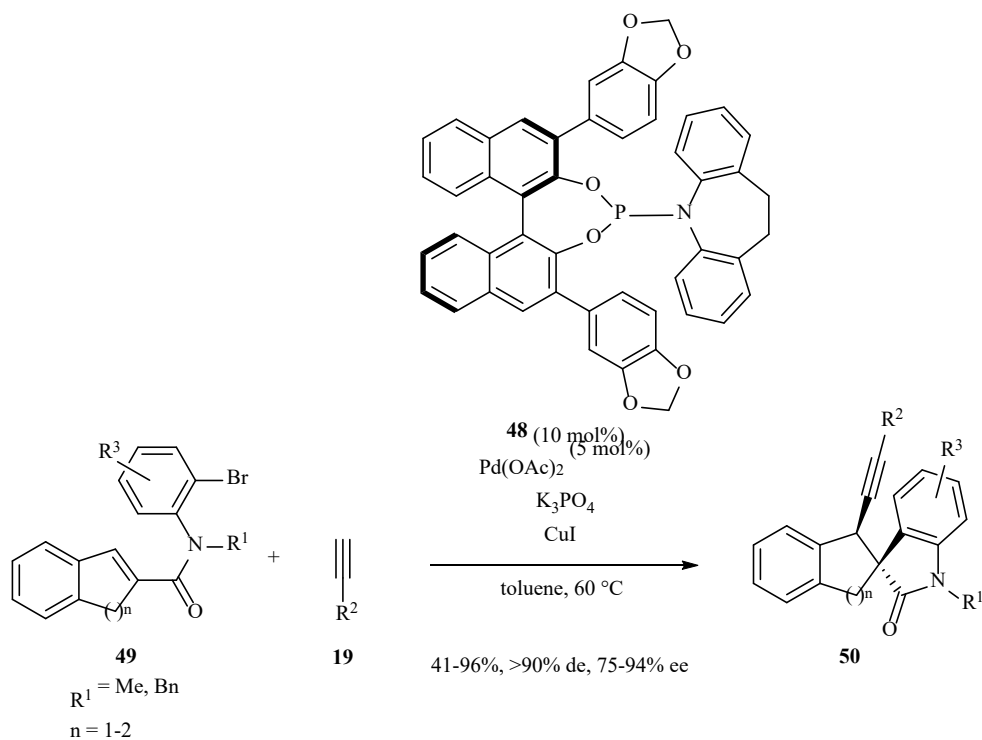
The same year, enantioselective domino Heck/Suzuki reaction of cyclic trisubstituted alkenes **36** with sodium tetraarylborates **37** was developed by Jia et al. (Scheme 9) [22]. The corresponding chiral 3,3'-spirooxindoles **39** exhibiting vicinal spiro quaternary and tertiary stereocenters were generated as almost single diastereomers (>90%

palladium complex in situ generated from 24 mol% of BINOL-based chiral phosphoramidite ligand **46** and 10 mol% of Pd(OAc)₂ (Scheme 11) [24]. This dearomative arylvinylation performed at 80 °C in 1,4-dioxane in the presence of K₃PO₄ as base afforded chiral 3-vinylated indolines **47** bearing two vicinal stereogenic centers as almost single diastereomers (>90% de) in 50-64% yields and 75-79% ee.



Scheme 11. Domino Heck/vinylation reaction of indoles with *N*-arylsulfonylhydrazones.

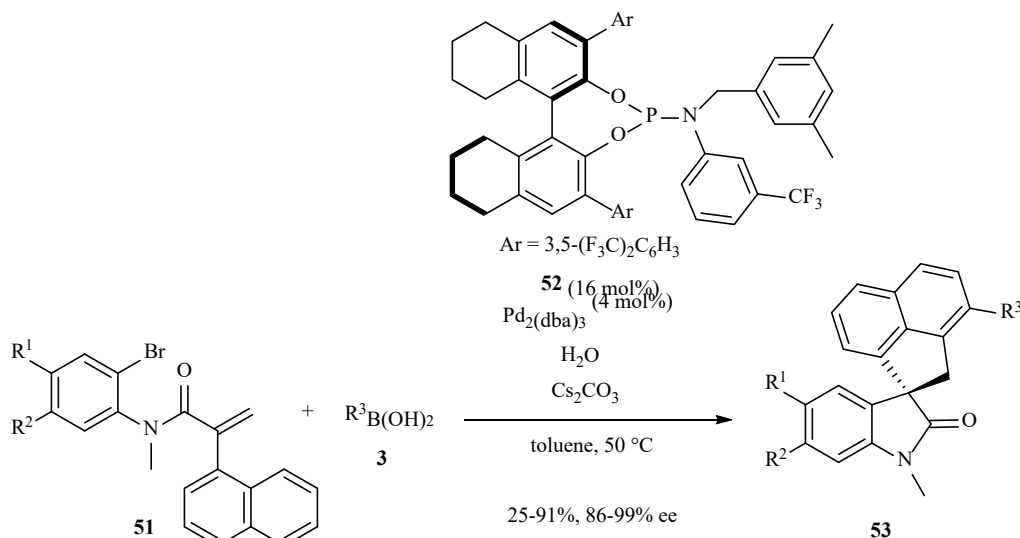
Other tetracyclic products, such as chiral 3,3'-spirooxindoles **50**, were synthesized by Jia et al. through asymmetric domino Heck/Sonogashira reaction between trisubstituted alkenes **49** and terminal aryl and aliphatic alkynes **19** by using a combination of 5 mol% of Pd(OAc)₂ with 10 mol% of BINOL-derived phosphoramidate ligand **48** (Scheme 12) [22]. Performed at 60 °C in the presence of K₃PO₄ as base in toluene as solvent, the 1,2-arylkynylation reaction afforded spiro tetracyclic products **50** bearing two stereocenters as almost single diastereomers (>90% de) in 41-96% yields and 75-94% ee.



Scheme 12. Domino Heck/Sonogashira reaction of trisubstituted alkenes with terminal alkynes.

2.1.4. Pentacyclic Molecules

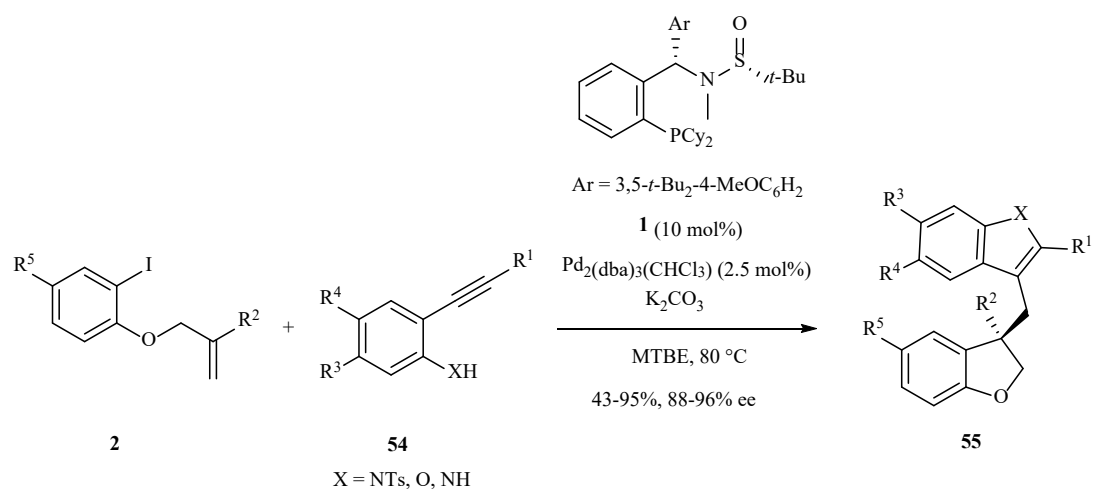
In 2021, pentacyclic chiral spirooxindoles **53** were synthesized by Guan et al. on the basis of a novel enantioselective palladium-catalyzed domino Heck/carbocyclization/Suzuki reaction of *N*-(2-bromoaryl)-2-naphthylacrylamides **51** with boronic acids **3** (Scheme 13) [25]. Performed at 50 °C in toluene in the presence of 4 mol% of Pd₂(dba)₃ and 16 mol% of novel phosphoramidite ligand **52** and Cs₂CO₃ as base, the cascade dearomative reaction afforded a variety of chiral spirooxindoles **53** in 25-91% yields and 86-99% ee (Scheme 13).



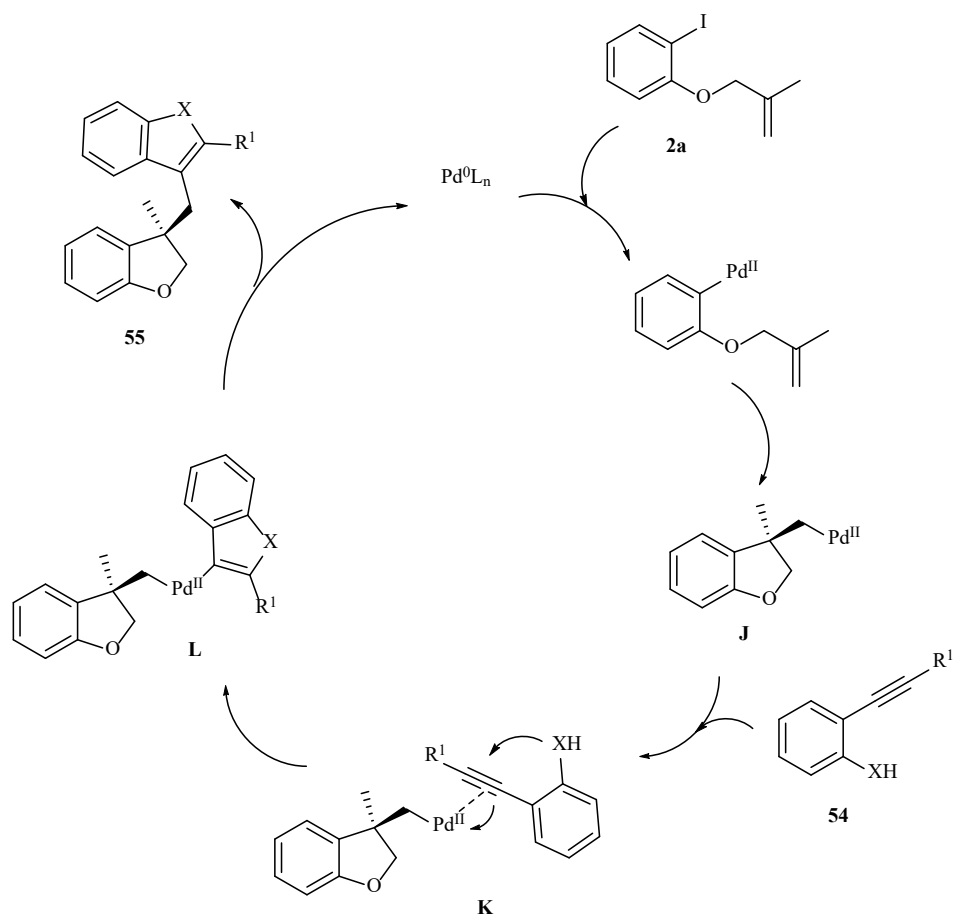
Scheme 13. Domino Heck/carbocyclization/Suzuki reaction of *N*-(2-bromoaryl)-2-naphthylacrylamides with boronic acids.

2.2. Carbon–Carbon and Carbon–Nitrogen/Oxygen Bond Formation

An enantioselective domino-Heck/nucleopalladation reaction of alkenyl-*O*-tethered aryl iodides **2** with alkyne-tethered nucleophiles **54**, such as phenols and sulfonamides, was described by Lautens et al., in 2021 (Scheme 14) [26]. Promoted by a chiral catalyst in situ generated from 2.5 mol% of Pd₂(dba)₃(CHCl₃) and 10 mol% of chiral ligand **1**, it resulted in the formation at 80 °C in MTBE (methyl *tert*-butyl ether) as solvent of chiral bisheterocyclic products **55** in 43-95% yields and 88-96% ee. A diversity of aryl halides and heteroatom-tethered alkynes were tolerated, thus allowing chiral benzofuran- (X = O) and indoline- (X = NTs, NH) containing products to be synthesized. This constituted the first example of highly enantioselective palladium-catalyzed domino reaction involving a carbopalladation between indoles and unactivated alkenes. The mechanism (Scheme 14) begins with the oxidative addition to aryl iodide **2a** (R¹ = R³ = R⁴ = H, R² = Me) and enantioselective carbopalladation leading to Pd(II) intermediate **J**. Then, alkyne **54** chelated to the palladium in **K** undergoes *anti*-nucleopalladation to form an alkenyl-alkyl palladium species **L**. The latter is then submitted to reductive elimination to form the final product.

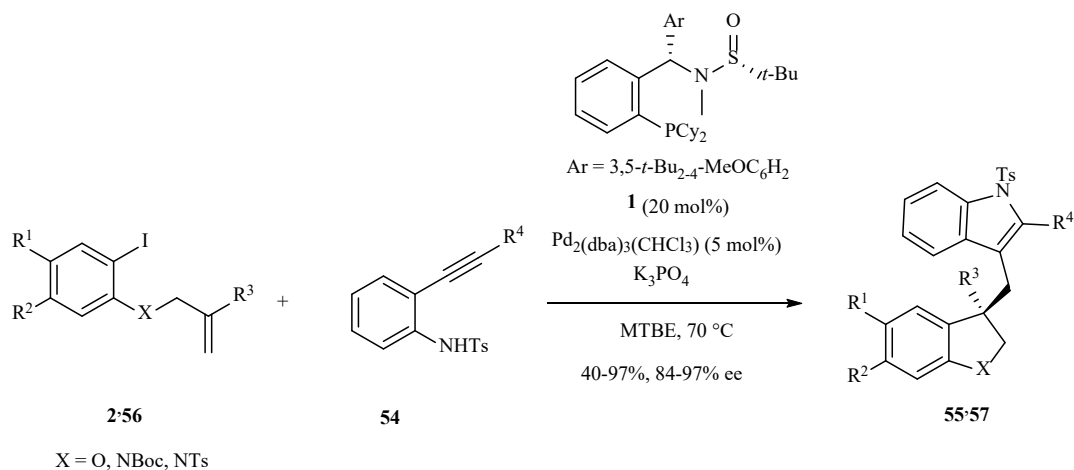


mechanism (with $\text{R}^2 = \text{Me}$, $\text{R}_3 = \text{R}_4 = \text{R}_5 = \text{H}$):



Scheme 14. Domino Heck/nucleopalladation reaction of alkenyl-*O*-tethered aryl iodides with alkyne-tethered nucleophiles.

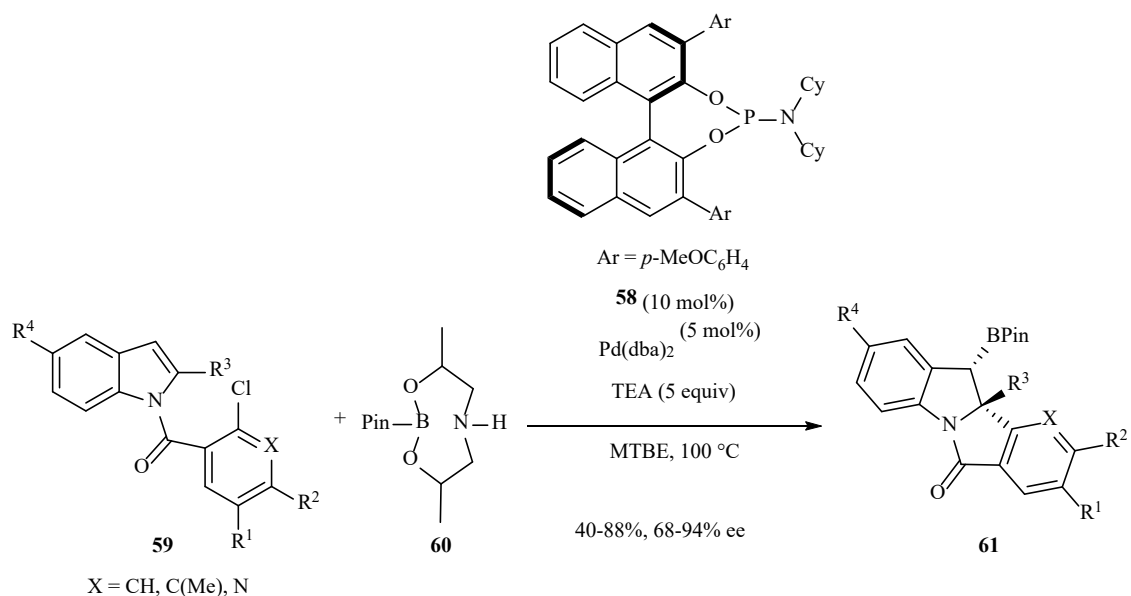
Similar results were almost concomitantly published by Zhang and Zhang using the same catalyst system, delivering chiral 2,3-dihydrobenzofuran-indoles **55** (X = O) but also indoline-substituted indoles **57** (X = NTs, NBoc) with comparable yields (40-97%) and enantioselectivities (84-97% ee), as shown in Scheme 15 [27].



Scheme 15. Domino Heck/nucleopalladation reaction of alkenyl-*O*- and *N*-tethered aryl iodides with alkyne-tethered amines.

2.3. Carbon–Carbon and Carbon–Boron Bond Formation

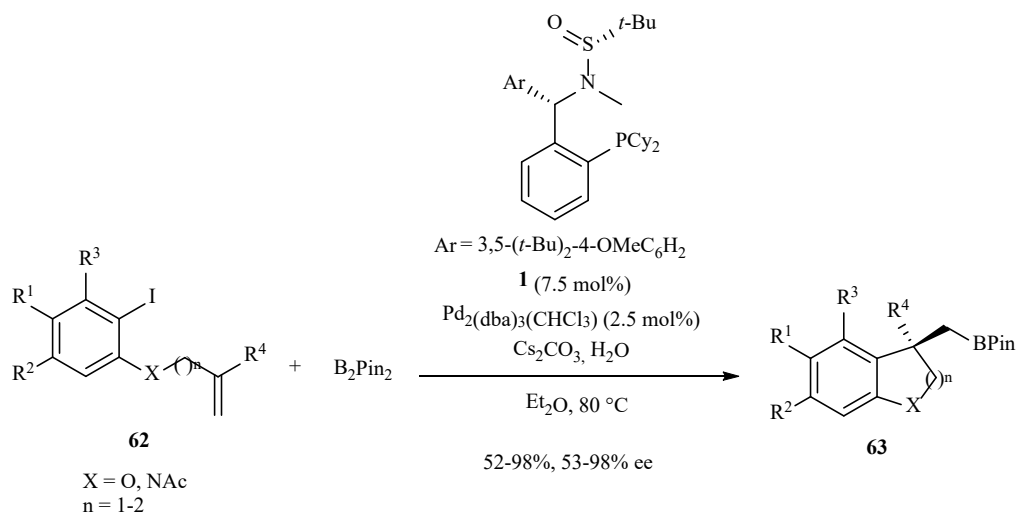
Aryl halides can react with boron reagents through domino Heck/borylation reaction to give Csp^3 -based organoboron derivatives [28]. For example, Lautens and Jia showed in 2019 that chlorinated *N*-tethered aryl indoles **59** reacted with boron reagent **60** to give chiral complex tetracyclic indolines **61** exhibiting two contiguous stereocenters (Scheme 16) [29]. When promoted at 100 °C by a chiral catalyst in situ generated from 5 mol% of $\text{Pd}(\text{dba})_2$ and 10 mol% of novel BINOL-derived chiral phosphoramidite ligand **58** in MTBE, the domino Heck/borylation reaction afforded these complex products in the presence of TEA (triethylamine) as base with 40-88% yields and 68-94% ee. Generally, lower enantioselectivities (68-79% ee) were observed in the case of steric hindrance at the halide ($\text{X} = \text{C}(\text{Me})$), as well as when substituents were present at the *para*-position of the amide tether ($\text{R}^1 = \text{OMe}, \text{F}$). Moreover, an heteroaromatic substrate ($\text{X} = \text{N}$) was tolerated but reacted with a lower enantioselectivity (82% ee).



Scheme 16. Domino Heck/borylation reaction of chlorinated *N*-tethered aryl indoles with a boron reagent.

Another domino Heck/borylation reaction was described by Zhang et al. in 2022, using 7.5 mol% of chiral P,N-ligand **1** combined with 2.5 mol% of $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (Scheme 17) [30]. The cascade reaction occurred between alkene-tethered aryl iodides **62** and B_2Pin_2 , leading to the corresponding chiral bicyclic boronic esters **63**

with 52-98% yields and 53-98% ee. Bicyclic 2,3-dihydrobenzofuranyl (X = O, n = 1), chromane (X = O, n = 2), indane (X = CH₂, n = 1) and indoline (X = N, n = 1) boronic esters could be easily synthesized.



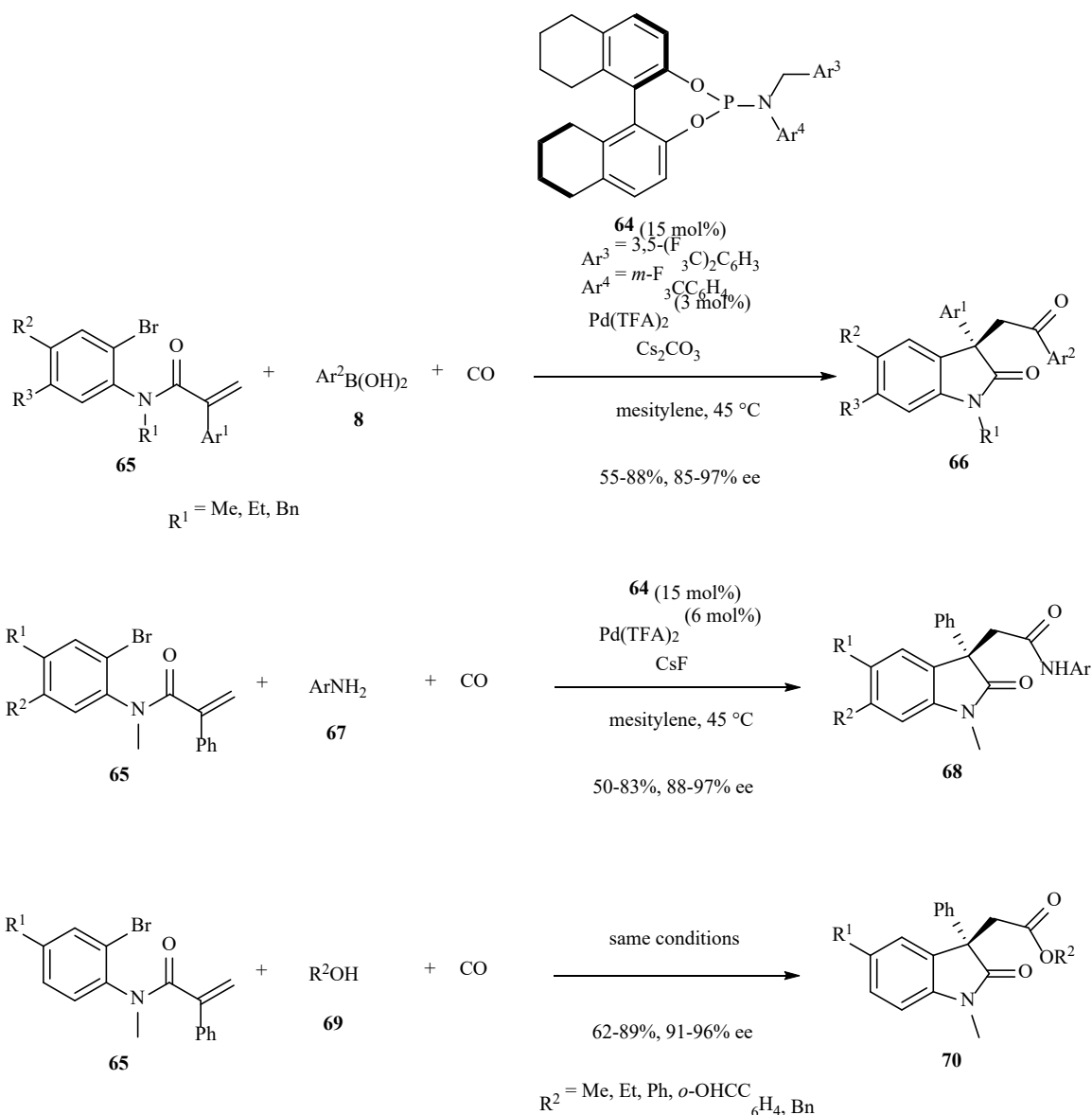
Scheme 17. Domino Heck/borylation reaction of alkene-tethered aryl iodides with B₂Pin₂.

3. THREE-COMPONENT DOMINO REACTIONS

3.1. Carbon–Carbon Bond Formation

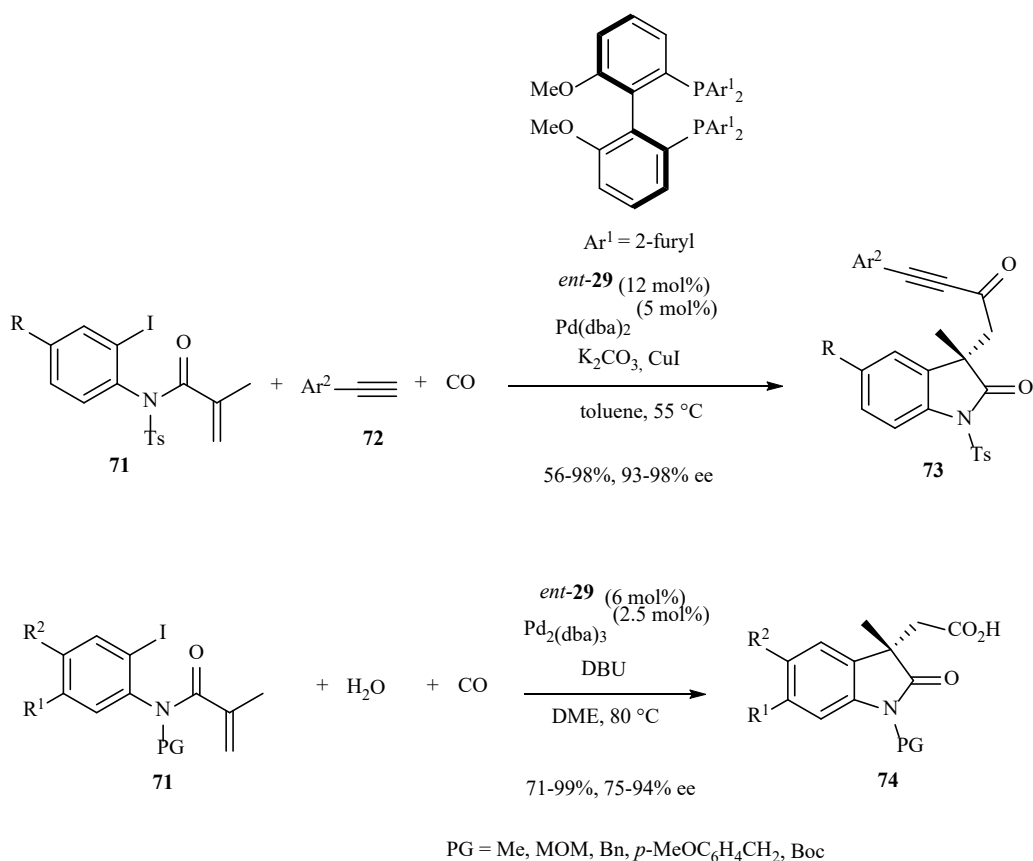
3.1.1. Bicyclic Molecules

Promoted by a chiral catalyst in situ generated from 15 mol% of novel chiral phosphoramidate **64** and 6 mol% of Pd(TFA)₂ (TFA: trifluoroacetic acid) in the presence of CsF as base, an unprecedented three-component enantioselective domino Heck/carbonylative Suzuki reaction between *N*-aryl acrylamides **65**, arylboronic acids **8** and CO was developed by Guan et al., in 2020 (Scheme 18) [31]. The process, performed at 45 °C in mesitylene, gave rise to the corresponding chiral oxindoles **66** exhibiting a β-carbonyl-substituted all-carbon quaternary stereocenter in 55-88% yields and 85-97% ee. The scope of the process could be extended to another type of nucleophiles, such as arylamines **67**, which resulted in the formation of chiral products **68** in 50-83% yields and 88-97% ee through related enantioselective domino Heck/amidation reaction (Scheme 18). Moreover, the use of nucleophiles, such as alcohols **69**, allowed chiral corresponding products **70** to be obtained in 62-89% yields and 91-96% ee through related domino Heck/esterification reaction (Scheme 18). In all cases of nucleophiles, a wide range of functional groups were tolerated on the substrates. This novel procedure was applied to the synthesis of biologically active hexahydropyrroloindole and its dimeric alkaloids.



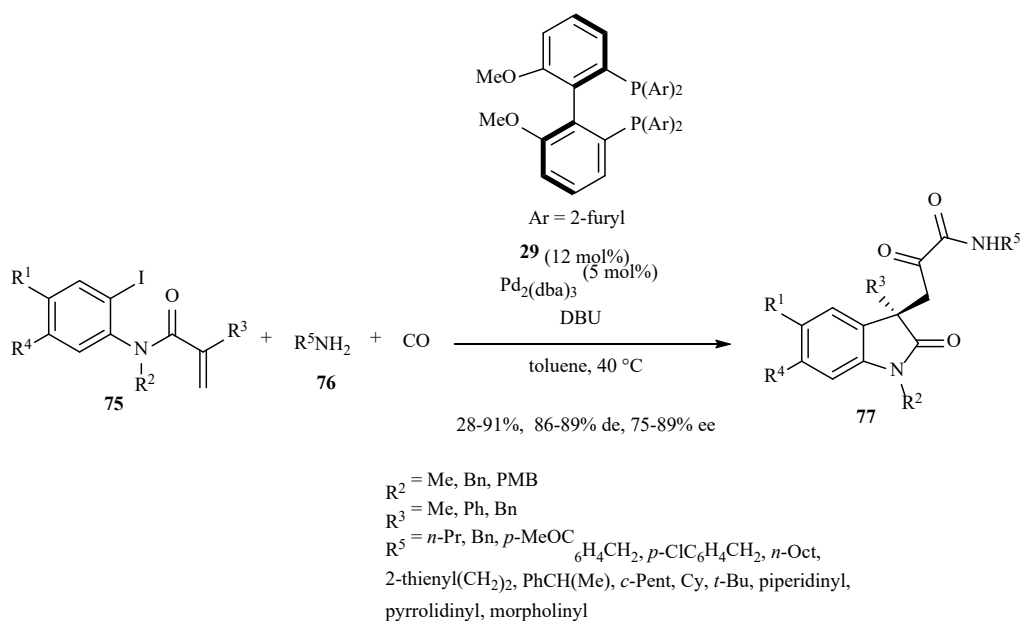
Scheme 18. Domino Heck/carbonylative Suzuki, Heck/amidation and Heck/esterification reactions of *N*-aryl acrylamides, arylboronic acids/arylamines/alcohols and CO.

In 2021, Wang and Ding employed chiral bisphosphine ligand *ent*-**29** to promote enantioselective three-component domino Heck/ carbonylative Sonogashira reaction between *N*-tosyl *o*-iodoacrylanilides **71**, terminal alkynes **72** and CO, which led to the corresponding chiral β -carbonylated 2-oxindoles **73** in 56-98% yields and 93-98% ee (Scheme 19) [32]. The reaction was carried out at 55 °C in toluene in the presence of a combination of 5 mol% of Pd(dba)₂ and 12 mol% of bisphosphine *ent*-**29** as catalyst system, K₂CO₃ as base and CuI as an additive. The presence of various types of substituents on the phenyl rings of both the two substrates were tolerated. In addition, the authors applied the same catalyst system to develop an asymmetric domino Heck/carbonylation reaction between *N*-protected *o*-iodoacrylanilides **71**, water as the nucleophile and CO. In this case, 6 mol % of ligand *ent*-**29** was used in combination with 2.5 mol% of Pd₂(dba)₃ to promote the process at higher temperature (80 vs 55 °C) in DME (dimethoxyethane) (Scheme 19). DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) was used as base but the reaction did not require the presence of CuI as an additive to occur. A series of chiral β -carbonylated 3,3-disubstituted oxindoles **74** were thus synthesized in 71-99% yields and 75-94% ee



Scheme 19. Domino Heck/carbonylation reactions of *o*-iodoacrylanilides, terminal alkynes/H₂O and CO.

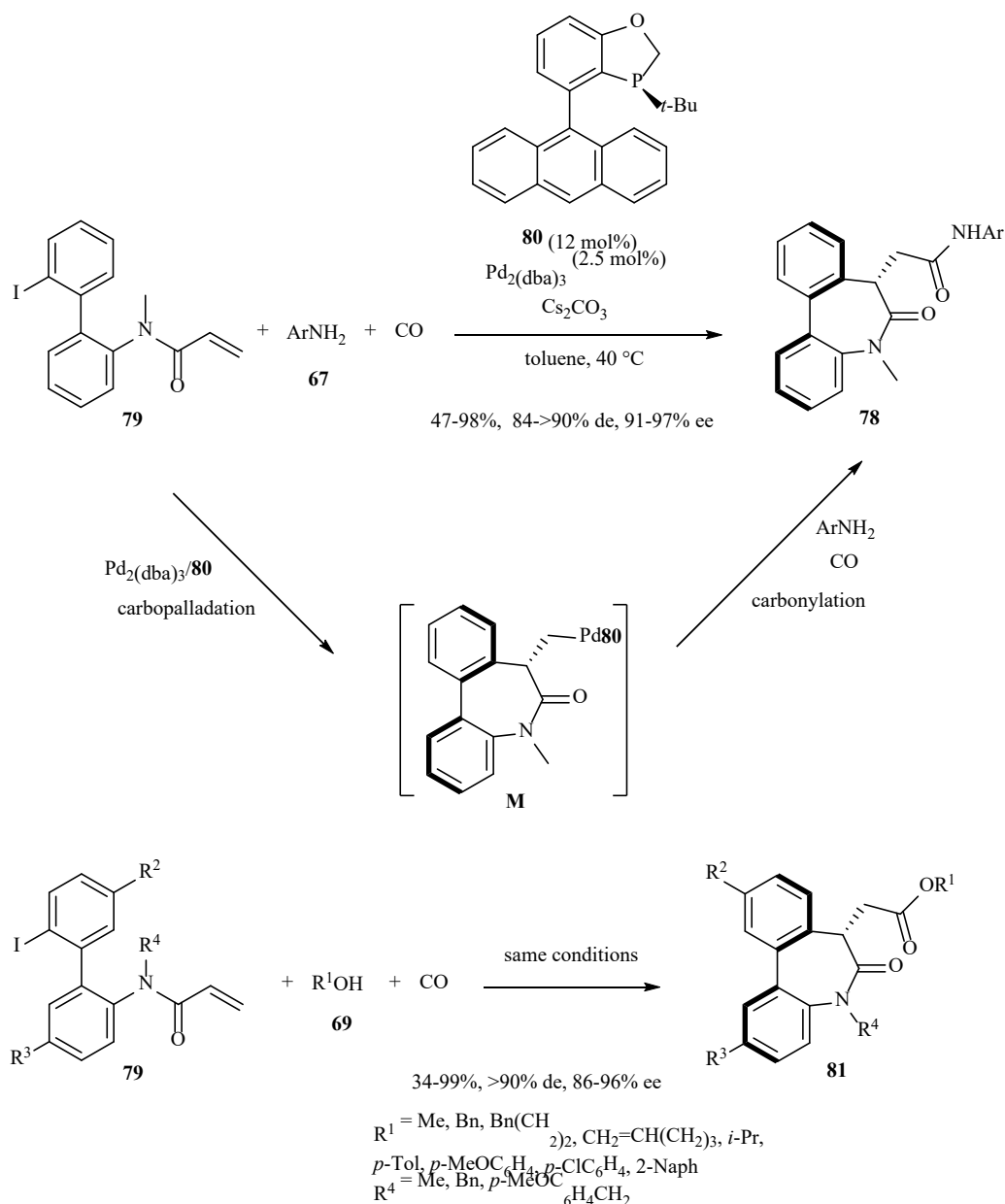
In 2022, Zhu and Luo disclosed an unprecedented three-component enantioselective domino Heck/carbonylation/aminocarbonylation reaction of *N*-protected *o*-iodoacrylanilides **75**, alkyl amines **76** and CO (Scheme 20) [33]. The catalyst system was composed of 12 mol% of chiral bisphosphine **29** and 5 mol% of Pd₂(dba)₃. Performed at 40 °C in toluene in the presence of DBU as base, the reaction afforded chiral α -ketoamides **77** in 28-91% yields, 86-89% de and 75-91% ee. This uncommon double CO insertion into the σ -alkylpalladium intermediate occurred selectively under atmospheric pressure of CO using an alkyl amine as the nucleophile. Primary, secondary as well as tertiary amines were compatible with comparable enantioselectivities obtained for primary (75-89% ee) and secondary amines (86-91% ee) while significant amounts of undesired monocarbonylated byproducts (double carbonylation : monocarbonylation = 5:1 to 15:1) were observed in the latter case.



Scheme 20. Domino Heck/carbonylation/aminocarbonylation reaction of *N*-protected *o*-iodoacrylanilides with alkyl amines and CO (Oct = octyl, Pent = pentyl).

3.1.2. Tricyclic Molecules

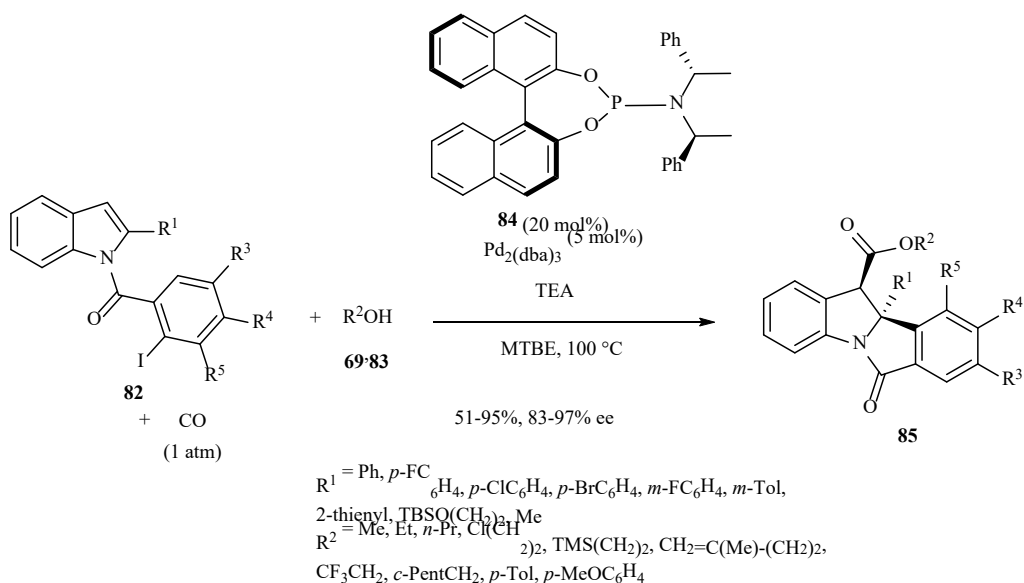
In 2021, Zhu and Luo reported the first synthesis of chiral bicyclic products **78** exhibiting a thermodynamically controlled stereogenic axis through enantioselective three-component palladium-catalyzed domino Heck/amidation reaction between *N*-methylacrylamides **79**, anilines **67** and CO (Scheme 21) [34]. This novel methodology, performed at 40 °C in toluene in the presence of Cs_2CO_3 as base, was promoted by 2.5 mol% of $\text{Pd}_2(\text{dba})_3$ combined with 12 mol% of chiral phosphine ligand **80** as catalyst system, leading to chiral dibenzo[*b,d*]azepin-6-ones **78** with 47-98% yields, 84->90% de and 91-97% ee. The authors proposed that the reaction evolved through cyclocarbopalladation, affording intermediate **M**, which then underwent carbonylation in the presence of anilines **67** and CO to form the final product. The scope of this methodology was extended to other nucleophiles, such as aliphatic as well as aromatic alcohols **69**, which resulted in the formation of chiral esters **81** through the corresponding domino Heck/esterification reaction with 34-99% yields, 90% de and 86-96% ee (Scheme 21).



Scheme 21. Domino Heck/amidation and domino Heck/esterification reactions of *N*-methylacrylamides, amines/alcohols and CO (Naph = naphthyl).

3.1.3. Tetracyclic Molecules

Another enantioselective three-component domino Heck/esterification reaction was described in 2022 by Yao and Lin, allowing the synthesis of tetracyclic chiral indoline-3-carboxylates **85** exhibiting two contiguous stereocenters (Scheme 22) [35]. The latter species were generated at 100 °C in MTBE in the presence of TEA as base from the corresponding variously substituted *N*-arylacyl indoles **82**, alcohols **69,83** and CO. The catalyst was constituted of a mixture of 20 mol% of chiral phosphoramidate ligand **84** and 5 mol% of Pd₂(dba)₃, allowing products **85** to be obtained with 51-95% yields and 83-97% ee.

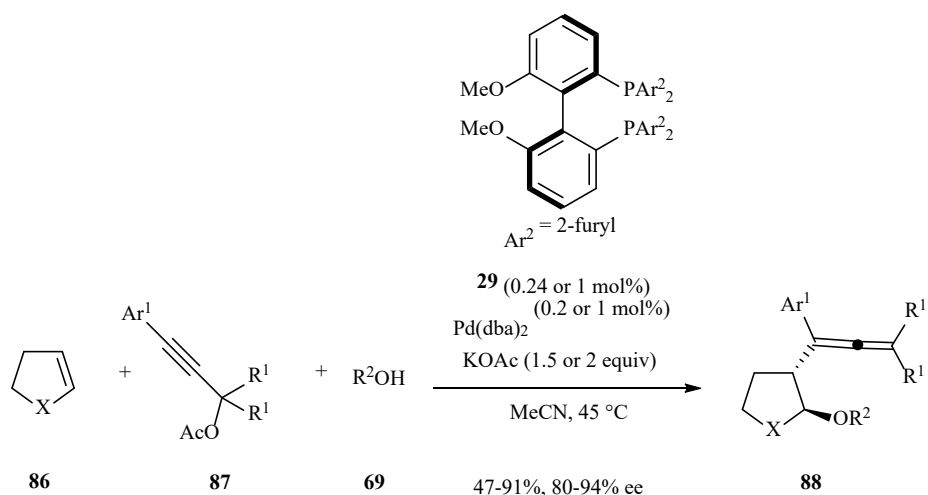


Scheme 22. Domino Heck/esterification reaction of *N*-arylacyl indoles, alcohols and CO (TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, Tol = tolyl).

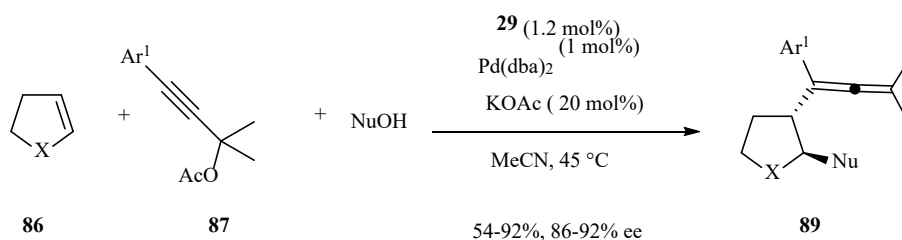
3.2. Carbon–Carbon and Carbon–Nitrogen/Oxygen Bond Formation

3.2.1. Monocyclic Molecules

Enantioselective three-component reactions between cyclic alkenes, propargylic acetates and various nucleophiles, spanning from alcohols, water, carboxylic acids to aryl amines, were developed in 2020 by Zhou et al., by using at 45 °C in acetonitrile a chiral palladium catalyst derived from Pd(dba)₂ and chiral ligand **29** [36]. A catalyst loading as low as 0.2 mol% was sufficient to promote the alkoxyallenylation reaction of nucleophiles as alkyl alcohols **69** with 2,3-dihydrofuran (X = O) **86** and propargylic acetates **87** to give the corresponding chiral *trans*-products **88** exclusively with 47-91% yields and 80-94% ee (Scheme 23). The reaction of another cyclic alkene, such as *N*-Boc-2,3-dihydropyrrole **86** (X = NBoc), with propargylic acetates **87** and aliphatic alcohols **69** also gave rise to the corresponding chiral products **88** in 55-88% yields and 87-92% ee but under catalysis with 1 mol% of Pd(dba)₂ combined with 2 mol% of chiral ligand **29** (Scheme 23). The scope of the methodology could be extended to other oxygen nucleophiles, such as phenols, water and carboxylic acids, as well as nitrogen nucleophiles, such as electron-poor aryl amines. As illustrated in Scheme 23, the three-component oxyallenylation of 2,3-dihydrofuran/*N*-Boc-2,3-dihydropyrrole **86** with propargylic acetates **87** and either phenol, acetic acid, or water in the presence of 1 mol% of Pd(dba)₂ and 1.2 mol% of chiral ligand **29** led to the desired products **89** in 54-92% and 86-92% ee. Using amines as nucleophiles allowed related asymmetric azaallenylation to occur under the same reaction conditions. The reaction of the latter nucleophiles with 2,3-dihydrofuran (X = O) **86** and propargylic acetates **87** yielded the corresponding products **89** with 60-81% yields and 86-91% ee. The mechanism of the reaction (Scheme 23) assumes the formation of allenic intermediate **N** after oxidative addition. The latter species was further subjected to attack by the nucleophile to give intermediate **O** which finally underwent reductive elimination to provide the product.

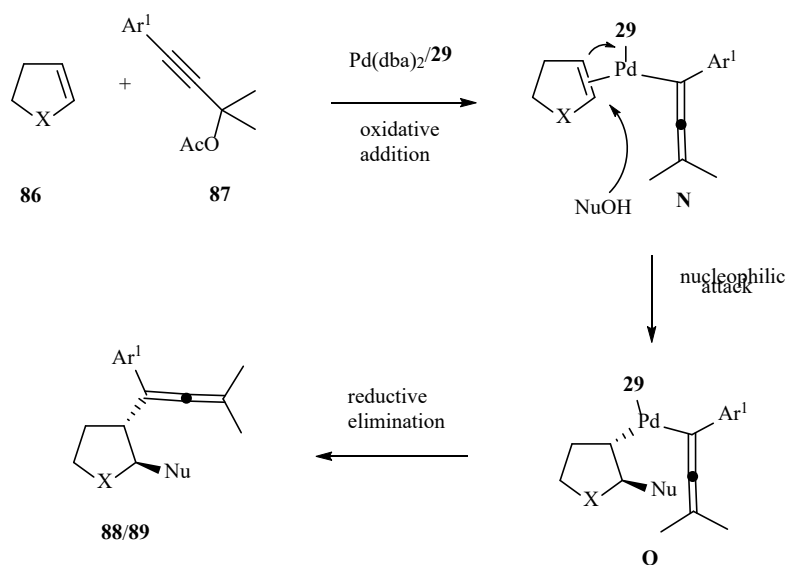


$\text{X} = \text{O}, \text{NBoc}$
 $\text{R}^2 = i\text{-Pr}, \text{Me}, \text{Et}, \text{Bn}, \text{Cy}, c\text{-Bu}, c\text{-Pent}, n\text{-Bu}$



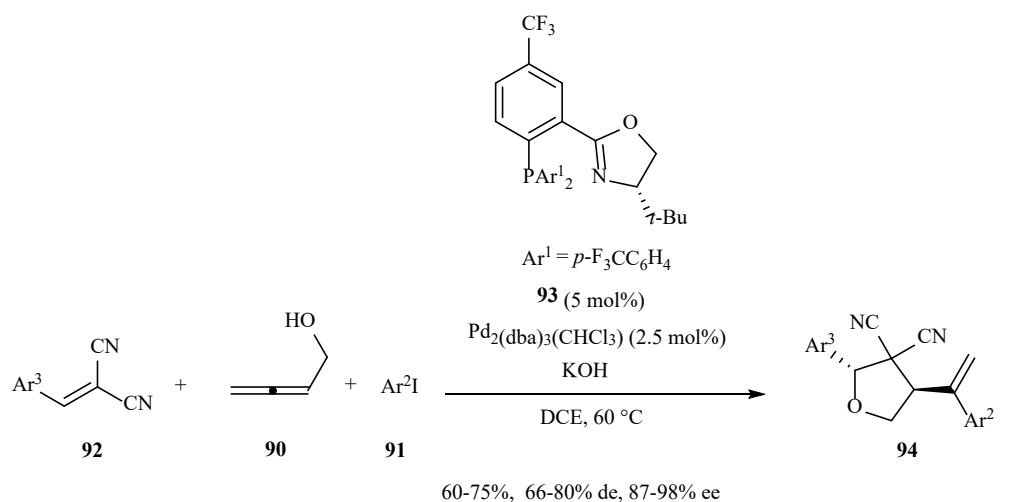
$\text{X} = \text{O}, \text{NBoc}$
 $\text{Ar}^1 = \text{Ph}, p\text{-FC}_6\text{H}_4$
 $\text{Nu} = \text{AcO}, \text{PhO}, \text{HO}, 3,5\text{-(F}_3\text{C)}_2\text{C}_6\text{H}_3\text{NH},$
 $3,5\text{-F}_2\text{C}_6\text{H}_3\text{NH}, p\text{-F}_3\text{CC}_6\text{H}_4\text{NH}$

mechanism:

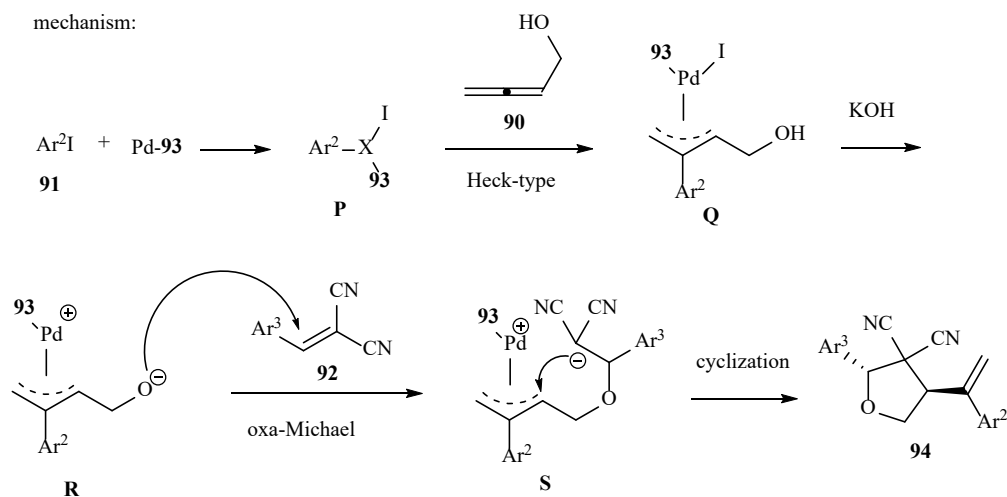


Scheme 23. Domino alkoxy-/oxy-/azaallenylation reactions of cyclic alkenes, propargylic acetates and nucleophiles (Nu = nucleophile).

Later in 2022, Zhang and Li described the first enantioselective palladium-catalyzed three-component reaction between 2,3-allenol **90**, aryl iodides **91**, and 2-arylmethylenemalononitriles **92** (Scheme 24) [37]. This domino Heck-type/oxa-Michael/cyclization reaction evolved at 60 °C in DCE in the presence of KOH as base and a combination of 5 mol% of phosphine ligand **93** and 2.5 mol% of Pd₂(dba)₃·CHCl₃. Chiral functionalized tetrahydrofurans **94** were produced in 60-75% yields, 66-80% de and 87-98% ee. A mechanism is proposed in Scheme 24, beginning with the oxidative addition of the chiral palladium complex to the aryl iodide to give intermediate **P** which then undergoes a Heck-type reaction with the allenol, providing π -allylpalladium intermediate **Q**. Then, the latter is converted into zwitterionic allyl palladium intermediate **R** in the presence of KOH. The oxa-Michael addition of intermediate **R** with the 2-arylmethylenemalononitrile affords intermediate **S**, which undergoes an intramolecular nucleophilic attack to give the final product. The utility of this novel methodology was demonstrated in a total synthesis of lignan (–)-2-episesaminone.



mechanism:

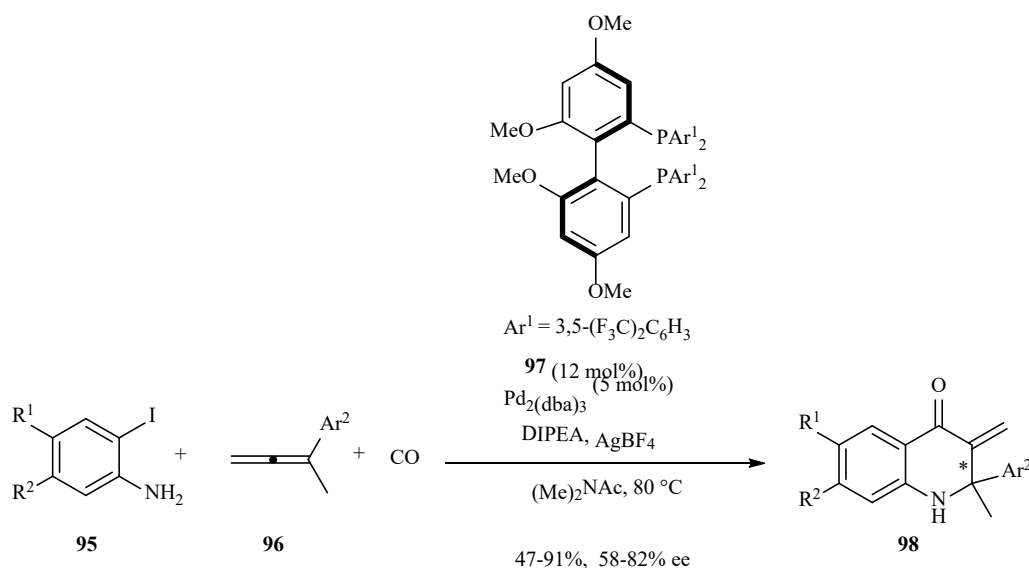


Scheme 24. Domino Heck-type/oxa-Michael/cyclization reaction of aryl iodides, a 2,3-allenol, and 2-arylmethylenemalononitriles.

3.2.2. Bicyclic Molecules

In 2021, Dong et al. developed an enantioselective domino Heck/carbonylation reaction between *o*-iodoanilines **95**, allenes **96** and CO (Scheme 25) [38]. The three-component process performed at 80 °C in *N,N*-dimethylacetamide as solvent was catalyzed by a chiral complex in situ generated from 5 mol% of Pd₂(dba)₃ and 12 mol% of chiral bisphosphine ligand **97** in the presence of DIPEA (diisopropylethylamine) as base and AgBF₄

as an additive. Under these conditions, chiral dihydroquinolinones **98** were obtained in 47-91% yields and 58-82% ee.



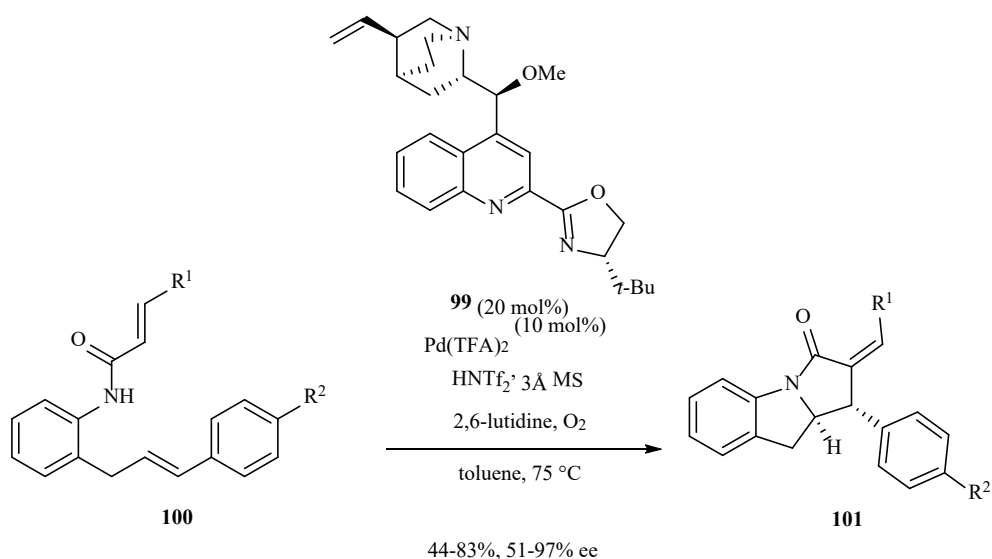
Scheme 25. Domino carbonylative Heck/aminocyclization reaction of *o*-iodoanilines, allenes and CO.

4. ONE- AND TWO-COMPONENT DOMINO MULTICYCLIZATION REACTIONS

4.1. Carbon–Carbon and Carbon–Nitrogen/Oxygen Bond Formation

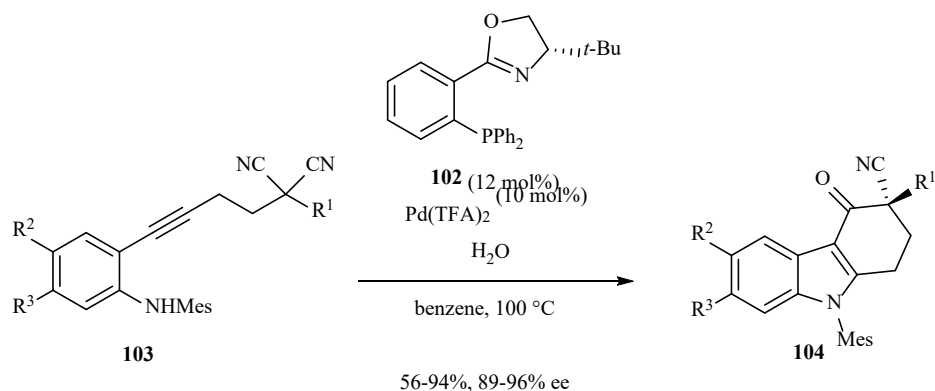
4.1.1. Tricyclic Molecules

Many types of chiral palladium complexes have been used to catalyze asymmetric oxidative cascade cyclizations [39]. In an example reported in 2019, He et al. disclosed the synthesis of novel cinchona alkaloid-derived oxazoline ligands to be investigated in an enantioselective intramolecular oxidative cyclization of aromatic nitrogen-containing dienes (Scheme 26) [40]. Optimal ligand **99** combined at 20 mol% of catalyst loading with 10 mol% of $\text{Pd}(\text{TFA})_2$ in toluene was found to be an efficient promoter for the domino reaction of aromatic alkenyl amides **100** with O_2 , providing the corresponding chiral dihydroindole polycyclic products **101** in 44-83% yields and 51-97% ee. It must be noted that these molecules represented relevant molecules for medicinal chemistry.



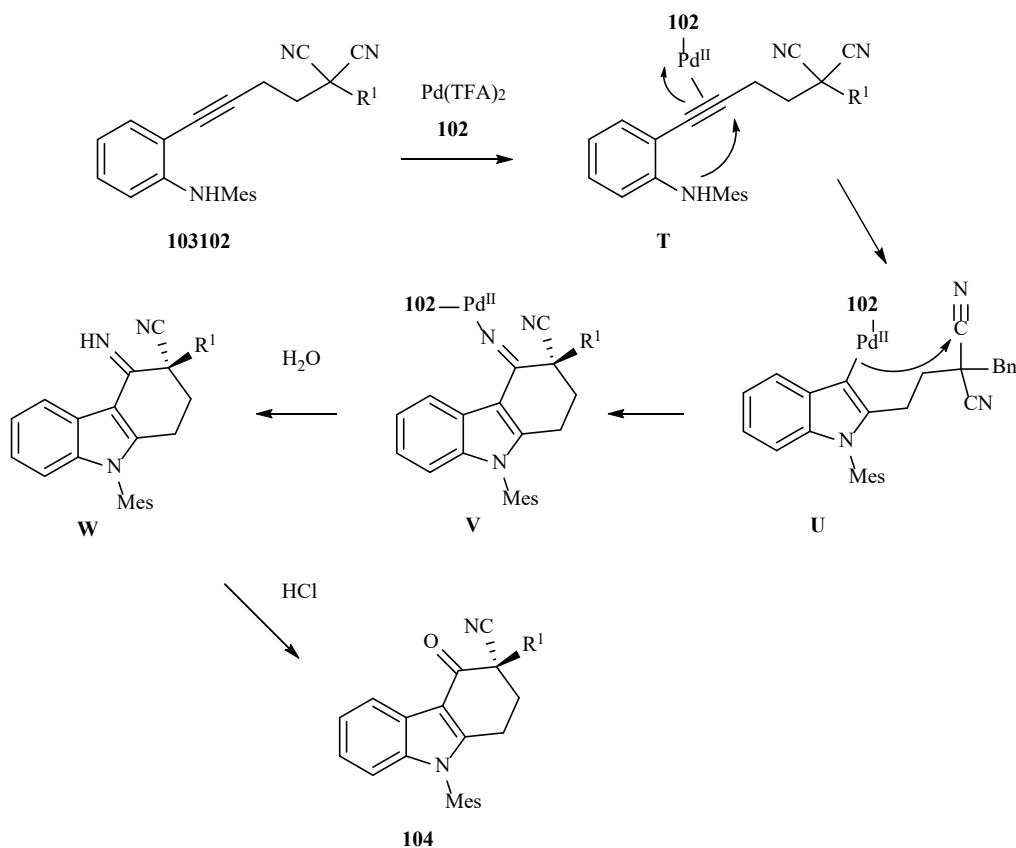
Scheme 26. Domino oxidative cyclization of aromatic nitrogen-containing dienes (MS = molecular sieves, Tf = trifluoromethanesulfonyl).

Another oxazoline ligand was employed in 2021 by Liu et al. in an enantioselective aminocyclization/intramolecular nucleophilic addition cascade reaction of alkyne-tethered malononitriles **103** (Scheme 27) [41]. Indeed, the chiral complex in situ generated from 10 mol% of Pd(TFA)₂ and 12 mol% of chiral ligand **102** was found efficient to promote aminocyclization and desymmetrizing nitrile addition cascade reaction of alkyne-tethered malononitriles **103** in benzene at 100 °C in the presence of water as an additive, which gave rise to the corresponding chiral carbazolones **104** exhibiting a quaternary stereocenter in 56-94% yields and 89-96% ee. After coordination of the Pd(II) chiral catalyst to the C≡C triple bond providing intermediate **T**, the cascade reaction involved a *trans*-aminopalladation to give indolylpalladium(II) species **U**, which further underwent intramolecular nucleophilic addition to the proximal nitrile, leading to intermediate **V**. In the presence of water, intermediate **V** was protonated to afford imine **W** along with recovered catalyst. Subsequent hydrolysis of **W** by aqueous HCl produced the final carbazolone.



$R^1 = \text{Bn, 3,4,5-(MeO)}_3\text{C}_6\text{H}_2\text{CH}_2, (2\text{-Naph})\text{CH}_2, (2\text{-thienyl})\text{CH}_2, (2\text{-furyl})\text{CH}_2, (\text{Me})_2\text{C}=\text{CHCH}_2, n\text{-Pr, CyCH}_2, c\text{-PrCH}_2, \text{Me, } i\text{-Pr, Ph, Ac}(\text{CH}_2)_2, \text{HO}(\text{CH}_2)_4, \text{PhthN}(\text{CH}_2)_3, \text{BnO}(\text{CH}_2)_2\text{N}(\text{Boc})(\text{CH}_2)_3, (\text{Cbz})\text{N}(\text{Boc})(\text{CH}_2)_3, \text{PhC}\equiv\text{C}(\text{CH}_2)_2, \text{[O]}_2(\text{CH}_2)_2$

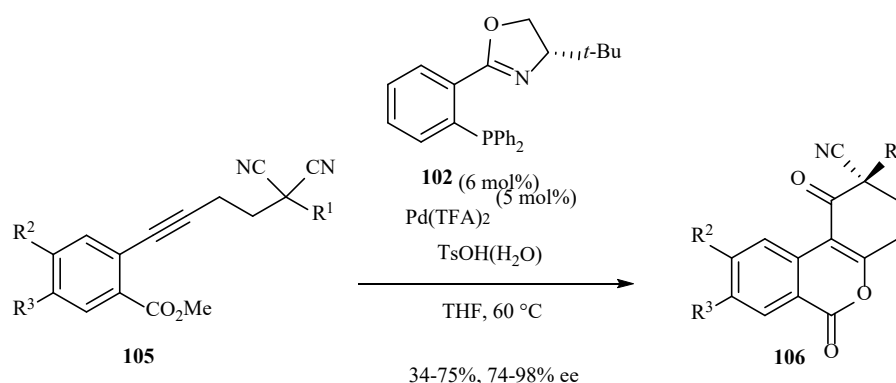
mechanism (with $R^2 = R^3 = \text{H}$):



Scheme 27. Domino aminocyclization/intramolecular nucleophilic addition reaction of alkyne-tethered malononitriles (Cbz = benzyloxycarbonyl, Mes = mesyl, Phth = phthalimido).

In addition, the same catalyst system was applied to develop enantioselective annulation of other alkyne-tethered malononitriles **105** (Scheme 28) [42]. In this case, only 5 mol% of Pd(TFA)_2 was sufficient in combination with 6 mol% of chiral phosphinoxazoline ligand **102** to induce the cascade reaction performed in THF

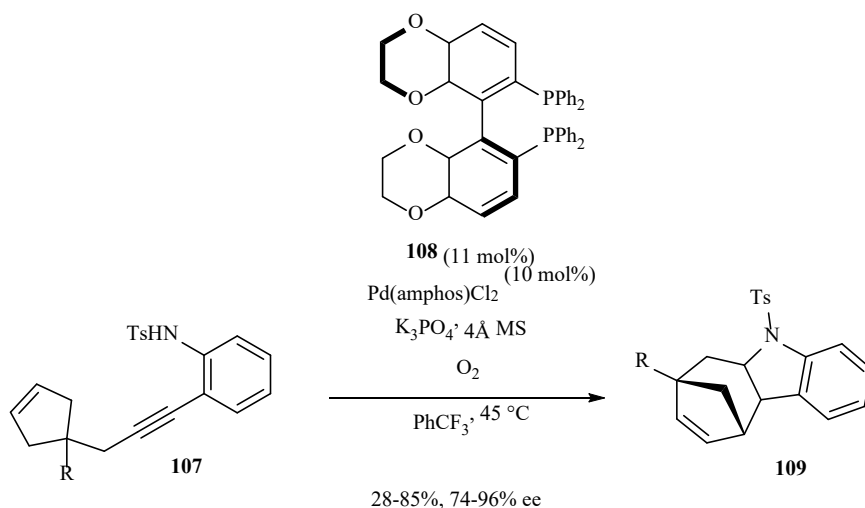
(tetrahydrofuran) as the solvent at a lower temperature (60 vs 100 °C). The reaction of methyl *o*-alkynylbenzoates **105** performed in the presence of TsOH·H₂O (Ts: tosyl) as an additive evolved through successive oxypalladation and intramolecular nitrile addition, thus leading to the corresponding chiral 3,4-ring-fused isocoumarins **106** exhibiting a quaternary stereocenter with 34-75% yields and 74-98% ee.



Scheme 28. Domino oxypalladation/intramolecular nucleophilic addition reaction of alkyne-tethered malononitriles.

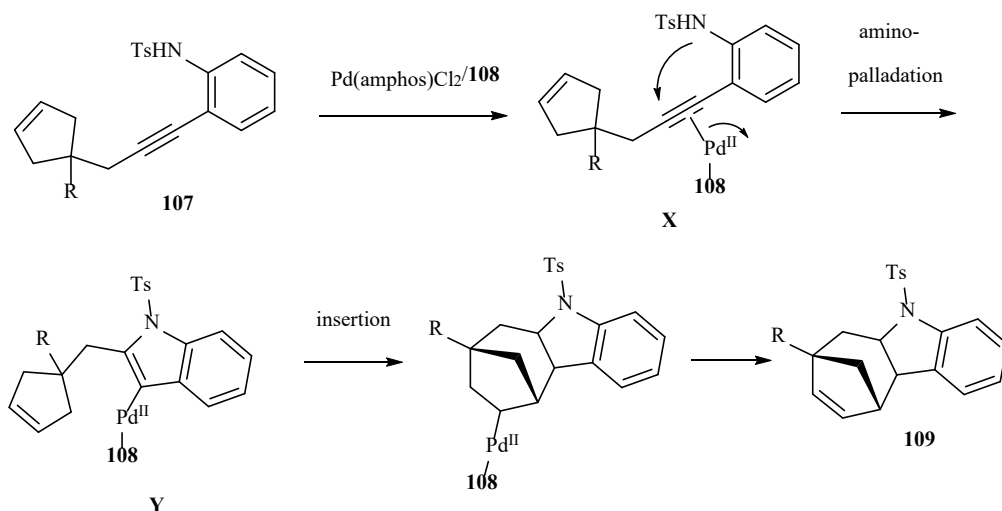
4.1.2. Tetracyclic Molecules

Indole-fused bicyclo[3.2.1]octanes constitute structural skeletons of natural and/or bioactive products. In 2021, an enantioselective cascade oxidative cyclization of *N*-sulfonyl-2-alkynylanilides **107** was developed by Ye et al. to reach this type of products (Scheme 29) [43]. The catalyst system was composed of 11 mol% of chiral bisphosphine ligand **108** and 10 mol% of Pd(amphos)Cl₂ (amphos: [4-(*N,N*-dimethylamino)phenyl]di-*tert*-butylphosphine) in CF₃Ph as solvent. Performed at 45 °C in the presence of K₃PO₄ as base under O₂ atmosphere, the cascade reaction of *N*-sulfonyl-2-alkynylanilides **107** underwent domino aminopalladation/Heck-type reaction, resulting in the formation of chiral indole-fused bicyclo[3.2.1]octanes **109** bearing a quaternary stereocenter in 28-85% yields and 74-96% ee. In the mechanism proposed in Scheme 29, the coordination of the palladium(II) catalyst to the C≡C triple bond of the substrate provided palladium intermediate **X**, which subsequently underwent aminopalladation to give palladium species **Y**. Then, the latter species was subjected to intramolecular C=C double-bond insertion followed by β-H elimination which afforded the final product.



$\text{R} = \text{CO}_2\text{Bn}, \text{CO}_2\text{Me}, \text{CO}_2\text{Et}, \text{CO}_2i\text{-Pr}, \text{CO}_2t\text{-Bu}, \text{Et}_2\text{NCO},$
 $\text{AcOCH}_2, \text{BnOCH}_2, \text{TBSOCH}_2, \text{O} \begin{array}{c} \diagup \\ \text{N} \\ \diagdown \end{array} \text{CH}_2, \text{O} \begin{array}{c} \diagup \\ \text{N} \\ \diagdown \end{array} \text{O}$

mechanism:

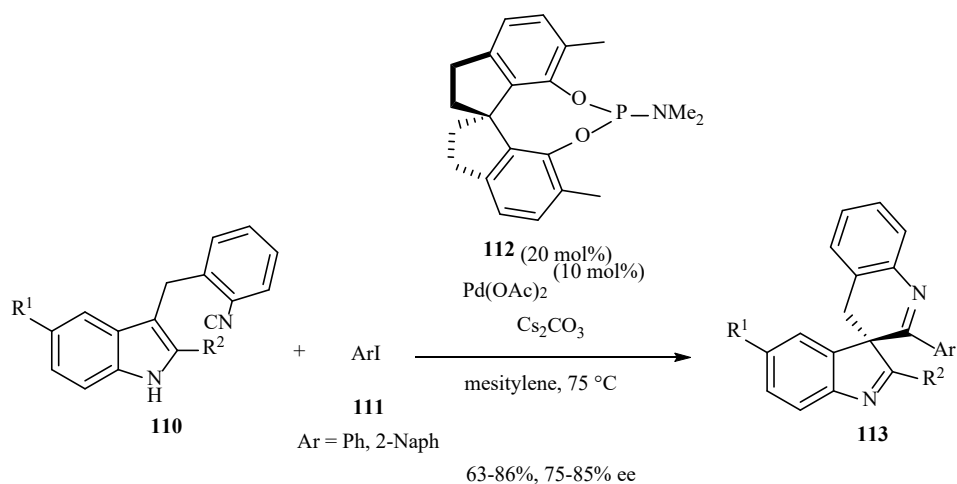


Scheme 29. Domino oxidative aminopalladation/Heck-type reaction of *N*-sulfonyl-2-alkynylanilides.

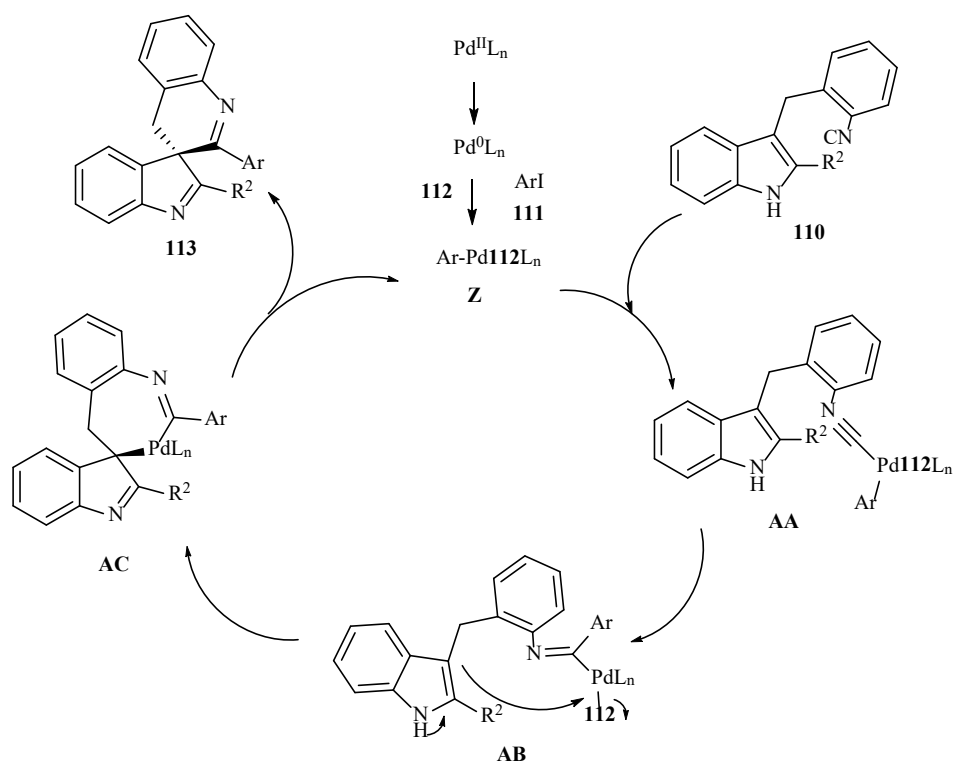
4.2. Carbon–Carbon Bond Formation

Spiroindolines are important structures in medicinal chemistry and, consequently, their synthesis is challenging. A novel methodology to prepare these molecules was described in 2021 by Wang et al. based on an enantioselective palladium-catalyzed dearomative imidoylative spirocyclization of 3-(2-isocyanoethyl)indoles **110** with aryl iodides **111** (Scheme 30) [44]. This cascade reaction involved an isocyanide insertion followed by a nucleophilic attack performed at 75 °C in mesitylene in the presence of Cs_2CO_3 as base. The catalyst in situ generated from 20 mol% of chiral phosphoramidite ligand **112** and 10 mol% of Pd(OAc)_2 allowed the formation of chiral 2'-aryl-substituted spiroindolines **113** in 63-86% yields and 75-85% ee. In the supposed mechanism depicted in Scheme 30, the cascade reaction began with the oxidative addition between the aryl iodide and chiral active palladium (II) species **Z** to give intermediate **AA**. Then, coordination of the isocyanide to the palladium and its migratory insertion provided imidoyl palladium intermediate **AB**. Dearomative nucleophilic attack of indole to

the palladium center resulted in the formation of seven-membered palladacyclic complex **AC** which was finally subjected to reductive elimination to afford the product along with regenerated catalyst.



proposed mechanism ($\text{R}^1 = \text{H}$):



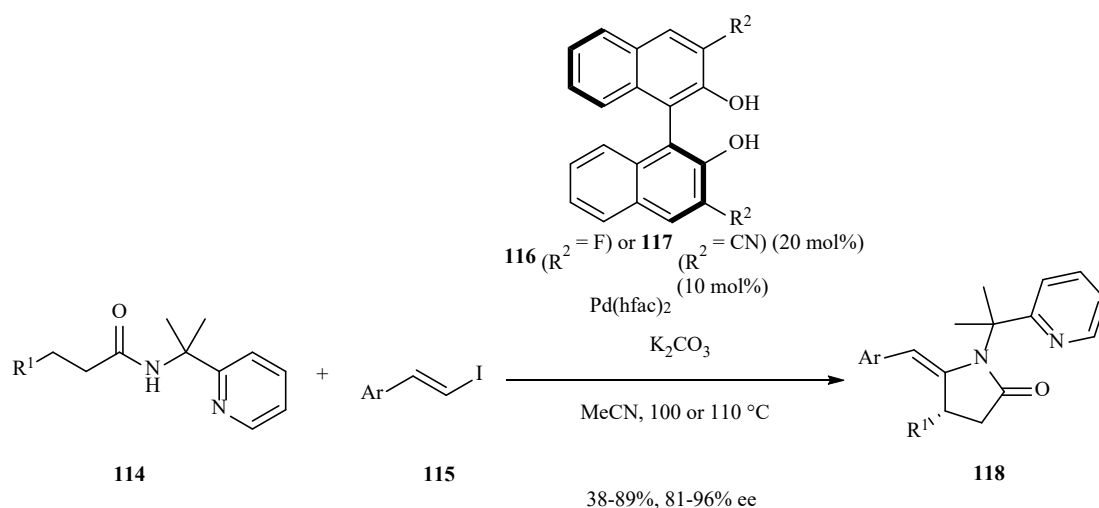
Scheme 30. Domino isocyanide insertion/nucleophilic attack reaction of 3-(2-isocyanoethyl)indoles with aryl iodides ($\text{L} = \text{ligand}$).

5. MISCELLANEOUS ONE- AND TWO-COMPONENT DOMINO REACTIONS

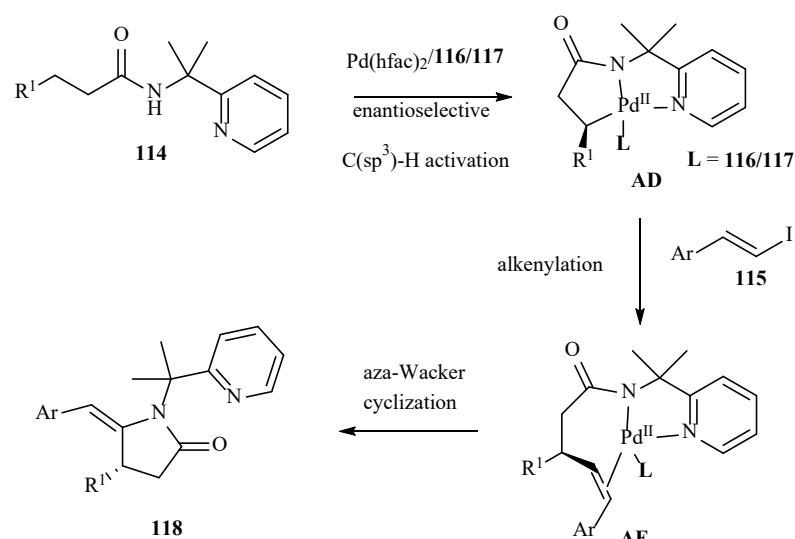
5.1. Carbon–Carbon and Carbon–Nitrogen Bond Formation

5.1.1. Monocyclic Molecules

The synthesis of γ -lactams is challenging related to their biological importance. In this context, Shi et al. disclosed in 2020 a novel methodology to prepare chiral γ -lactams containing a β -stereocenter dealing with an enantioselective domino methylene $C(sp^3)\text{-H}$ alkenylation/aza-Wacker cyclization reaction between 2-pyridinylisopropyl-derived aliphatic amides **114** and aryl vinyl iodides **115** (Scheme 31) [45]. The catalyst system was composed of 10 mol% of $\text{Pd}(\text{hfac})_2$ (hfac: hexafluoroacetylacetonate) and 20 mol% of chiral BINOL(1,1'-bi-2-naphthol)-derived ligand **116** ($R^2 = \text{F}$) or **117** ($R^2 = \text{CN}$). Performed in acetonitrile in the presence of K_2CO_3 as base, the reaction led to chiral β -stereogenic γ -lactams **118** with 38-89% yields and high 81-96% ee. A mechanism is proposed in Scheme 31, beginning with asymmetric $C(sp^3)\text{-H}$ activation of the β -methylene, leading to chiral palladacycle intermediate **AD**. The latter species then reacted with the aryl vinyl iodide to give the corresponding intermediate **AE**. A subsequent palladium-catalyzed aza-Wacker-type cyclization finally yielded the final γ -lactam. Generally, the use of chiral ligand **117** allowed higher yields albeit combined with slightly reduced enantioselectivities to be obtained in comparison with chiral ligand **116**. A range of aryl vinyl iodides bearing either electron-withdrawing or electron-donating substituents on the phenyl ring were compatible whereas no reaction occurred in the case of alkyl vinyl iodides.

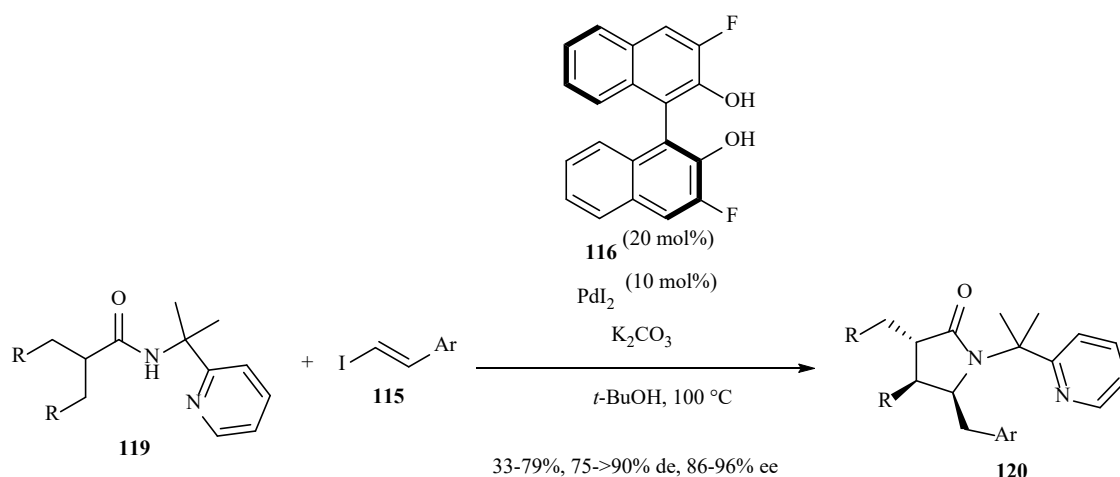


mechanism:

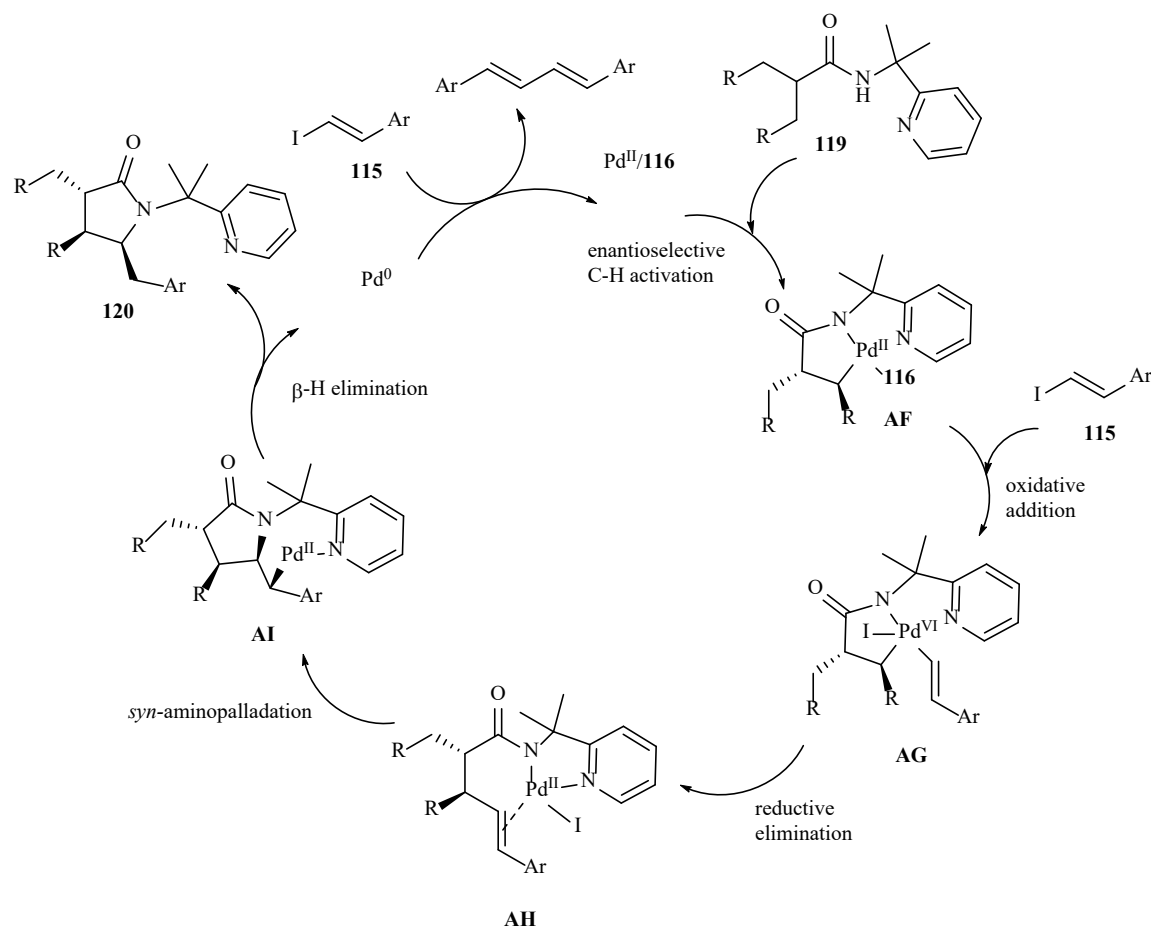


Scheme 31. Domino alkenylation/aza-Wacker cyclization reaction of 2-pyridinylisopropyl-derived aliphatic amides with aryl vinyl iodides.

In 2021, these authors applied a related methodology to synthesize chiral γ -lactams containing α,β -contiguous stereocenters [46]. In this case, the domino methylene $C(sp^3)$ -H alkenylation/aza-Wacker cyclization reaction occurred between another type of 2-pyridinylisopropyl-derived aliphatic amides, such as gem-dialkyl aliphatic amides **119**, and aryl vinyl iodides **115** (Scheme 32). By using at 100 °C a combination of 10 mol% of PdI_2 and 20 mol% of chiral BINOL-derived ligand **116** as catalyst system in *tert*-butanol as solvent in the presence of K_2CO_3 as base, the reaction afforded chiral γ -lactams **120** in 33-79% yields, 75->90% and 86-96% ee. The presence of either electron-donating or electron-withdrawing substituents on the phenyl ring of the aryl iodides was tolerated, leading to the corresponding chiral γ -lactams with enantioselectivities of 87-95% ee and 90-95% ee, respectively, combined with diastereoselectivities of 84->90% de and 88->90% de, respectively. On the other hand, alkyl vinyl iodides were not compatible. Moreover, gem-dialkyl aliphatic amides **119** could exhibit either alkyl or aryl substituents (R). A possible mechanism depicted in Scheme 32 begins with the cleavage of one of the four β -methylene $C(sp^3)$ -H bonds assisted by the chiral ligand, which leads to the formation of chiral palladacycle intermediate **AF**. Then, oxidative addition of the aryl vinyl iodide onto **AF** affords Pd(IV) species **AG**, which subsequently undergoes reductive elimination to generate palladium intermediate **C**. The coordination of the amide and alkene to palladium in **AH** facilitates intramolecular *syn*-aminopalladation to occur, providing palladium intermediate **AI**. The latter is further subjected to β -H elimination, affording the final chiral γ -lactam. In addition, the Pd(0) species is reoxidized to Pd(II) by consuming 2 equivalents of aryl vinyl iodide to close the catalytic cycle with generation of a 1,3-diene.



mechanism:

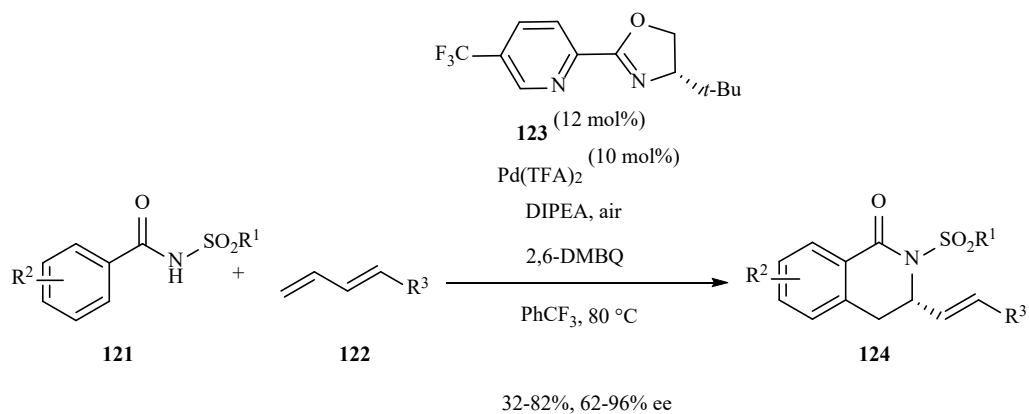


Scheme 32. Domino methylene alkenylation/aza-Wacker cyclization reaction of other 2-pyridinylisopropyl-derived aliphatic amides with aryl vinyl iodides.

5.1.2. Bicyclic Molecules

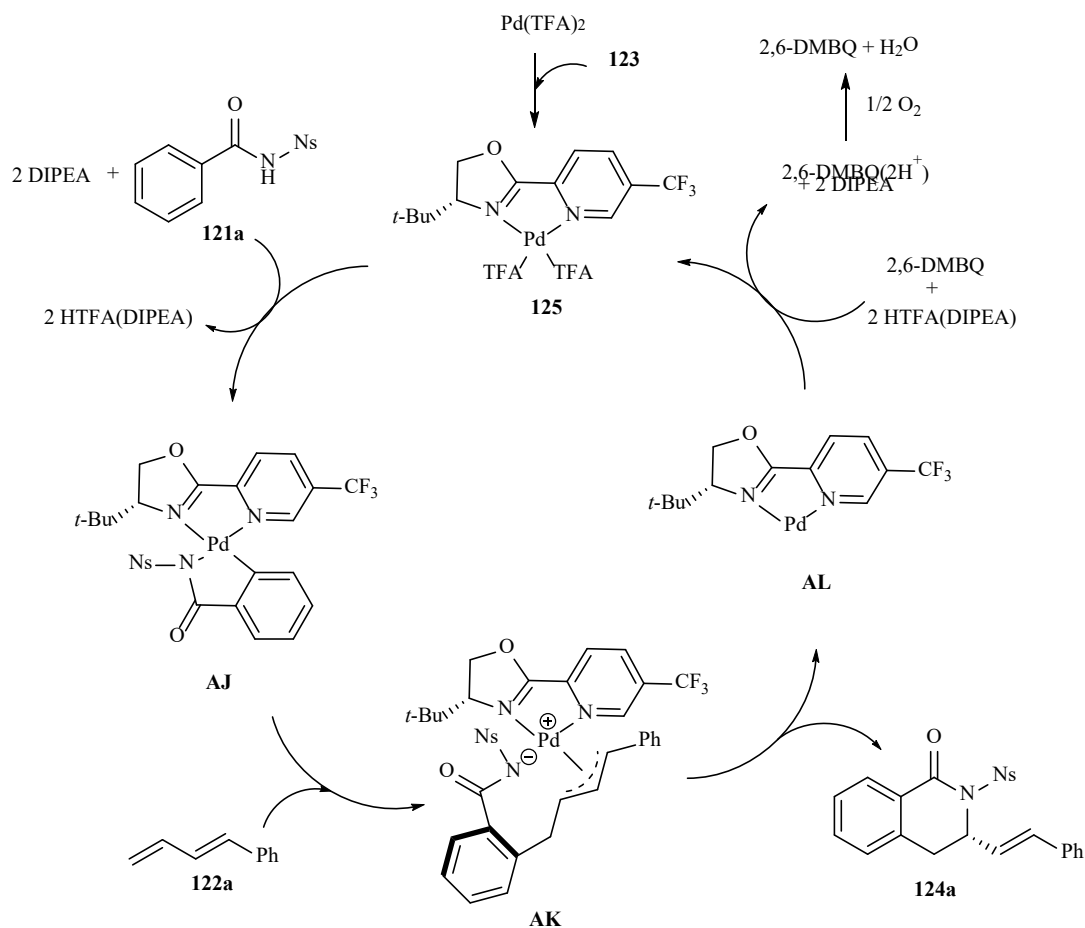
Chiral isoquinolines, and especially 3,4-dihydroisoquinolones, play a significant role in medicinal chemistry, which makes their synthesis challenging. In 2019, Yang et al. developed a novel methodology to synthesize these molecules based on an asymmetric C-H functionalization/intramolecular allylation cascade reaction between *N*-

sulfonyl benzamides **121** and 1,3-dienes **122** (Scheme 33) [47]. This was promoted by a chiral palladium catalyst in situ generated from 12 mol% of chiral pyridine/oxazoline ligand **123** and 10 mol% of Pd(TFA)₂ in the presence of DIPEA as base and 2,6-dimethoxy-1,4-benzoquinone (2,6-DMBQ) (DMBQ: dimethoxy-1,4-benzoquinone) as oxidant, thus resulting in the formation of the corresponding chiral 3,4-dihydroisoquinolones **124** with 32-82% yields and 62-96% ee. Benzamides with electron-donating substituents (R²) on the phenyl ring reacted with better yields (62-81%) and enantioselectivities (80-87% ee) than benzamides with electron-withdrawing substituents (33-52% and 62-85% ee). Along with aromatic 1,3-dienes, an aliphatic 1,3-diene (R³ = Bn) underwent the reaction with 64% yield and 90% ee. The mechanism proposed in Scheme 33 begins with the coordination of the chiral ligand to the precatalyst to generate active chiral palladium(II) catalyst **125**. Then, deprotonation of the N–H bond and metalation of the sp² C–H bond delivers five-membered palladacycle **AJ** (R¹ = *p*-O₂NC₆H₄, R² = H) which further undergoes migratory insertion of the 1,3-diene **122a** (R³ = Ph), leading to the π-allyl palladium complex **AK**. Finally, attack of the nitrogen nucleophile to the π-allyl palladium moiety affords domino product **124a** along with palladium(0) species **AL**, which can be oxidized to regenerate Pd(II) catalyst **125**.



$\text{R}^1 = n\text{-Non}, p\text{-Tol}, 2\text{-Naph}, p\text{-F}_3\text{CC}_6\text{H}_4, o\text{-O}_2\text{NC}_6\text{H}_4, \text{CF}_3$

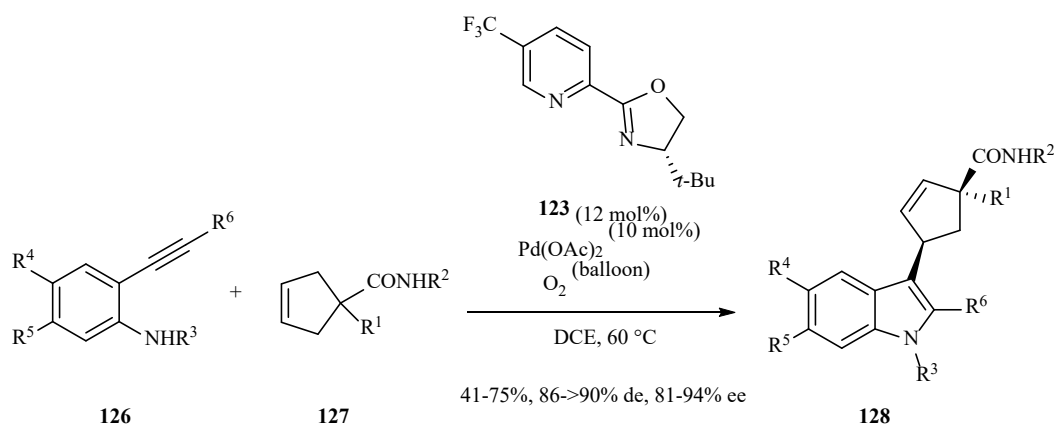
mechanism (with $\text{R}^1 = p\text{-O}_2\text{NC}_6\text{H}_4, \text{R}^2 = \text{H}, \text{R}_3 = \text{Ph}$):



Scheme 33. Domino C–H functionalization/intramolecular allylation reaction of *N*-sulfonyl benzamides with 1,3-dienes (Non = nonyl).

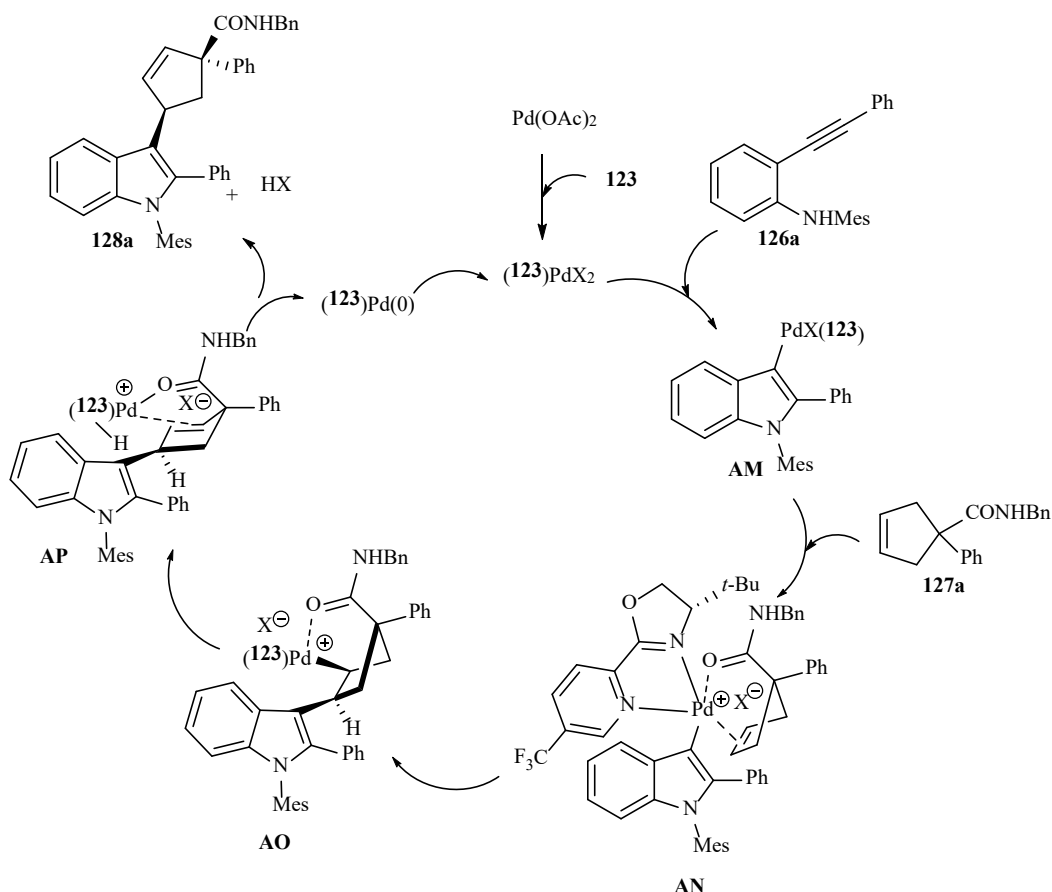
In another area, Zhu et al. described in 2021 an asymmetric domino indolization/oxidative Heck reaction between substituted cyclopentenes **127** and 2-alkynylanilines **126** catalyzed by a chiral palladium complex derived from 12 mol% of chiral bidentate ligand **123** and 10 mol% of Pd(OAc)_2 (Scheme 34) [48]. The reaction was carried out at 60°C in DCE in the presence of oxygen as oxidant, leading to chiral indole-cyclopentene conjugates **128**

bearing two stereocenters with 41-75% yields, 86->90% de and 81-94% ee. The mechanism described in Scheme 34 involves an intramolecular aminopalladation of **126a**, catalyzed by (2)PdX₂ in situ generated from chelation of pybox (2,6-bis(2-oxazolyl)pyridine) ligand **2** to Pd(OAc)₂, which affords the indolylPdX species **AM**. Then, coordination of the latter to the double bond of **127a** directed by the amide function generates Pd(II) complex **AN** which defined the face selectivity of the subsequent *syn*-carbopalladation to afford Pd(II) species **AO**. This intermediate subsequently underwent a β-hydride elimination to give intermediate **AP** which, upon decomplexation and reductive elimination of HX from the resulting HPdX provides final product **128a** along with Pd(0). The latter is then oxidized by oxygen and acetic acid to regenerate the catalyst.



$R^1 = \text{Ph, } p\text{-MeOC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, m\text{-Tol, } o\text{-O}_2\text{NC}_6\text{H}_4, 2\text{-Naph, Me, Bn, } t\text{-BuO}_2\text{CCH}_2, \text{H}$
 $R^2 = \text{Bn, } i\text{-Bu}$
 $R^6 = \text{Ph, } p\text{-MeOC}_6\text{H}_4, p\text{-MeO}_2\text{CC}_6\text{H}_4, 2\text{-thienyl, } n\text{-Bu, Cl(CH}_2)_3, \text{BnO(CH}_2)_2, \text{MeO}_2\text{C(CH}_2)_3$

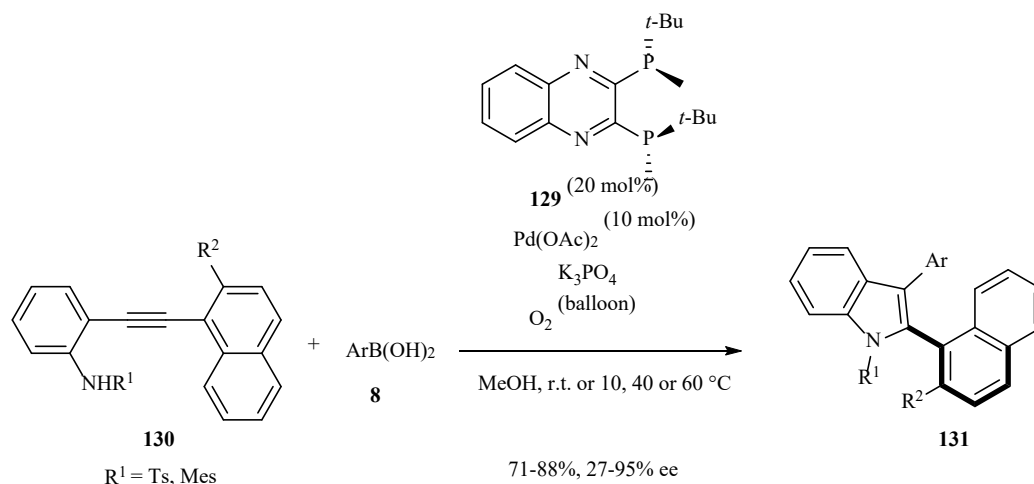
mechanism (with $R^1 = R_6 = \text{Ph, } R_2 = \text{Bn, } R_3 = \text{Mes, } R_4 = R_5 = \text{H}$):



Scheme 34. Domino indolization/oxidative Heck reaction of 2-alkynylanilines with substituted cyclopentenes.

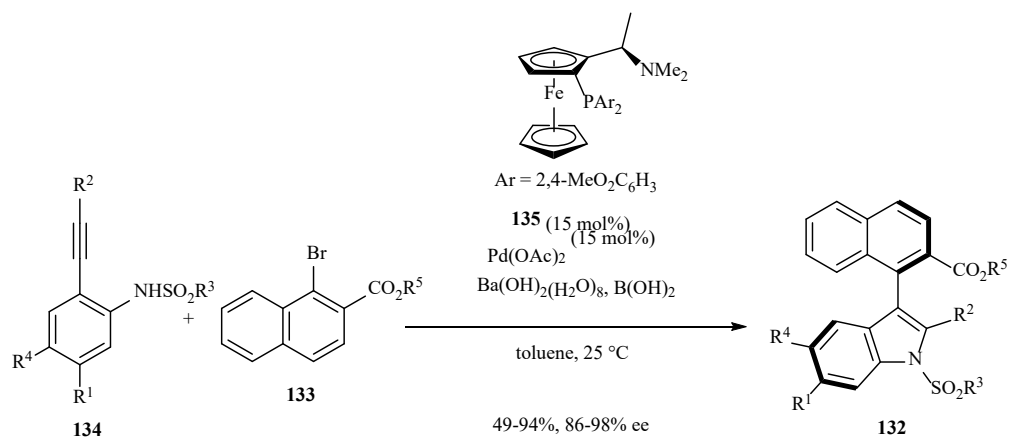
In 2020, Zhu et al. reported the first example of enantioselective palladium-catalyzed Cacchi-type reaction applied to the synthesis of indoles bearing an achiral C2-aryl axis (Scheme 35) [49]. The cascade reaction employed as catalyst system a combination of 10 mol% of Pd(OAc)_2 with 20 mol% and (*R,R*)-QuinoxP*

(QUINOX: (quinolin-2-yl)-oxazoline) ligand **129** in methanol as solvent. In the presence of two equivalents of K_3PO_4 under oxygen atmosphere, the domino cyclization/cross-coupling reaction of *N*-sulfonyl-2-alkynylanilides **130** with (hetero)arylboronic acids **8** afforded the corresponding chiral 2,3-disubstituted indoles **131** in 71-88% yields and 27-95% ee. The nature of the alkoxy group (R^2) on the naphthyl ring of the *N*-sulfonyl-2-alkynylanilide was found to dramatically influenced the enantioselectivity of the reaction, with the best ee values achieved with a benzyloxy group ($R^2 = OBn$, 75-94% ee), whereas the lowest enantioselectivities (27-33% ee) were obtained in the reaction of a *N*-sulfonyl-2-alkynylanilide bearing a methoxy group ($R^2 = OMe$) with 2-methylphenylboronic acid (Ar = *o*-Tol). Arylboronic acids bearing either electron-withdrawing or electron-donating substituents at different positions of the phenyl ring were well tolerated (83-94% ee) as well as 2-naphthyl boronic acid (Ar = 2-Naph, 90% ee) and heteroaromatic boronic acids (Ar = 2-furyl, 89-95% ee).



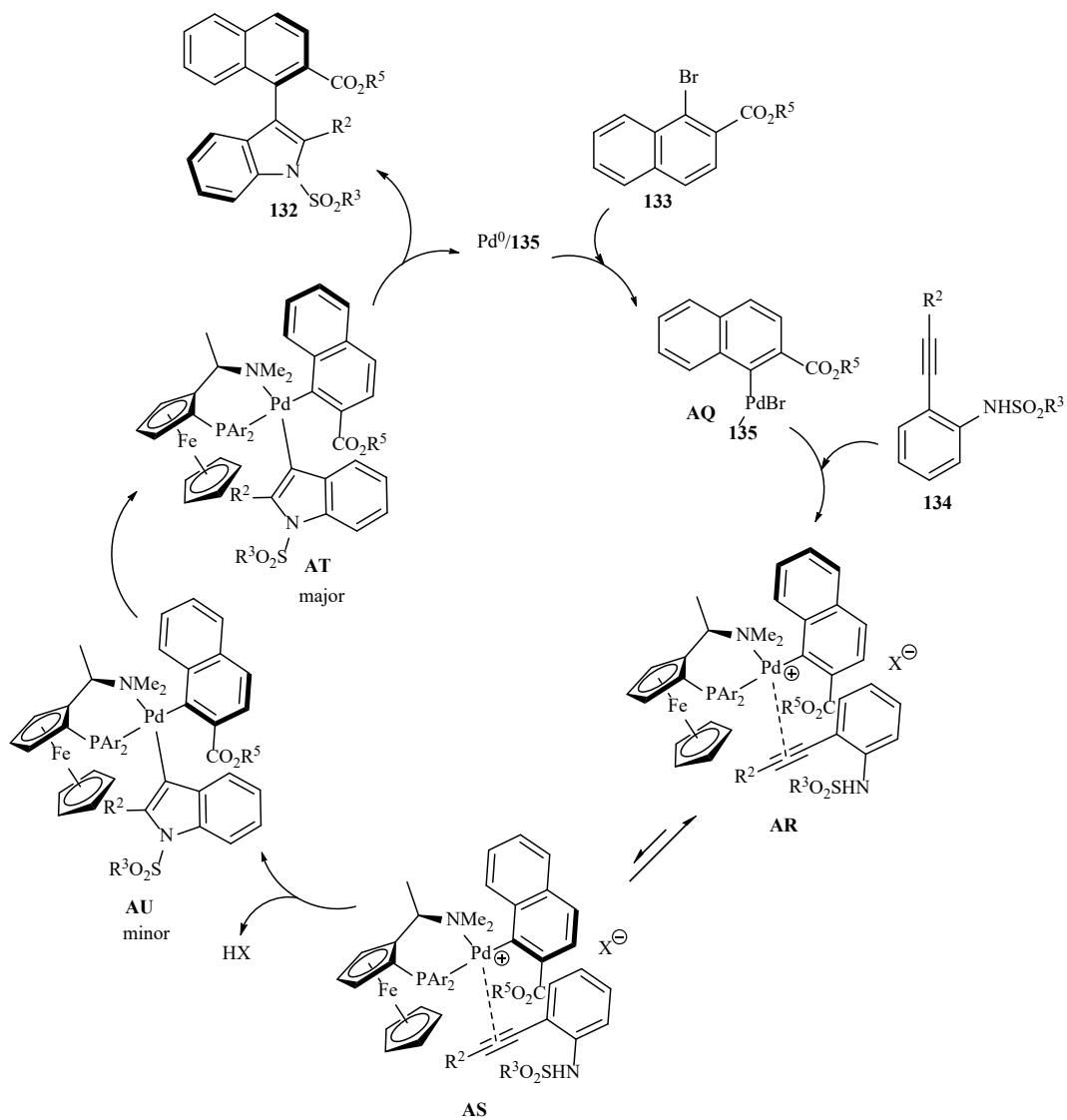
Scheme 35. Domino cyclization/cross-coupling reaction of *N*-sulfonyl-2-alkynylanilides with arylboronic acids.

The synthesis of other axially chiral 2,3-disubstituted indoles **132** was disclosed in 2021 by Qi and Li on the basis of a related Cacchi-type reaction between aryl bromides **133** and *o*-alkynylanilines **134** (Scheme 36) [50]. In this case, 15 mol% of a chiral catalyst prepared from $Pd(OAc)_2$ and ferrocene-based N,P-ligand **135** was used to promote the reaction at 25 °C in toluene in the presence of a base, such as $Ba(OH)_2 \cdot 8H_2O$, and $B(OH)_3$ as an additive. Under these conditions, *o*-alkynylanilines bearing various substituents at positions 4 and 5 reacted smoothly with variously substituted alkynes to afford axially chiral 2,3-disubstituted indoles **132** with 49-94% yields and 86-98% ee. The mechanism of this domino cyclization/cross-coupling reaction is proposed in Scheme 36, beginning with the in situ generation of a chiral $Pd(0)$ active catalyst followed by the oxidative addition of the arylbromide to give arylpalladium(II) species **AQ**. The subsequent coordination of the latter to the $C\equiv C$ triple bond of the alkyne resulted in the formation of intermediates **AR** and **AS**. Due to less steric interactions, complex **AR** was more stable than **AS**. Then, the palladium-activated alkyne underwent nucleophilic attack of the nitrogen atom, leading to major intermediate **AT** along with minor intermediate **AU**. Final reductive elimination afforded product **132** along with regenerated catalyst.



$\text{R}^2 = \text{Ph}, p\text{-MeOC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, m\text{-Tol},$
 $m\text{-ClC}_6\text{H}_4, 2\text{-thienyl}, n\text{-Pr}, \text{Cy}, i\text{-Bu}, \text{BnCH}_2$
 $\text{R}^3 = p\text{-Tol}, p\text{-MeOC}_6\text{H}_4, \text{Ph}$
 $\text{R}^5 = \text{Me}, \text{Et}, \text{Bn}, \text{Ph}, \text{t-Bu}, \text{Cy}$

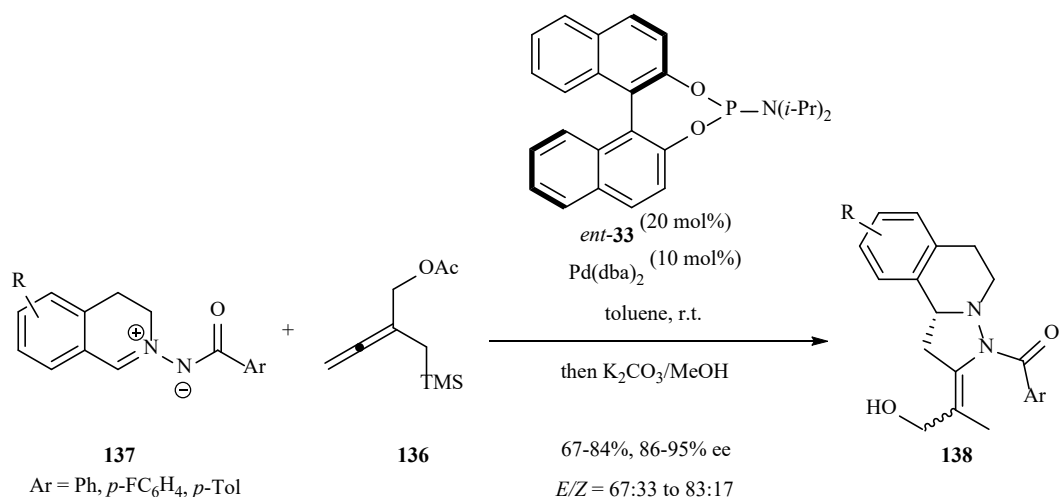
mechanism (with $\text{R}^1 = \text{R}_4 = \text{H}$):



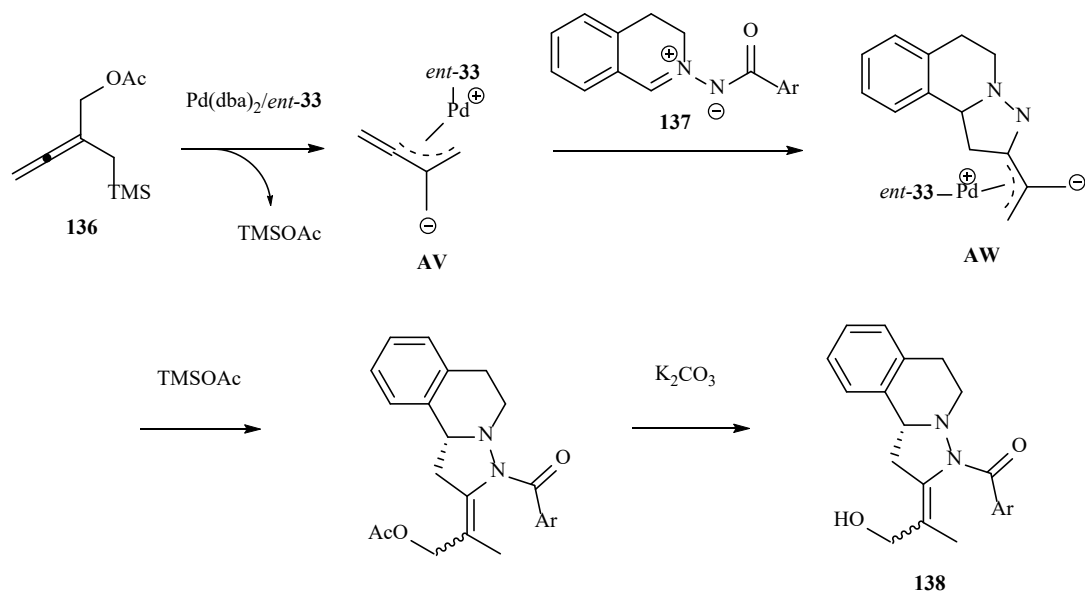
Scheme 36. Domino cyclization/cross-coupling reaction of *o*-alkynylanilines with aryl bromides.

5.1.3. Tricyclic Molecules

The cycloaddition of palladium-trimethylenemethane species represent a powerful tool for the synthesis of cyclic products. The first example of enantioselective palladium-catalyzed [3+2] cycloaddition of methylene-trimethylenemethane species with dipoles was reported by Guo et al., in 2019 (Scheme 37) [51]. It occurred between methylene-trimethylenemethane donors **136** and azomethine imines **137**, constituting the first step of an unprecedented enantioselective domino [3+2] cycloaddition/allylation reaction catalyzed by 10 mol% of Pd(dba)₂ combined with 20 mol% of chiral BINOL-derived phosphoramidite ligand *ent*-**33**. Performed in toluene at room temperature, the process allowed the synthesis of chiral hexahydropyrazolo[5,1-*a*]isoquinolines **138** as major (*E*)-diastereomers (*E/Z* = 67:13 to 83:17) in 67-84% yields and 86-95% ee. The azomethine imines tolerated the presence of different substituents on both the two phenyl rings. The mechanism of the one-pot process depicted in Scheme 37 shows that the methylene-trimethylenemethane donor was converted in the presence of the chiral palladium catalyst, into palladium-methylene-trimethylenemethane intermediate **AV** with simultaneous release of TMSOAc. Intermediate **AV** subsequently underwent [3+2] cycloaddition with the azomethine imine, affording intermediate **AW**. Then, allylation of the acetyloxy anion afforded the final product.



mechanism (with R = H):



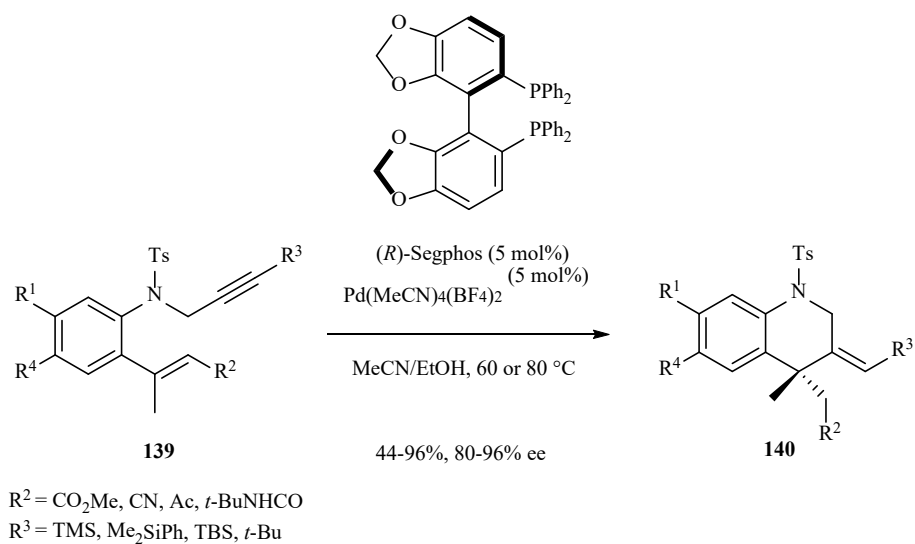
Scheme 37. Domino [3+2] cycloaddition/allylation reaction of methylene-trimethylenemethane donors with azomethine imines (r.t. = room temperature).

5.2. Carbon–Carbon Bond Formation

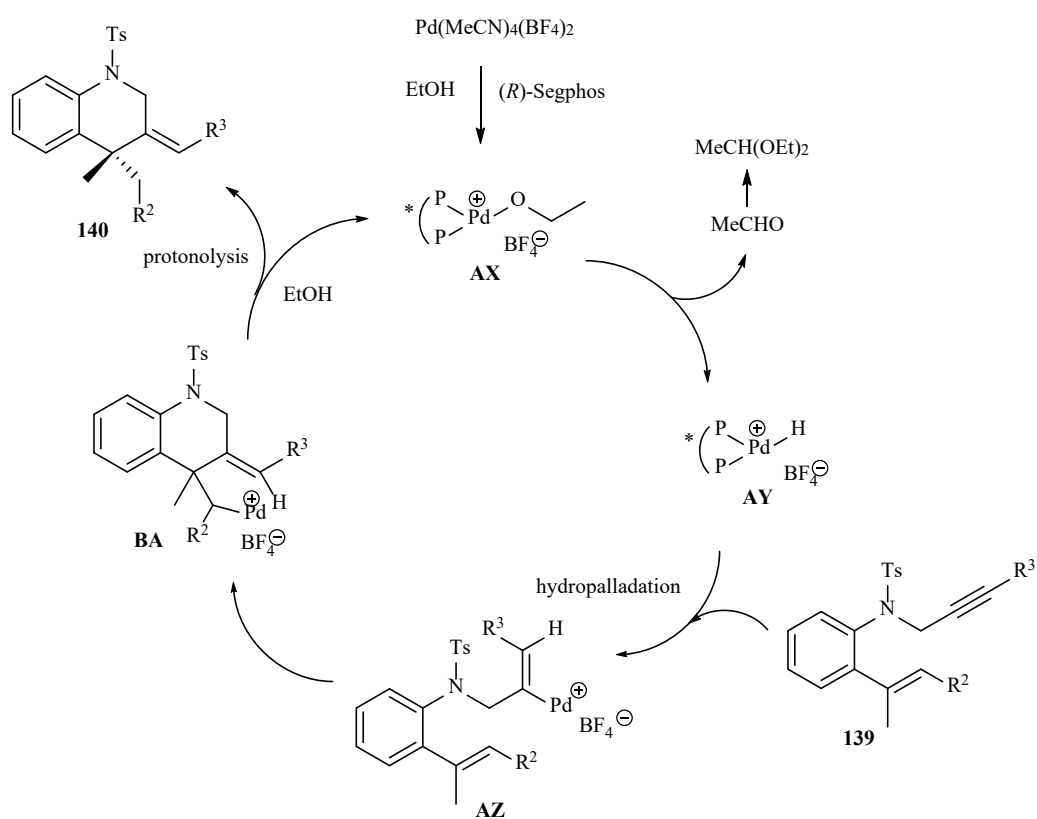
5.2.1. Bicyclic Molecules

1,2,3,4-Tetrahydroquinolines constitute the skeletons of many relevant biologically active products. In 2019, Lu and Han reported a novel methodology to prepare these heterocyclic molecules based on an asymmetric domino reaction of *N*-tosyl-tethered 1,7-enynes **139** [52]. Heating these substrates at 60 or 80 °C in acetonitrile as solvent and ethanol as the hydrogen source in the presence of 5 mol% of a catalyst system composed of $\text{Pd}(\text{MeCN})_4(\text{BF}_4)_2$ and (*R*)-Segphos underwent an hydropalladation followed by a 1,4-addition which produced the corresponding chiral 1,2,3,4-tetrahydroquinolines **140** possessing a quaternary stereocenter in 44-96% yields and 80-96% ee

(Scheme 38). This unprecedented enantioselective palladium-catalyzed reductive cyclization of *N*-tosyl-tethered 1,7-enynes can be explained by the mechanism depicted in Scheme 38, beginning with the generation of palladium species **AX** from the precatalyst and ethanol. Then, complex **AX** leads to palladium intermediate hydride complex **AY** via β -H elimination. Subsequently, intermediate **AZ** is generated through insertion of the carbon-carbon triple bond of substrate **139** into a hydrogen-palladium bond in intermediate **AY**. Then, the carbon-palladium bond adds to the intramolecular alkene to provide intermediate **BA** which is further submitted to protonolysis to afford the final product along with regenerated catalyst.



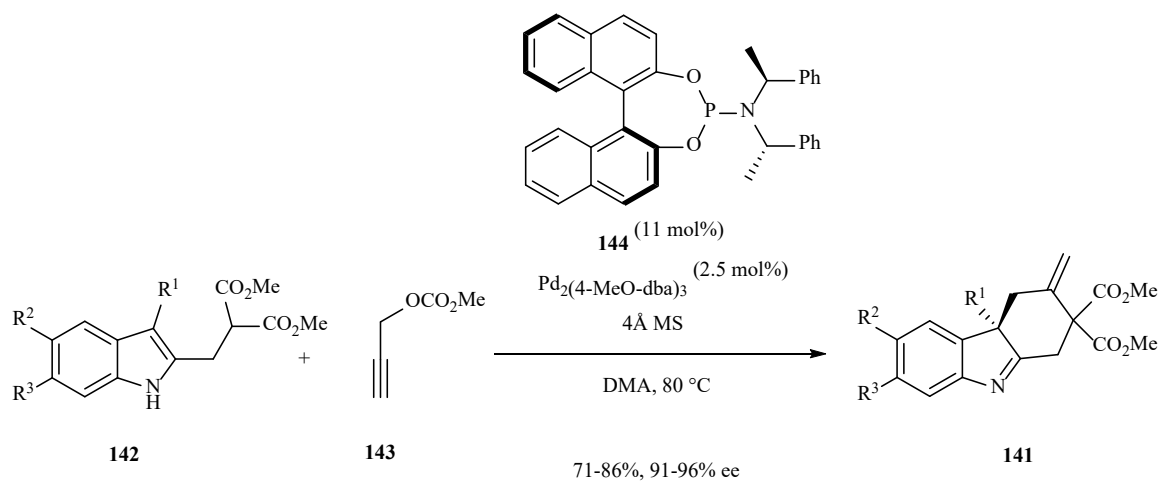
mechanism (with $\text{R}^1 = \text{R}_4 = \text{H}$):



Scheme 38. Domino hydropalladation/1,4-addition reaction of *N*-tosyl-tethered 1,7-enynes.

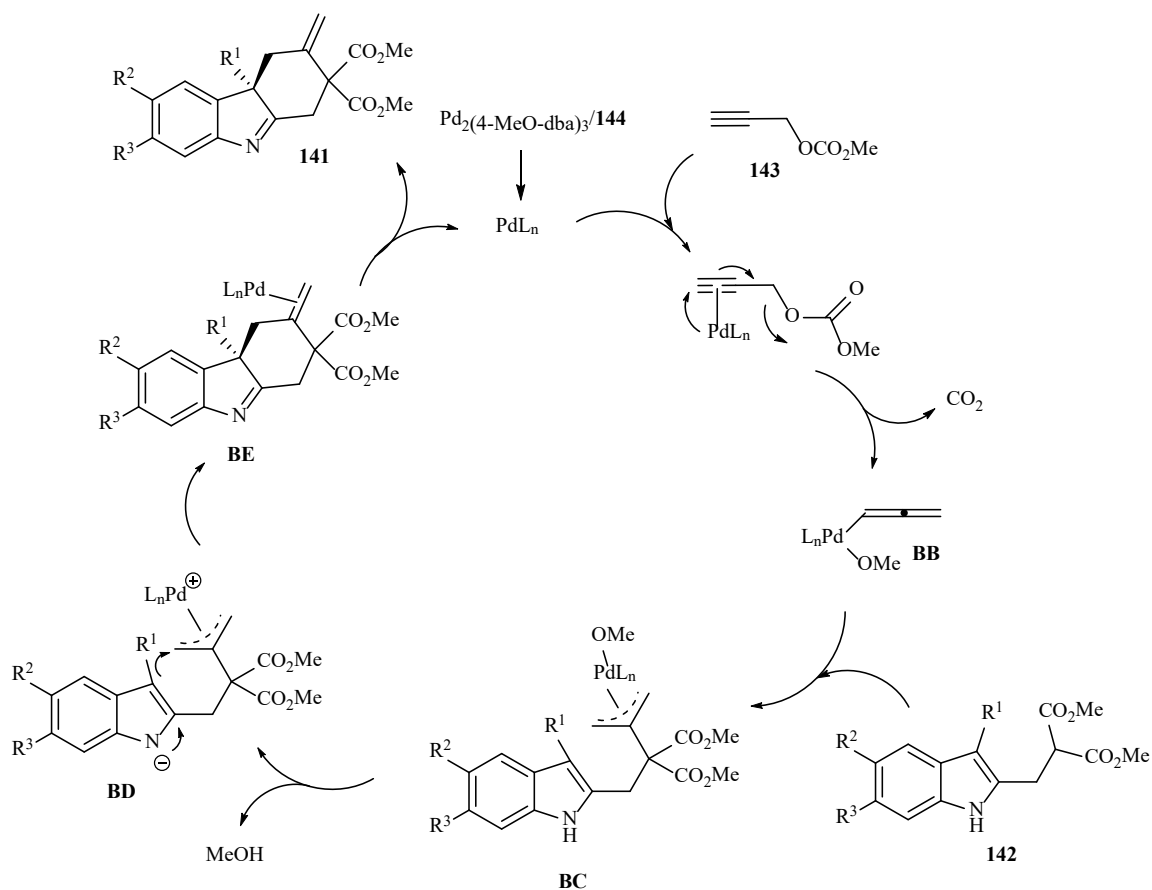
5.2.2. Tricyclic Molecules

Tricyclic densely substituted fused indolenines **141** were synthesized in 2019 by You et al. on the basis of an asymmetric cascade dearomatization between indoles **142** bearing a nucleophile at the C2 position and methyl propargyl carbonate **143** (Scheme 39) [53]. The reaction was promoted at 80 °C by a chiral catalyst in situ formed from 11 mol% of chiral BINOL-derived phosphoramidite ligand **144** and 2.5 mol% of Pd₂(4-MeO-dba)₃ in dimethylacetamide (DMA) as the solvent, thus affording chiral multisubstituted fused indolenines **141** with 71-86% and 91-96% ee. Indoles bearing either electron-donating or electron-withdrawing substituents on the benzyl group (R¹ = ArCH₂) reacted with excellent enantioselectivities (93-95% ee). Moreover, the presence of an aliphatic group at the C3 position (R¹) was well tolerated since the corresponding products were produced with 92-94% ee. A possible mechanism depicted in Scheme 39 shows that the methyl propargyl carbonate was activated by Pd(0) to give intermediate **BB**. Then, the nucleophilic side chain of the indole attacked this intermediate to generate π-allyl palladium species **BC**. Upon deprotonation of the N-H group of indole, the C3 position of indole in **BD** attacked the π-allyl palladium moiety to give intermediate **BE**. Finally, the liberation of the palladium catalyst delivered the product.



$R^1 = \text{Bn}, p\text{-MeO}_2\text{C}_6\text{H}_4\text{CH}_2, p\text{-TolCH}_2, m\text{-TolCH}_2, p\text{-FC}_6\text{H}_4\text{CH}_2, p\text{-ClC}_6\text{H}_4\text{CH}_2,$
 $(2\text{-thienyl})\text{CH}_2, (2\text{-Naph})\text{CH}_2, \text{Me}, \text{Et}, n\text{-Pr}, i\text{-Bu}, \text{CyCH}_2, \text{MOM}$
 $R^2 = \text{H}, \text{OMe}, \text{Me}, \text{F}, \text{Cl}, \text{Br}$
 $R^3 = \text{H}, \text{F}, \text{Cl}$

mechanism:



Scheme 39. Domino dearomatization reaction of indoles with methyl propargyl carbonate (MOM = methoxymethyl).

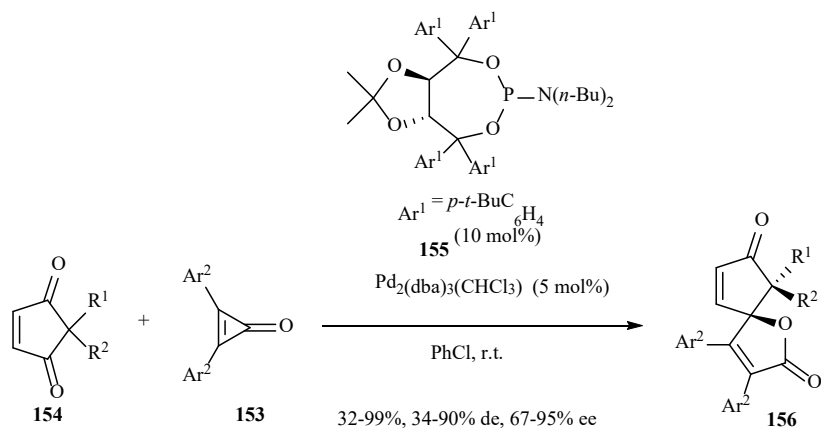
5.3. Carbon–Carbon and Carbon–Oxygen Bond Formation

5.3.1. Bicyclic Molecules

In 2019, Guo et al. developed the synthesis of chiral nine-membered bicyclo[5.2.2]tetrahydrooxonines **148** via an asymmetric domino [3+2] cycloaddition/Cope rearrangement reaction between the corresponding vinyl ethylene carbonates **145** and coumalates **146** catalyzed by 2.5 mol% of Pd₂(dba)₃·CHCl₃ combined with 15 mol% of BINOL-derived chiral phosphoramidite ligand **147** (Scheme 40) [54]. This cascade reaction was carried out at 25 °C in chloroform, thus forming a range of chiral bicyclic products **148** with 54-95% yields and 87-99% ee. The carbonate partners could exhibit a wide variety of (hetero)aryl groups (R¹) and different ester group (R²) in coumalates were well tolerated. A mechanism is proposed in Scheme 40, beginning with the ring-opening of vinyl ethylene carbonate **145** in the presence of the palladium catalyst to give zwitterionic allylpalladium intermediate **BF**. Subsequently, the latter species attacks coumalate **146** to provide palladium intermediate **BG**. Then, this intermediate undergoes a [3+2] cycloaddition to afford bicyclic intermediate **149** through palladium intermediate **BH**. The latter is then subjected to a Cope rearrangement to yield the final nine-membered product. By changing the nature and catalyst loading (20 vs 15 mol%) of the chiral ligand (**150** instead of **147**), the scope of the methodology could be extended to pyrones **151** (Scheme 40). As illustrated in Scheme 40, the latter reacted at 25 °C with vinyl ethylene carbonate **145a** (R¹ = Ph) to give the corresponding chiral products **152** with 50-99% yields and 83-99% ee when treated by 15 mol% of related chiral phosphoramidite ligand **150** combined with 5 mol% of Pd₂(dba)₃·CHCl₃ in chloroform as solvent.

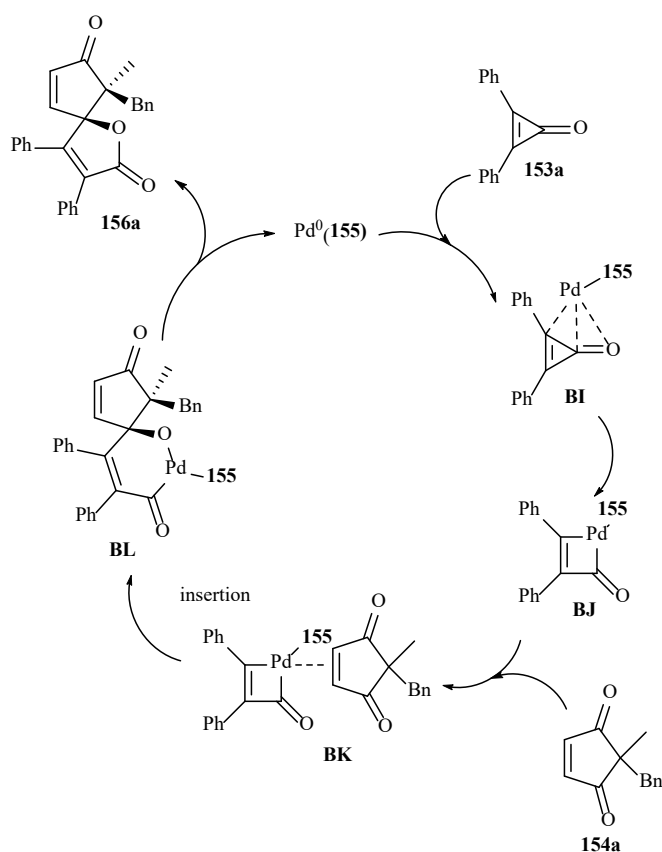
Scheme 40. Domino [3+2] cycloaddition/Cope rearrangement reactions of vinyl ethylene carbonates with coumalates/pyrones (Bz = benzoyl).

In 2021, Xu et al. described unprecedented enantioselective palladium-catalyzed domino [3+2] spiro-annulation reaction of cyclopropanones **153** with cyclopentene-1,3-diones **154** catalyzed by 5 mol% of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ and 10 mol% of chiral TADDOL($\alpha, \alpha, \alpha', \alpha'$ -tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol)-derived phosphoramidite ligand **155** (Scheme 41) [55]. Performed at room temperature in chlorobenzene, the domino carbon-carbon bond cleavage/[3+2] annulation afforded chiral oxaspiro-products **156** exhibiting two adjacent quaternary centers with 32-99% yields, 34-90% de and 67-95% ee. Good results were achieved for a series of cyclopropanones bearing different substituents at any positions of the phenyl rings. A supposed mechanism depicted in Scheme 41 begins with the coordination of the cyclopropanone to palladium(0) complex to give palladium complex **BI**. Then, oxidative addition with carbon-carbon bond activation provided palladium intermediate **BJ**. The latter species further coordinated to the C=C double bond of the cyclopentene-1,3-dione to provide complex **BK** which underwent migratory insertion of the Pd-C bond to give intermediate **BL**. Finally, the product was obtained by reductive elimination along with regenerated palladium(0) catalyst.



$R^1 = \text{Me, Et}$
 $R^2 = \text{Bn, } o\text{-TolCH}_2, m\text{-TolCH}_2, p\text{-TolCH}_2, p\text{-FC}_6\text{H}_4\text{CH}_2, p\text{-ClC}_6\text{H}_4\text{CH}_2, o\text{-FC}_6\text{H}_4\text{CH}_2, p\text{-ClC}_6\text{H}_4\text{CH}_2, m\text{-ClC}_6\text{H}_4\text{CH}_2, o\text{-BrC}_6\text{H}_4\text{CH}_2, p\text{-BrC}_6\text{H}_4\text{CH}_2, 3,5\text{-Me}_2\text{C}_6\text{H}_3\text{CH}_2, (2\text{-Naph})\text{CH}_2, p\text{-PhC}_6\text{H}_4\text{CH}_2, 2\text{-Cl-4-FC}_6\text{H}_3\text{CH}_2, p\text{-MeO}_2\text{CC}_6\text{H}_4\text{CH}_2, o\text{-O}_2\text{NC}_6\text{H}_4\text{CH}_2, (2\text{-thienyl})\text{CH}_2, m\text{-F}_3\text{CC}_6\text{H}_4\text{CH}_2, p\text{-MeOC}_6\text{H}_4\text{CH}_2, p\text{-NCC}_6\text{H}_4\text{CH}_2, \text{MeC}\equiv\text{CCH}_2$
 $\text{Ar}^2 = p\text{-FC}_6\text{H}_4, p\text{-Tol, } m\text{-Tol, Ph}$

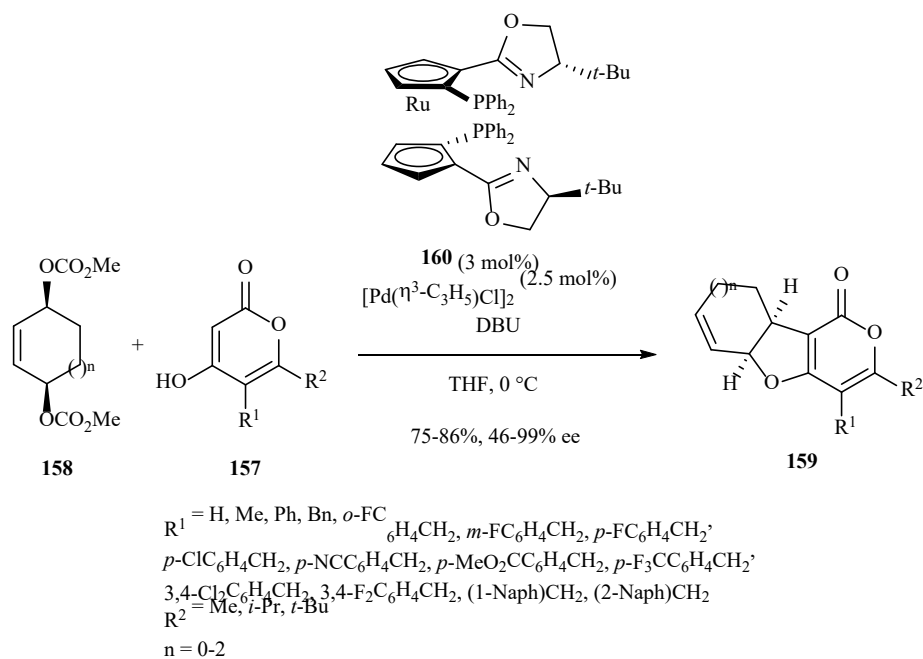
mechanism (with $\text{Ar}^2 = \text{Ph}, R_1 = \text{Me}, R_2 = \text{Bn}$):



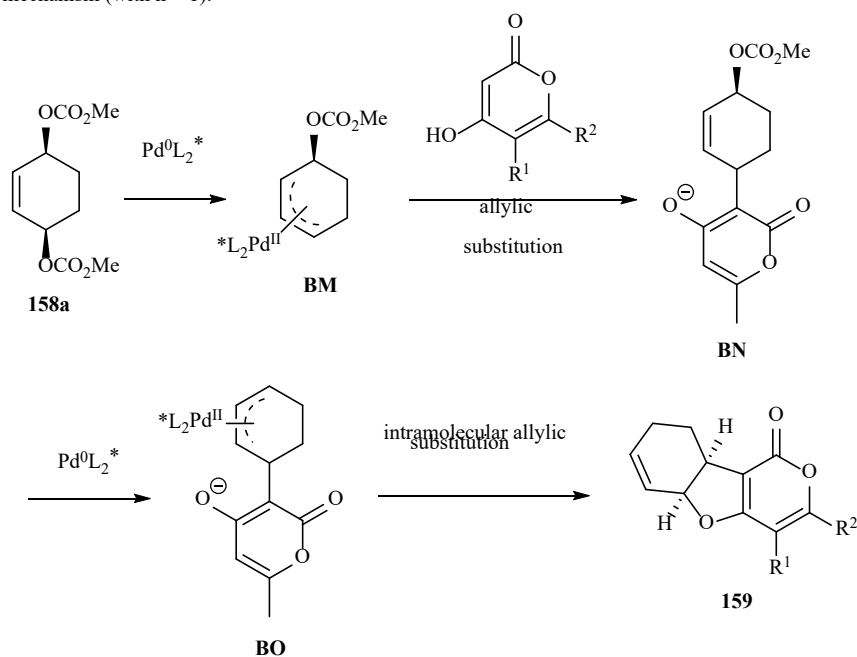
Scheme 41. Domino carbon–carbon bond cleavage/[3+2] annulation of cyclopropanones with cyclopentene-1,3-diones (r.t. = room temperature).

5.3.2. Tricyclic Molecules

In 2022, Liu et al. developed a novel synthesis of chiral furo[3,2-c]pyrans through unprecedented asymmetric domino double allylic substitution reaction of 4-hydroxy-2H-pyrones **157** ($n = 1$) with *meso*-allyl dicarbonates **158** (Scheme 42) [56]. The reaction was promoted at 0 °C in THF in the presence of DBU as base by a chiral palladium catalyst derived from 3 mol% of chiral ligand **160** and 2.5 mol% of $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$, leading to chiral fused-ring products **159** with 75-86% yields and 46-99% ee. Actually, uniformly high ee values (82-99% ee) were achieved in the reaction of 4-hydroxy-2H-pyrones ($n = 1$) while five-membered ($n = 0$) and seven-membered substrates ($n = 2$) reacted with much lower enantioselectivities (46-60% ee). Moreover, a variety of alkyl substituents (R^1, R^2) were tolerated on the 4-hydroxy-2H-pyrones. In Scheme 42 is proposed a mechanism beginning with the formation of π -allylpalladium complex **BM** from the reaction of activated Pd complex L^*Pd^0 with the *meso*-allyl decarbonate. Then, complex **BM** reacted with the 4-hydroxy-2H-pyrone to give monosubstituted intermediate product **BN**. The latter species further generated novel π -allylpalladium complex **BO** by reaction with the catalyst, which then underwent an intramolecular allylic substitution, yielding the final cyclized product.



mechanism (with $n = 1$):

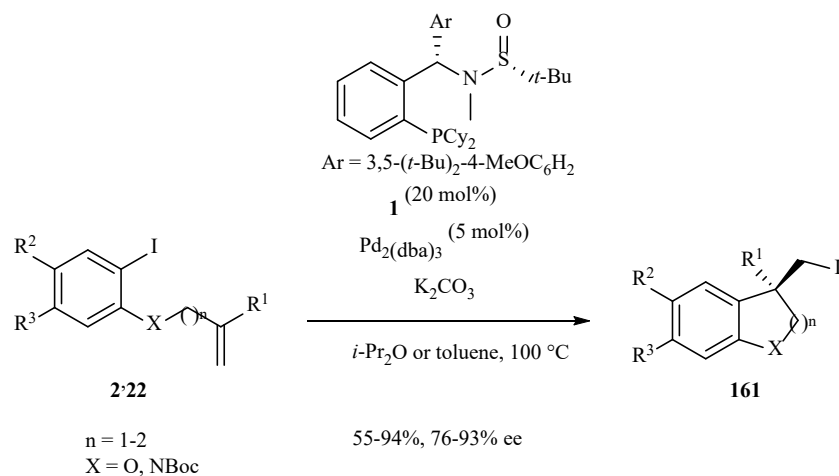


Scheme 42. Domino double allylic substitution reaction of 4-hydroxy-2H-pyrones and derivatives with *meso*-allyl dicarbonates.

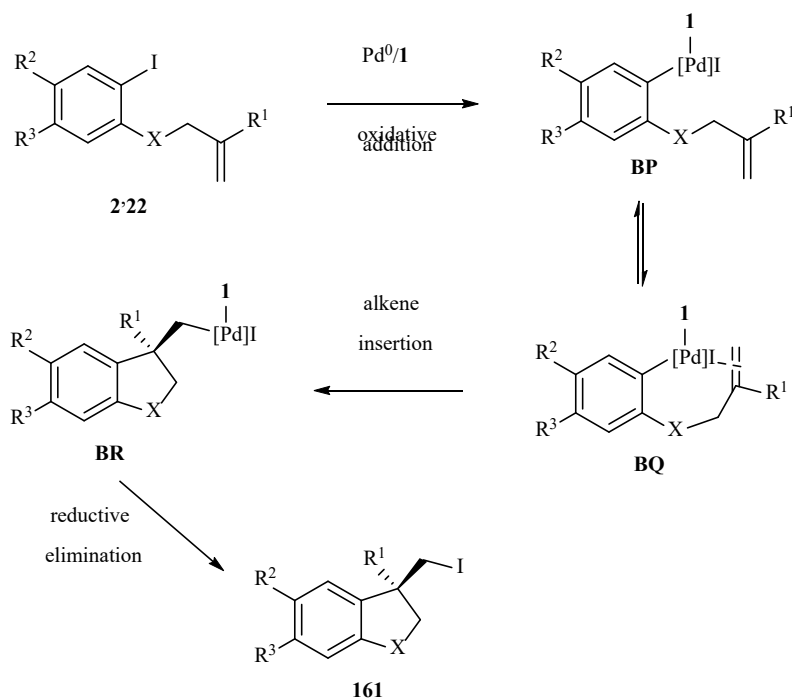
5.4. Carbon–Carbon and Carbon–Iodide Bond Formation

In 2019, Zhang and Li described the first example of highly enantioselective carboiodination of olefin-tethered aryl iodides, which was promoted by a combination of 20 mol% of chiral ligand **1** with 5 mol% of $\text{Pd}_2(\text{dba})_3$ (Scheme 43) [57]. Performed at 100 °C in diisopropylether as the solvent in the presence of K_2CO_3 , the domino iodine atom transfer/cycloisomerization reaction of unactivated alkenes **2,22** led to the corresponding chiral 3,3-disubstituted 2,3-dihydrobenzofurans **161** ($X = \text{O}$, $n = 1$), indolines ($X = \text{NBoc}$, $n = 1$) or chromanes ($X = \text{O}$, $n =$

2) bearing an alkyl iodide group and a quaternary stereocenter with 55-94% and 76-93% ee. The reaction of olefin-tethered aryl iodides with a nitrogen linker ($X = \text{NBoc}$) required the use of toluene instead of diisopropylether as solvent and provided generally lower enantioselectivities (76-87% ee vs 90-93% ee) than that of substrates exhibiting an oxygen linker ($X = \text{O}$). A possible mechanism is proposed in Scheme 43, involving the oxidative addition of the aryl iodide to give palladium intermediate **BP**. Then, the latter undergoes coordination of the double C=C bond to the palladium atom to give intermediate **BQ**. Subsequently, alkene insertion occurs to provide cyclized intermediate **BR** which is further submitted to reductive elimination to produce the final product.



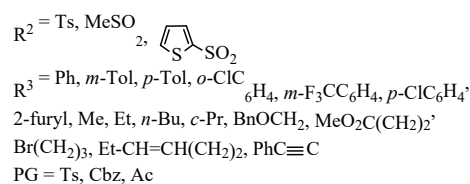
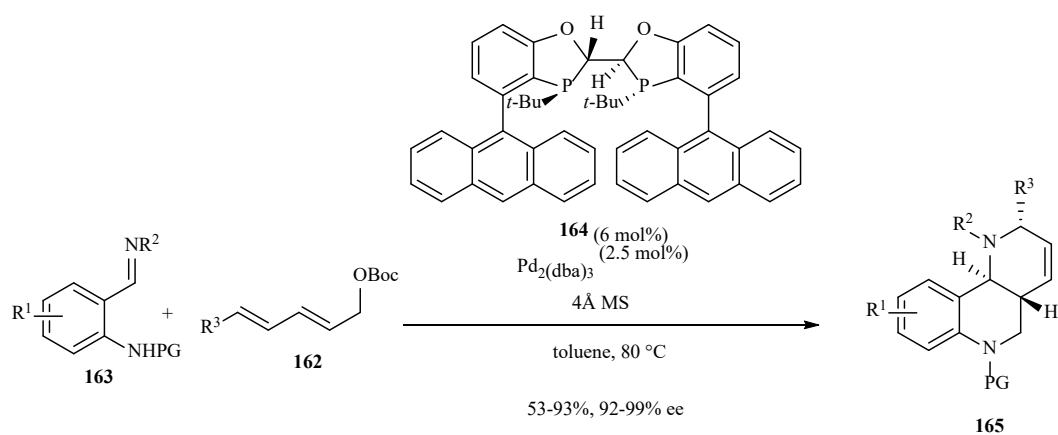
mechanism (n = 1):



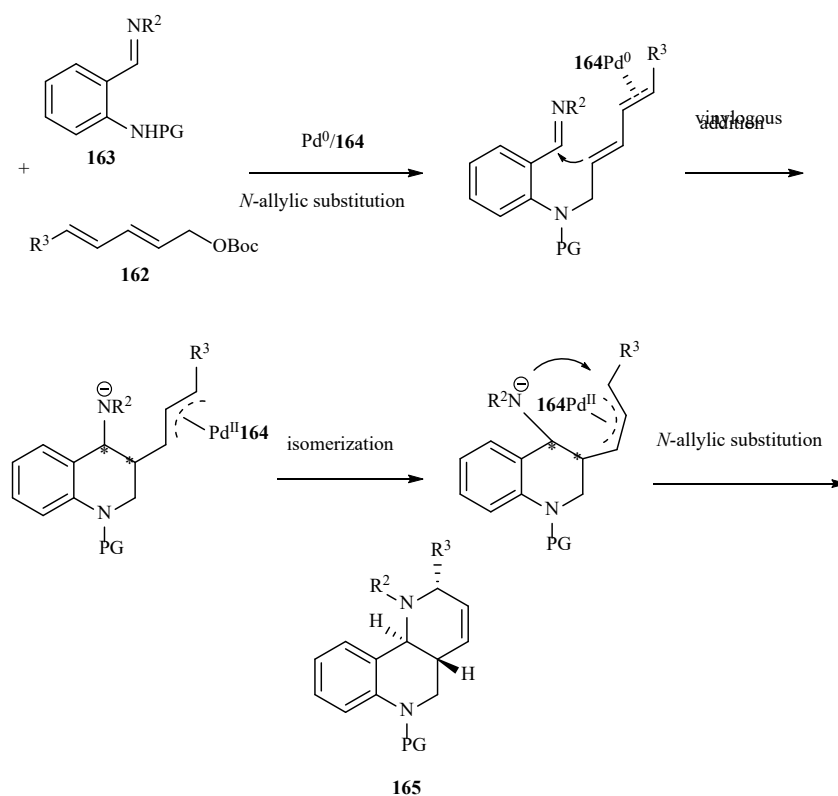
Scheme 43. Domino iodine transfer/cycloisomerization reaction of olefin-tethered aryl iodides.

5.5. Carbon–Nitrogen Formation

An asymmetric cascade reaction between 2,4-dienyl carbonates **162** and *o*-TsNH aryl aldimines **163** (PG = Ts), was developed by Chen and Chen, in 2022 (Scheme 44) [58]. Promoted at 80 °C in toluene by a catalyst system composed of 2.5 mol% of Pd₂(dba)₃ and 6 mol% of chiral bisphosphine ligand **164**, it provided through successive *N*-allylation, vinylogous addition, π - σ - π isomerization, and another *N*-allylation chiral densely functionalized tricyclic products **165** with 53-93% yields and 92-99% ee. A range of functional groups were tolerated on the substituent (R³) of the 2,4-dienyl carbonates.



mechanism (with $\text{R}^1 = \text{H}$):



Scheme 44. Domino *N*-allylation/vinylogous addition/isomerization/*N*-allylation reaction of 2,4-dienyl carbonates with *o*-TsNH aryl aldimines.

6. CONCLUSIONS

Novel palladium-catalyzed domino reactions are continuously emerging in the literature, opening new transformations with unexpected activations. The almost total economy of these cascade processes and their applications in medicine, biology, agriculture, science of new materials, among other fields convert this machinery in a precious tool in organic synthesis, allowing very complex molecules to be generated in single steps from simple starting materials. This review shows that during the last few years and due the versatility, wide scope, and high tolerance of palladium, a range of novel asymmetric palladium-catalyzed domino processes have been developed with an increasing diversity reflecting that of ligands employed to induce them. For example, chiral P,N-ligands, phosphoramidates, and bisphosphines have been successfully applied to promote enantioselective Heck-initiated reactions of many types. Moreover, oxazolines, bisphosphines, BINOL derivatives as well as P,N-ligands and phosphoramidites have been employed in a myriad of asymmetric one-, two-, three- and four-component domino reactions. With the discovery of novel chiral palladium catalysts and the combination of various types of reactions, the field of asymmetric cascade palladium catalysis will undoubtedly continue to grow with more applications in total synthesis. In particular, the special and emerging area of multicatalyzed tandem reactions based on the combination of palladium catalysts with other types of catalysts is blooming, enabling even more transformations that would be inaccessible through classic approaches. In the near future, palladium will continue to be combined with organocatalysts, nickel, copper, rhodium, gold, silver, ruthenium, and lanthanide complexes among other catalysts, making organic synthesis more resources efficient.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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