



# Recent Developments in Enantioselective Domino Reactions. Part A: Noble Metal Catalysts

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# Recent Developments in Enantioselective Domino Reactions. Part A: Noble Metal Catalysts

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In respectful memory of Dr Zoltan Hajos

**Abstract:** This review updates the field of enantioselective domino reactions promoted by chiral catalysts derived from noble metals, including palladium, silver, rhodium, ruthenium, iridium and gold, published since the beginning of 2019. It illustrates how much a diversity of these catalysts allow unprecedented asymmetric domino reactions of many types to be achieved with excellent enantioselectivity, giving a direct access to a wide variety of complex chiral molecules.

**Keywords:** domino reactions; multicomponent reactions; transition metals; noble metals; asymmetric synthesis

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## 1 Introduction

Combining asymmetric metal catalysis with the concept of domino reactions results in the rapid and economic construction of very complex chiral molecules often obtained with remarkable levels of stereoselectivity.<sup>[1]</sup> In the last decade, many types of enantioselective domino processes have been catalyzed by a wide variety of chiral metal complexes. Introduced by Tietze in 1990s, the concept of domino reactions consists in one-step two or more bond-forming transformations occurring under strictly the same reaction conditions.<sup>[2]</sup> These sophisticated one-pot reactions have allowed many biologically important and/or natural products to be simply synthesized without requiring the purification of intermediates.<sup>[3]</sup> The goal of this review is to collect the recent advances in enantioselective domino reactions catalyzed by noble metals, including palladium, silver, rhodium, ruthenium, iridium and gold, published since the beginning of 2019 since this field was most recently updated this year, covering the literature until the end of 2018.<sup>[3w]</sup> It is divided into six parts, dealing successively with enantioselective palladium-catalyzed domino reactions, silver-catalyzed domino reactions, rhodium-catalyzed domino reactions, ruthenium-catalyzed domino reactions, iridium-catalyzed domino reactions and gold-catalyzed domino reactions. The two first parts are subdivided according to the type of reactions. It must be noted that this review does not include multicatalyzed enantioselective domino reactions.

## 2 Enantioselective Palladium-Catalyzed Domino Reactions

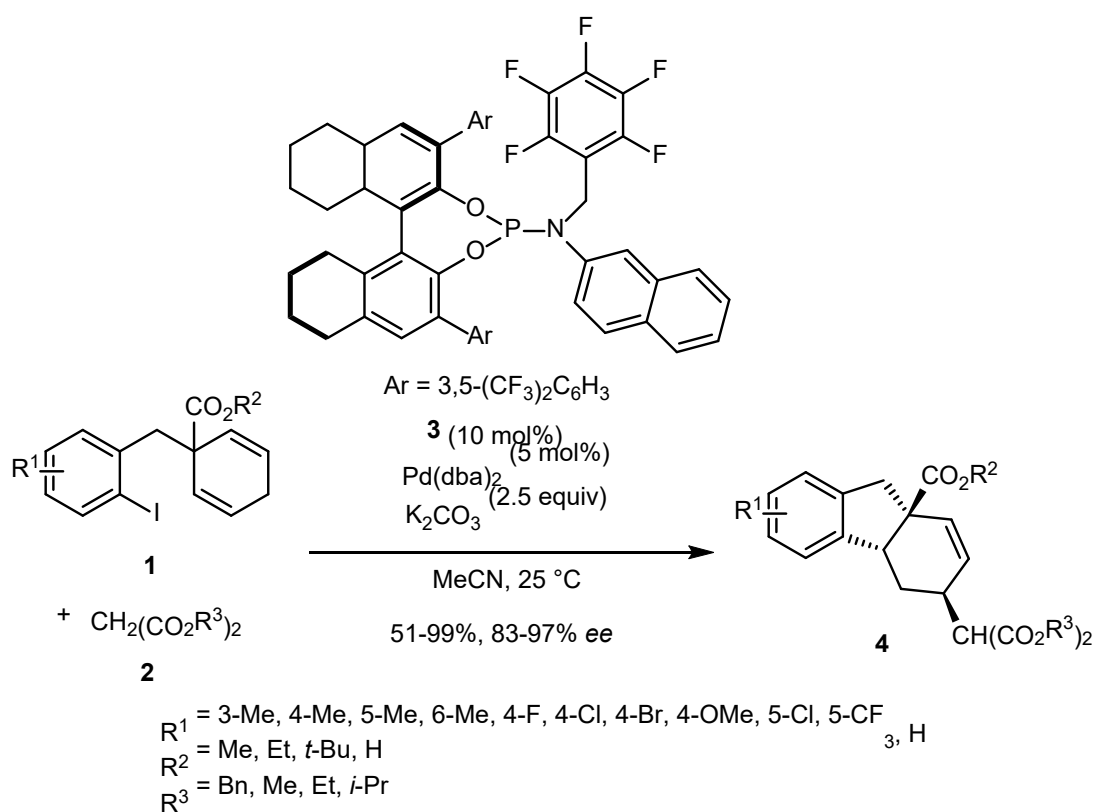
Related to its versatile chemistry and high tolerance to functional groups, palladium has been widely applied to promote many types of transformations,<sup>[4]</sup> including C–H activations,<sup>[5]</sup> cross-coupling reactions,<sup>[6]</sup> and annulations.<sup>[7]</sup> Especially, the mode of reactivity of palladium is well suited to cascade processes often initiated by a Heck reaction.<sup>[8]</sup> Among them, a wide number of highly efficient asymmetric versions of palladium-catalyzed domino reactions have been developed, allowing an easy access to many types of chiral complex architectures.<sup>[9]</sup>

### 2.1 Enantioselective Heck-Initiated Domino Reactions

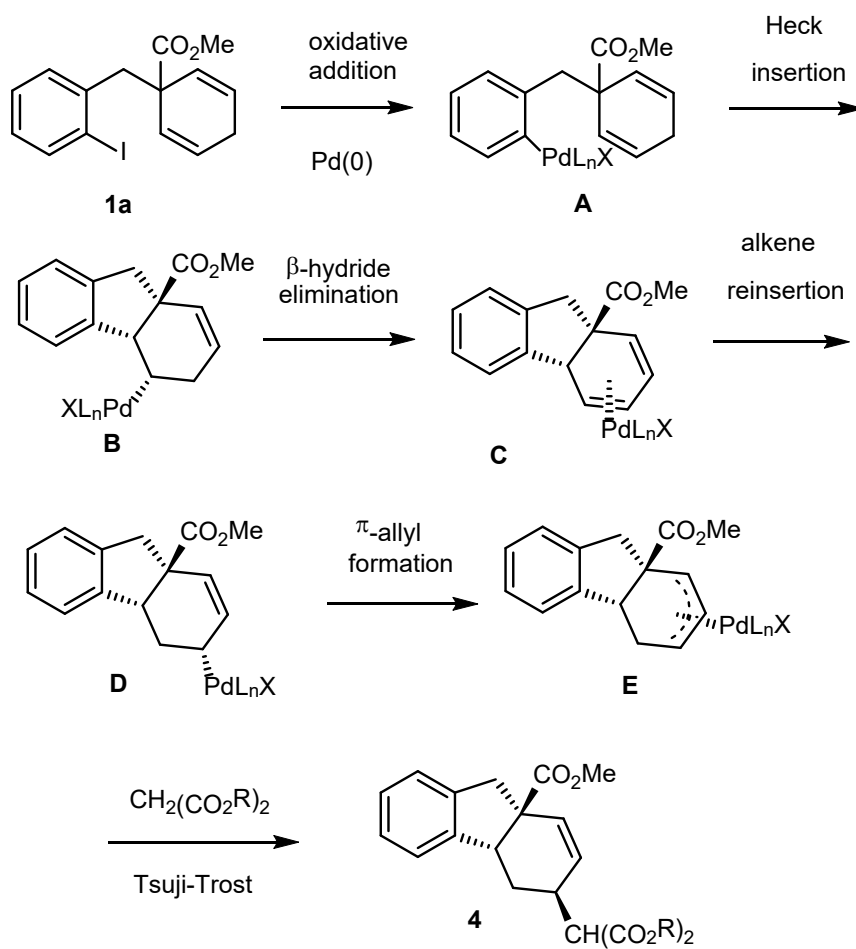
#### 2.1.1 Phosphoramidite Ligands

Among enantioselective palladium-catalyzed domino reactions, Heck-initiated processes have been the most developed. Indeed, the Heck reaction is well suited to initiate a cascade of reactions since it

generates, after the carbopalladation of a double bond, an active  $\sigma$ -alkylpalladium species that can be further diversely functionalized. For example, the palladium-catalyzed intramolecular Heck-type cascade reaction is one of the most reliable methods to construct five- and six-membered rings containing an all-carbon quaternary stereogenic center.<sup>[10]</sup> The  $\sigma$ -alkylpalladium intermediate generated by cyclocarbopalladation usually lacks a  $\beta$ -H moiety for elimination to ensure that the following transformations occur selectively. In 2019, Wu et al. reported an asymmetric domino Heck/Tsuji–Trost reaction which allowed the synthesis of potentially bioactive chiral functionalized tetrahydrofluorenes.<sup>[11]</sup> It involved the enantioselective palladium-catalyzed coupling of 2,5-cyclohexadienyl-substituted aryl iodides **1** with malonates **2** performed at 25 °C in acetonitrile as solvent in the presence of a chiral palladium catalyst *in situ* generated from 5 mol% of Pd(dba)<sub>2</sub> and 10 mol% of chiral H<sub>8</sub>-BINOL-based phosphoramidite ligand **3** (Scheme 1). In the presence of a base such as K<sub>2</sub>CO<sub>3</sub>, the reaction proceeded through an asymmetric Heck insertion followed by a Tsuji–Trost allylation, leading to chiral tetrahydrofluorenes **4** as single diastereomers with high enantioselectivities (83-97% *ee*) and moderate to quantitative yields (51-99%). The presence of either electron-donating or electron-withdrawing substituents on the phenyl ring of the aryl iodides was tolerated. The authors proposed the mechanism depicted in Scheme 1, beginning with the oxidative addition of Pd(0) to 2,5-cyclohexadienyl-substituted aryl iodide **1a** (R<sup>1</sup> = H, R<sup>2</sup> = Me) to give palladium intermediate **A** which then underwent a Heck reaction leading to homoallylic palladium intermediate **B**. The latter was subsequently submitted to  $\beta$ -hydride elimination to afford palladium intermediate **C**, which was further submitted to alkene reinsertion to give **D**. Then, intermediate **D** afforded  $\pi$ -allyl palladium species **E**, which finally delivered the domino product through backside intermolecular nucleophilic attack with malonate **2**.

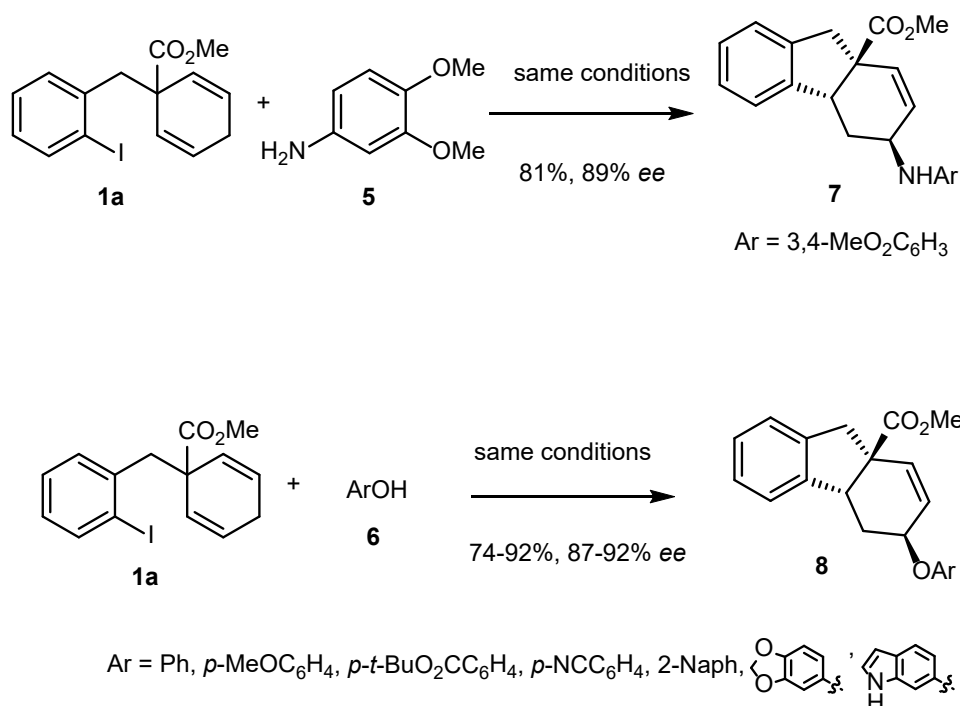


mechanism (with  $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{Me}$ ):



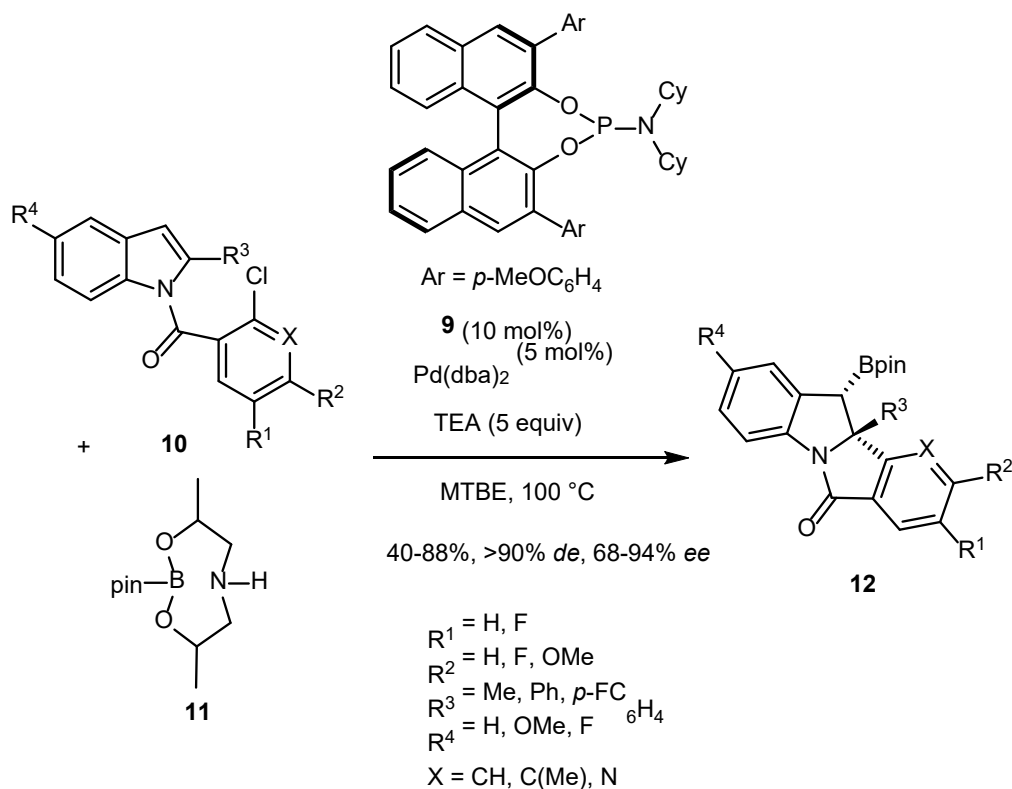
**Scheme 1.** Domino Heck/Tsuji–Trost reaction of 2,5-cyclohexadienyl-substituted aryl iodides with malonates.

The scope of this methodology could be extended to heteroatom nucleophiles, such as electron-rich aniline **5** and aromatic alcohols **6**, which afforded by reaction with methyl 1-(2-iodobenzyl)-cyclohexa-2,5-diene-1-carboxylate **1a** the corresponding chiral tetrahydrofluorenes **7** and **8**, respectively (Scheme 2).<sup>[11]</sup> The latter were obtained in both high yields (81% for **7** and 74–92% for **8**) and *ee* values (89% *ee* for **7** and 87–92% *ee* for **8**).



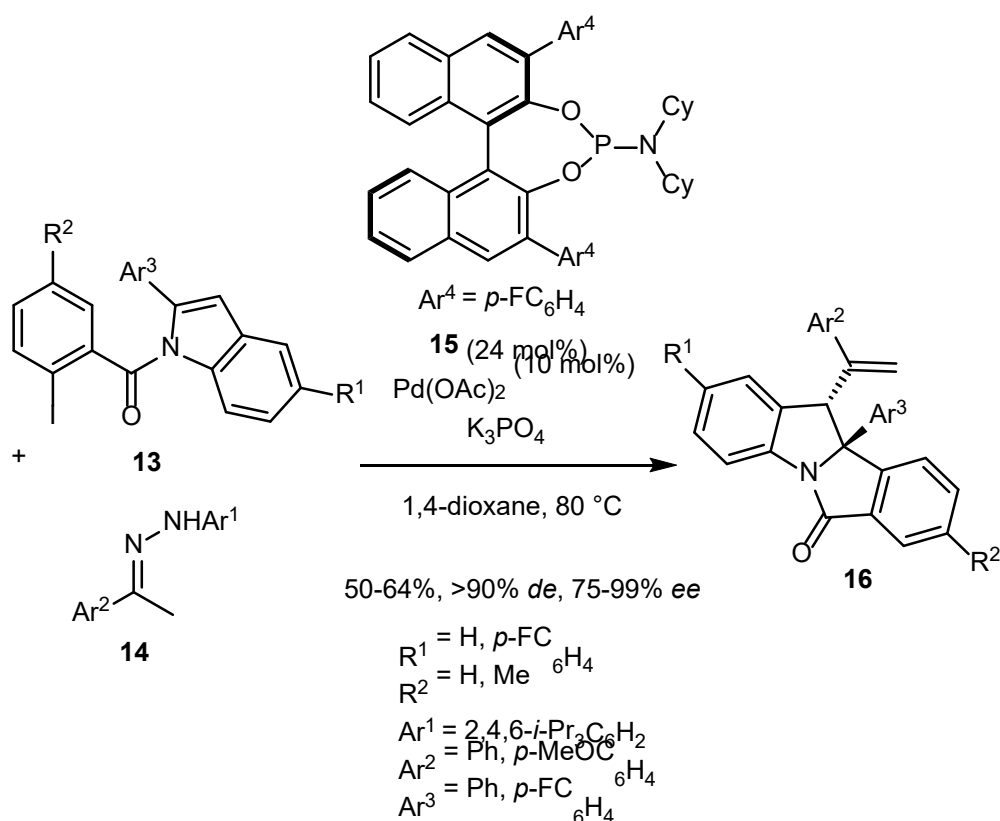
**Scheme 2.** Domino Heck/Tsuji–Trost reactions of a 2,5-cyclohexadienyl-substituted aryl iodide with heteroatom nucleophiles.

In 2019, Lautens and Jia developed an enantioselective domino Heck/borylation reaction of chlorinated *N*-tethered aryl indoles **10** with pre-activated  $sp^2$ – $sp^3$  mixed-boron reagent **11** performed in the presence of 10 mol% of novel BINOL-derived chiral phosphoramidite ligand **9** in combination with 5 mol% of Pd(dba)<sub>2</sub> in MTBE as the solvent (Scheme 3).<sup>[12]</sup> The reaction led at 100 °C in the presence of TEA as base to the corresponding chiral tetracyclic indolines **12** as almost single diastereomers (>90% *de*) possessing vicinal borylated trisubstituted and tetrasubstituted stereocenters with both moderate to high yields (40–88%) and enantioselectivities (68–94% *ee*). The catalyst system tolerated the presence of different substituents on the phenyl ring of the aryl-chloride substrates. In case of steric hindrance at the halide (X = C(Me)), or when substituents were present at the *para*-position of the amide tether ( $R^2$  = OMe, F), lower enantioselectivities (68–79% *ee*) were obtained. In contrast, substitution at the *meta*-position of the chloride ( $R^1$  = F) or on the indole moiety ( $R^4$  = F, OMe) resulted in the formation of the corresponding products with excellent enantioselectivities (91–93% *ee*). Furthermore, an aryl functionality at the  $R^3$  position ( $R^3$  = Ph, *p*-FC<sub>6</sub>H<sub>4</sub>) allowed the best enantioselectivity (94% *ee*) to be achieved. In addition, an heteroaromatic substrate (X = N) was compatible, albeit leading to the corresponding product with a lower enantioselectivity (82% *ee*).



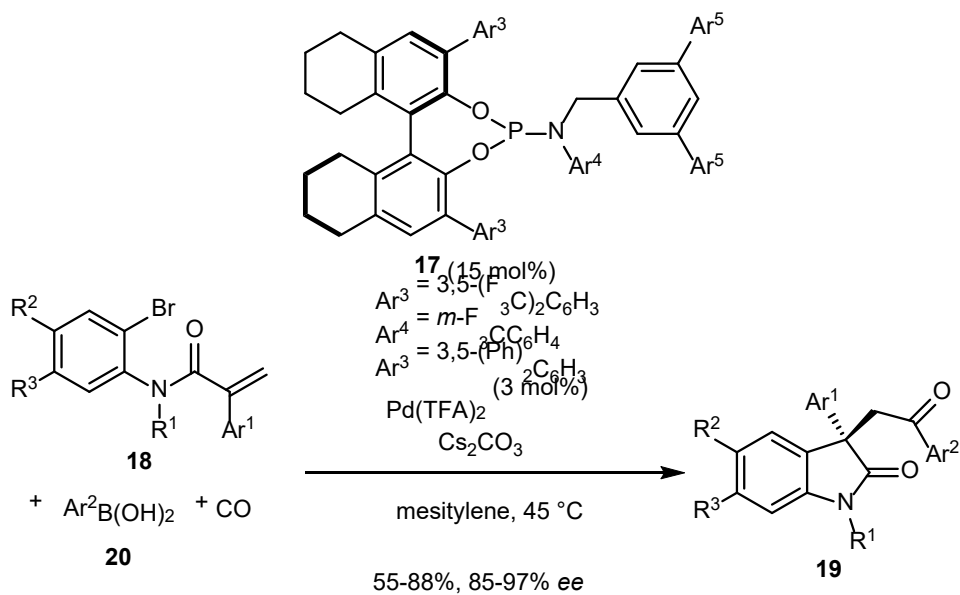
**Scheme 3.** Domino Heck/borylation reaction of chlorinated *N*-tethered aryl indoles with a boron reagent.

In the same year, an enantioselective palladium-catalyzed domino Heck/vinylation reaction of indoles **13** with *N*-arylsulfonylhydrazones **14** was reported by Jia et al. (Scheme 4).<sup>[13]</sup> Using 10 mol% of Pd(OAc)<sub>2</sub> combined with 24 mol% of BINOL-based chiral phosphoramidite ligand **15** as catalyst system, this dearomative arylvinylation reaction performed at 80 °C in 1,4-dioxane as solvent in the presence of K<sub>3</sub>PO<sub>4</sub> as base afforded the corresponding chiral 3-vinylated indolines **16** bearing vicinal quaternary and tertiary carbon centers as almost single diastereomers (>90% *de*) in moderate yields (50-64%) combined with moderate to good enantioselectivities (75-79% *ee*).

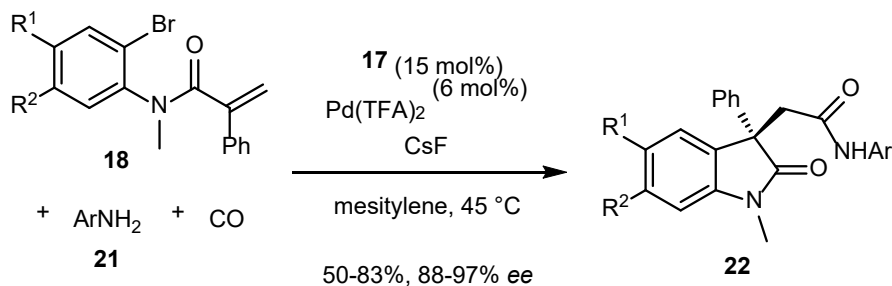


**Scheme 4.** Domino Heck/vinylation reaction of indoles with *N*-arylsulfonylhydrazones.

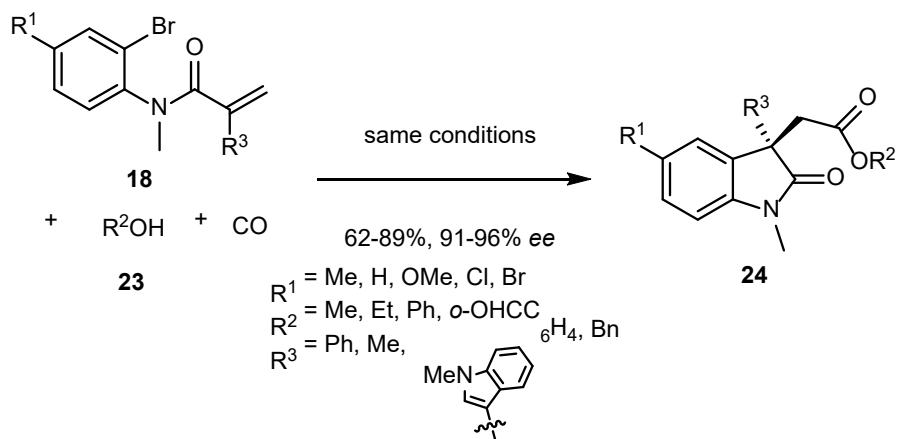
In 2020, novel enantioselective domino Heck/carbonylative Suzuki reactions between *N*-aryl acrylamides, various nucleophiles and CO were developed by Guan et al. in the presence of novel chiral monodentate phosphoramidite ligand **17** (Scheme 5).<sup>[14]</sup> Promoted by a combination of 15 mol% of this chiral ligand and 3 mol% of  $\text{Pd}(\text{TFA})_2$  in the presence of CsF as base, the three-component domino Heck carbonylative/Suzuki reaction between *N*-aryl acrylamides **18**, arylboronic acids **20** and CO performed at 45 °C in mesitylene as solvent afforded the corresponding chiral oxindoles **19** exhibiting a  $\beta$ -carbonyl-substituted all-carbon quaternary stereocenter in good to high yields (55-88%) and high enantioselectivities (85-97% *ee*). The scope of the process could be extended to another type of nucleophiles, such as arylamines **21**, which allowed the synthesis of the corresponding chiral products **22** in good yields (50-83%) and high enantioselectivities (88-97% *ee*) through asymmetric domino Heck/amidation reaction (Scheme 5). Furthermore, a third class of nucleophiles, such as alcohols **23**, could be applied, leading to desired products **24** in good yields (62-89%) and excellent *ee* values (91-96% *ee*) through domino Heck/esterification reaction, as shown in Scheme 5. In all cases of nucleophiles, a wide range of functional groups were tolerated on the substrates. It must be noted that these results represented the first enantioselective palladium-catalyzed domino Heck carbonylation reactions in the presence of CO promoted by a chiral monodentate ligand. The synthetic utility of this novel methodology was demonstrated by its application in the synthesis of three bioactive alkaloids, such as (+)-physovenine, (+)-physostigmine and (+)-folicanthine.



$\text{R}^1 = \text{Me, Et, Bn}$   
 $\text{R}^2 = \text{Me, H, Et, } i\text{-Pr, } n\text{-Bu, } t\text{-Bu, OMe, OEt, F, Cl, CF}_3, \text{Br}$   
 $\text{R}^3 = \text{Me, H, OMe, F}$   
 $\text{Ar}^1 = \text{Ph, } p\text{-Tol, } p\text{-F-C}_6\text{H}_4, p\text{-Cl-C}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-EtOC}_6\text{H}_4, p\text{-BnOC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-Cl-C}_6\text{H}_4, p\text{-Br-C}_6\text{H}_4, 2\text{-Naph, } 1\text{-Naph,}$   
 $\text{Ar}^2 = \text{Ph, } p\text{-Tol, } m\text{-Tol, } o\text{-Tol, } p\text{-Et-C}_6\text{H}_4, p\text{-t-BuC}_6\text{H}_4, p\text{-PhC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-EtOC}_6\text{H}_4, p\text{-BnOC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-Cl-C}_6\text{H}_4, p\text{-Br-C}_6\text{H}_4, 2\text{-Naph, } 1\text{-Naph,}$

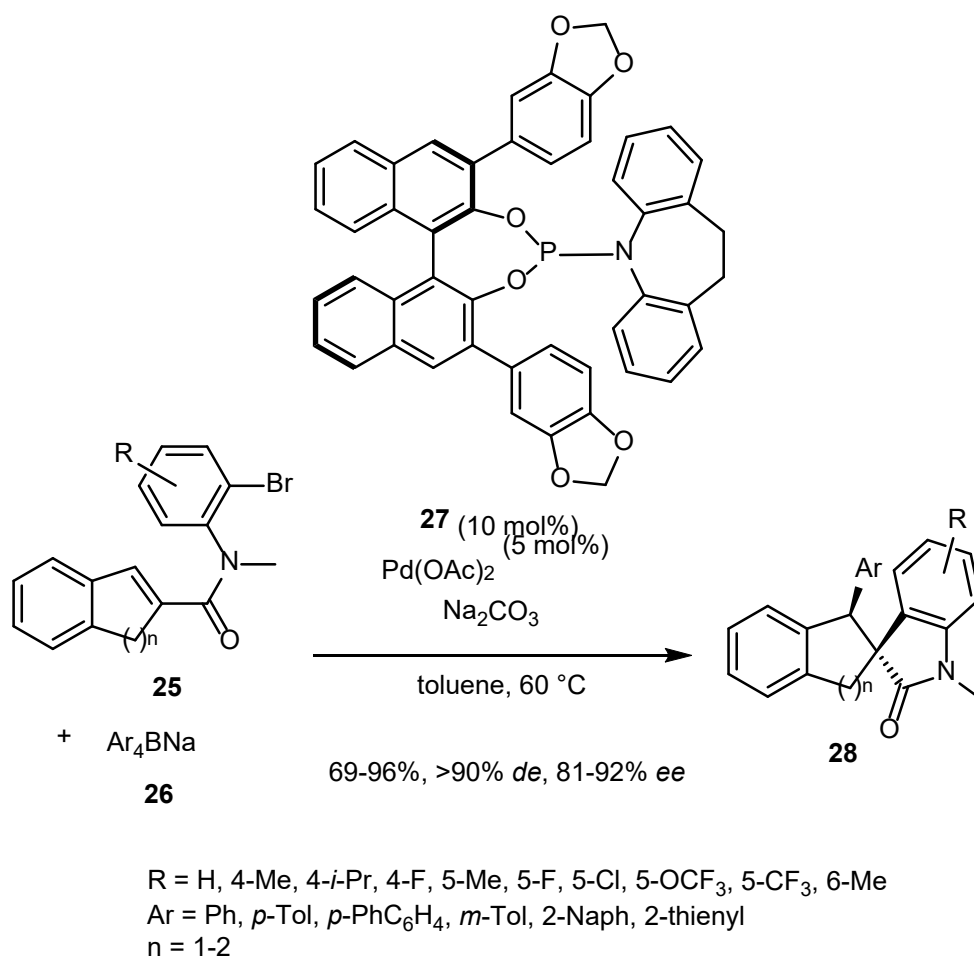


$\text{R}^1 = \text{Me, H, } t\text{-Bu, OMe, F, Cl, Br, CF}_3$   
 $\text{R}^2 = \text{H, Me, OMe}$   
 $\text{Ar} = \text{Ph, } p\text{-Cl-C}_6\text{H}_4, p\text{-Br-C}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-O}_2\text{NC}_6\text{H}_4, p\text{-MeO}_2\text{CC}_6\text{H}_4, p\text{-NCC}_6\text{H}_4, p\text{-AcOC}_6\text{H}_4, p\text{-BocNHC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, o\text{-Tol, } m\text{-Tol, } m\text{-EtC}_6\text{H}_4, m\text{-i-PrC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4, m\text{-Cl-C}_6\text{H}_4, 3,5\text{-Me}_2\text{C}_6\text{H}_3$



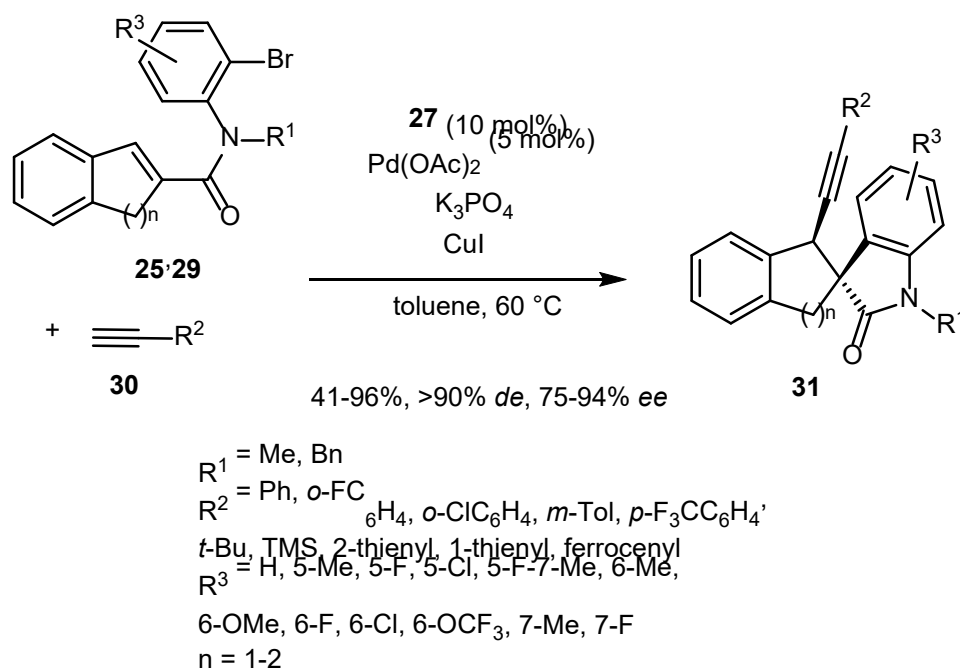
**Scheme 5.** Three-component domino Heck/carbonylative Suzuki, domino Heck/esterification and domino Heck/amidation reactions of *N*-aryl acrylamides.

In another area, Jia et al. developed in 2021 an enantioselective domino Heck/Suzuki reaction of sterically hindered cyclic trisubstituted alkenes **25** with sodium tetraarylborates **26** (Scheme 6).<sup>[15]</sup> Carried out at 60 °C in toluene as solvent, this 1,2-diarylation reaction was catalyzed by a combination of 5 mol% of Pd(OAc)<sub>2</sub> and 10 mol% of chiral BINOL-derived phosphoramidate ligand **27**, resulting in the formation of a variety of chiral 3,3'-spirooxindoles **28** exhibiting vicinal spiro quaternary and tertiary stereocenters with good to high yields (69-96%) and both high diastereo- (>90% *de*) and enantioselectivities (81-92% *ee*).



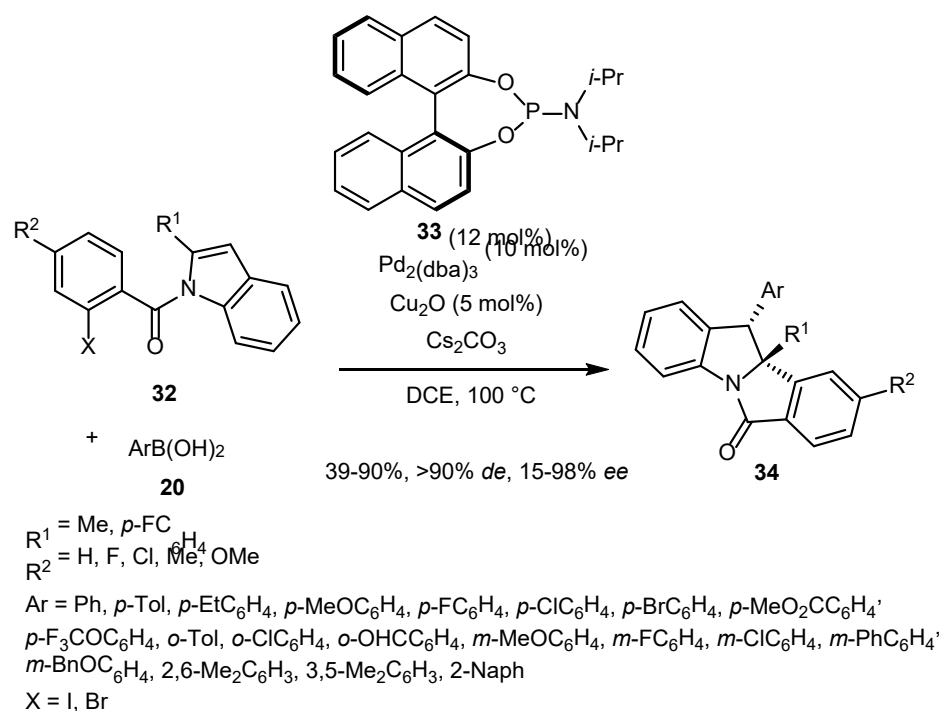
**Scheme 6.** Domino Heck/Suzuki reaction of trisubstituted alkenes with sodium tetraarylborates.

In addition, the same authors also developed enantioselective Heck/Sonogashira reactions of sterically hindered trisubstituted alkenes **25,29** with terminal alkynes **30** by using the same catalyst system (Scheme 7).<sup>[15]</sup> Performed at 60 °C in the presence of K<sub>3</sub>PO<sub>4</sub> as base in toluene as solvent, the 1,2-arylalkynylation reaction afforded the corresponding chiral 3,3'-spirooxindoles **31** exhibiting two consecutive stereogenic carbon centers as almost single diastereomers (>90% *de*) with moderate to excellent yields (41-96%) and good to high *ee* values (75-94% *ee*). The catalyst tolerated both aryl and aliphatic alkynes.

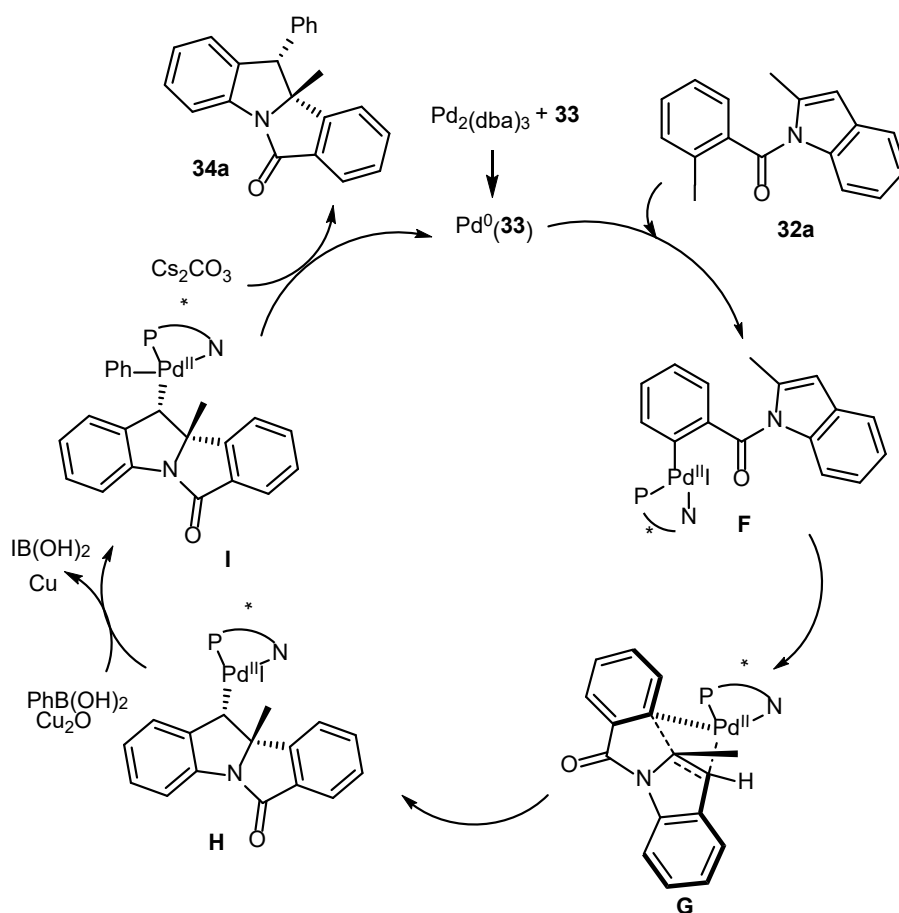


**Scheme 7.** Domino Heck/Sonogashira reaction of trisubstituted alkenes with terminal alkynes.

In 2021, an unprecedented enantioselective palladium-catalyzed domino Heck/Suzuki reaction between aryl halides **32** and arylboronic acids **20** was developed by Zhao and Han in the presence of chiral phosphoramidite ligand **21** (Scheme 8).<sup>[16]</sup> The process was performed at 100 °C in the presence of 10 mol% of  $\text{Pd}_2(\text{dba})_3$ , 12 mol% of chiral BINOL-based phosphoramidite ligand **33**, 5 mol% of  $\text{Cu}_2\text{O}$  as an additive, and  $\text{Cs}_2\text{CO}_3$  as base in DCE as the solvent. This asymmetric domino Heck-type/Suzuki reaction afforded a wide variety of chiral indolines **34** bearing an all-carbon quaternary stereogenic center as almost single diastereomers (>90% *de*) with both moderate to excellent enantioselectivities (15-98% *ee*) and yields (39-90%). The catalyst system tolerated a broad diversity of functional groups. Comparable *ee* values were obtained for either aryl iodides ( $\text{X} = \text{I}$ , 15-98% *ee*) and aryl bromides ( $\text{X} = \text{Br}$ , 26-98% *ee*) while the former generally reacted with better yields (53-90% vs 39-66%). A mechanism is depicted in Scheme 8, showing the initial formation of a chiral  $\text{Pd}(0)$  species from ligand **33** and  $\text{Pd}_2(\text{dba})_3$ . Then, this active chiral catalyst underwent oxidative addition to the C–I bond of aryl iodide **32a** ( $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{H}$ ,  $\text{X} = \text{I}$ ) to form chiral aryl–palladium complex **F**, which was subsequently submitted to intramolecular *syn*-insertion into the C=C bond of the indole to provide dearomative benzylic  $\text{Pd}(\text{II})$  intermediate **G**. Then, migratory insertion in intermediate **G** afforded intermediate **H**, followed by intermolecular coordination and insertion of a phenyl copper species, *in situ* generated from the reaction between phenylboronic acid and  $\text{Cu}_2\text{O}$ , which led to intermediate **I**. Finally, the desired product **34a** was obtained via reductive elimination of intermediate **I** along with regenerated catalyst.

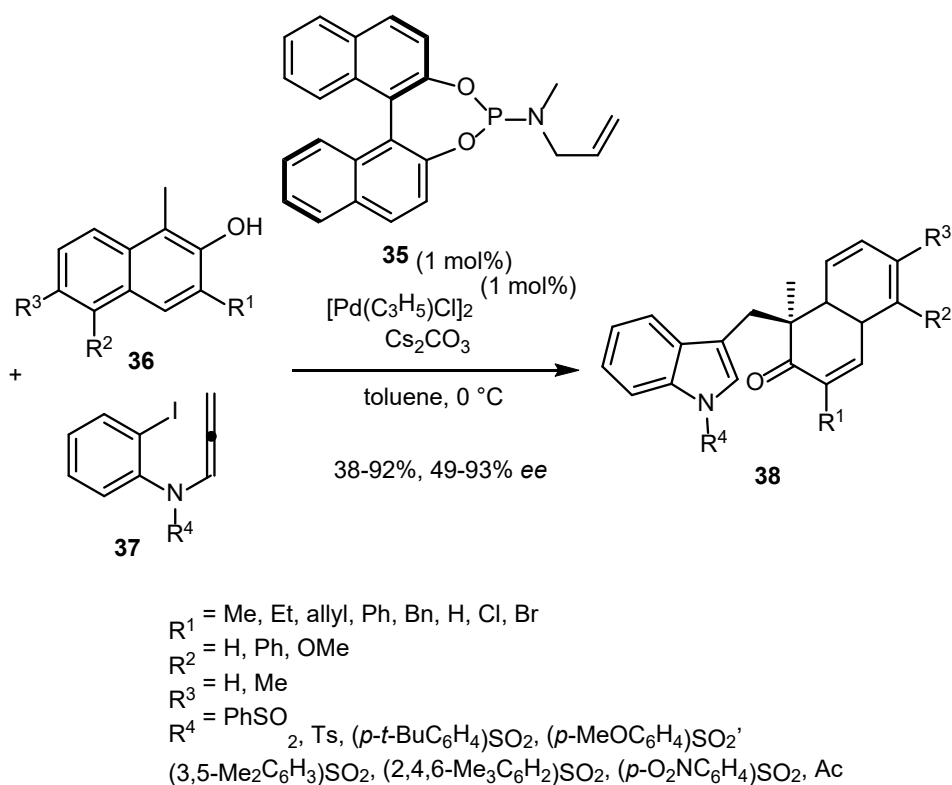


mechanism (with  $\text{R}^1 = \text{Me}$ ,  $\text{R}_2 = \text{H}$ ,  $\text{X} = \text{I}$ ,  $\text{Ar} = \text{Ph}$ ):



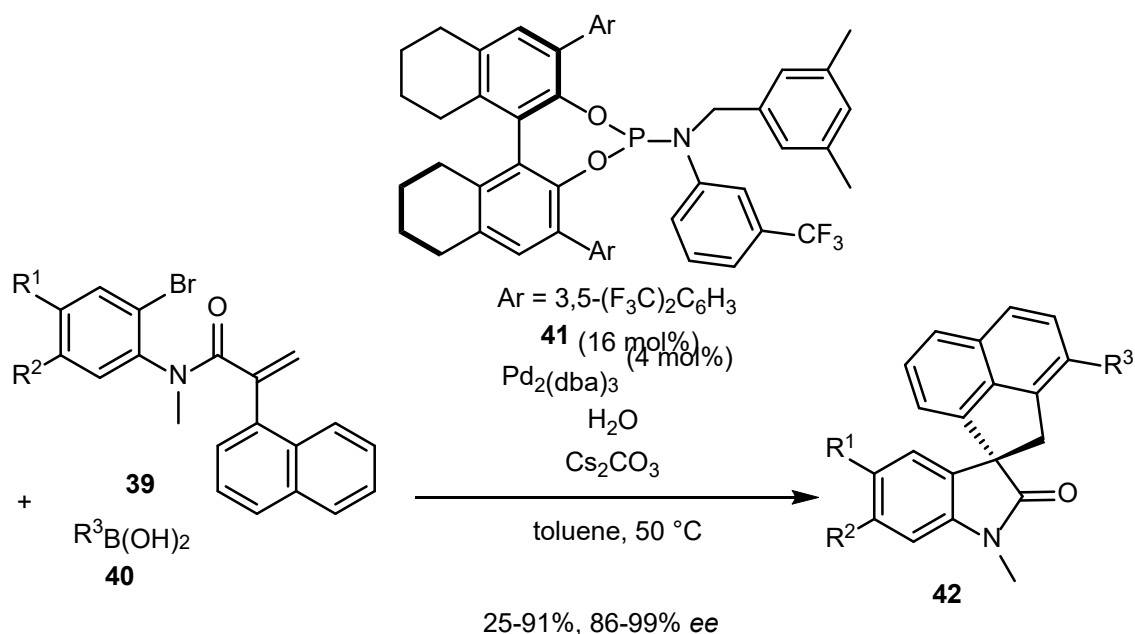
**Scheme 8.** Domino Heck/Suzuki reaction of aryl halides with arylboronic acids.

In 2021, Wang and Guo disclosed novel enantioselective palladium-catalyzed domino Heck/dearomatization reactions (Scheme 9).<sup>[17]</sup> These reactions involved at 0 °C a chiral palladium catalyst *in situ* generated from only 1 mol% of  $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$  and the same quantity of chiral phosphoramidite ligand **35** in toluene as solvent. In the presence of  $\text{Cs}_2\text{CO}_3$  as base,  $\beta$ -naphthols **36** reacted with *N*-(2-iodophenyl)allenamides **37** through asymmetric domino Heck/dearomatization reaction to give the corresponding chiral dearomatized products **38** with both moderate to high yields (38-92%) and enantioselectivities (49-93% *ee*). These indole-functionalized  $\beta$ -naphthalenone products exhibiting an all-carbon quaternary stereocenter possess the skeleton of important indole-terpenoid analogues. The nature of the *N*-protecting group ( $\text{R}^4$ ) of the allenamide substrate was found to have a great influence on the enantioselectivity of the reaction, since sulfonamides ( $\text{R}^4 = \text{SO}_2\text{Ar}$ ) provided 69-93% *ee* while lower *ee* values (49-70% *ee*) were obtained in the reaction of acetamides ( $\text{R}^4 = \text{Ac}$ ). The process was supposed to evolve through a Heck reaction followed by a nucleophilic trapping of the C-Pd intermediate thus-generated by the  $\beta$ -naphthol as prochiral nucleophile.



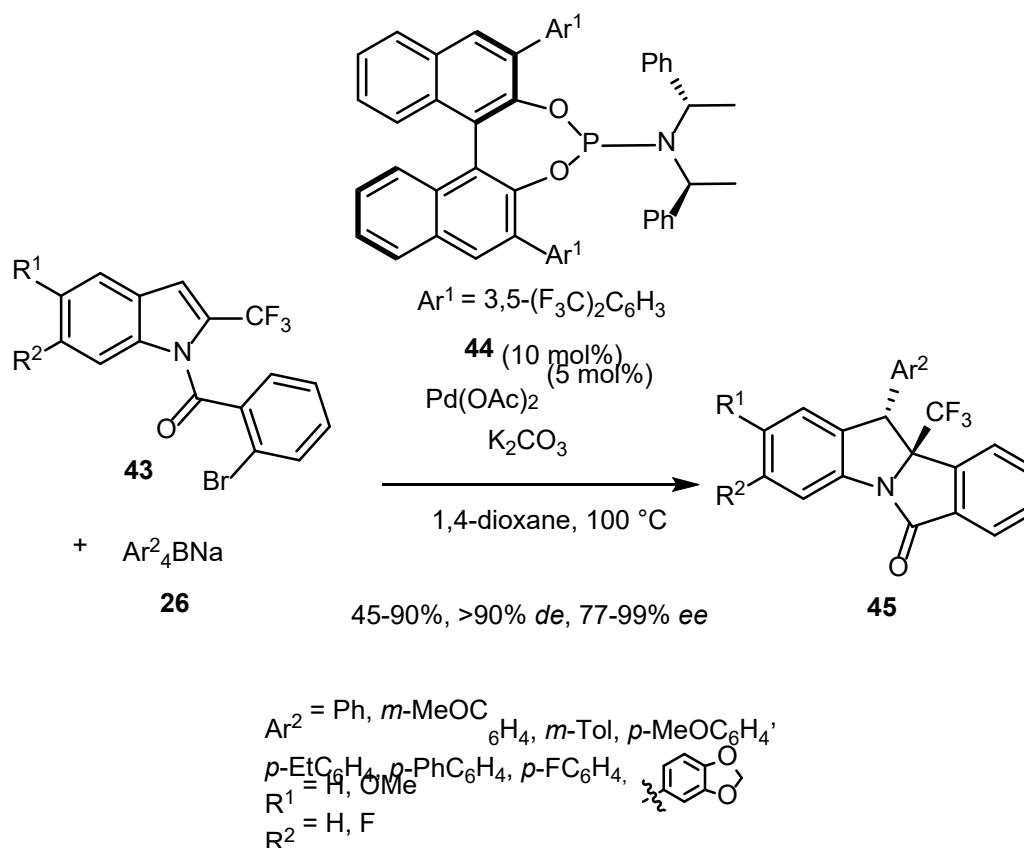
**Scheme 9.** Domino Heck/dearomatization reaction of  $\beta$ -naphthols with *N*-(2-iodophenyl)allenamides.

In the same year, Guan et al. disclosed an unprecedented enantioselective palladium-catalyzed domino Heck/carbocyclization/Suzuki reaction of *N*-(2-bromoaryl)-2-naphthylacrylamides **39** with arylboronic acids **40** (Scheme 10).<sup>[18]</sup> The reaction was promoted at 50 °C in toluene by a combination of 4 mol% of  $\text{Pd}_2(\text{dba})_3$  and 16 mol% of novel phosphoramidite ligand **41** in the presence of  $\text{Cs}_2\text{CO}_3$  as base. This dearomatization strategy of nonactivated naphthalenes allowed chiral spirooxindoles **42** to be synthesized with variable yields (25-91%) and uniformly high enantioselectivities (86-99% *ee*).



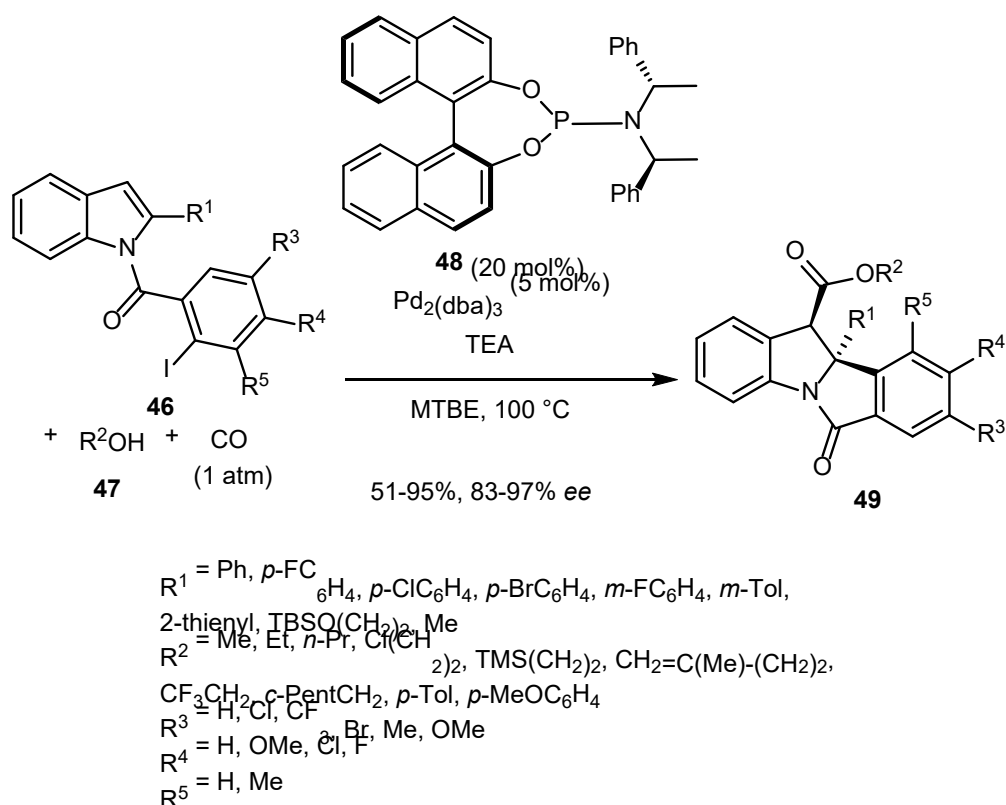
**Scheme 10.** Domino Heck/carbocyclization/Suzuki reaction of *N*-(2-bromoaryl)-2-naphthylacrylamides with arylboronic acids.

Later in 2022, Jia et al. reported an enantioselective palladium-catalyzed domino Heck/Suzuki reaction of *N*-(*o*-bromoaryl)-2- $CF_3$ -indoles **43** with sodium tetraarylborates **26** (Scheme 11).<sup>[19]</sup> A chiral catalyst *in situ* generated from 5 mol% of  $Pd(OAc)_2$  and 10 mol% of chiral phosphoramidate ligand **44** was employed at 100 °C in 1,4-dioxane as solvent. In the presence of  $K_2CO_3$  as base, the reaction delivered chiral indolines **45** containing two vicinal carbon centers as single diastereomers (>90% *de*) with moderate to high yields (45-90%) and good to high enantioselectivities (77-99% *ee*).



**Scheme 11.** Domino Heck/Suzuki reaction of *N*-(*o*-bromoaryl)-2- $\text{CF}_3$ -indoles with sodium tetraarylborates.

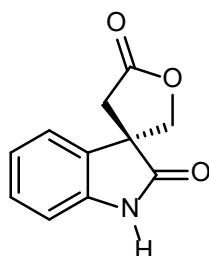
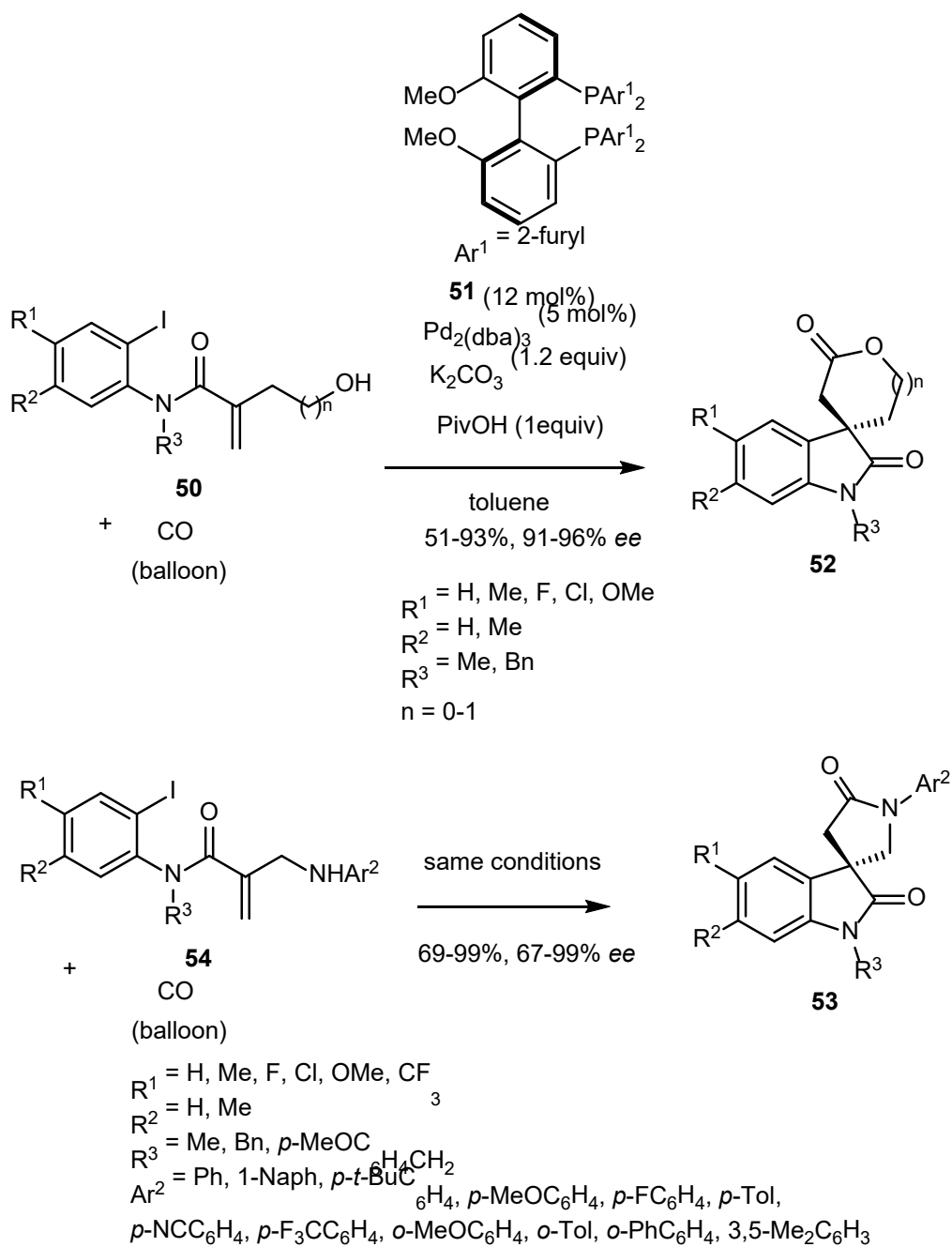
A novel methodology for the asymmetric dearomatization of *N*-arylacyl indoles was described in 2022 by Yao and Lin on the basis of an enantioselective palladium-catalyzed domino Heck/esterification reaction.<sup>[20]</sup> This three-component reaction occurred at 100 °C in MTBE as solvent between *N*-arylacyl indoles **46**, alcohols **47** and CO (1 atm) in the presence of TEA as base and a chiral catalyst *in situ* generated from 5 mol% of  $\text{Pd}_2(\text{dba})_3$  and 20 mol% of chiral phosphoramidate ligand **48**. It resulted in the formation of a wide range of chiral indoline-3-carboxylates **49** bearing vicinal C2-aza-quaternary and C3 tertiary stereocenters with moderate to excellent yields (51-95%) and uniformly high enantioselectivities (83-97% *ee*), as illustrated in Scheme 12. This arylation carbonylation reaction tolerated a series of substituents on the *N*-arylacyl indoles as well as either aliphatic or aromatic alcohols.



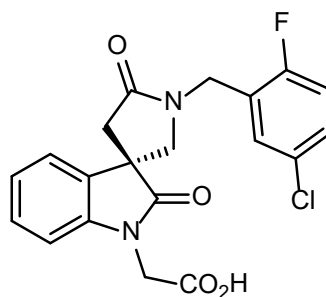
**Scheme 12.** Three-component domino Heck/esterification reaction of *N*-arylacyl indoles, alcohols and CO.

### 2.1.2 Bisphosphine Ligands

The development of efficient methods to synthesize chiral oxindoles is challenging related to their numerous biological activities.<sup>[21]</sup> In this context, Zhu and Luo investigated in 2019 the asymmetric reaction of *N*-(2-iodophenyl)-*N*-alkyl-acrylamides **50** exhibiting a branched homoallylic alcohol under CO pressure promoted by a chiral bisphosphine palladium catalyst in toluene as the solvent.<sup>[22]</sup> The latter was *in situ* generated from 5 mol% of  $\text{Pd}_2(\text{dba})_3$  as precatalyst and 12 mol% of chiral bisphosphine **51**. In the presence of  $\text{K}_2\text{CO}_3$  as base, an intramolecular carbopalladation followed by a carbonylative lactonization occurred to give the corresponding chiral spirooxindole  $\delta$ - or  $\gamma$ -lactones **52** with moderate to high yields (51-93%) and high enantioselectivities (91-96% *ee*), as shown in Scheme 13. This novel and highly enantioselective domino palladium-catalyzed Heck/carbonylative lactonization reaction was applied to the total synthesis of natural product coixspiro lactam as well as that of receptor antagonist CRTH2. In addition to chiral spirooxindole  $\gamma$ - and  $\delta$ -lactones, their lactam analogues **53** could also be synthesized by extending the same methodology to related substrates **54** bearing an intramolecular nitrogen nucleophile instead of an alcohol group. Indeed, the enantioselective domino palladium-catalyzed Heck/carbonylative lactamization reaction of aromatic amines **54** afforded the corresponding chiral spirooxindole  $\delta$ -lactams **53** with good to quantitative yields (69-99%) and moderate to excellent enantioselectivities (67-99% *ee*), as presented in Scheme 13.



coixspirolactam

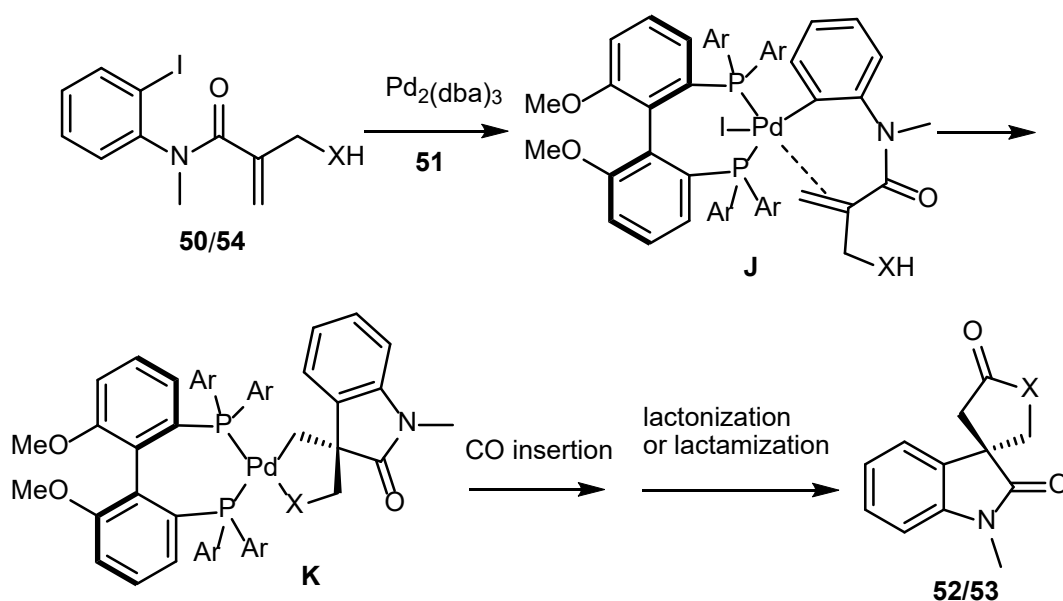


receptor antagonist CRTHZ

**Scheme 13.** Domino Heck/carbonylative lactonization/lactamization reactions of *N*-(2-iodophenyl)-*N*-alkyl-acrylamides.

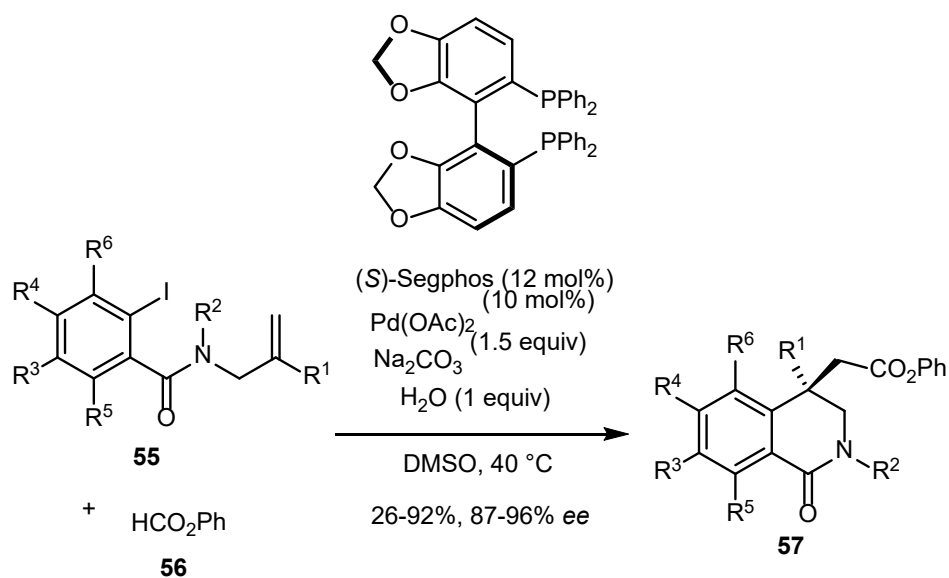
A mechanism for the precedent methodology is proposed in Scheme 14, showing that after oxidative addition, the terminal alkene chelated to the Pd(II) center coordinated to the bidentate chiral bisphosphine ligand in **J**, according to an orientation with the side-chain stretching to the open area away from the ligand. Subsequently, a migratory insertion of the alkenyl moiety to Ar-Pd(II) generated the quaternary carbon center, and an alkyl Pd(II) species **K** then underwent CO insertion and nucleophilic cyclization to deliver the final domino product **52** or **53**.

mechanism (with  $n = 0$ ,  $R^1 = R^2 = H$ ,  $R^3 = Me$ ):



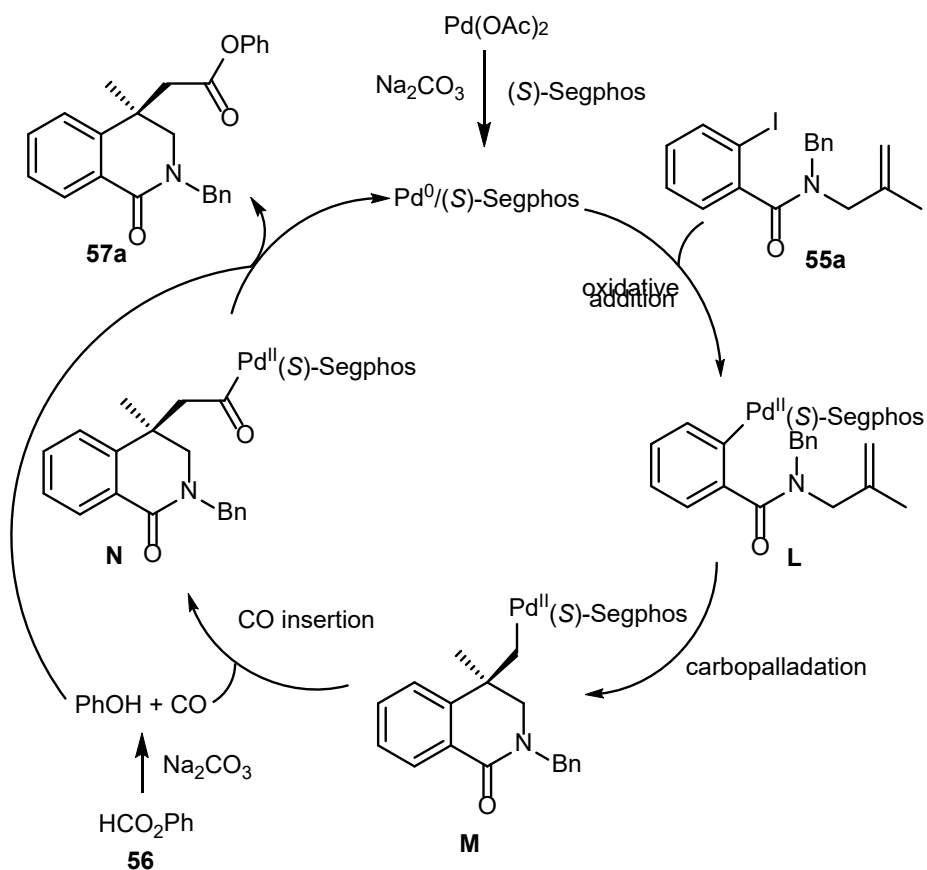
**Scheme 14.** Mechanism for domino Heck/carbonylative lactonization/lactamization reactions of *N*-(2-iodophenyl)-*N*-alkyl-acrylamides.

In 2019, Zhang et al. reported an enantioselective domino Heck/carboxyphenylation reaction of *N*-allyl benzamides **55** using phenyl formate **56** as the CO source dedicated to the construction of chiral six-membered isoquinolinone skeletons bearing an all-carbon quaternary stereocenter.<sup>[23]</sup> The carbonylative Heck reaction was performed at 40 °C in DMSO as solvent in the presence of  $Na_2CO_3$ . Catalyzed by a chiral complex *in situ* formed from 10 mol% of  $Pd(OAc)_2$  and 12 mol% of (*S*)-Segphos as ligand, it resulted in the formation of chiral carbonylated 3,4-dihydroisoquinolines **57** with variable yields (26-92%) and high enantioselectivities (87-96% *ee*). These products constitute the core skeleton in ubiquitous bioactive compounds. It must be noted that this novel methodology represented a rare example of asymmetric six-membered cyclization reactions based on a domino intramolecular Heck-nucleophilic capture sequence. A possible mechanism is depicted in Scheme 15, beginning with the oxidative addition of aryl iodide **55a** ( $R^1 = Me$ ,  $R^2 = Bn$ ,  $R^3 = R^4 = R^5 = R^6 = H$ ) to an *in situ* generated Pd(0) species which led to Pd(II) intermediate **L**. The latter underwent intramolecular carbopalladation to afford  $\sigma$ -alkyl Pd(II) complex **M**. In the presence of  $Na_2CO_3$ , phenyl formate **56** produced CO and phenol. The migratory insertion of CO into the  $\sigma$ -alkyl-Pd bond provided acylpalladium complex **N**. Then, nucleophilic attack of phenol followed by reductive elimination gave the final product along with regenerated Pd(0) catalyst.



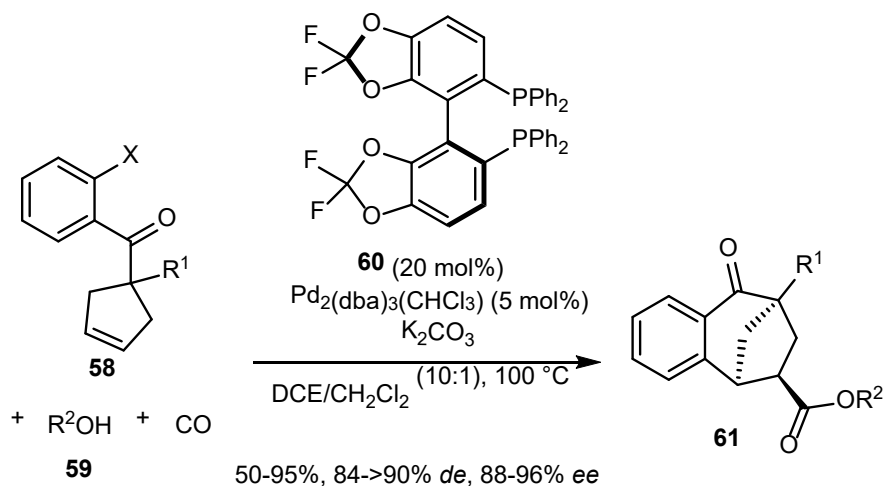
$R^1$  = Me, Et, *n*-Bu, Bn, MOM, *p*-MeOC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>  
 $R^2$  = Bn, Me, CH<sub>2</sub>  
 $R^3$  = H, OMe,  $R^4$  = H, F, OMe  
 $R^5$  = H, Me  
 $R^6$  = H, Me

mechanism (with  $R^1$  = Me,  $R^2$  = Bn,  $R^3$  =  $R^4$  =  $R^5$  =  $R^6$  = H):

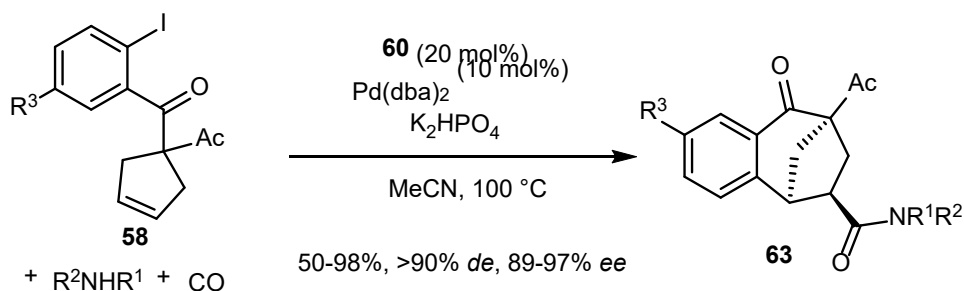


**Scheme 15.** Domino Heck/carboxyphenylation reaction of *N*-allyl benzamides with phenyl formate.

An enantioselective palladium-catalyzed domino Heck/esterification reaction of cyclopentenones **58** with alcohols **59** under CO atmosphere was disclosed by Lin and Yao, in 2020 (Scheme 16).<sup>[24]</sup> This three-component process was performed at 100 °C in a 10:1 mixture of DCE and dichloromethane as the solvent and K<sub>2</sub>CO<sub>3</sub> as base. It was promoted by a combination of 5 mol% of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> and 20 mol% of chiral bisphosphine ligand **60**, which resulted in the formation of a range of chiral functionalized bicyclo[3.2.1]octanes **61** bearing one all-carbon quaternary and two tertiary carbon stereogenic centers as almost single diastereomers (84->90% *de*) in moderate to high yields (50-95%) and high enantioselectivities (88-96% *ee*). A wide variety of alcohols were compatible, spanning from simple primary aliphatic alcohols, including primary alcohols with various functional groups, such as alkenyl, trifluoromethyl, halogen, trimethylsilyl, and even highly sterically hindered adamantyl groups, to cyclic and acyclic secondary alcohols and also phenols bearing substituents on the phenyl ring. Moreover, the scope of the methodology could be extended to nitrogen nucleophiles, such as secondary amines **62**, which afforded by reaction with cyclopentenones **58** and CO the corresponding chiral amides **63** as single diastereomers (>90% *de*) with excellent enantioselectivities (89-97% *ee*) and moderate to quantitative yields (50-98%). In this case, the active catalyst was *in situ* generated from 10 mol% of Pd(dba)<sub>2</sub> as precatalyst and 20 mol% of chiral bisphosphine ligand **60** in acetonitrile as solvent and in the presence of K<sub>2</sub>HPO<sub>4</sub> as base. Both acyclic and cyclic secondary alkylamines were compatible to the domino Heck/amidation reaction. The authors proposed a mechanism beginning with oxidative addition of the active palladium catalyst to the cyclopentene, which generated cationic Pd(II) intermediate **O** (Scheme 16). Subsequent intramolecular *syn*-migratory insertion of **O** resulted in the formation of alkylpalladium intermediate **P**. Then, the latter was submitted to insertion of CO followed by that of the nucleophile to afford intermediate **Q**, which finally delivered the product.

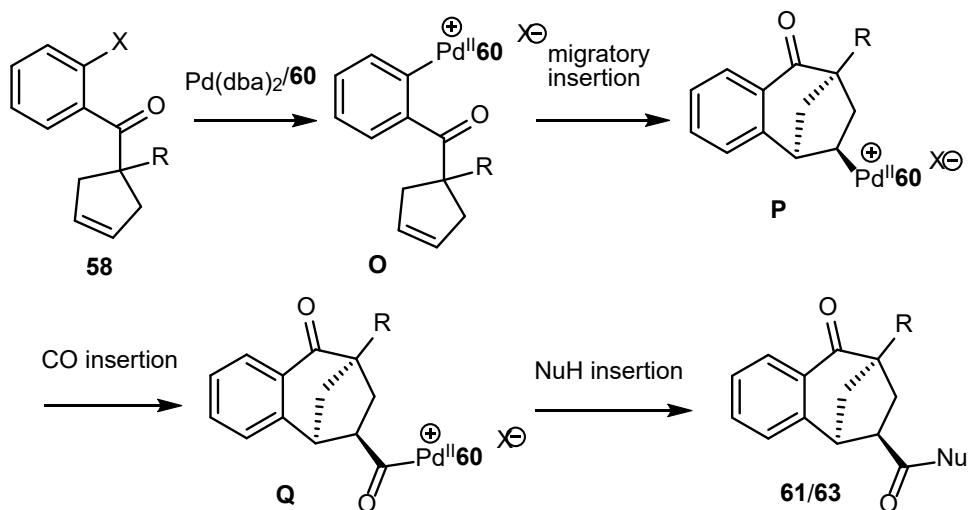


$R^1 = Ac, CO$   
 $R^2 = Me, Et, n\text{-}Pr, Bn, CH_2=CH(CH_2)_3, CF_3CH_2, Cl(CH_2)_3, TMS(CH_2)_2, (adamantyl)CH_2, i\text{-}Pr, c\text{-}Pr, c\text{-}Bu, c\text{-}Pent, Cy, Ph, p\text{-}Tol, p\text{-}t\text{-}BuC_6H_4, p\text{-}MeOC_6H_4, p\text{-}ClC_6H_4, p\text{-}AcC_6H_4, p\text{-}PhC_6H_4, m\text{-}ClC_6H_4, p\text{-}BnOC_6H_4, 3,5\text{-}Me_2C_6H_3, 2\text{-}Naph$   
 $X = I, Br$



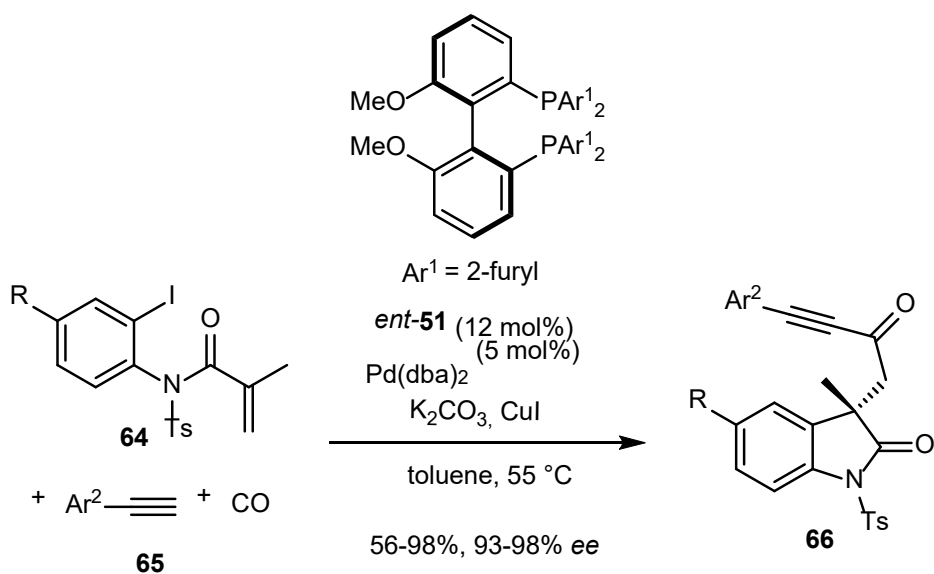
**62**  
 $R^1 = Et, Bn, Me, H$   
 $R^2 = Et, Bn, Ph, n\text{-}Pr, p\text{-}EtO$   
 $R^1, R^2 = (CH_2)_4, (CH_2)_5, (CH_2)_6, (CH_2)_2O(CH_2)_2, (CH_2)_2S(CH_2)_2$   
 $R^3 = H, OMe$

mechanism:

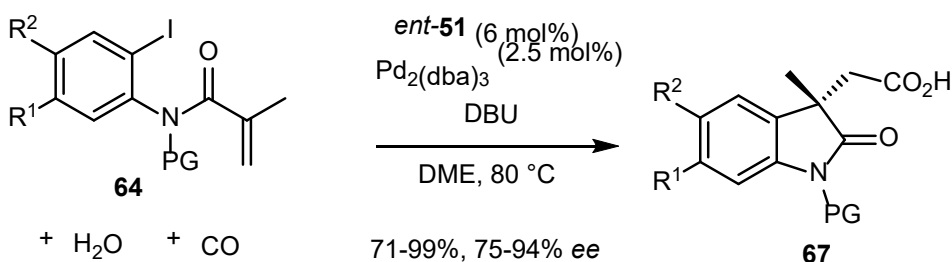


**Scheme 16.** Three-component domino Heck/esterification and domino Heck/amidation reactions of cyclopentenenes, alcohols/secondary amines and CO.

Later in 2022, an enantioselective palladium-catalyzed domino Heck/carbonylation reaction of *N*-tosyl-protected *o*-iodoacrylanilides **64** with terminal alkynes **65** and CO was reported by Wang and Ding, leading to the corresponding chiral  $\beta$ -carbonylated 2-oxindoles **66** bearing a 3,3-disubstituted all-carbon quaternary stereocenter with excellent enantioselectivities (93-98% *ee*) and moderate to quantitative yields (56-98%), as illustrated in Scheme 17.<sup>[25]</sup> The three-component domino Heck/carbonylative Sonogashira reaction required the use of 12 mol% of chiral biphosphine *ent*-**51** as ligand and 5 mol% of Pd(dba)<sub>2</sub> as precatalyst to occur at 55 °C in toluene as solvent with K<sub>2</sub>CO<sub>3</sub> as base and CuI as additive. The presence of various types of substituents on the phenyl rings of both the two substrates were tolerated. With the aim of extending the scope of this methodology, the authors investigated the use of water as nucleophile. In this case, the optimal reaction conditions were achieved by using 6 mol% of the same chiral ligand albeit combined with 2.5 mol% of Pd<sub>2</sub>(dba)<sub>3</sub> as precatalyst in DME as the solvent (Scheme 17). Furthermore, the process was performed at higher temperature (80 vs 55 °C) with DBU as base and did not require the presence of CuI as an additive. Under these conditions, a series of *N*-protected *o*-iodoacrylanilides **64** reacted with water under CO pressure to give the corresponding chiral  $\beta$ -carbonylated 3,3-disubstituted oxindoles **67** in both good to high yields (71-99%) and *ee* values (75-94% *ee*). These products presented the advantage to exhibit a carboxyl group which can act as a pharmacophore in many drugs.



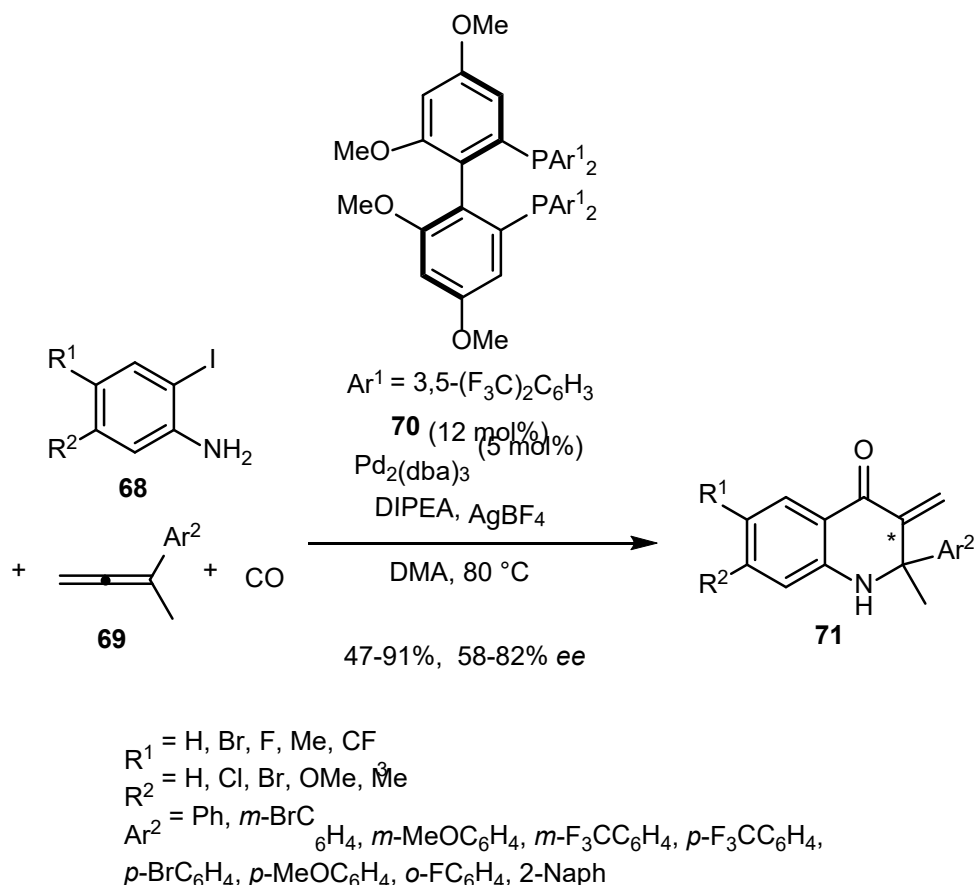
$\text{R} = \text{H, F, Cl, Br, CF}_3$   
 $\text{Ar}^2 = \text{Ph, } o\text{-Tol, } o\text{-MeOC}_6\text{H}_4, o\text{-FC}_6\text{H}_4, o\text{-BocHNC}_6\text{H}_4, m\text{-Tol,}$   
 $m\text{-FC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4, p\text{-Me}_2\text{NC}_6\text{H}_4, p\text{-PhC}_6\text{H}_4, p\text{-FC}_6\text{H}_4,$   
 $p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, 2\text{-thienyl}$



$\text{R}^1 = \text{Me, H, Bn, OMe, Cl, Br}$   
 $\text{R}^2 = \text{H, Me, OMe, F, Cl, Br, CF}_3, \text{NO}_2$   
 $\text{PG} = \text{Me, MOM, Bn, } p\text{-MeOC}_6\text{H}_4\text{CH}_2, \text{Boc}$

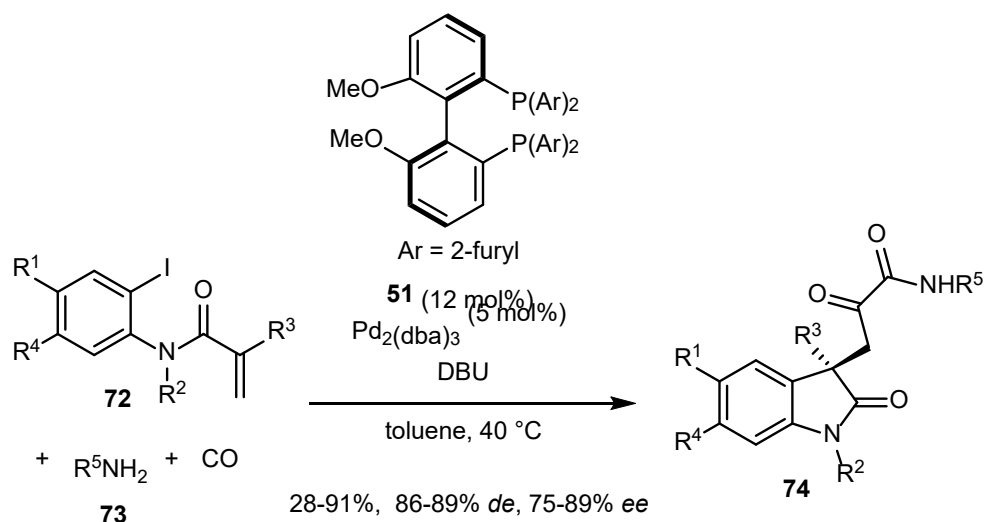
**Scheme 17.** Three-component domino Heck/carbonylation reactions of *o*-iodoacrylanilides, terminal alkynes/water and CO.

In 2021, Dong et al. developed a novel route to aza-quaternary carbon center via C–N bond formation based on an enantioselective palladium-catalyzed carbonylative Heck/aminocyclization reaction of *o*-iodoanilines **68** with allenes **69** and CO (Scheme 18).<sup>[26]</sup> The three-component reaction was promoted at 80 °C in *N,N*-dimethylacetamide (DMA) as solvent by a chiral catalyst *in situ* generated from 5 mol% of  $\text{Pd}_2(\text{dba})_3$  and 12 mol% of chiral bisphosphine ligand **70**. In the presence of DIPEA as base and  $\text{AgBF}_4$  as additive, the domino Heck/aminocyclization reaction of *o*-iodoanilines **68** with allenes **69** under CO atmosphere yielded the corresponding chiral dihydroquinolinones **71** with both moderate to high yields (47-91%) and enantioselectivities (58-82% *ee*).



**Scheme 18.** Three-component domino carbonylative Heck/aminocyclization reaction of *o*-iodoanilines, allenes and CO.

In 2022, Zhu and Luo described a rare example of asymmetric palladium-catalyzed double carbonylation of  $\sigma$ -alkylpalladium Heck intermediates (Scheme 19).<sup>[27]</sup> Indeed, an unprecedented enantioselective domino Heck/carbonylation/aminocarbonylation reaction of *N*-protected *o*-iodoacrylanilides **72** with alkyl amines **73** and CO was successfully developed in the presence of 5 mol% of  $\text{Pd}_2(\text{dba})_3$  and 12 mol% of chiral bisphosphine **51**. The process was performed at 40 °C in toluene as solvent in the presence of DBU as base, delivering the corresponding chiral  $\alpha$ -ketoamides **74** in variable yields (28-91%) combined with both good to high diastereo- (86-89% *de*) and enantioselectivities (75-91% *ee*). This rare double CO insertion into the  $\sigma$ -alkylpalladium intermediate occurred selectively under atmospheric pressure of CO using an alkyl amine as the nucleophile. The catalyst system tolerated a wide variety of alkyl amines, spanning from primary to tertiary ones. Comparable *ee* values were obtained in the reaction of 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.

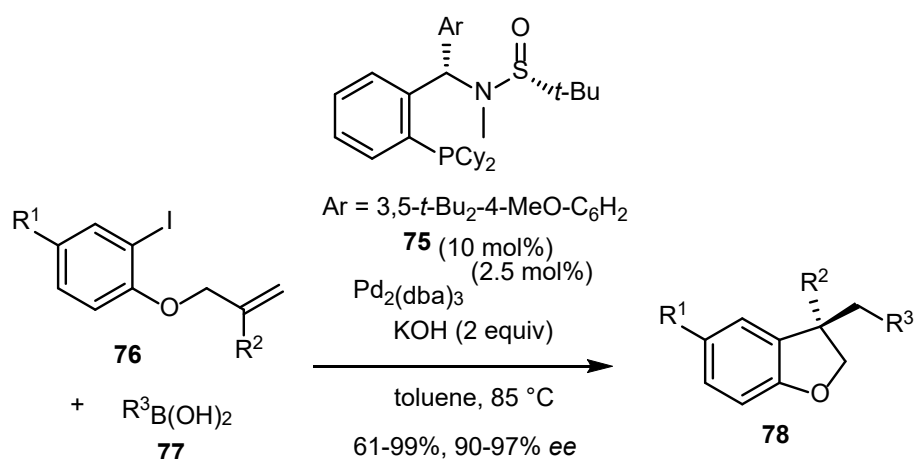


$\text{R}^1 = \text{H, Me, OMe, Cl, Cl, F, CF}_3, \text{CN, CO}_2\text{Me}$   
 $\text{R}^2 = \text{Me, Bn, PMB}$   
 $\text{R}^3 = \text{Me, Ph, Bn}$   
 $\text{R}^4 = \text{H, Me}$   
 $\text{R}^5 = n\text{-Pr, Bn, } p\text{-MeOC}_6\text{H}_4\text{CH}_2, p\text{-ClC}_6\text{H}_4\text{CH}_2, n\text{-Oct, 2-thienyl(CH}_2)_2, \text{PhCH(Me), c-Pent, Cy, } t\text{-Bu, piperidinyl, pyrrolidinyl, morpholinyl,}$

**Scheme 19.** Three-component domino Heck/carbonylation/aminocarbonylation reaction of *N*-protected *o*-iodoacrylanilides with alkyl amines and CO.

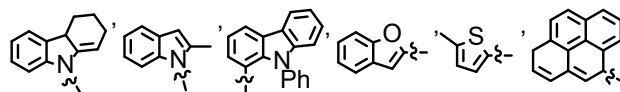
### 2.1.3 P,N-ligands

3,3-Disubstituted dihydrobenzofurans are found in many bioactive products, including retinoids, morphine, CB2 receptor agonists, DNA-PK inhibitors, among others. In 2019, Zhang et al. developed the first example of highly enantioselective palladium-catalyzed dicarbofunctionalization of olefin-tethered aryl halides with alkyl, aryl or alkenylboronic acids, which resulted in the synthesis of various chiral benzene-fused cyclic compounds with an all-carbon quaternary stereocenter, including dihydrobenzofurans.<sup>[28]</sup> The domino Heck/Suzuki coupling process was promoted at 85 °C in toluene as solvent by a combination of 2.5 mol% of  $\text{Pd}_2(\text{dba})_3$  and 10 mol% of chiral P,N-ligand **75**. In the presence of KOH as base, the domino cyclization/cross-coupling reaction of unactivated alkenes with alkyl-, alkenyl- or arylboronic acids allowed a direct route to many types of chiral (hetero)cyclic complex products, including biologically interesting dihydrobenzofurans, indolines, chromanes, and indanes bearing a quaternary stereocenter with moderate to quantitative yields (52-99%) and uniformly high enantioselectivities (80-97% *ee*). In a first time, the reaction conditions were applied to chemo- and stereoselective diarylation, aryl alkenylation and aryl alkylation of a wide range of *o*-iodophenol-derived allyl ethers **76** which afforded by reaction with aryl, alkenyl- and alkylboronic acids **77** the corresponding chiral dihydrobenzofurans **78** with good to quantitative yields (61-99%) and high *ee* values (90-97% *ee*), as shown in Scheme 20. With the aim of synthesizing other potent bioactive molecules, the authors extended the scope of the methodology to the synthesis of chiral indolines, chromanes, and indanes **80** bearing a quaternary stereocenter starting from the corresponding substrates **79**. Indeed, a range of chiral indolines ( $\text{Y} = \text{NBoc}$ ,  $n = 0$ ) were produced with 80-98% yields and 80-94% *ee*, as well as chromanes ( $\text{Y} = \text{O}$ ,  $n = 1$ ) with 52-99% yields combined with 92-94% *ee*, and indanes ( $\text{Y} = \text{CH}_2$ ,  $n = 0$ ) with 60-78% yields and 83-85% *ee* (Scheme 20). The wide scope of the process demonstrated its remarkable high functional-group tolerance.

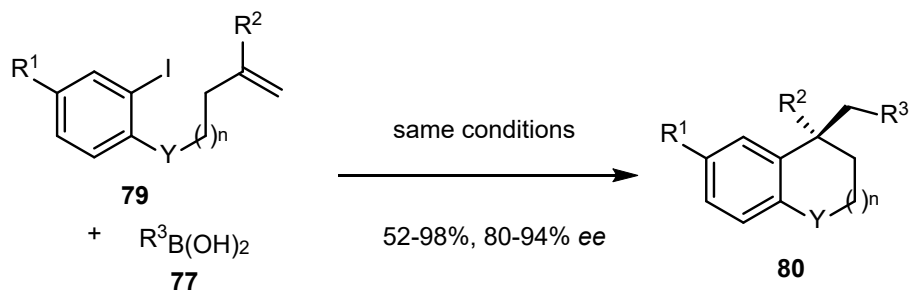
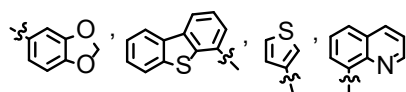


$\text{R}^1 = \text{H, Cl, Ph, CN, NO}$

$\text{R}^2 = \text{Me, Et, } n\text{-Pr, } n\text{-Bu, } n\text{-Pent, } i\text{-Pr, } t\text{-Bu, } p\text{-Tol, } p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4,$   
 $p\text{-Et}_2\text{OCC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, o\text{-Tol, } o\text{-MeOC}_6\text{H}_4, o\text{-FC}_6\text{H}_4, m\text{-Tol, } m\text{-O}_2\text{NC}_6\text{H}_4,$   
 $3,5\text{-Me}_2\text{C}_6\text{H}_3, 3,5\text{-MeO}_2\text{C}_6\text{H}_3, 3,4,5\text{-F}_3\text{C}_6\text{H}_2, 2\text{-Naph,}$



$\text{R}^3 = \text{Ph, } p\text{-Tol, } p\text{-MeOC}_6\text{H}_4, p\text{-Et}_2\text{OCC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, o\text{-Tol, } o\text{-MeOC}_6\text{H}_4,$   
 $m\text{-Tol, } m\text{-MeOC}_6\text{H}_4, m\text{-t-BuC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, m\text{-PhC}_6\text{H}_4, m\text{-O}_2\text{NC}_6\text{H}_4,$   
 $3,5\text{-F}_2\text{C}_6\text{H}_3, 3\text{-F-4-MeC}_6\text{H}_3, 3,4,5\text{-F}_3\text{C}_6\text{H}_2, 2\text{-Naph, } 1\text{-Naph, } 1\text{-cyclohexenyl,}$   
 $1\text{-cyclopentenyl, } (E)\text{-}n\text{-PrCH=CH, } c\text{-Pr, } n\text{-Bu,}$



with  $\text{Y} = \text{NBoc}$ ,  $n = 0$ : 80-98%, 80-94% ee

$\text{R}^1 = \text{H, CF}_3$

$\text{R}^2 = i\text{-Pr, Me, } n\text{-Bu, } n\text{-Pent, } t\text{-Bu}$

$\text{R}^3 = 1\text{-cyclohexenyl, } (E)\text{-PrCH=CH, Ph, } \text{benzothiophene}$

with  $\text{Y} = \text{O}$ ,  $n = 1$ : 52-99%, 92-94% ee

$\text{R}^1 = \text{H}$

$\text{R}^2 = \text{Me}$

$\text{R}^3 = 1\text{-cyclohexenyl, } (E)\text{-PrCH=CH, Ph, } p\text{-MeOC}_6\text{H}_4, p\text{-Et}_2\text{OCC}_6\text{H}_4,$   
 $m\text{-MeOC}_6\text{H}_4, o\text{-MeOC}_6\text{H}_4, \text{benzothiophene}$

with  $\text{Y} = \text{CH}_2$ ,  $n = 0$ : 60-78%, 83-85% ee

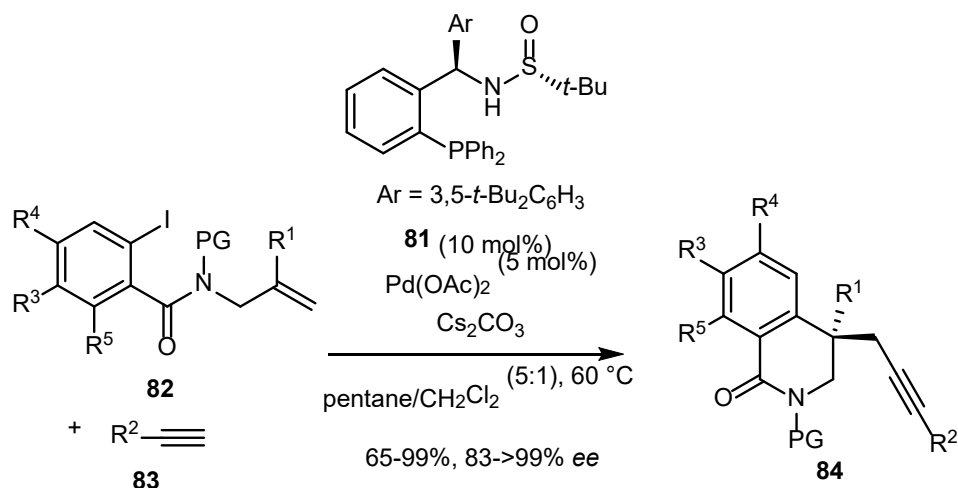
$\text{R}^1 = \text{H}$

$\text{R}^2 = \text{Me}$

$\text{R}^3 = 1\text{-cyclohexenyl, } (E)\text{-PrCH=CH, Ph, } \text{benzothiophene}$

**Scheme 20.** Domino Heck/Suzuki reactions of olefin-tethered aryl halides with alkyl/aryl/alkenylboronic acids.

In 2020, Zhang and Zhang developed one of the first highly chemo- and enantioselective palladium-catalyzed aryl-alkynylation of alkenes based on an enantioselective palladium-catalyzed domino Heck/Sonogashira reaction (Scheme 21).<sup>[29]</sup> This methodology resulted in the formation of benzene-fused cyclic chiral products bearing a propargyl all-carbon quaternary stereocenter. In the presence of a chiral palladium catalyst *in situ* generated from 5 mol% of Pd(OAc)<sub>2</sub> and 10 mol% of chiral ligand **81** and Cs<sub>2</sub>CO<sub>3</sub> as base in a 5:1 mixture of pentane and dichloromethane as the solvent, the aryl-alkynylation reaction of *N*-allyl carboxamides **82** with various alkynes **83** afforded at 60 °C the corresponding chiral bicyclic functionalized products **84** exhibiting a quaternary stereocenter with good to quantitative yields (65-99%) and high enantioselectivities (83->99% *ee*). The scope of the methodology was remarkably wide. For example, an impressive range of arylacetylenes bearing diverse functional groups on the phenyl ring were well tolerated as well as heteroarenes. Moreover, alkenyl alkynes (R<sup>2</sup> = CH<sub>2</sub>=C(Me), 1-cyclohexenyl) underwent the reaction with excellent *ee* values (90-94% *ee*). Aliphatic alkynes (R<sup>2</sup> = *n*-Hex, *n*-decyl, Cl(CH<sub>2</sub>)<sub>3</sub>) also reacted smoothly with high enantioselectivities (88-94% *ee*). In addition, the presence of either electron-withdrawing or electron-donating substituents on the phenyl ring of the *N*-allyl carboxamides was compatible as well as a range of alkyl substituents (R<sup>1</sup>) attached to the alkene moiety. Encouraged by these results, the authors demonstrated that by using closely related chiral ligand **85** (10 mol%) in combination with Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (2.5 mol%) as catalyst system allowed the asymmetric construction of 3,3-disubstituted dihydrobenzofuran, indoline, and chromane derivatives, constituting core motifs in ubiquitous bioactive alkaloids. Indeed, promoted at 80 °C in ethyl acetate as the solvent by this chiral catalyst combination in the presence of K<sub>3</sub>PO<sub>4</sub> as base, a range of *O*- or *N*-tethered alkenes **86** underwent an enantioselective domino Heck/Sonogashira reaction with a wide variety of alkynes **83** to afford the corresponding chiral bicyclic products **87** with good to excellent yields (68-99%) and high *ee* values (88-96% *ee*). Indeed, chiral 3,3-disubstituted dihydrobenzofurans (X = O, n = 1), chromanes (X = O, n = 2) as well as indolines (X = NBoc, n = 1) were synthesized through this one-pot aryl-alkynylation reaction. Once again, the scope of the domino process was found wide since aryl, heteroaryl, alkenyl, and linear/branched alkyl alkynes were all tolerated as well as the presence of different substituents on the alkene moiety (R<sup>2</sup>) of the *N*-/*O*-tethered alkenes.



R<sup>1</sup> = H, *t*-Bu, Ph, Cl, Br, F

R<sup>2</sup> = Ph, *p*-Tol, *p*-EtC

*H*<sub>4</sub>, *p*-*i*-PrC<sub>6</sub>H<sub>4</sub>, *p*-BuC<sub>6</sub>H<sub>4</sub>, *p*-PentC<sub>6</sub>H<sub>4</sub>, *p*-F<sub>3</sub>COC<sub>6</sub>H<sub>4</sub>,

*p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-PhC<sub>6</sub>H<sub>4</sub>, *p*-*t*-BuC<sub>6</sub>H<sub>4</sub>, *p*-Me<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, *p*-NCC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>,

*p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-BrC<sub>6</sub>H<sub>4</sub>, *p*-NCCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, *m*-Tol, *m*-MeOC<sub>6</sub>H<sub>4</sub>, *m*-FC<sub>6</sub>H<sub>4</sub>,

*m*-MeO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>, 3,5-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, *p*-MeOC<sub>6</sub>H<sub>4</sub>, 2-Naph, 1-Naph, 2-thienyl,

1-thienyl, CH<sub>2</sub>=C(Me), 1-cyclohexenyl, *n*-Hex, *n*-decyl, Cl(CH<sub>2</sub>)<sub>3</sub>, TMS,

R<sup>3</sup> = H, Me, F, Cl, Br

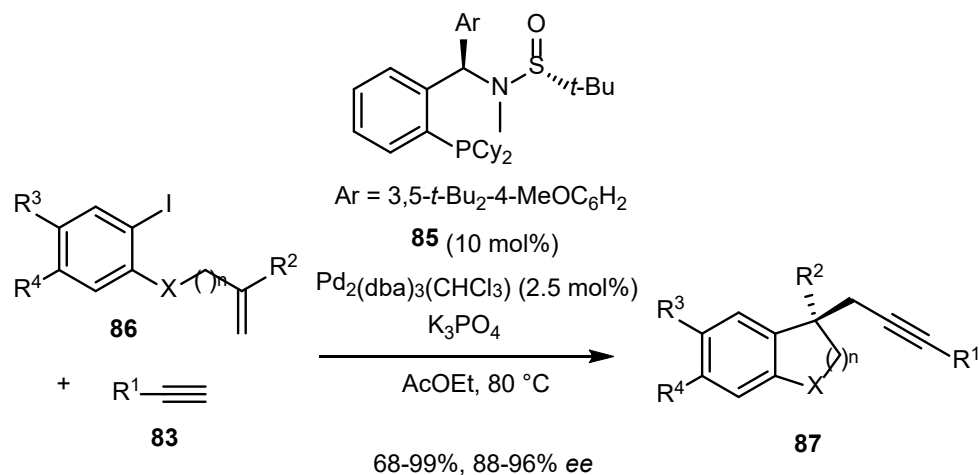
R<sup>4</sup> = H, Cl

R<sup>3</sup>, R<sup>4</sup> = OCH<sub>2</sub>O

R<sup>5</sup> = H

R<sup>3</sup>, R<sup>5</sup> = OCH<sub>2</sub>O

PG = Bn, *p*-MeOC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>



R<sup>1</sup> = Ph, *p*-Tol, *p*-PentC

*H*<sub>4</sub>, *p*-PhC<sub>6</sub>H<sub>4</sub>, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>,

*p*-MeO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, *p*-NCC<sub>6</sub>H<sub>4</sub>, *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-OHCC<sub>6</sub>H<sub>4</sub>, *m*-Tol,

*m*-ClC<sub>6</sub>H<sub>4</sub>, *o*-MeOC<sub>6</sub>H<sub>4</sub>, *o*-FC<sub>6</sub>H<sub>4</sub>, *o*-ClC<sub>6</sub>H<sub>4</sub>, *o*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 2-Naph, 2-pyridyl,

2-thienyl, 1-cyclohexenyl, *t*-Bu, *n*-Bu, Cl(CH<sub>2</sub>)<sub>3</sub>, MeO(CH<sub>2</sub>)<sub>3</sub>, TMS

R<sup>2</sup> = Me, Et, *i*-Pr, *n*-Bu, *n*-Pent, *t*-Bu, Bn, (2-Naph)CH<sub>2</sub>,

(2-thienyl)CH<sub>2</sub>, Ph, Cl

R<sup>3</sup> = H, Me, OMe, Cl

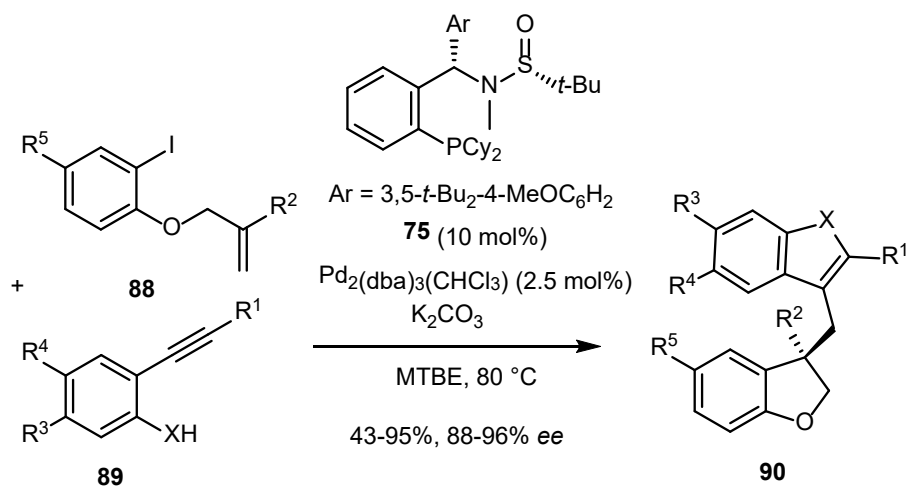
R<sup>4</sup> = H, Me

X = O, NBoc

n = 1-2

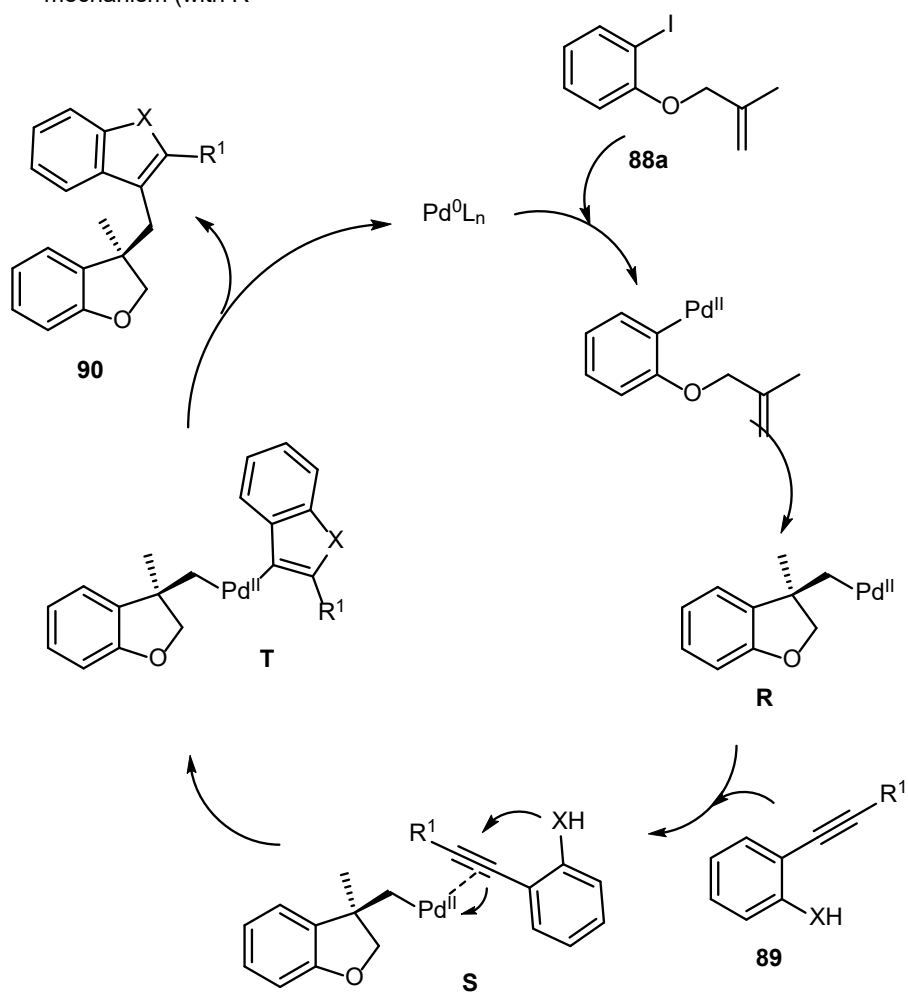
**Scheme 21.** Domino Heck/Sonogashira reactions of *N*-allyl carboxamides/*N*- or *O*-tethered alkenes with alkynes.

In 2021, Lautens et al. reported an enantioselective domino-Heck/nucleopalladation reaction of alkenyl-*O*-tethered aryl iodides **88** with a series of alkyne-tethered nucleophiles **89**, such as phenols and sulfonamides, to give a wide variety of the corresponding chiral bisheterocyclic products **90** (Scheme 22).<sup>[30]</sup> The latter were generated with uniformly excellent enantioselectivities (88-96% *ee*) combined with moderate to high yields (43-95%) when the reaction was catalyzed at 80 °C in MTBE as solvent by a combination of 2.5 mol% of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> and 10 mol% of chiral ligand **75**. This catalyst system tolerated both various aryl halides and heteroatom-tethered alkynes, leading to a collection of chiral benzofuran- (X = O) and indoline- (X = NTs, NH) containing scaffolds. It must be noted that this result constituted the first highly enantioselective example of a domino reaction, involving a chiral palladium catalyst which promoted a carbopalladation between indoles and unactivated alkenes. In the mechanism proposed in Scheme 22, an oxidative addition to aryl iodide **88a** and enantioselective carbopalladation led to alkylpalladium(II) intermediate **R**. Then, alkyne substrate **89** chelated to the palladium in **S** and underwent an *anti*-nucleopalladation to form an alkenyl-alkyl palladium species **T**. The latter was subsequently submitted to reductive elimination to form the final product.



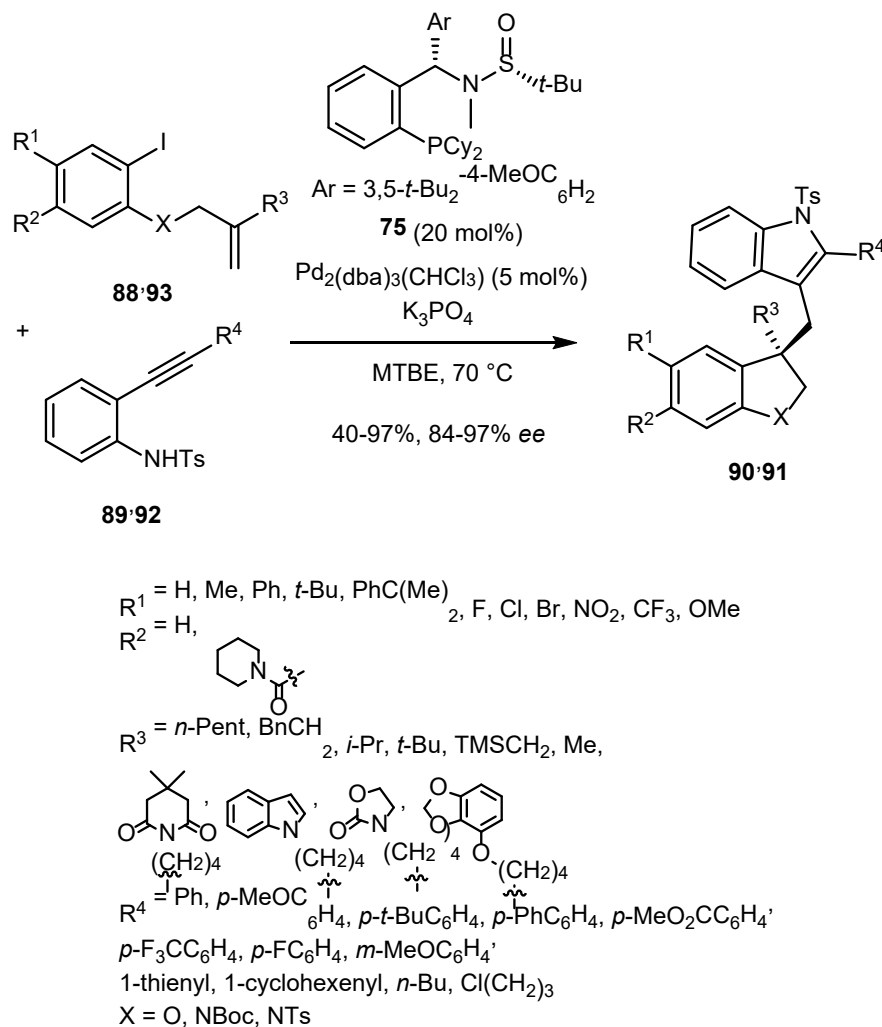
$\text{R}^1 = \text{Ph, TMS, Cl}(\text{CH}_2)_4, \text{TBSO}(\text{CH}_2)_2, 1\text{-cyclohexenyl, PhthN}(\text{CH}_2)_3,$   
 $1\text{-thienyl, 3-O}_2\text{N-4-MeC}_6\text{H}_3, p\text{-MeOC}_6\text{H}_4, m\text{-NCC}_6\text{H}_4$   
 $\text{R}^2 = \text{Me, Bn, } n\text{-Bu, } i\text{-Pr, Et}$   
 $\text{R}^3 = \text{H, Cl}$   
 $\text{R}^4 = \text{H, Cl, CF}_3$   
 $\text{R}^5 = \text{H, Cl, CF}_3$   
 $\text{X} = \text{NTs, O, NH}$

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



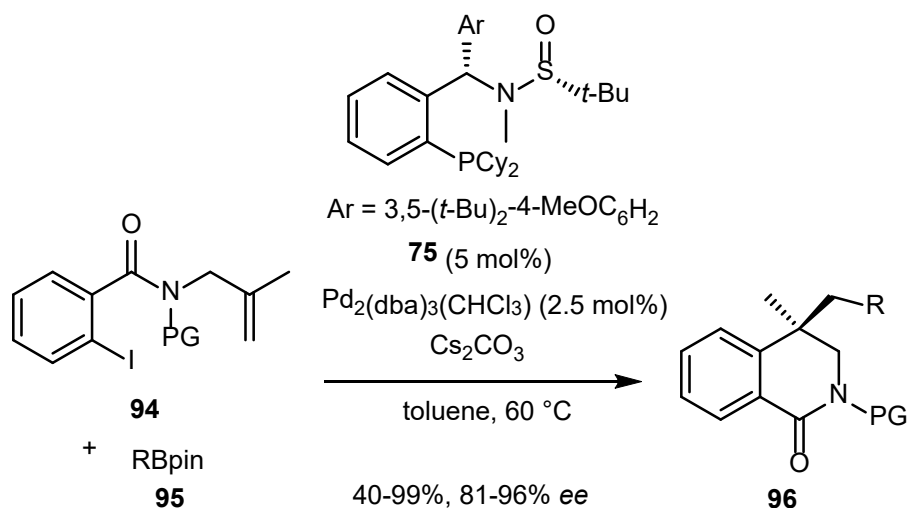
**Scheme 22.** Domino Heck/nucleopalladation reaction of alkenyl-*O*-tethered aryl iodides with alkyne-tethered nucleophiles.

Similar results were almost concomitantly published by Zhang and Zhang using the same catalyst system, delivering chiral 2,3-dihydrobenzofuran-indoles **90** (X = O) but also indoline-substituted indoles **91** (X = NTs, NBoc) from the corresponding alkyne-tethered amines **89,92** and alkenyl-*O*- and *N*-tethered aryl iodides **88,93** with comparable yields (40-97%) and enantioselectivities (84-97% *ee*), as presented in Scheme 23.<sup>[31]</sup>



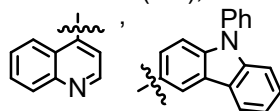
**Scheme 23.** Domino Heck/nucleopalladation reaction of alkenyl-*O*- and *N*-tethered aryl iodides with alkyne-tethered amines.

In 2021, Guo, Yang and Zhang reported a rare example of synthesis of chiral disubstituted dihydroisoquinolinones, which constitute the structural motifs of many natural and/or biologically active products.<sup>[32]</sup> This was achieved through enantioselective domino Heck/Suzuki reaction of 2-iodobenzamides **94** with aryl/alkenylboronic acid pinacol esters **95** catalyzed by a combination of 2.5 mol% of  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  and 5 mol% of chiral P,N-ligand **75** in toluene at 60 °C. The process afforded the corresponding chiral disubstituted dihydroisoquinolinones **96** with moderate to quantitative yields (40-99%) and uniformly high *ee* values (81-96% *ee*), as shown in Scheme 24. The catalyst system showed a high functional group tolerance, and was compatible with various aryl and alkenyl borates.



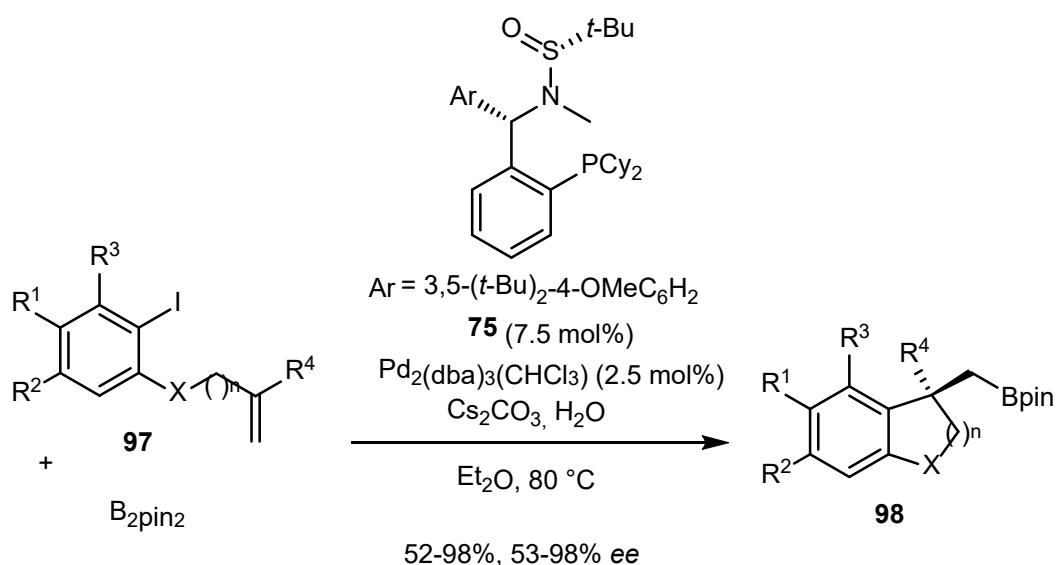
PG = Bn, PMB

R = Ph, *p*-Tol, *p*-*t*-BuC<sub>6</sub>H<sub>4</sub>, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-BrC<sub>6</sub>H<sub>4</sub>,  
*p*-PhC<sub>6</sub>H<sub>4</sub>, *p*-EtO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-NCC<sub>6</sub>H<sub>4</sub>, *m*-Tol, *m*-MeOC<sub>6</sub>H<sub>4</sub>, *m*-PhC<sub>6</sub>H<sub>4</sub>,  
*m*-NCC<sub>6</sub>H<sub>4</sub>, *o*-MeOC<sub>6</sub>H<sub>4</sub>, *o*-H<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 2,5-(MeO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 2-Naph,  
 2'-CHO-2-thienyl, CH<sub>2</sub>=CH, CH<sub>2</sub>=C(Me), CH<sub>2</sub>=C(Ph), EtO<sub>2</sub>CCH=CH,  
 (Me)C=CH, PhCH=CH,



**Scheme24.** Domino Heck/Suzuki reaction of 2-iodobenzamides with aryl/alkenylboronic acid pinacol esters.

Later in 2022, Zhang et al. applied another chiral P,N-ligand exhibiting a bulky 3,5-*t*-Bu<sub>2</sub>-4-OMe-C<sub>6</sub>H<sub>2</sub> group to promote an enantioselective palladium-catalyzed domino Heck/borylation reaction of alkene-tethered aryl iodides **97** with B<sub>2</sub>pin<sub>2</sub>.<sup>[33]</sup> The reaction employed 2.5 mol% of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> as precatalyst and 7.5 mol% of chiral ligand **75** in diethyl ether as solvent and led at 80 °C to the corresponding chiral bicyclic boronic esters **98** with both moderate to excellent yields (52-98%) and enantioselectivities (53-98% *ee*), as shown in Scheme 25. The scope of the methodology was found extremely wide since various types of boronic esters could be easily synthesized, spanning from 2,3-dihydrobenzofuranyl boronic esters (X = O, n = 1) to chromane (X = O, n = 2), indane (X = CH<sub>2</sub>, n = 1) and indoline (X = N, n = 1) boronic esters.



$\text{X} = \text{O}, \text{CH}_2, \text{NAC}$

$n = 1\text{-}2$

$\text{R}^1 = \text{H}, \text{Me}, \text{Ph}, \text{PhC}(\text{Me})_2$

$\text{R}^2 = \text{H}, t\text{-Bu}$

$\text{R}^1, \text{R}^2 = (\text{CH}=\text{CH})_2$   
 $\text{R}^3 = \text{H}$

$\text{R}^3, \text{R}^1 = \text{CH}=\text{CH}-\text{NSO}_2\text{Ph}$

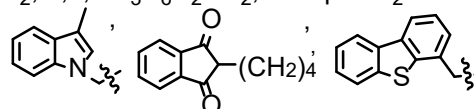
$\text{R}^4 = \text{Me}, \text{Et}, n\text{-Pr}, n\text{-Bu}, i\text{-Pr}, t\text{-Bu}, \text{Bn}, p\text{-TolCH}_2$

$p\text{-ClC}_6\text{H}_4\text{CH}_2, p\text{-F}_3\text{CC}_6\text{H}_4\text{CH}_2, m\text{-FC}_6\text{H}_4\text{CH}_2, m\text{-ClC}_6\text{H}_4\text{CH}_2$

$m\text{-O}_2\text{NC}_6\text{H}_4\text{CH}_2, m\text{-TolCH}_2, m\text{-MeOC}_6\text{H}_4\text{CH}_2, m\text{-}t\text{-BuC}_6\text{H}_4\text{CH}_2$

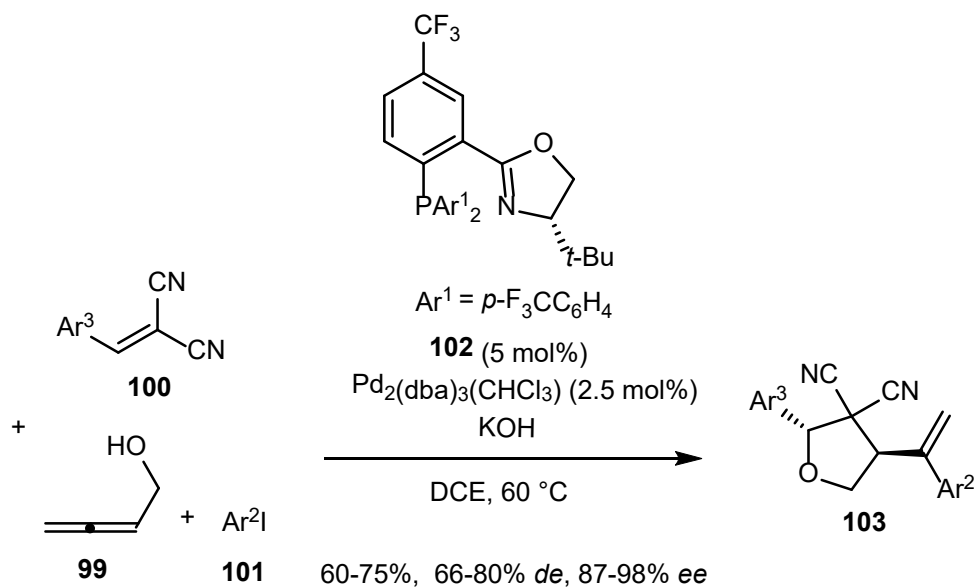
$o\text{-TolCH}_2, 3,5\text{-F}_2\text{C}_6\text{H}_3\text{CH}_2, 2,3,4\text{-F}_3\text{C}_6\text{H}_2\text{CH}_2, 2\text{-NaphCH}_2$

$\text{TMSCH}_2, \text{Cl}(\text{CH}_2)_4, \text{Ph},$



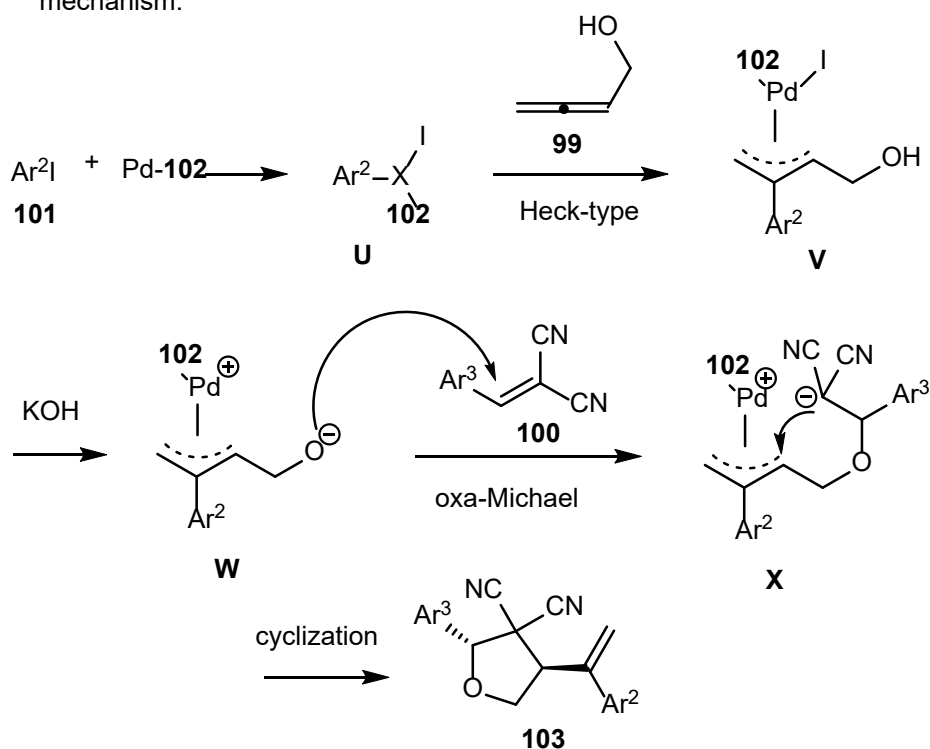
**Scheme 25.** Domino Heck/borylation reaction of alkene-tethered aryl iodides with  $\text{B}_2\text{pin}_2$ .

In the same year, Zhang and Li reported the first enantioselective palladium-catalyzed three-component reaction between 2,3-allenol **99**, 2-arylmethylenemalononitriles **100** and aryl iodides **101** (Scheme 26).<sup>[34]</sup> It dealt with an asymmetric domino Heck-type/oxa-Michael/cyclization reaction catalyzed by a chiral complex *in situ* generated from 2.5 mol% of  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  and 5 mol% of chiral P,N-ligand **102**. Performed at  $60^\circ\text{C}$  in DCE as solvent in the presence of KOH as base, it yielded chiral functionalized substituted tetrahydrofurans **103** in good yields (60-75%), uniformly high enantioselectivities (87-98% *ee*) combined with moderate to high diastereoselectivities (66-80% *de*). A mechanism depicted in Scheme 26 was proposed by the authors, beginning with the oxidative addition of palladium complex to the aryl iodide to give intermediate **U**. Then, the latter underwent a Heck-type reaction with the allenol substrate to provide  $\pi$ -allylpalladium intermediate **V**. In the presence of KOH as base, this intermediate was converted into zwitterionic allyl palladium intermediate **W** which was subsequently submitted to an oxa-Michael addition to the 2-arylmethylenemalononitrile to afford intermediate **X**. Then, the latter underwent an intramolecular nucleophilic attack to deliver the final cyclic product. The utility of this novel methodology was demonstrated in a concise total synthesis of lignan (–)-2-episesaminone.



$\text{Ar}^2 = \text{Ph}, p\text{-MeOC}_6\text{H}_4, o\text{-Tol}, m\text{-Tol}, p\text{-Tol}, m\text{-FC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-AcC}_6\text{H}_4, p\text{-MeO}_2\text{CC}_6\text{H}_4, p\text{-NCC}_6\text{H}_4, 2\text{-Naph}, 1\text{-Naph}, 2\text{-pyridyl}, 2\text{-thienyl}, 3,4\text{-(MeO)}_2\text{C}_6\text{H}_2$   
 $\text{Ar}^3 = \text{Ph}, o\text{-Tol}, m\text{-Tol}, p\text{-Tol}, p\text{-ClC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, 2\text{-Naph}, 2\text{-furyl}$

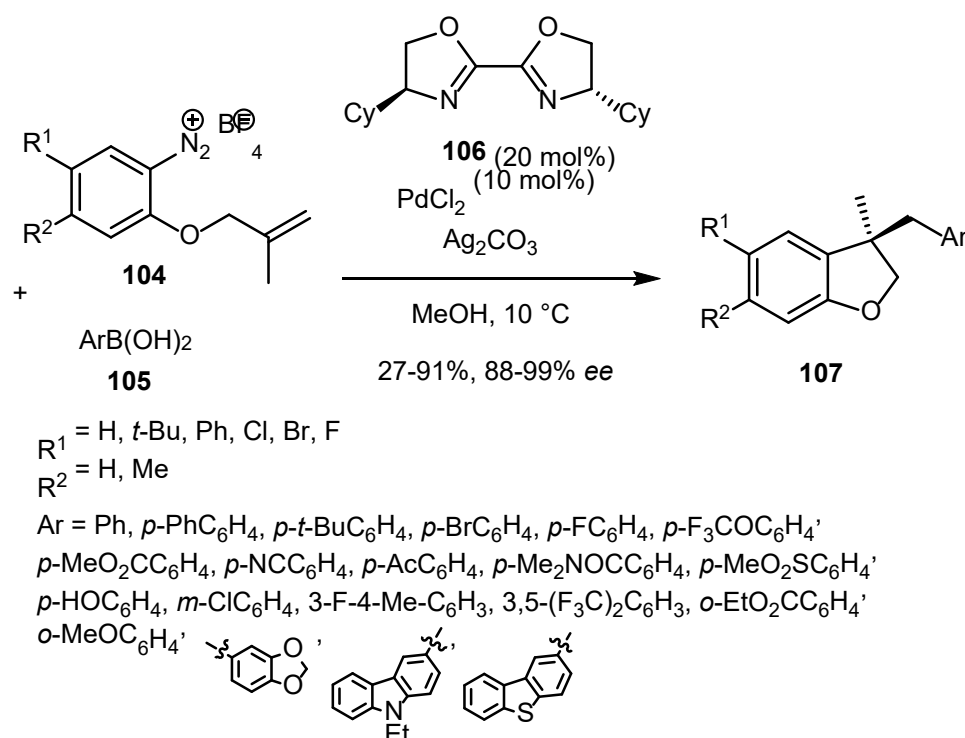
mechanism:



**Scheme 26.** Three-component domino Heck-type/oxa-Michael/cyclization reaction of a 2,3-allenol, aryl iodides and 2-arylmethylenemalononitriles.

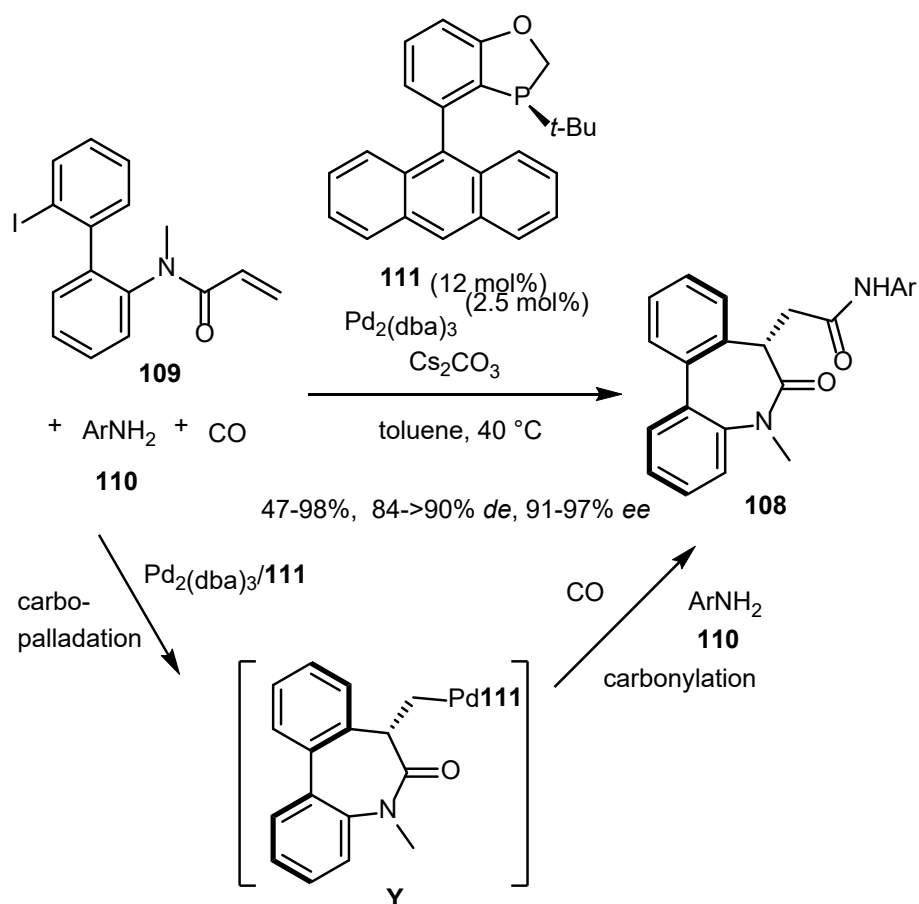
#### 2.1.4 Other Ligands

Chiral bisoxazolines<sup>[35]</sup> have been widely employed as ligands in various types of asymmetric metal-catalyzed transformations.<sup>[36]</sup> In 2019, Chen and Kong reported a rare example of enantioselective palladium-catalyzed diarylation of unactivated alkenes with arylboronic acids, delivering chiral dihydrobenzofurans (Scheme 27).<sup>[37]</sup> It involved a domino Heck-type/Suzuki reaction occurring at 10 °C in methanol as the solvent between arenediazonium salts **104** and (hetero)arylboronic acids **105** in the presence of 10 mol% of PdCl<sub>2</sub> and 20 mol% of chiral bisoxazoline ligand **106**, which led to the corresponding chiral dihydrobenzofurans **107** bearing an all-carbon quaternary center. The latter were obtained in moderate to high yields (27-91%) and uniformly high enantioselectivities (88-99% *ee*). Remarkably, a range of functional groups including fluoro, bromo, trifluoromethoxy, cyano, ester, ketone, amide, sulfonyl, and free hydroxyl groups were all compatible. In addition, heteroarylboronic acids, such as dioxolane, benzothiophene and carbazole heterocycles, were tolerated, providing the corresponding products with 92-95% *ee*.

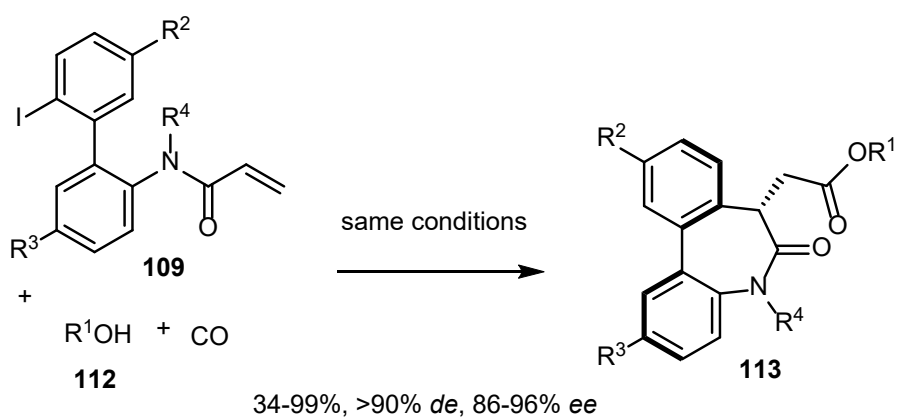


**Scheme 27.** Domino Heck-type/Suzuki reaction of arenediazonium salts with arylboronic acids.

In 2021, Zhu and Luo reported the first enantioselective palladium-catalyzed 7-*exo*-trig carbopalladation/carbonylation domino reaction, allowing the synthesis of dibenzo[b,d]azepin-6-ones with thermodynamically controlled atropisomerism to be achieved (Scheme 28).<sup>[38]</sup> Products **108** containing a thermodynamically controlled stereogenic axis arose from the three-component domino Heck/amidation reaction of the corresponding *N*-methylacrylamides **109** exhibiting a rigid biaryl backbone with anilines **110** under CO atmosphere performed in the presence of a chiral palladium catalyst *in situ* generated from 2.5 mol% of Pd<sub>2</sub>(dba)<sub>3</sub> and 12 mol% of chiral phosphine ligand **111**. By using Cs<sub>2</sub>CO<sub>3</sub> as base, a range of chiral products **108** were formed with moderate to quantitative yields (47-98%) and both high diastereo- (84->90% *de*) and enantioselectivities (91-97% *ee*). The process evolved through cyclocarbopalladation, leading to palladium intermediate **Y**, which then underwent carbonylation in the presence of aniline **110** and CO to provide the final product. The same reaction conditions were applied to other nucleophiles, such as aliphatic as well as aromatic alcohols **112**, which afforded through domino Heck/esterification reaction the corresponding chiral esters **113** with moderate to quantitative yields (34-99%) and both high diastereo- (>90% *de*) and enantioselectivities (86-96% *ee*), as presented in Scheme 28.



Ar = Ph, *o*-Tol, *o*-MeOC<sub>6</sub>H<sub>4</sub>, *o*-ClC<sub>6</sub>H<sub>4</sub>, *o*-PhC<sub>6</sub>H<sub>4</sub>, *p*-Tol, *p*-BrC<sub>6</sub>H<sub>4</sub>,  
*p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-MeO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-NCC<sub>6</sub>H<sub>4</sub>, *p*-AcC<sub>6</sub>H<sub>4</sub>, 2,4-MeO<sub>2</sub>C<sub>6</sub>H<sub>3</sub>,  
 3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 2-Naph, 1-Naph



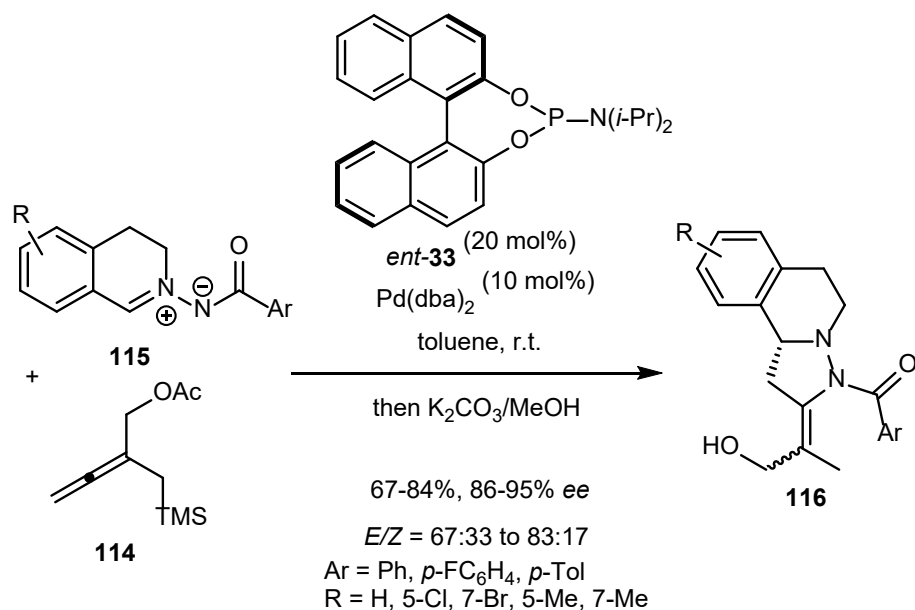
$\text{R}^1$  = Me, Bn, Bn(CH<sub>2</sub>)<sub>2</sub>, CH<sub>2</sub>=CH(CH<sub>2</sub>)<sub>3</sub>, *i*-Pr, *p*-Tol,  
*p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, 2-Naph  
 $\text{R}^2$  = H, Me, OMe  
 $\text{R}^3$  = H, Me  
 $\text{R}^4$  = Me, Bn, *p*-MeOC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>

**Scheme 28.** Three-component domino Heck/carbonylation reactions of *N*-methylacrylamides, amines/alcohols and CO.

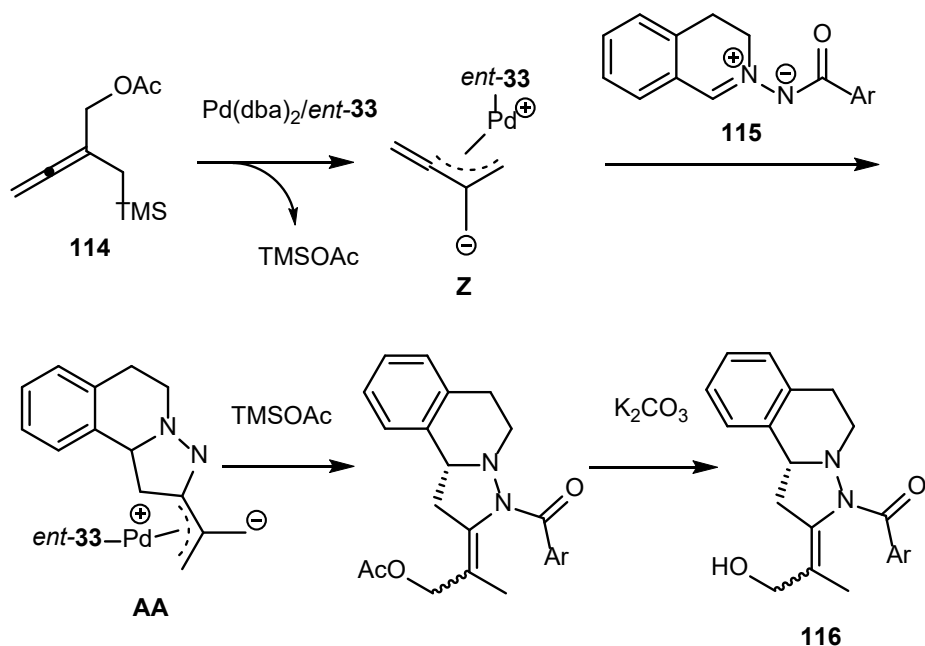
## 2.2 Miscellaneous Enantioselective Domino Reactions

### 2.2.1 Phosphoramidite Ligands

In 2019, Guo et al. described the first example of enantioselective palladium-catalyzed [3+2] cycloaddition of methylene-trimethylenemethane species as dipolarophiles with dipoles.<sup>[39]</sup> Actually, this cycloaddition, occurring between methylene-trimethylenemethane donors **114** and azomethine imines **115**, constituted the first step of an unprecedented enantioselective domino [3+2] cycloaddition/allylation reaction performed in toluene at room temperature in the presence of 10 mol% of Pd(dba)<sub>2</sub> and 20 mol% of chiral BINOL-derived phosphoramidite ligand *ent*-**33** (Scheme 29). It resulted in the formation of biologically relevant functionalized chiral hexahydropyrazolo[5,1-*a*]isoquinolines **116** as major (*E*)-diastereomers (*E/Z* = 67:13 to 83:17) in good yields (67-84%) and high enantioselectivities (86-95% *ee*). The azomethine imines tolerated the presence of different substituents on both the two phenyl rings. A mechanism is proposed in Scheme 29, showing that the methylene-trimethylenemethane donor was converted in the presence of a palladium catalyst into palladium-methylene-trimethylenemethane complex **Z** with simultaneous release of TMSOAc. Intermediate **Z** subsequently underwent [3+2] cycloaddition with the azomethine imine, affording intermediate **AA**. Then, allylation of the acetyloxy anion afforded the final product.



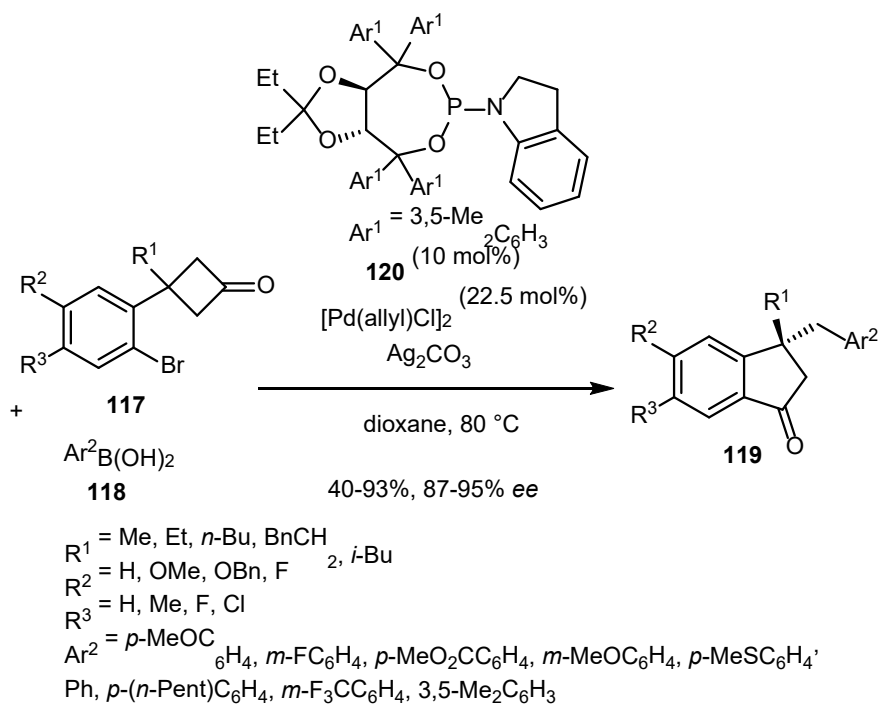
mechanism (with R = H):



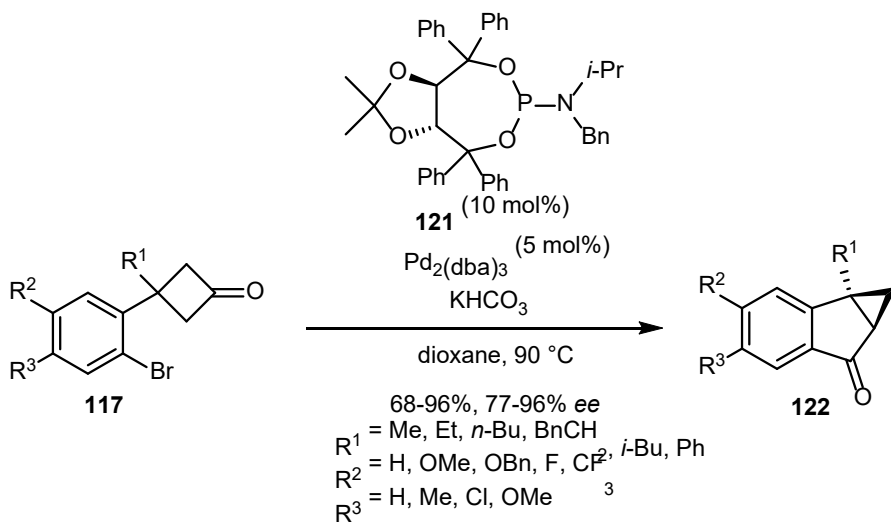
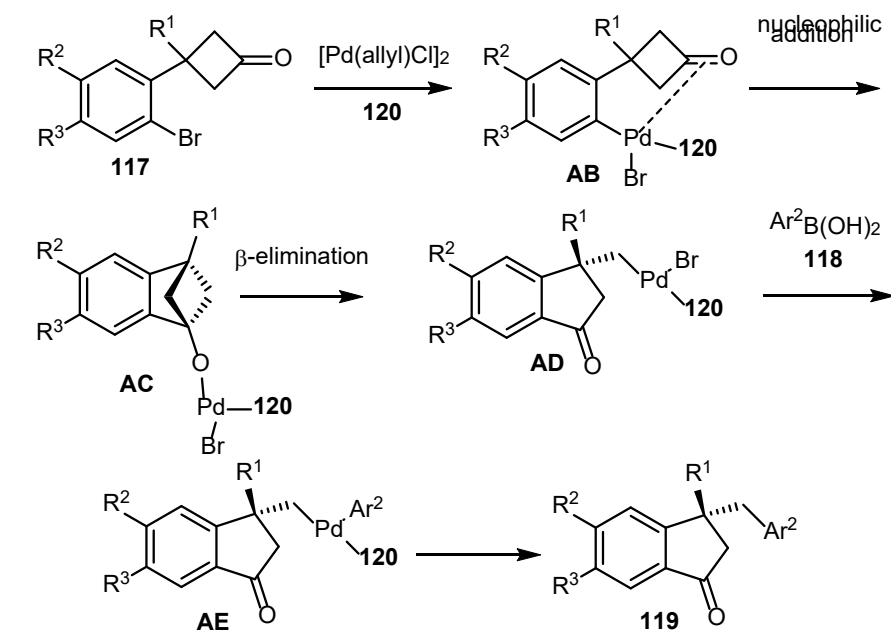
**Scheme 29.** Domino [3+2] cycloaddition/allylation reaction of methylene-trimethylenemethane donors with azomethine imines.

The same year, Cao and Xu developed an enantioselective palladium-catalyzed domino ring-opening/cross-coupling reaction of cyclobutanones **117** with arylboronic acids **118** (Scheme 30).<sup>[40]</sup> It allowed the synthesis of chiral indanones **119** bearing a  $\beta$ -quaternary carbon stereocenter with moderate to high yields (40-93%) and homogeneously high enantioselectivities (87-95% *ee*). The reaction was promoted by a chiral catalyst *in situ* generated from 10 mol% of chiral TADDOL-derived phosphoramidite **120** and 22.5 mol% of  $[\text{Pd(allyl)Cl}]_2$  in dioxane as the solvent. Various arylboronic acids bearing either electron-donating or electron-withdrawing groups at any position of the phenyl ring reacted smoothly at 80 °C with high *ee* values. Concerning the cyclobutanone partner, different

alkyl groups at the R<sup>1</sup> position were compatible as well as different substituents, including halogen, alkyl and alkoxy groups, on the phenyl ring. A mechanism is proposed in Scheme 30, beginning with the oxidative addition of the cyclobutanone to give arylpalladium species **AB**. Subsequently, nucleophilic addition of the latter to the carbonyl group of the cyclobutanone afforded highly strained alkoxypalladium intermediates **AC**. Then, carbon elimination led to  $\sigma$ -alkylpalladium species **AD**, which were further trapped by the aryl boronic acid to form intermediates **AE**. Finally, reductive elimination generated the product. In addition, the authors demonstrated that in the absence of external nucleophiles, such as arylboronic acids, cyclobutanones **117** underwent at 90 °C an enantioselective intramolecular domino ring-opening/cyclopropanation reaction to afford the corresponding chiral cyclopropane-fused indanones **122** (Scheme 30). These products were generated in the presence of 5 mol% of Pd<sub>2</sub>(dba)<sub>3</sub> as precatalyst, 10 mol% of related TADDOL-derived phosphoramidite ligand **121** and KHCO<sub>3</sub> as base in dioxane as solvent with both good to high yields (68-96%) and enantioselectivities (77-96% *ee*).

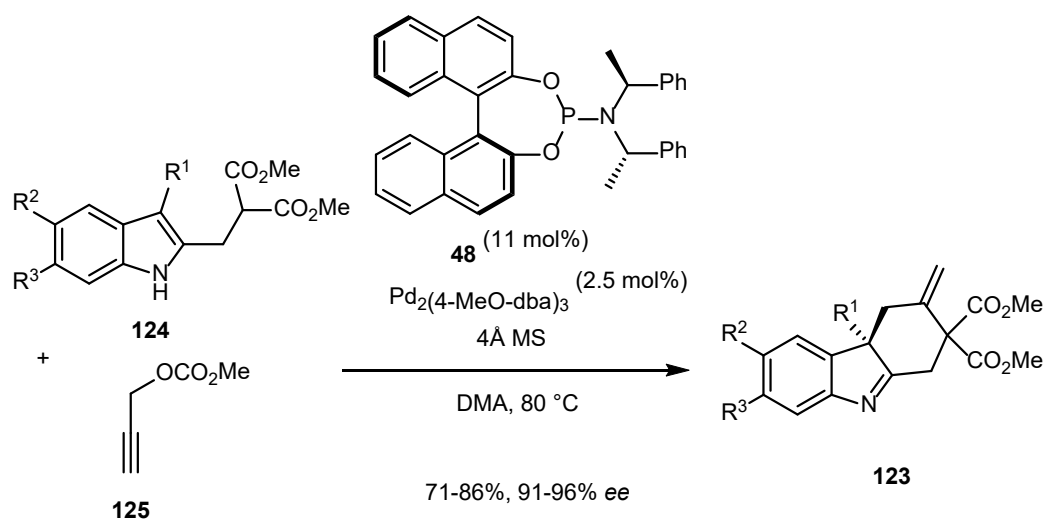


mechanism:



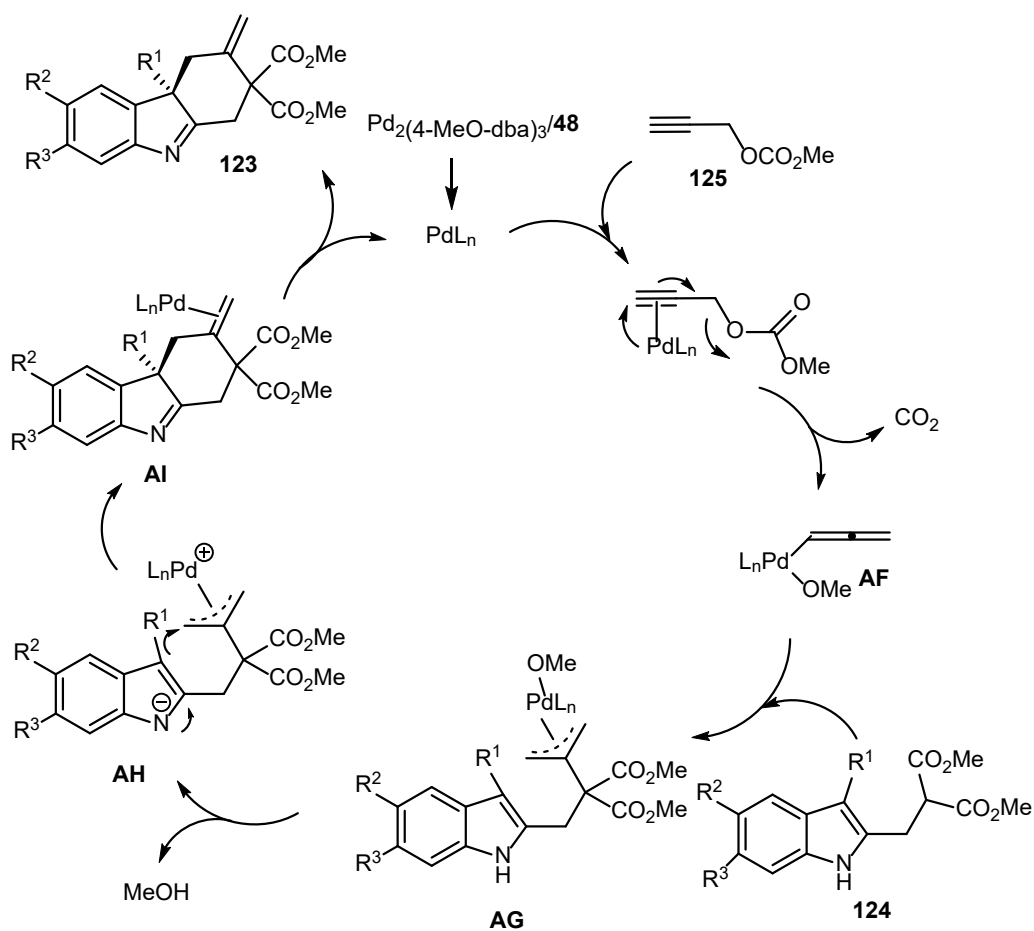
**Scheme 30.** Domino ring-opening/cross-coupling reaction of cyclobutanones with arylboronic acids and domino ring-opening/cyclopropanation reaction of cyclobutanones.

In 2019, You et al. reported a chemo- and enantioselective synthesis of multisubstituted fused indolenines **123** through palladium-catalyzed cascade dearomatization of indoles **124** bearing a nucleophile at the C2 position with methyl propargyl carbonate **125** (Scheme 31).<sup>[41]</sup> Carried out at 80 °C in DMA as the solvent, the domino reaction was promoted by a chiral catalyst *in situ* generated from 2.5 mol% of Pd<sub>2</sub>(4-MeO-dba)<sub>3</sub> and 11 mol% of chiral BINOL-derived phosphoramidite ligand **48**. In this context, densely substituted fused indolenines **123** were synthesized in good to excellent yields (71-86%) with excellent chemo- and enantioselectivities (91-96% *ee*). Indoles bearing either electron-withdrawing or electron-donating substituents on the benzyl group (R<sup>1</sup> = ArCH<sub>2</sub>) smoothly reacted with excellent enantioselectivities (93-95% *ee*). Moreover, the presence of an aliphatic group at the C3 position (R<sup>1</sup>) was well tolerated since the corresponding products were produced with 92-94% *ee*. The authors proposed the mechanism depicted in Scheme 31, highlighting that the methyl propargyl carbonate was activated by Pd(0) to give intermediate **AF**. Then, the nucleophilic side chain of the indole attacked this intermediate to generate  $\pi$ -allyl palladium species **AG**. Upon deprotonation of the N-H group of indole, the C3 position of indole in **AH** attacked the  $\pi$ -allyl palladium moiety to deliver palladium intermediate **AI**. Finally, the liberation of the palladium catalyst afforded the product.



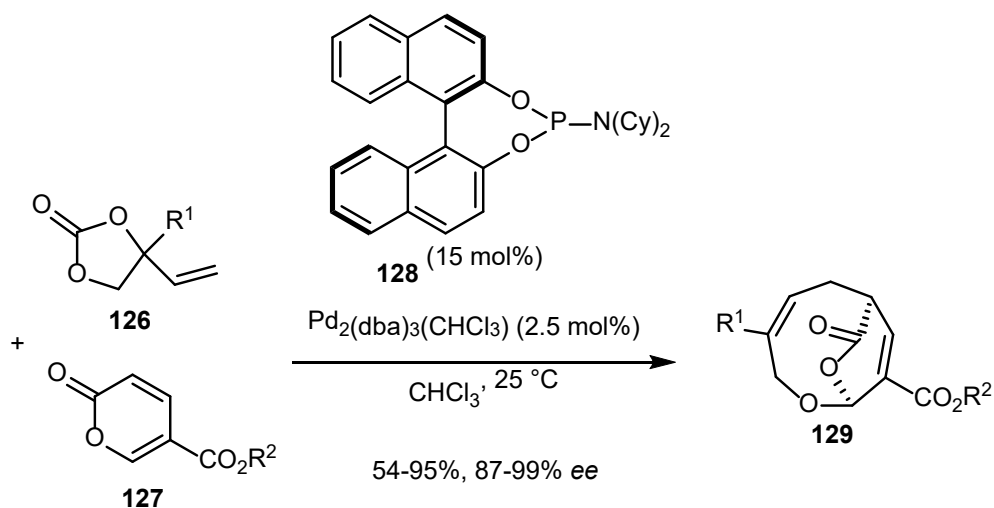
$\text{R}^1 = \text{Bn}, p\text{-MeO}_2\text{CC}_6\text{H}_4\text{CH}_2, p\text{-TolCH}_2, m\text{-TolCH}_2, p\text{-FC}_6\text{H}_4\text{CH}_2, p\text{-ClC}_6\text{H}_4\text{CH}_2,$   
 $(2\text{-thienyl})\text{CH}_2, (2\text{-Naph})\text{CH}_2, \text{Me, Et, } n\text{-Pr, } i\text{-Bu, CyCH}_2, \text{MOM}$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

mechanism:



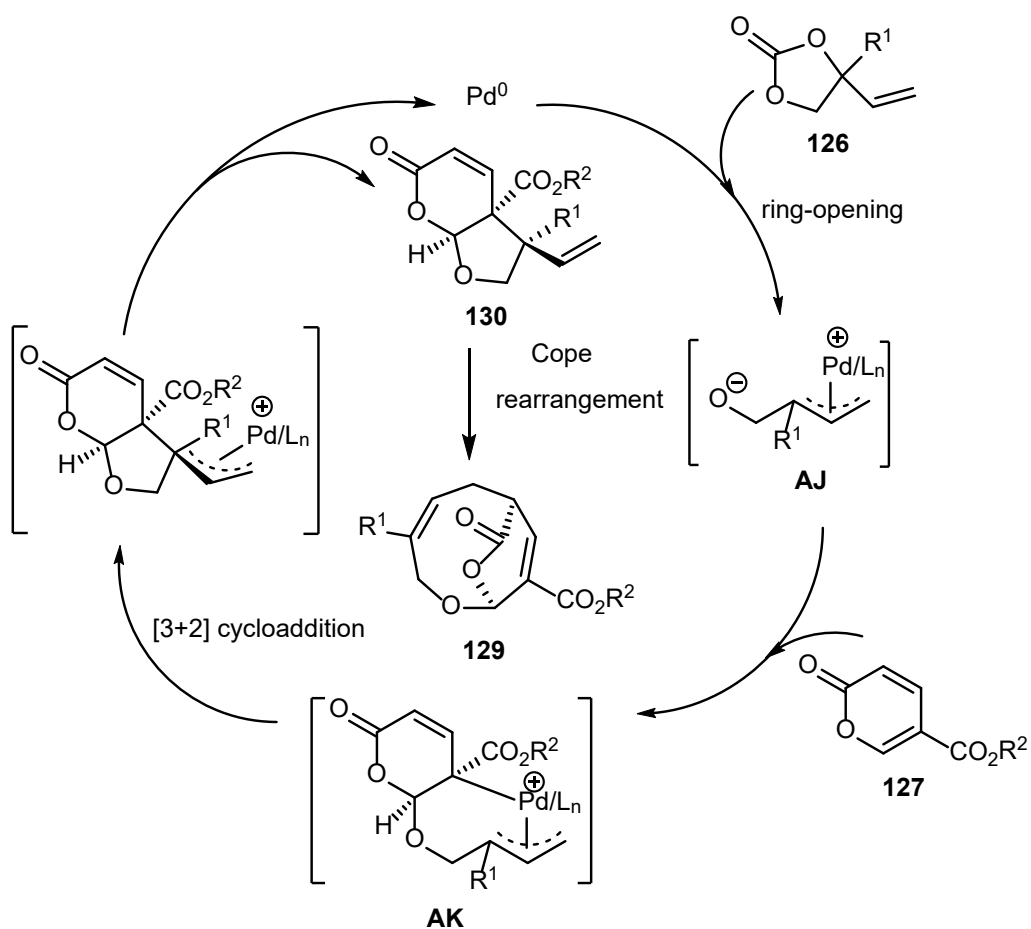
**Scheme 31.** Domino dearomatization reaction of indoles with methyl propargyl carbonate.

The synthesis of medium-sized cyclic ethers is challenging since they constitute the skeleton of many biologically important natural products. In this context, Guo et al. developed in 2019 a novel route to these products consisting in an enantioselective palladium-catalyzed domino reaction based on a [3+2] cycloaddition (Scheme 32).<sup>[42]</sup> The process occurred at 25 °C between vinyl ethylene carbonates **126** and coumalates **127** in chloroform as the solvent. It was catalyzed by a combination of 2.5 mol% of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> and 15 mol% of BINOL-derived chiral phosphoramidite ligand **128**, leading to a wide range of chiral nine-membered bicyclo[5.2.2]tetrahydrooxonines **129** with moderate to quantitative yields (54-95%) and excellent enantioselectivities (87-99% *ee*). These products arose from an enantioselective domino [3+2] cycloaddition/Cope rearrangement reaction. Its scope was wide since all types of ester group (R<sup>2</sup>) in coumalates were compatible and vinyl ethylene carbonates could exhibit a large variety of (hetero)aryl groups (R<sup>1</sup>). The reaction followed the mechanism detailed in Scheme 32, which begins with the ring-opening of vinyl ethylene carbonate **126** in the presence of the palladium catalyst to give zwitterionic allylpalladium intermediate **AJ**. The latter further attacks coumalate **127** to provide palladium intermediate **AK**. Subsequently, this intermediate undergoes a [3+2] cycloaddition to afford intermediate **130**. The latter is then submitted to a Cope rearrangement to produce the final product.



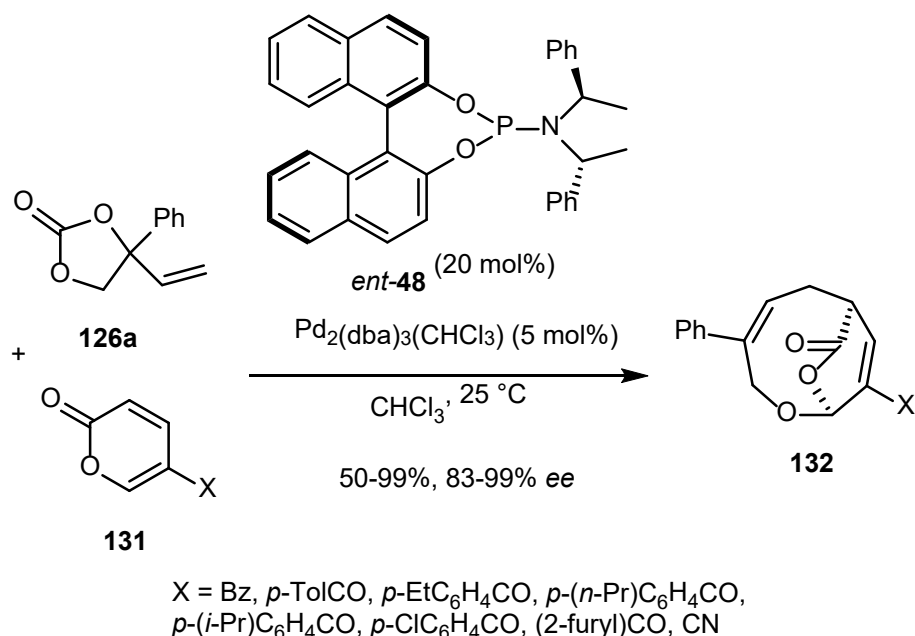
$\text{R}^1 = \text{Ph}, p\text{-MeOC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-Tol}, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-NCC}_6\text{H}_4, m\text{-Tol}, m\text{-MeOC}_6\text{H}_4, m\text{-FC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, o\text{-FC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, o\text{-MeOC}_6\text{H}_4, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, 2,4\text{-F}_2\text{C}_6\text{H}_3, 2\text{-Naph}, 2\text{-thienyl}, (E)\text{-PhCH=CH}$   
 $\text{R}^2 = \text{Me}, \text{Et}, \text{Ph}, \text{Bn}, \text{Cl}(\text{CH}_2)_4$

mechanism:



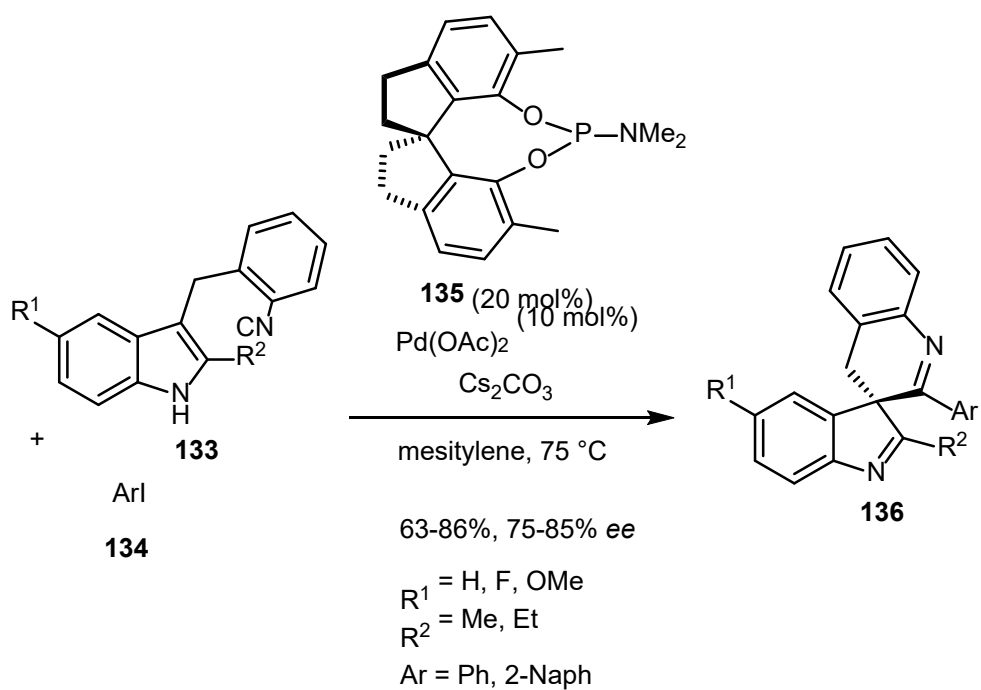
**Scheme 32.** Domino [3+2] cycloaddition/Cope rearrangement reaction of vinyl ethylene carbonates with coumalates.

By changing the nature and catalyst loading (20 vs 15 mol%) of the chiral ligand (*ent*-**48** instead of **128**), the scope of the precedent methodology could be extended to pyrones **131** (Scheme 33).<sup>[42]</sup> Indeed, in the presence of 15 mol% of related chiral phosphoramidite ligand *ent*-**48** combined with 5 mol% of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> in chloroform as solvent, a series of pyrones **131** reacted at 25 °C with vinyl ethylene carbonate **126a** to afford the corresponding chiral domino products **132** with moderate to quantitative yields (50-99%) and high enantioselectivities (83-99% *ee*). In addition to (hetero)aryl-substituted vinyl ethylene carbonates, a vinyl-substituted substrate (R<sup>1</sup> = (*E*)-PhCH=CH) successfully underwent the reaction to give the corresponding product in 80% yield and 87% *ee*. The presence of either electron-withdrawing or electron-donating substituents on the phenyl ring of pyrones was well tolerated. Furthermore, a 2-furyl-substituted pyrone (X = (2-furyl)CO) as well as a cyano-substituted pyrone (X = CN) were compatible, leading to the desired bridged cyclic products with 83 and 98% *ee*, respectively.

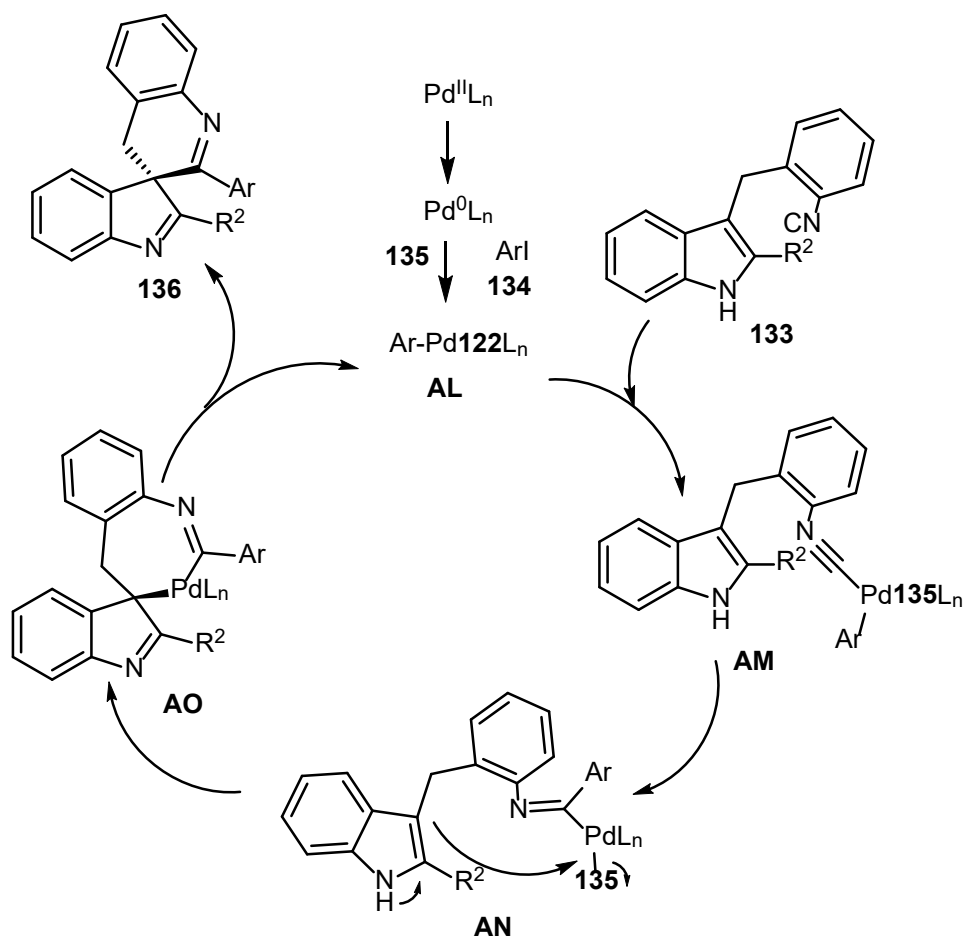


**Scheme 33.** Domino [3+2] cycloaddition/Cope rearrangement reaction of a vinyl ethylene carbonate with pyrones.

Chiral spiroindolines constitute important molecules in medicinal chemistry. In 2021, Wang et al. described a novel route to these products based on an enantioselective palladium-catalyzed dearomative imidoylative spirocyclization of 3-(2-isocyanoethyl)indoles **133** with aryl iodides **134** (Scheme 34).<sup>[43]</sup> This domino isocyanide insertion/nucleophilic attack reaction was achieved at 75 °C in the presence of Cs<sub>2</sub>CO<sub>3</sub> as base in mesitylene as the solvent. It employed a chiral complex *in situ* generated from 20 mol% of chiral phosphoramidite ligand **135** and 10 mol% of Pd(OAc)<sub>2</sub>. Under these conditions, the reaction afforded chiral 2'-aryl-substituted spiroindolines **136** in both good yields (63-86%) and enantioselectivities (75-85% *ee*). The mechanism proposed in Scheme 34 shows that the cascade reaction began with the oxidative addition of the aryl iodide to chiral active palladium (II) species **AL** to give intermediate **AM**. Then, coordination of the isocyanide to the palladium atom and its migratory insertion provided imidoyl palladium intermediate **AN**. Dearomative nucleophilic attack of indole to the palladium center resulted in six-membered palladacyclic complex **AO**. Finally, the domino product was produced through a reductive elimination along with regenerated catalyst.

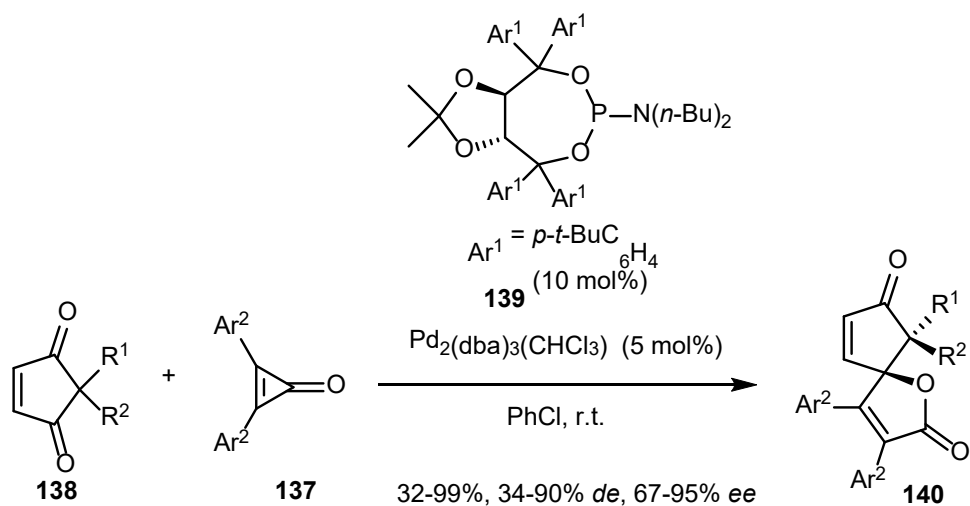


proposed mechanism ( $R^1 = \text{H}$ ):



**Scheme 34.** Domino isocyanide insertion/nucleophilic attack reaction of 3-(2-isocyanoethyl)indoles with aryl iodides.

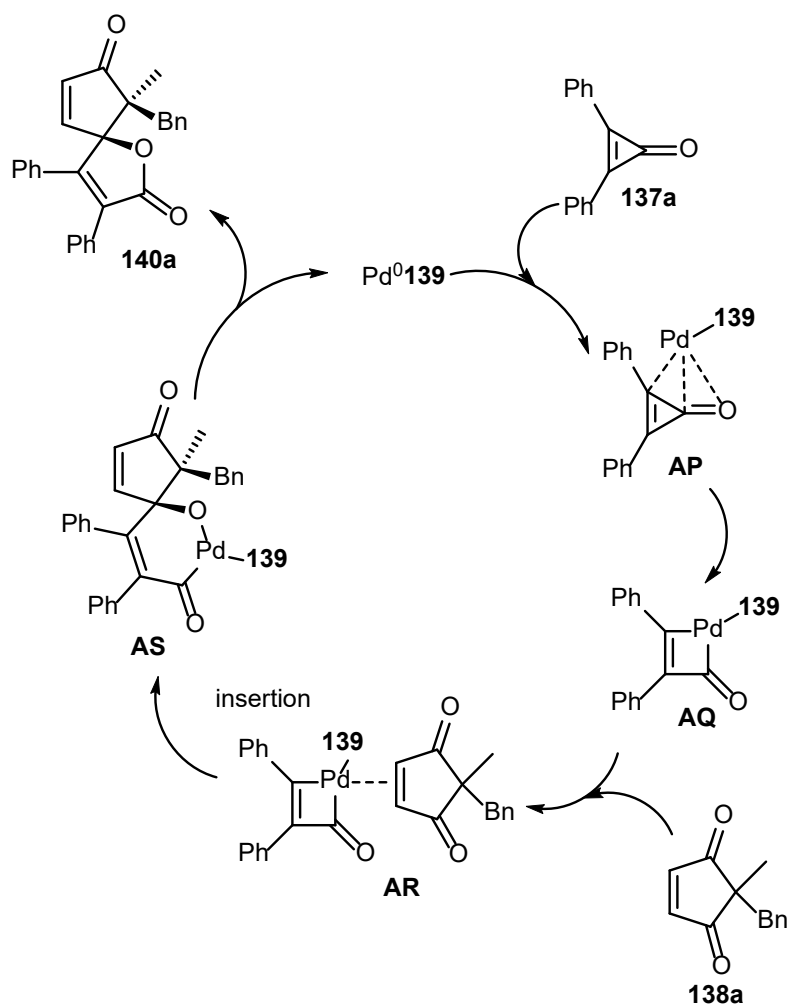
In 2021, Xu et al. reported the use of a chiral TADDOL-derived phosphoramidite ligand in a novel enantioselective palladium-catalyzed domino [3+2] spiro-annulation reaction between cyclopropenones **137** and cyclopentene-1,3-diones **138**.<sup>[44]</sup> The process was performed at room temperature in chlorobenzene as the solvent in the presence of a combination of 10 mol% of ligand **139** and 5 mol% of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>. As illustrated in Scheme 35, the domino carbon–carbon bond cleavage/[3+2] annulation afforded complex chiral oxaspiro-products **140** exhibiting two adjacent quaternary centers and a cyclopentenone–lactone scaffold with moderate to quantitative yields (32–99%), low to high diastereoselectivities (34–90% *de*) and moderate to high enantioselectivities (67–95% *ee*). Good results were achieved for a series of cyclopropenones bearing electron-neutral, electron-withdrawing or electron-donating groups at any positions of the phenyl rings. A possible mechanism is depicted in Scheme 35, beginning with the coordination of the three-membered cyclopropenone to palladium(0) complex to give palladium complex **AP**. Then, oxidative addition with carbon–carbon bond activation provided palladium intermediate **AQ**. The latter subsequently coordinated the carbon–carbon double bond of the cyclopentene-1,3-dione to give complex **AR** which underwent migratory insertion of the Pd–C bond, providing intermediate **AS**. Finally, the product was obtained by reductive elimination along with regenerated palladium(0) catalyst. It must be noted that this work represented the first example of an enantioselective palladium-catalyzed [3+2] annulation reaction between cyclopropenones and ketones, allowing the construction of oxaspiro molecules bearing two vicinal carbon quaternary stereocenters.



$\text{R}^1 = \text{Me, Et}$   
 $\text{R}^2 = \text{Bn, } o\text{-TolCH}_2$

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

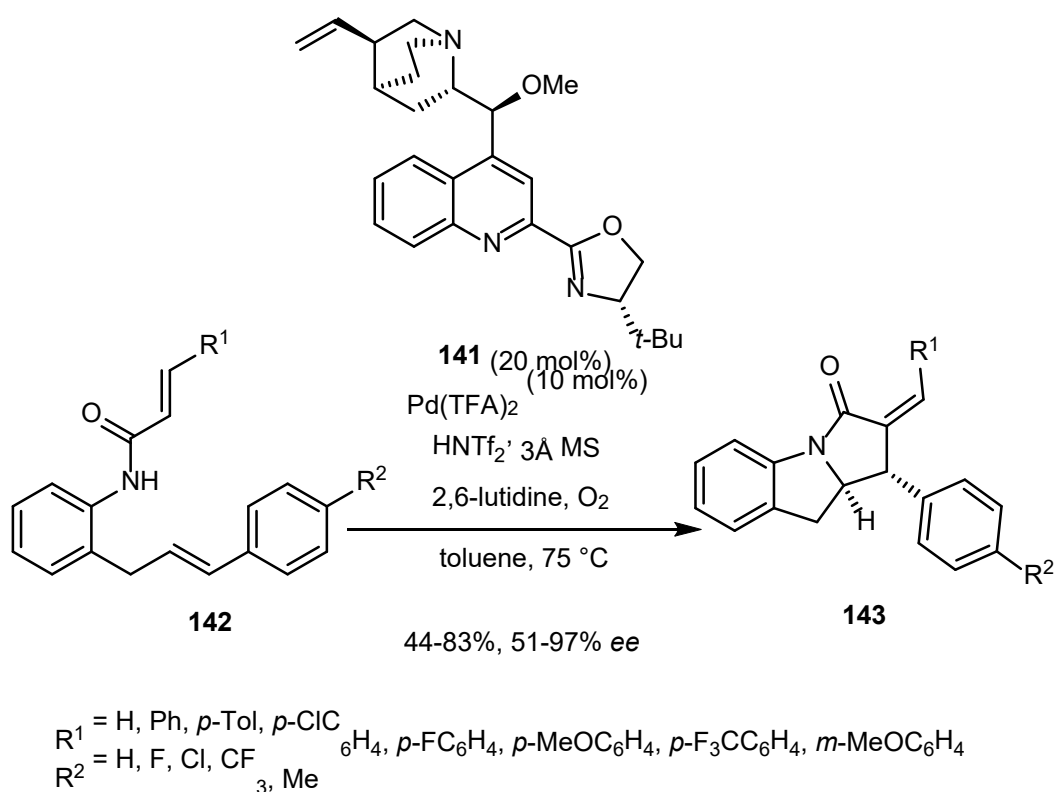
mechanism (with  $\text{Ar}^2 = \text{Ph}$ ,  $\text{R}_1 = \text{Me}$ ,  $\text{R}_2 = \text{Bn}$ ):



**Scheme 35.** Domino carbon–carbon bond cleavage/[3+2] annulation of cyclopropanones with cyclopentene-1,3-diones.

## 2.2.2 Oxazoline Ligands

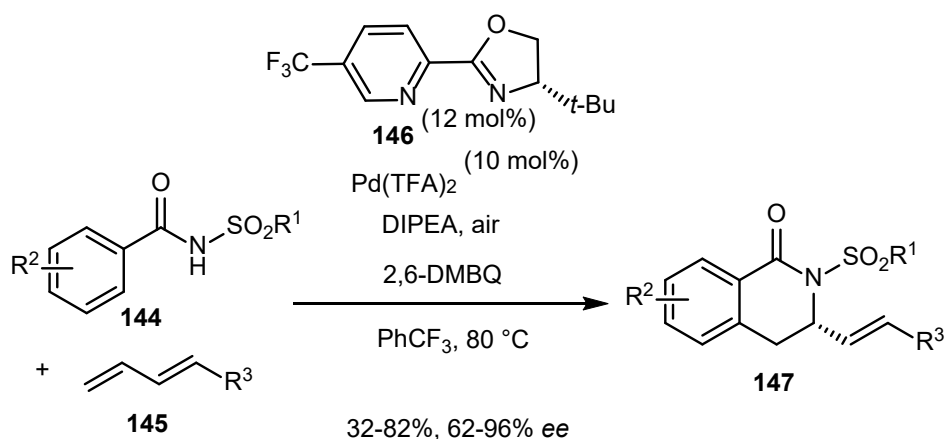
A number of asymmetric cascade cyclizations have been promoted by chiral palladium catalysts.<sup>[45]</sup> In an example reported in 2019 by He et al., novel cinchona alkaloid-derived oxazoline ligands were investigated in enantioselective intramolecular palladium-catalyzed oxidative cyclization of aromatic nitrogen-containing dienes (Scheme 36).<sup>[46]</sup> Chiral pyridine/oxazoline **141** was selected as optimal ligand employed at 20 mol% of catalyst loading in combination with 10 mol% of Pd(TFA)<sub>2</sub> in toluene as the solvent. In the presence of HNTf<sub>2</sub> and 2,6-lutidine as additives, the reaction of variously substituted aromatic alkenyl amides **142** performed at 75 °C resulted under oxygen atmosphere in the formation of the corresponding chiral dihydroindole polycyclic products **143** in both moderate to high yields (44-83%) and enantioselectivities (51-97% *ee*). These complex heterocyclic products generated through oxidative cascade cyclization constituted relevant molecules for medicinal chemistry.



**Scheme 36.** Domino oxidative cyclization of aromatic nitrogen-containing dienes.

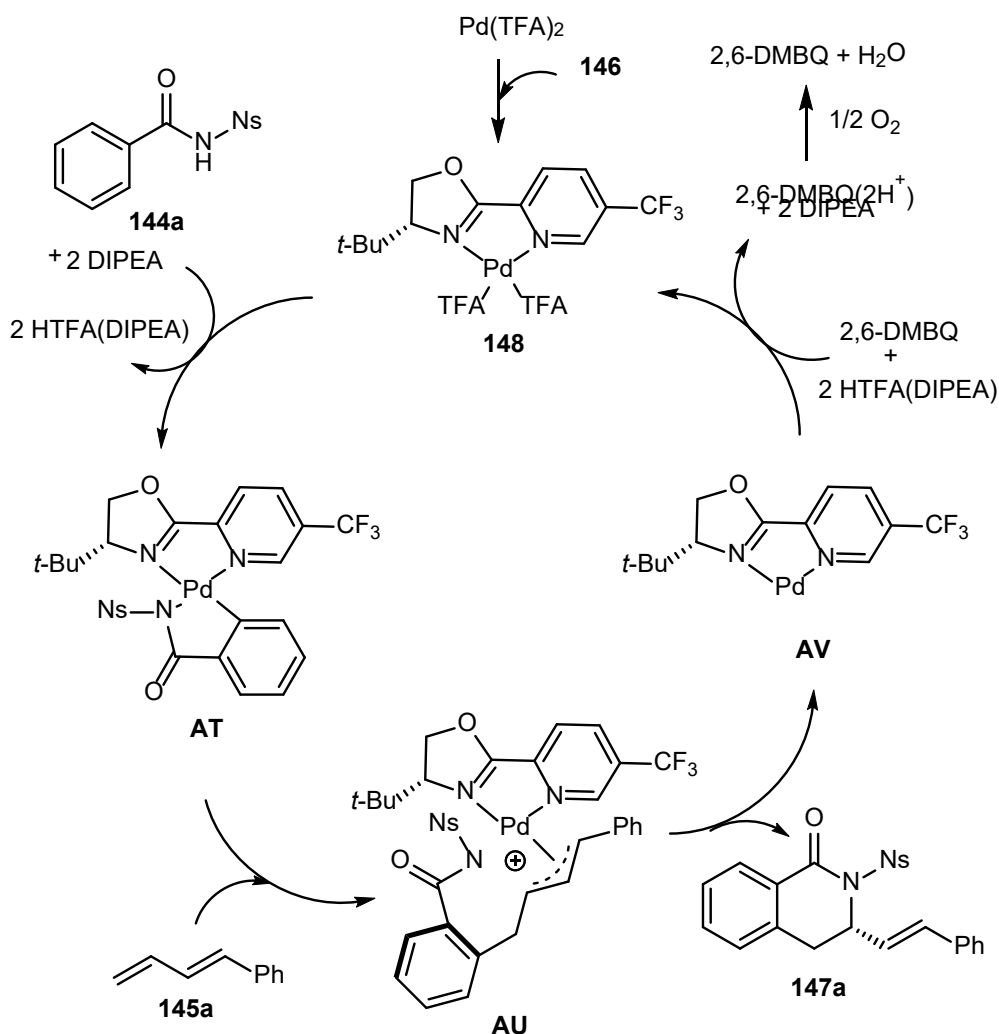
The synthesis of chiral isoquinolines, and especially 3,4-dihydroisoquinolones, is challenging since these molecules play a significant role in medicinal chemistry. In 2019, Yang et al. developed a novel direct route to this class of products on the basis of an enantioselective palladium-catalyzed domino reaction.<sup>[47]</sup> This dealt with an asymmetric domino C–H functionalization/intramolecular allylation reaction of *N*-sulfonyl benzamides **144** with 1,3-dienes **145** promoted by a chiral palladium catalyst *in situ* generated from 10 mol% of Pd(TFA)<sub>2</sub> and 12 mol% of chiral pyridine/oxazoline ligand **146** in the presence of DIPEA as base and 2,6-dimethoxy-1,4-benzoquinone (2,6-DMBQ) as oxidant. The reaction resulted in the formation of a range of chiral 3,4-dihydroisoquinolones **147** with moderate to high yields (32-82%) and generally high enantioselectivities (62-96% *ee*), as illustrated in Scheme 37.

The reaction of benzamides bearing electron-donating substituents ( $R^2$ ) on the phenyl ring afforded the desired chiral 3,4-dihydroisoquinolones with both good yields (62-81%) and enantioselectivities (80-87% *ee*) whereas benzamides with electron-withdrawing substituents reacted with both lower yields (33-52%) and *ee* values (62-85% *ee*). Moreover, a collection of variously substituted aromatic 1,3-dienes were tolerated including an aliphatic 1,3-diene ( $R^3 = \text{Bn}$ ) which underwent the reaction to give the corresponding product with 64% yield and 90% *ee*. The mechanism proposed in Scheme 37 begins with the coordination of the chiral ligand to the precatalyst to generate active chiral palladium(II) catalyst **148**. Then, deprotonation of the N–H bond and metalation of the  $\text{sp}^2$  C–H bond provides five-membered palladacycle **AT** which subsequently undergoes migratory insertion of the 1,3-diene **145a** ( $R^3 = \text{Ph}$ ), leading to  $\pi$ -allyl palladium complex **AU**. Finally, back attack of the nitrogen nucleophile to the  $\pi$ -allyl palladium moiety affords domino product **147a** along with palladium(0) species **AV**, which can be oxidized to regenerated Pd(II) catalyst **148**.



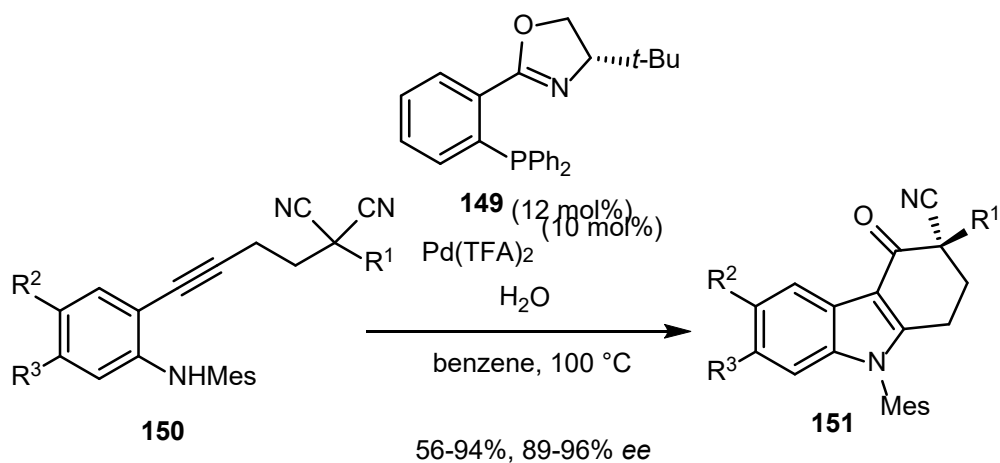
$\text{R}^1 = n\text{-Non}, p\text{-Tol}, 2\text{-Naph}, p\text{-F}_3\text{CC}_6\text{H}_4, o\text{-O}_2\text{NC}_6\text{H}_4, \text{CF}_3$   
 $\text{R}^2 = 4\text{-Me}, 4\text{-Et}, 4\text{-}t\text{-Bu}, 4\text{-OMe}, 3\text{-Me}, 2\text{-Me}, 2,4\text{-Me}_2, 4\text{-F}, 4\text{-Cl}, 4\text{-Br},$   
 $4\text{-NO}_2, 4\text{-Br}, 4\text{-CO}_2\text{Me}, 4\text{-CF}_3, 3\text{-F-4-OMe}$   
 $\text{R}^3 = \text{Ph}, p\text{-Tol}, p\text{-MeOC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, o\text{-Tol},$   
 $o\text{-MeOC}_6\text{H}_4, o\text{-F}_3\text{CC}_6\text{H}_4, o\text{-FC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, o\text{-BrC}_6\text{H}_4,$   
 $2\text{-Br-5-OMeC}_6\text{H}_3, \text{Bn}, \text{CO}_2\text{Et}$

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 37.** Domino C–H functionalization/intramolecular allylation reaction of *N*-sulfonyl benzamides with 1,3-dienes.

In 2021, Liu et al. described the use of a chiral palladium catalyst derived from 10 mol% of Pd(TFA)<sub>2</sub> and 12 mol% of chiral phosphinooxazoline ligand **149** to promote an enantioselective palladium-catalyzed aminocyclization and desymmetrizing nitrile addition cascade reaction of alkyne-tethered malononitriles **150** (Scheme 38).<sup>[48]</sup> The domino reaction was performed at 100 °C in benzene as solvent in the presence of water as an additive, affording chiral carbazolones **151** exhibiting an  $\alpha$ -all-carbon quaternary stereocenter. Moderate to quantitative yields (56-94%) combined with uniformly high *ee* values (89-96% *ee*) were obtained for an impressively wide variety of substituted substrates. The authors proposed that the cascade reaction began with the coordination of the Pd(II) chiral catalyst to the alkyne to form palladium complex **AW** (Scheme 38). Then, *trans*-aminopalladation occurred to generate indolylpalladium(II) species **AX**, which further underwent intramolecular nucleophilic addition to the proximal nitrile, providing intermediate **AY**. In the presence of water, intermediate **AY** was protonated to give imine **AZ** along with recovered catalyst. Subsequent hydrolysis of **AZ** by aqueous HCl allowed the final carbazolone to be produced. It must be noted that this work could also be situated in section 2.2.5 dealing with P,N-ligands.

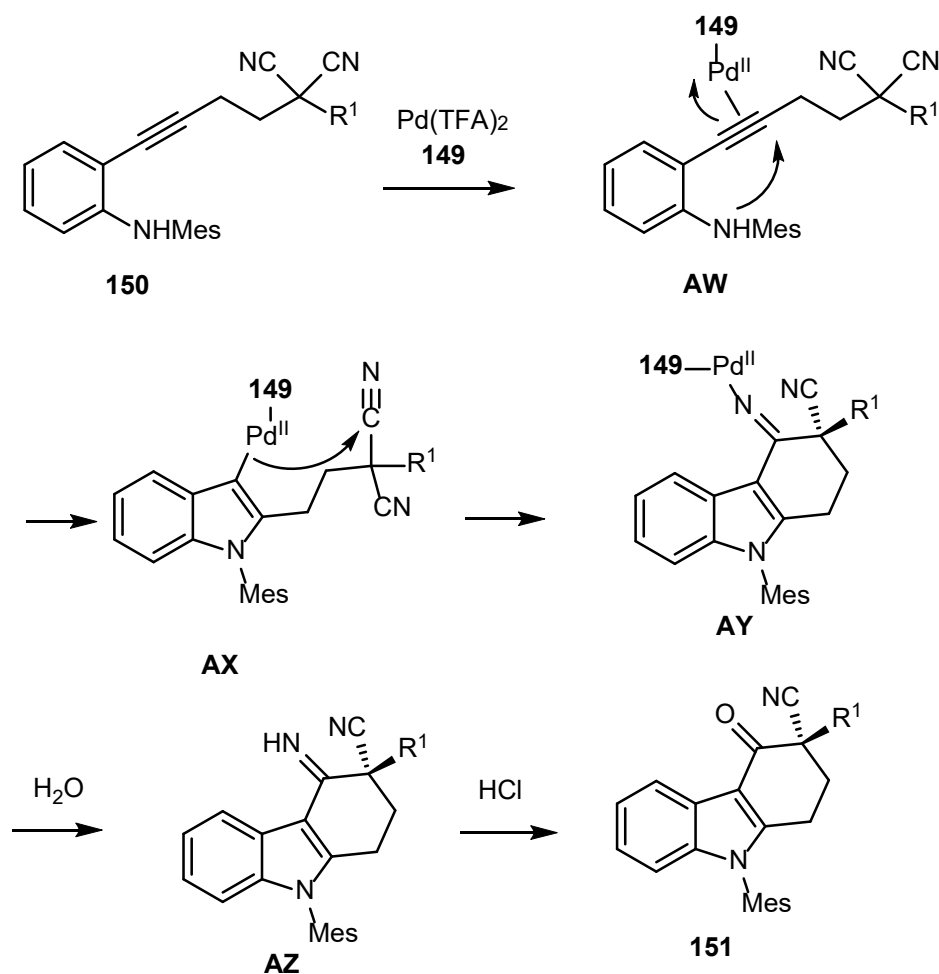


$\text{R}^1 = \text{Bn}, 3,4,5\text{-(MeO)}_3\text{C}_6\text{H}_2\text{CH}_2, (2\text{-Naph})\text{CH}_2, (2\text{-thienyl})\text{CH}_2, (2\text{-furyl})\text{CH}_2, (\text{Me})_2\text{C}=\text{CHCH}_2, n\text{-Pr}, \text{CyCH}_2, c\text{-PrCH}_2, \text{Me}, i\text{-Pr}, \text{Ph}, \text{Ac}(\text{CH}_2)_2,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

$\text{R}^2 = \text{H}, \text{Me}, \text{F}, \text{Cl}, \text{Br}, \text{CF}$

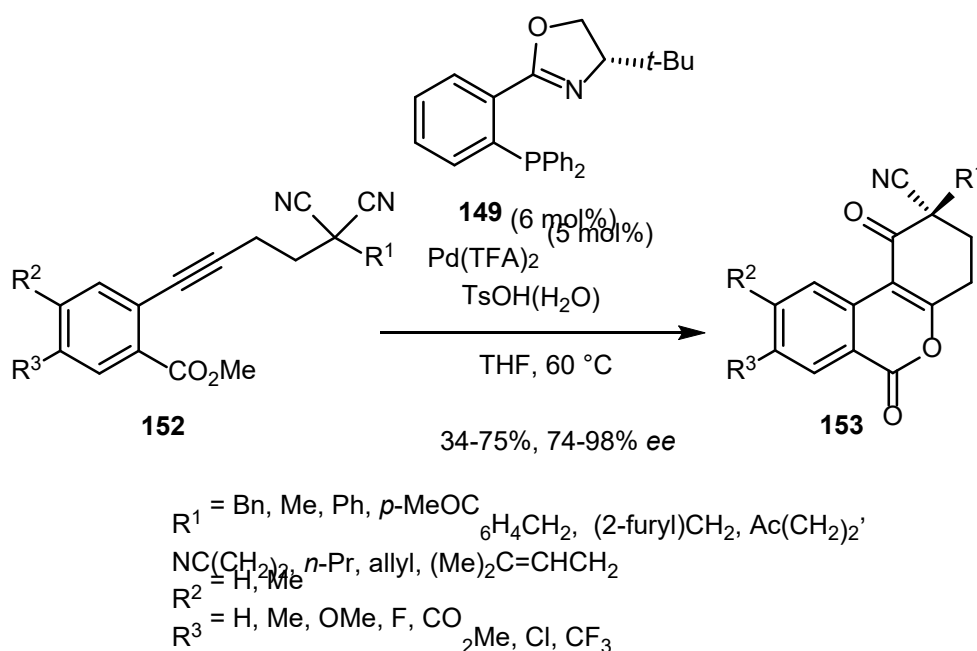
$\text{R}^3 = \text{H}, \text{Me}, \text{OMe}, \text{F}, \text{CO}_2\text{Me}$

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



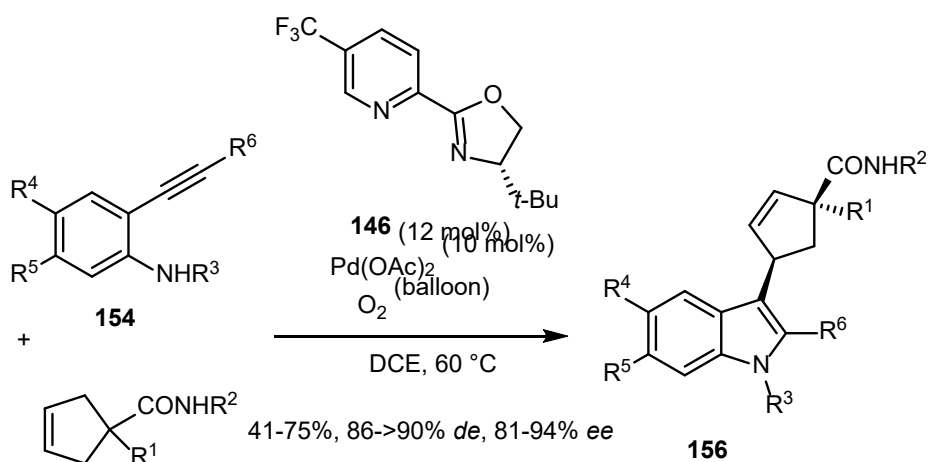
**Scheme 38.** Domino aminocyclization/intramolecular nucleophilic addition reaction of alkyne-tethered malononitriles.

In 2021, these authors applied the same chiral ligand to promote related enantioselective palladium-catalyzed annulation of other alkyne-tethered malononitriles **152** (Scheme 39).<sup>[49]</sup> In this case, only 6 mol% of chiral phosphinooxazoline ligand **149** combined with 5 mol% of Pd(TFA)<sub>2</sub> as precatalyst were sufficient to promote the cascade reaction performed in THF as the solvent at lower reaction temperature (60 vs 100 °C). In the presence of TsOH·H<sub>2</sub>O as additive, the domino reaction of diversely substituted methyl *o*-alkynylbenzoates **152** evolved through successive oxypalladation and intramolecular nitrile addition, delivering the corresponding chiral 3,4-ring-fused isocoumarins **153** exhibiting a nitrile-containing quaternary stereogenic center with moderate to good yields (34-75%) and high *ee* values (74-98% *ee*). These results could also be situated in section 2.2.5 dealing with P,N-ligands.



**Scheme 39.** Domino oxypalladation/intramolecular nucleophilic addition reaction of alkyne-tethered malononitriles.

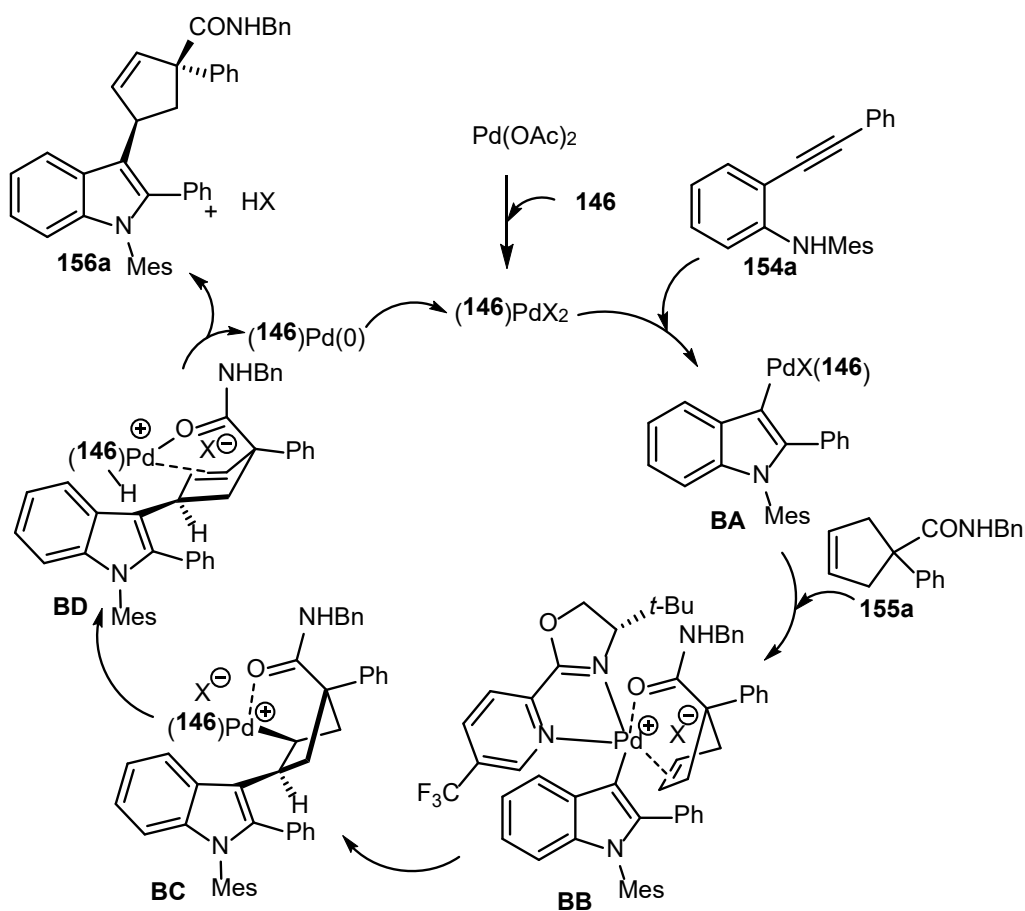
An enantioselective palladium-catalyzed domino amino-palladation/oxidative Heck reaction between 2-alkynylanilines **154** and substituted cyclopentenones **155** was developed by Zhu et al., in 2021 (Scheme 40).<sup>[50]</sup> Carried out at 60 °C in DCE as solvent in the presence of 10 mol% of Pd(OAc)<sub>2</sub>, 12 mol% of chiral pyridine/oxazoline ligand **146** and O<sub>2</sub> as terminal oxidant, the asymmetric domino indolization/oxidative Heck reaction resulted in the formation of chiral indole-cyclopentene derivatives **156** bearing two stereocenters with moderate to good yields (41-75%) and both uniformly high diastereo- (86->90% *de*) and enantioselectivities (81-94% *ee*). A mechanism proposed in Scheme 40 involves an intramolecular aminopalladation of **154a** (R<sup>3</sup> = Mes, R<sup>4</sup> = R<sup>5</sup> = H, R<sup>6</sup> = Ph) catalyzed by (146)PdX<sub>2</sub> *in situ* generated from chelation of ligand **146** to Pd(OAc)<sub>2</sub>, which afforded indolylPdX species **BA**. Then, coordination of the latter to the double bond of **155a** (R<sup>1</sup> = Ph, R<sup>2</sup> = Bn) directed by the amide function generated Pd(II) complex **BB** which defined the face selectivity of the subsequent *syn*-carbopalladation to afford Pd(II) species **BC**. This intermediate subsequently underwent a β-hydride elimination to give intermediate **BD** which, upon decomplexation and reductive elimination of HX from the resulting HPdX, provided final product **146a** along with Pd(0). The latter was then oxidized by oxygen and acetic acid to regenerate the catalyst.



**155**

$\text{R}^1 = \text{Ph}, p\text{-MeOC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, m\text{-Tol}, o\text{-O}_2\text{NC}_6\text{H}_4, 2\text{-Naph}, \text{Me}, \text{Bn}, t\text{-BuO}_2\text{CCH}_2, \text{H}$   
 $\text{R}^2 = \text{Bn}, i\text{-Bu}$   
 $\text{R}^3 = \text{Mes}, \text{Ts}, \text{Ns}$   
 $\text{R}^4 = \text{H}, \text{Cl}, \text{CF}_3, \text{CO}_2\text{Me}, \text{Me}$   
 $\text{R}^3, \text{R}^4 = \text{OCH}_3, \text{OCH}_2\text{O}$   
 $\text{R}^5 = \text{H}, \text{F}$   
 $\text{R}^6 = \text{Ph}, p\text{-MeOC}_6\text{H}_4, p\text{-MeO}_2\text{CC}_6\text{H}_4, 2\text{-thienyl}, n\text{-Bu}, \text{Cl}(\text{CH}_2)_3, \text{BnO}(\text{CH}_2)_2, \text{MeO}_2\text{C}(\text{CH}_2)_3$

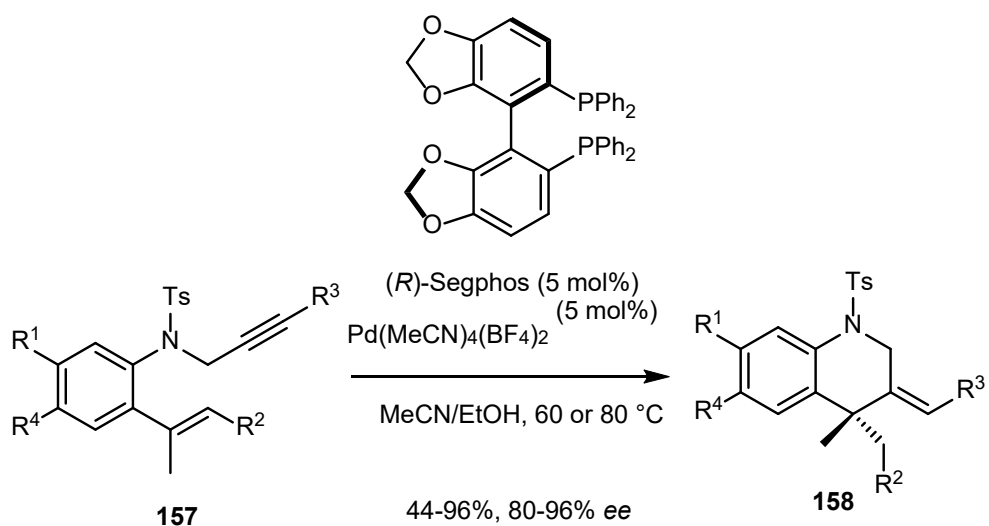
mechanism (with  $\text{R}^1 = \text{R}_6 = \text{Ph}, \text{R}_2 = \text{Bn}, \text{R}_3 = \text{Mes}, \text{R}_4 = \text{R}_5 = \text{H}$ ):



**Scheme 40.** Domino indolization/oxidative Heck reaction of 2-alkynylanilines with substituted cyclopentenes.

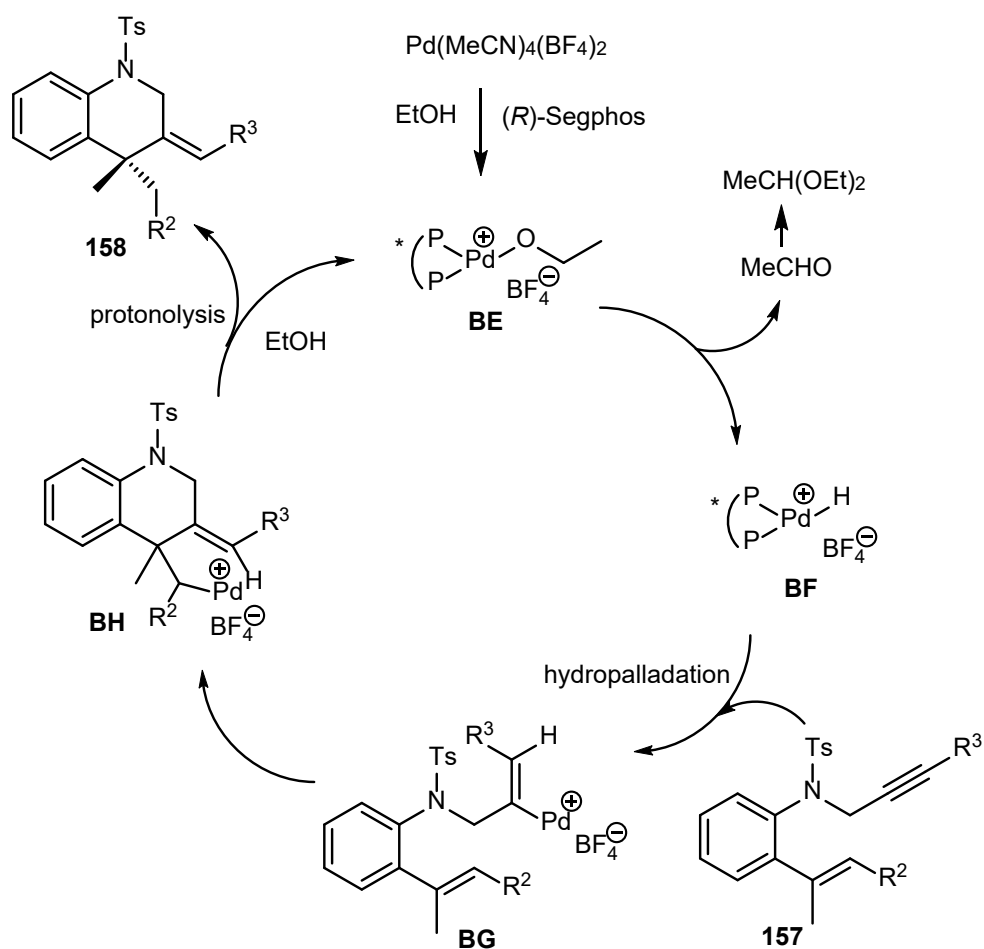
### 2.2.3 Bisphosphine Ligands

Chiral 1,2,3,4-tetrahydroquinolines play an important role in medicinal chemistry. In 2019, Lu and Han disclosed a novel route to these molecules based on an enantioselective intramolecular palladium-catalyzed domino reaction of *N*-tosyl-tethered 1,7-enynes **157** (Scheme 41).<sup>[51]</sup> Indeed, when these substrates were heated at 60 or 80 °C in acetonitrile as the solvent and ethanol as the hydrogen source in the presence of 5 mol% of (*R*)-Segphos as chiral ligand and the same quantity of Pd(MeCN)<sub>4</sub>(BF<sub>4</sub>)<sub>2</sub> as precatalyst, they underwent hydropalladation followed by 1,4-addition which yielded the corresponding chiral 1,2,3,4-tetrahydroquinolines **158** exhibiting a chiral quaternary carbon center. These products were obtained with moderate to high yields (44-96%) and homogeneously high enantioselectivities (80-96% *ee*). This unprecedented enantioselective palladium-catalyzed reductive cyclization of *N*-tosyl-tethered 1,7-enynes can be explained by the mechanism depicted in Scheme 41. In a first time, palladium ethoxide complex **BE** is generated from the precatalyst and ethanol. Then, complex **BE** leads to palladium intermediate hydride complex **BF** via β-H elimination. Subsequently, intermediate **BG** is generated through insertion of the carbon–carbon triple bond of substrate **157** into a hydrogen–palladium bond in intermediate **BF**. Then, the carbon–palladium bond adds to the intramolecular alkene to provide intermediate **BH** which is further submitted to protonolysis to afford the final product along with regenerated palladium(II) catalyst.



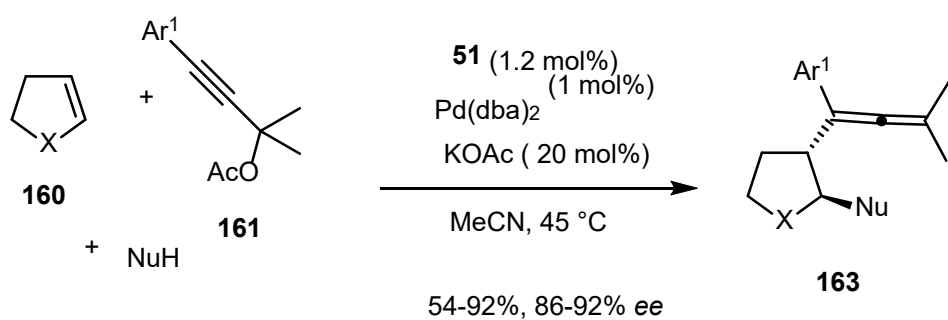
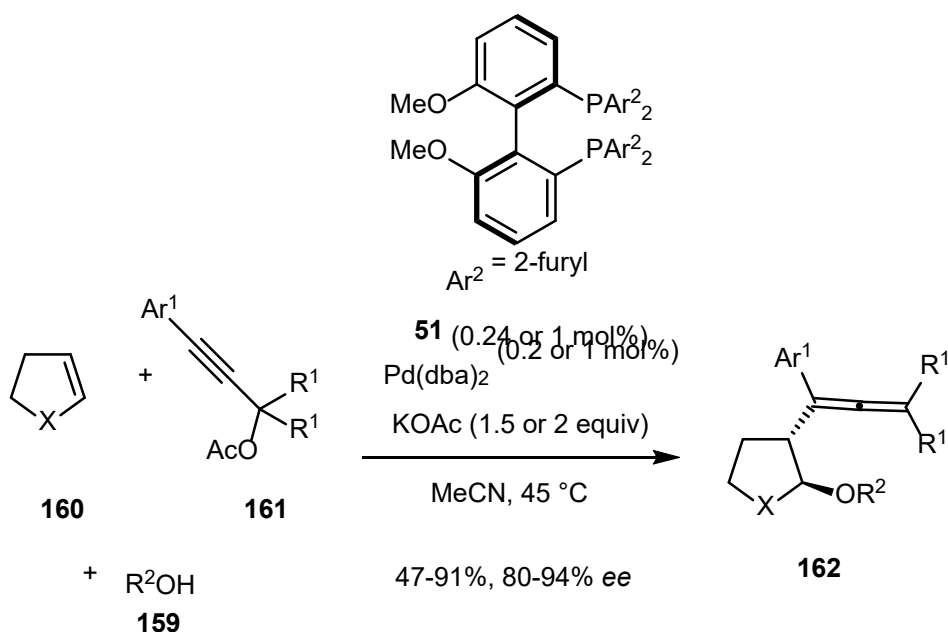
$R^1 = \text{H, Me}$   
 $R^2 = \text{CO}_2\text{Me, CN, Ac, } t\text{-BuNHCO}$   
 $R^3 = \text{TMS, Me}_2\text{SiPh, TBS, } t\text{-Bu}$   
 $R^4 = \text{H, Me, OMe, F, Cl, Br, CF}_3, \text{Ph}$

mechanism (with  $R^1 = R_4 = \text{H}$ ):



**Scheme 41.** Domino hydropalladation/1,4-addition reaction of *N*-tosyl-tethered 1,7-enynes.

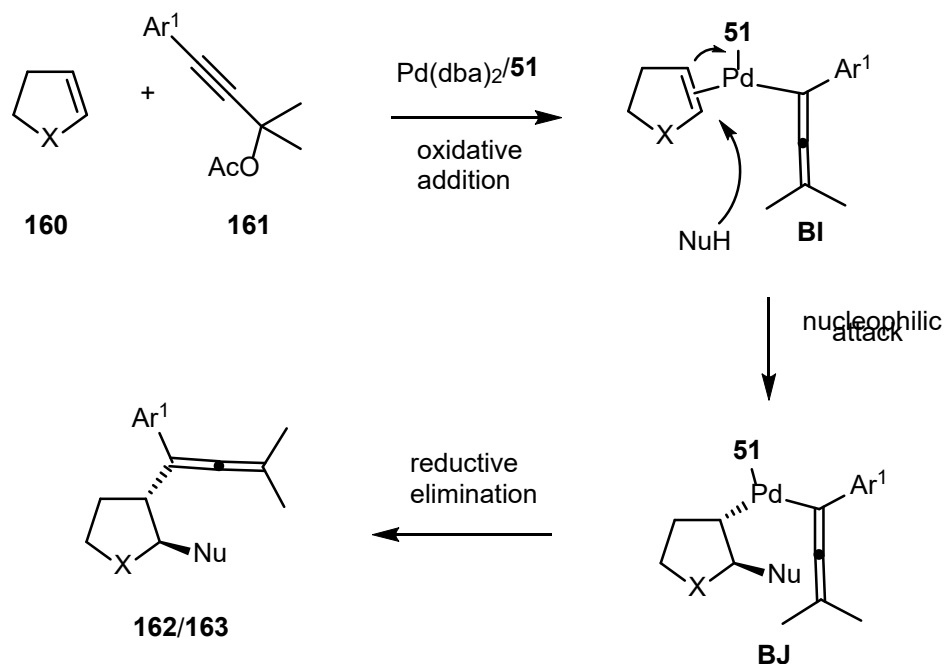
In 2020, Zhou et al. employed chiral bisphosphine ligand **51** to promote asymmetric palladium-catalyzed three-component reactions between cyclic alkenes, propargylic acetates and various external nucleophiles, such as alkyl alcohols, phenols, carboxylic acids, water, and electron-deficient aryl amines.<sup>[52]</sup> When alkyl alcohols **159** were used as nucleophiles, an enantioselective alkoxyallenylation occurred at 45 °C in the presence of 2,3-dihydrofuran **160** (X = O) and propargylic acetates **161** in acetonitrile as solvent and by using only 0.24 mol% of chiral ligand **51** combined with 0.2 mol% of Pd(dba)<sub>2</sub> as catalyst system. The reaction afforded the corresponding chiral *trans*-products **162** exclusively with moderate to high yields (47-91%) and high enantioselectivities (80-94% *ee*). Another cyclic alkene, such as *N*-Boc-2,3-dihydropyrrole **160** (X = NBoc), was also compatible to asymmetric alkoxyallenylation with propargylic acetates **161** and alkyl alcohols **159**, but in this case a higher catalyst loading was required, such as 1 mol% of Pd(dba)<sub>2</sub> combined with 1.2 mol% of chiral ligand **51**. Under these conditions, the corresponding chiral products **162** were produced in comparable yields (55-88%) and *ee* values (87-92% *ee*), as shown in Scheme 42. Moreover, the reaction was also applicable to other oxygen nucleophiles, such as water, phenols, and carboxylic acids, as well as nitrogen nucleophiles, such as electron-poor aryl amines. Indeed, the three-component oxyallenylation of 2,3-dihydrofuran/*N*-Boc-2,3-dihydropyrrole **160** with propargylic acetates **161** and either acetic acid, phenol or water in the presence of 1 mol% of Pd(dba)<sub>2</sub> and 1.2 mol% of chiral ligand **51** in acetonitrile at 45 °C led to the desired products **163** in moderate to high yields (54-92%) and high enantioselectivities (86-92% *ee*). Using amines as nucleophiles allowed related asymmetric azaallenylation to occur under the same reaction conditions. As shown in Scheme 42, the reaction of amines with 2,3-dihydrofuran **160** (X = O) and propargylic acetates **161** yielded the corresponding products **163** with 60-81% yields and 86-91% *ee*. It must be noted that these results constituted the first example of asymmetric Wacker-type attack of truly external nucleophiles on monoolefins occurring without the aid of directing groups.



**Scheme 42.** Three-component domino alkoxy/oxy-/azaallenenylation reactions of cyclic alkenes, propargylic acetates and various oxygen and nitrogen nucleophiles.

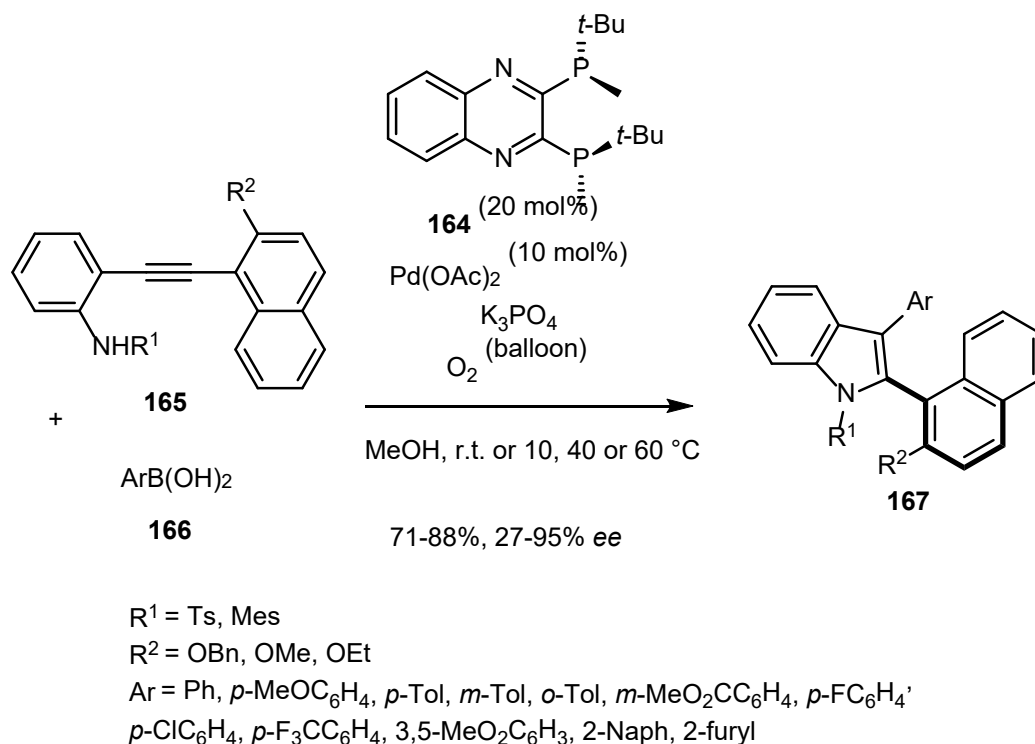
The mechanism of the precedent reaction between cyclic alkenes **160** and propargylic acetates **161** is shown in Scheme 43, beginning with oxidative addition in the presence of the chiral palladium catalyst, leading to allenic palladium intermediate **BI**.<sup>[52]</sup> The latter was subsequently submitted to

nucleophilic attack to afford allenic palladium intermediate **BJ** which further underwent reductive elimination to give the final product.



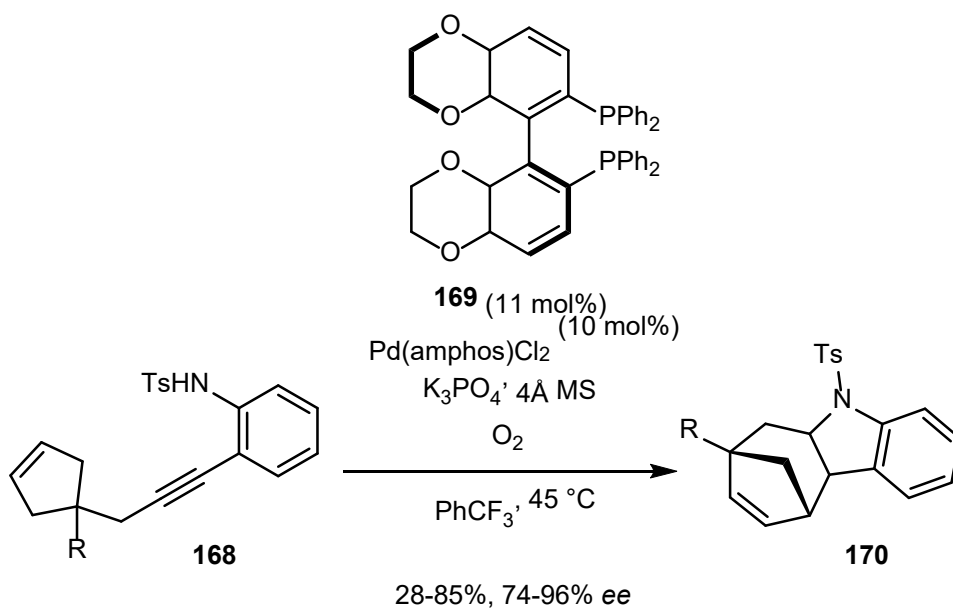
**Scheme 43.** Mechanism for three-component reaction of cyclic alkenes, propargylic acetates and nucleophiles.

The first example of enantioselective palladium-catalyzed Cacchi-type reaction applied to the synthesis of indoles bearing an achiral C2-aryl axis was described by Zhu et al., in 2020 (Scheme 44).<sup>[53]</sup> Catalyzed by a combination of 10 mol% of Pd(OAc)<sub>2</sub> and 20 mol% of chiral bisphosphine ligand **164**, in the presence of two equivalents of K<sub>3</sub>PO<sub>4</sub> under oxygen atmosphere, the domino cyclization/cross-coupling reaction of *N*-sulfonyl-2-alkynylanilides **165** with (hetero)arylboronic acids **166** afforded the corresponding chiral 2,3-disubstituted indoles **167** in good yields (71-88%) and low to excellent enantioselectivities (27-95% *ee*). Studying the scope of this asymmetric cyclizative cross-coupling reaction, the authors found that the nature of the alkoxy group (R<sup>2</sup>) on the naphthyl ring of the *N*-sulfonyl-2-alkynylanilide dramatically influenced the enantioselectivity of the reaction, with the best *ee* values (75-94% *ee*) achieved in the case of a benzyloxy group (R<sup>2</sup> = OBn). In contrast, the lowest enantioselectivities (27-33% *ee*) were obtained in the reaction of a *N*-sulfonyl-2-alkynylanilide bearing a methoxy group (R<sup>2</sup> = 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*).



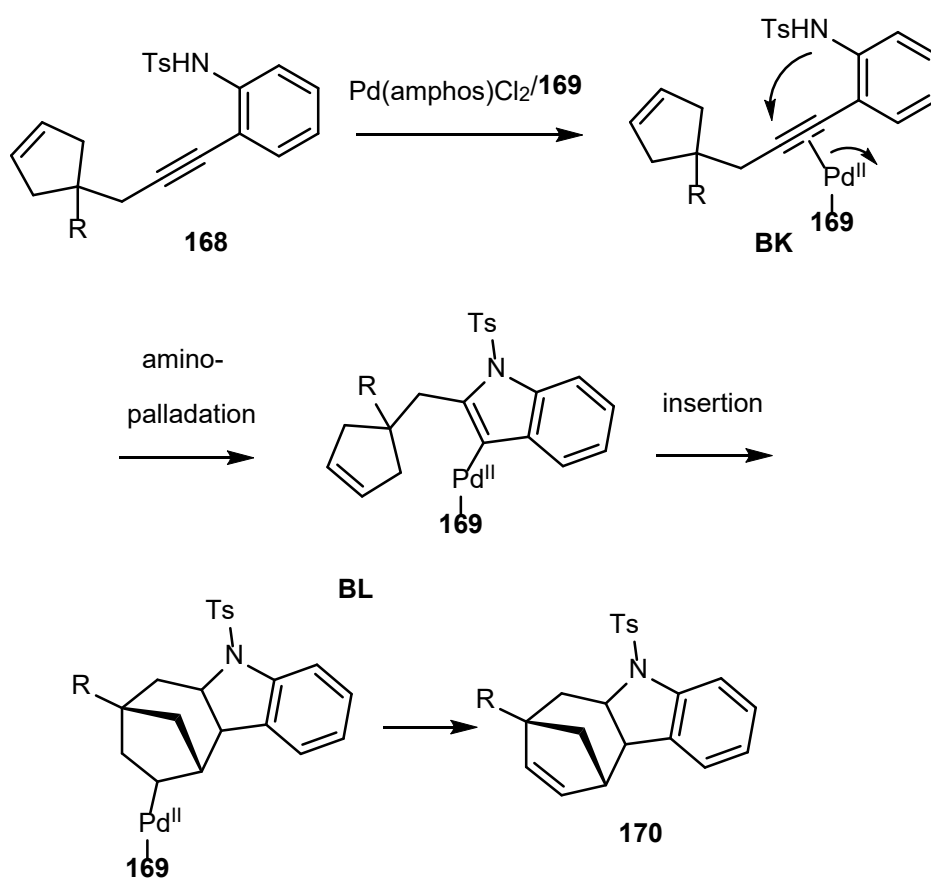
**Scheme 44.** Domino cyclization/cross-coupling reaction of *N*-sulfonyl-2-alkynylanilides with arylboronic acids.

Indole-fused bicyclo[3.2.1]octanes constitute important structural skeletons of many natural and/or bioactive products. In 2021, Ye et al. reported a novel route to these molecules based on an enantioselective palladium-catalyzed cascade oxidative cyclization involving *N*-sulfonyl-2-alkynylanilides **168** as substrates (Scheme 45).<sup>[54]</sup> The reaction was promoted at 45 °C in CF<sub>3</sub>Ph as solvent by a chiral catalyst derived from 10 mol% of Pd(amphos)Cl<sub>2</sub> and 11 mol% of chiral bisphosphine ligand **169**. Performed under oxygen atmosphere in the presence of K<sub>3</sub>PO<sub>4</sub> as base, a range of variously substituted *N*-sulfonyl-2-alkynylanilides **168** underwent domino aminopalladation/Heck-type reaction, allowing the desired chiral indole-fused bicyclo[3.2.1]octanes **170** bearing an all-carbon quaternary bridgehead stereocenter to be synthesized in moderate to good yields (28-85%) and good to excellent enantioselectivities (74-96% *ee*). The catalyst system was particularly tolerant for a wide range of functional groups. A mechanism is proposed in Scheme 45 beginning with the coordination of the palladium(II) catalyst with the triple bond of the *N*-sulfonyl-2-alkynylanilide which generated palladium intermediate **BK**. Then, the latter underwent aminopalladation to afford indol-3-yl palladium species **BL**. The subsequent intramolecular C=C double-bond insertion of intermediate **BL** followed by β-H elimination led to the final product.



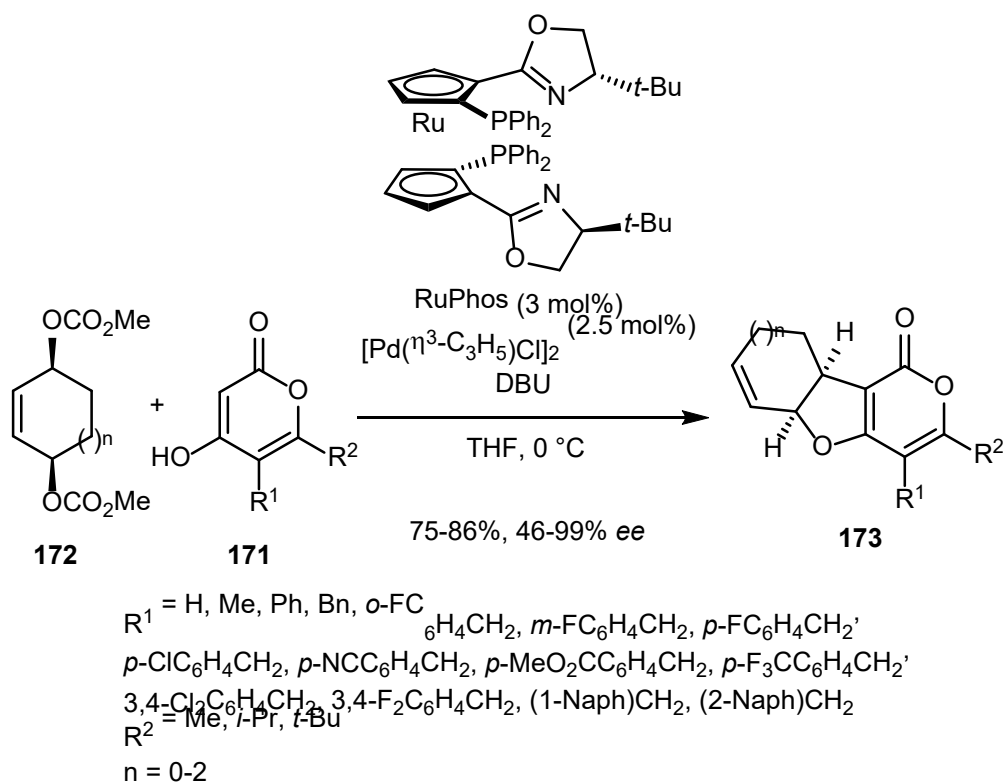
R = CO<sub>2</sub>Bn, CO<sub>2</sub>Me, CO<sub>2</sub>Et, CO<sub>2</sub>*i*-Pr, CO<sub>2</sub>*t*-Bu, Et<sub>2</sub>NCO,  
 AcOCH<sub>2</sub>, BnOCH<sub>2</sub>, TBSOCH<sub>2</sub>, ,

mechanism:

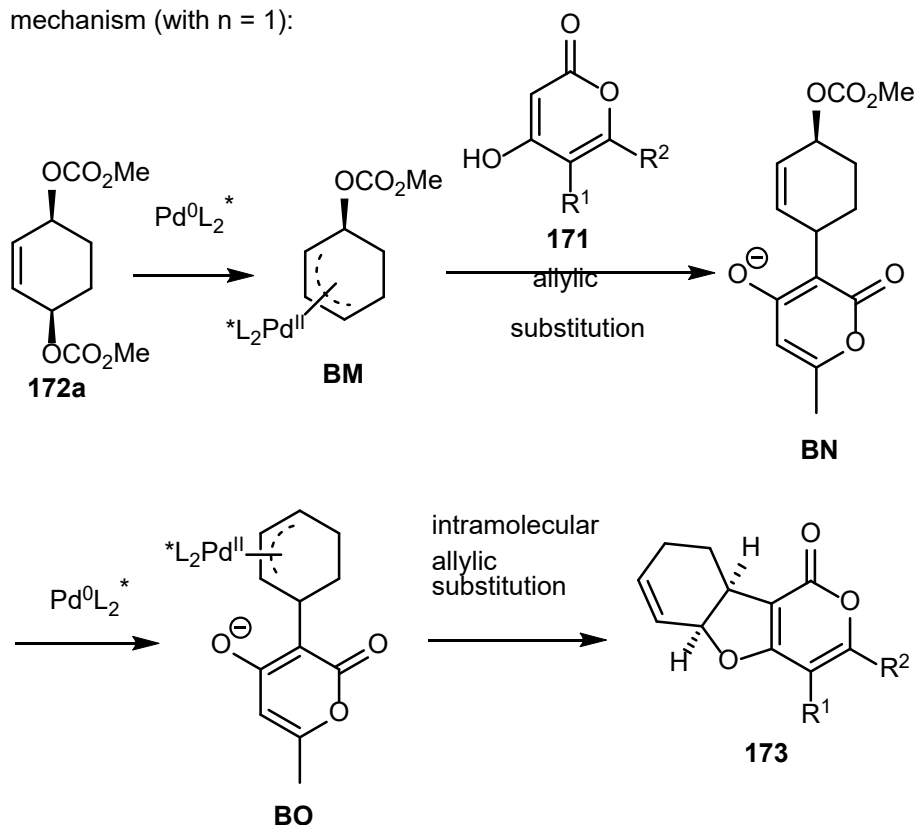


**Scheme 45.** Domino oxidative aminopalladation/Heck-type reaction of *N*-sulfonyl-2-alkynylanilides.

With the aim of developing an efficient synthetic methodology to prepare biologically interesting chiral fused-ring products, such as furo[3,2-*c*]pyrans, Liu et al. described in 2022 a novel enantioselective palladium-catalyzed domino double allylic substitution reaction of 4-hydroxy-2H-pyrones **171** with *meso*-allyl dicarbonates **172**.<sup>[55]</sup> The optimal catalyst system was constituted by 3 mol% of chiral ligand RuPhos and 2.5 mol% of  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$  employed at 0 °C in THF. The reaction performed in the presence of DBU as base afforded the corresponding chiral fused-ring products **173** with good yields (75-86%) and moderate to excellent enantioselectivities (46-99% *ee*), as shown in Scheme 46. Actually, this desymmetrization of *meso*-allyl dicarbonates provided uniformly high *ee* values (82-99% *ee*) in the case of six-membered cyclic decarbonates (*n* = 1) as substrates while five-membered (*n* = 0) and seven-membered substrates (*n* = 2) reacted with much lower enantioselectivities (46-60% *ee*). The substrate scope of the 4-hydroxy-2H-pyrones was wide since a variety of alkyl substituents ( $\text{R}^1, \text{R}^2$ ) were tolerated. The reaction could follow the mechanism depicted in Scheme 46 with the initial formation of  $\pi$ -allylpalladium complex **BM** from the reaction of activated Pd complex  $\text{L}^*\text{Pd}^0$  with the *meso*-allyl decarbonate. Then, complex **BM** reacted with the 4-hydroxy-2H-pyrone to give monosubstituted intermediate product **BN**. The latter subsequently formed novel  $\pi$ -allylpalladium complex **BO** by reaction with the catalyst, which further underwent an intramolecular allylic substitution, yielding the final cyclized product. It must be noted that this work could also be situated in Section 2.2.2 dealing with oxazoline ligands.



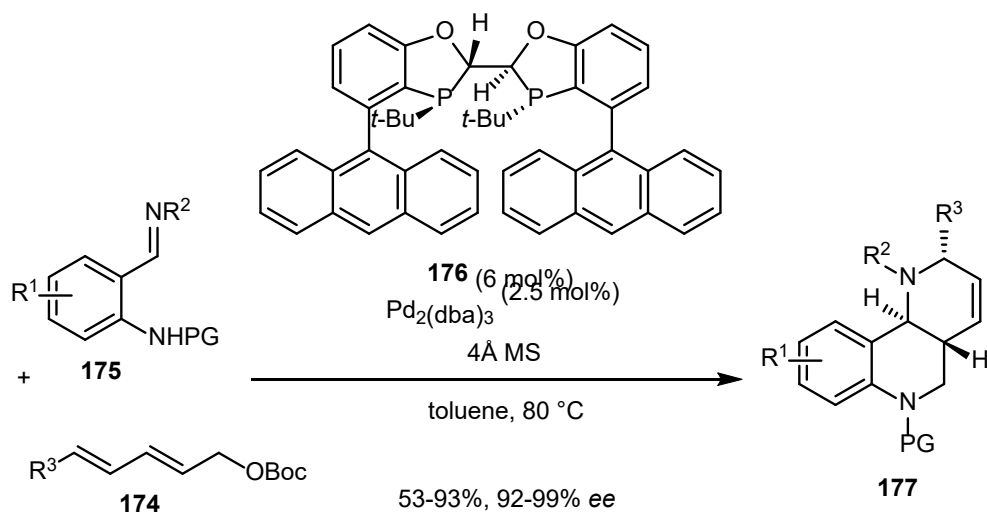
mechanism (with  $n = 1$ ):



**Scheme 46.** Domino double allylic substitution reaction of 4-hydroxy-2H-pyrones with *meso*-allyl dicarbonates.

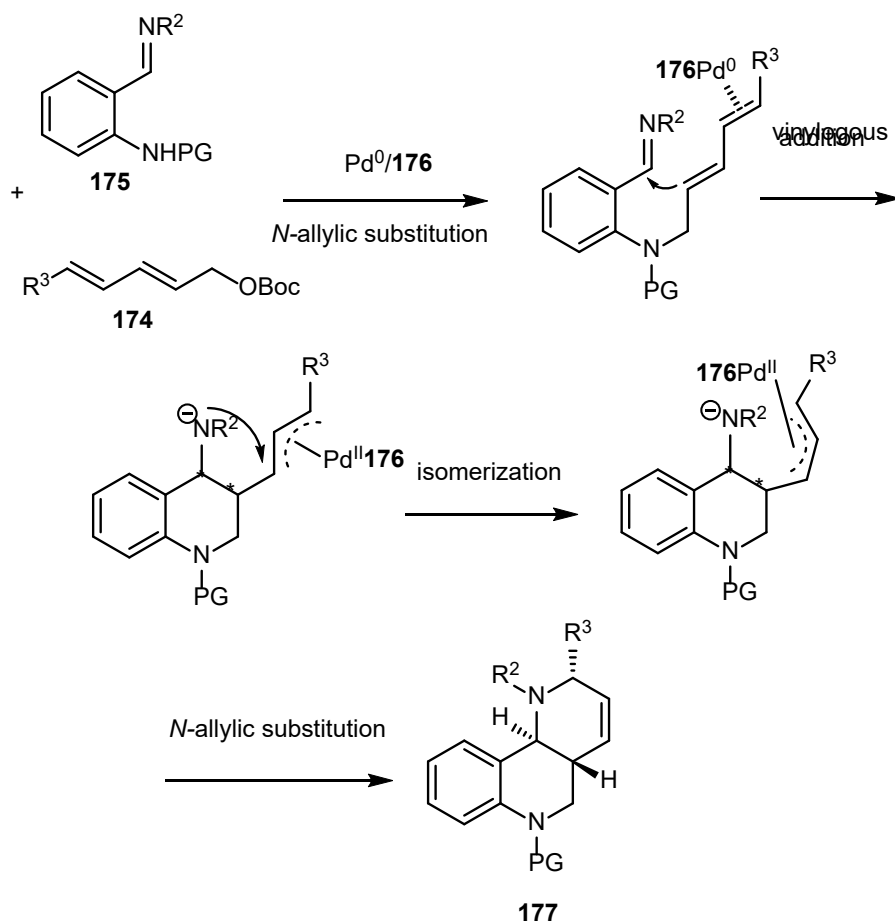
Other biologically challenging tricyclic architectures were synthesized in 2022 by Chen and Chen through auto-tandem palladium catalysis.<sup>[56]</sup> The methodology involved an enantioselective domino

reaction of 2,4-dienyl carbonates **174** with *o*-TsNH aryl aldimines **175** (PG = Ts) evolving through successive *N*-allylation, vinylogous addition,  $\pi$ - $\sigma$ - $\pi$  isomerization, and another *N*-allylation (Scheme 47). By using 6 mol% of chiral bisphosphine ligand **176** combined with 2.5 mol% of Pd<sub>2</sub>(dba)<sub>3</sub> as catalyst system, the reaction performed at 80 °C in toluene resulted in the formation of chiral densely functionalized tricyclic products **177** with moderate to high yields (53-93%) and uniformly excellent enantioselectivities (92-99% *ee*). A broad range of functional groups were tolerated on the substituent (R<sup>3</sup>) of the 2,4-dienyl carbonates.



$\text{R}^1$  = H, 4-Me, 4-OMe, 5-OMe, 5-Cl, 5-CF<sub>3</sub>, 4,5-F<sub>2</sub>, 6-F  
 $\text{R}^2$  = Ts, MeSO<sub>2</sub>, 2-thienyl, 2-thienyl-SO<sub>2</sub>  
 $\text{R}^3$  = Ph, *m*-Tol, *p*-Tol, *o*-ClC<sub>6</sub>H<sub>4</sub>, *m*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, 2-furyl, Me, Et, *n*-Bu, *c*-Pr, BnOCH<sub>2</sub>, MeO<sub>2</sub>C(CH<sub>2</sub>)<sub>2</sub>, Br(CH<sub>2</sub>)<sub>3</sub>, Et-CH=CH(CH<sub>2</sub>)<sub>2</sub>, PhC≡C  
 PG = Ts, Cbz, Ac

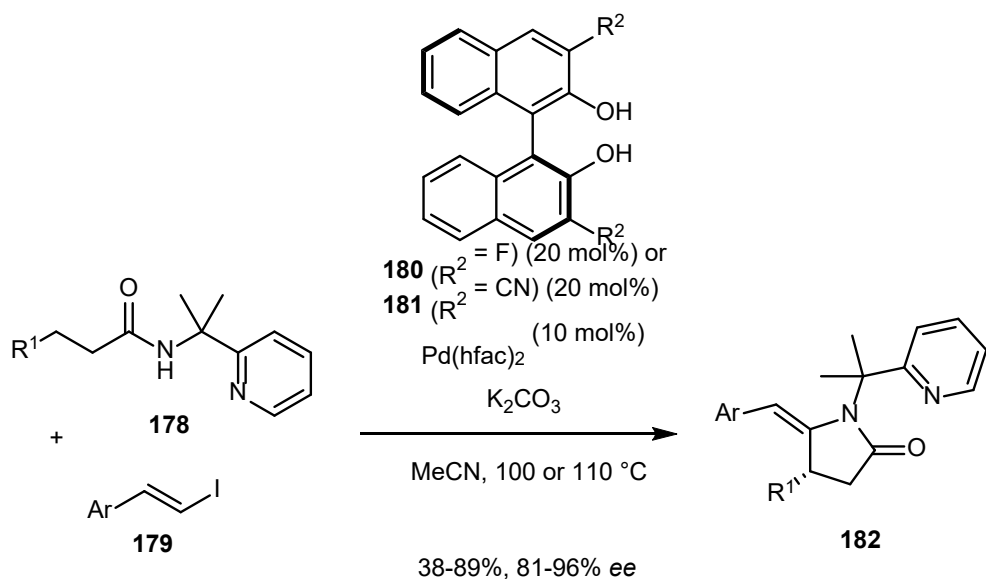
mechanism (with  $\text{R}^1$  = H) :



**Scheme 47.** Domino *N*-allylation/vinylogous addition/ $\pi$ - $\sigma$ - $\pi$  isomerization/*N*-allylation reaction of 2,4-dienyl carbonates with *o*-TsNH aryl aldimines.

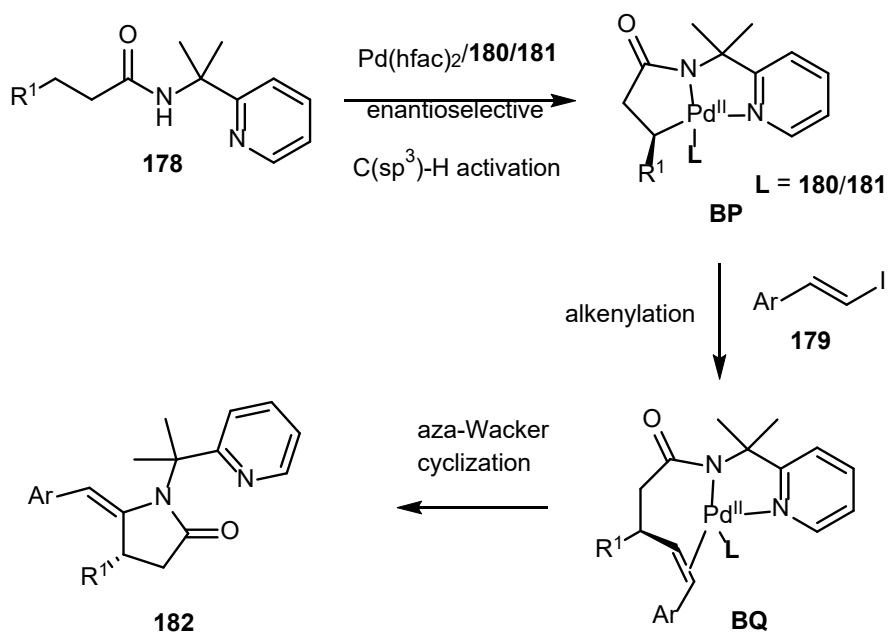
#### 2.2.4 BINOL-Derived Ligands

Related to the biological importance of  $\gamma$ -lactams, intensive efforts have been dedicated to their asymmetric synthesis. In 2020, Shi et al. disclosed a one-step formation of chiral  $\gamma$ -lactams containing a  $\beta$ -stereocenter through an unprecedented enantioselective domino methylene C(sp<sup>3</sup>)-H alkenylation/aza-Wacker cyclization reaction.<sup>[57]</sup> It involved 2-pyridinylisopropyl-derived aliphatic amides **178** and aryl vinyl iodides **179** as substrates in acetonitrile as the solvent (Scheme 48). The reaction was promoted at 100 or 110 °C by a chiral catalyst *in situ* generated from 10 mol% of Pd(hfac)<sub>2</sub> and 20 mol% of chiral BINOL-derived ligand **180** (R<sup>2</sup> = F). or **181** (R<sup>2</sup> = CN) in the presence of a base such as K<sub>2</sub>CO<sub>3</sub>, resulting in the formation of chiral  $\beta$ -stereogenic  $\gamma$ -lactams **182** with moderate to high yields (38-89%) and high enantioselectivities (81-96% *ee*). It evolved through enantioselective C(sp<sup>3</sup>)-H activation of the  $\beta$ -methylene, leading to chiral palladacycle intermediate **BP**. Then, the latter reacted with the aryl vinyl iodide to give the corresponding alkenylation species **BQ**. A subsequent palladium-catalyzed aza-Wacker-type cyclization yielded the final  $\beta$ -stereogenic  $\gamma$ -lactam. A series of 2-pyridinylisopropyl-derived aliphatic amides **178** were compatible. It was found that chiral ligand **181** allowed higher yields albeit combined with slightly reduced enantioselectivities to be obtained in comparison with chiral ligand **180**. A range of aryl vinyl iodides bearing either electron-withdrawing or electron-donating substituents on the phenyl ring were well tolerated whereas no reaction occurred in the case of alkyl vinyl iodides. It must be noted that this work represented the first palladium-catalyzed cascade cyclization reaction relying on enantioselective methylene C(sp<sup>3</sup>)-H activation.



$R^1 = \text{Me, Et, Pr, Bu, amyl, BnCH}_2, \text{Bn(CH}_2)_2, (2\text{-Naph})\text{CH}_2, i\text{-Pr, } i\text{-Bu, Ph}_2\text{CHCH}_2, (p\text{-FC}_6\text{H}_4)_2\text{CHCH}_2, \text{Cy(CH}_2)_2, p\text{-FC}_6\text{H}_4\text{CH}_2, p\text{-ClC}_6\text{H}_4\text{CH}_2, p\text{-BrC}_6\text{H}_4\text{CH}_2, p\text{-TolCH}_2, \text{TBSO(CH}_2)_3$   
 $\text{Ar} = p\text{-Tol, } o\text{-Tol, } m\text{-Tol, } p\text{-(}i\text{-Pr)}\text{C}_6\text{H}_4, p\text{-(}t\text{-Bu)}\text{C}_6\text{H}_4, 3,5\text{-(Me)}_2\text{C}_6\text{H}_3, o\text{-FC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, 3\text{-F-4-MeOC}_6\text{H}_3, 2\text{-Naph}$

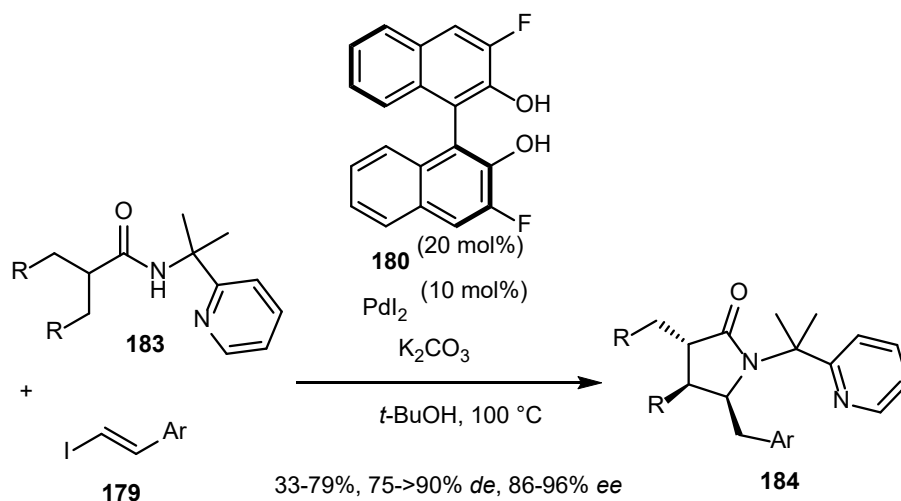
mechanism:



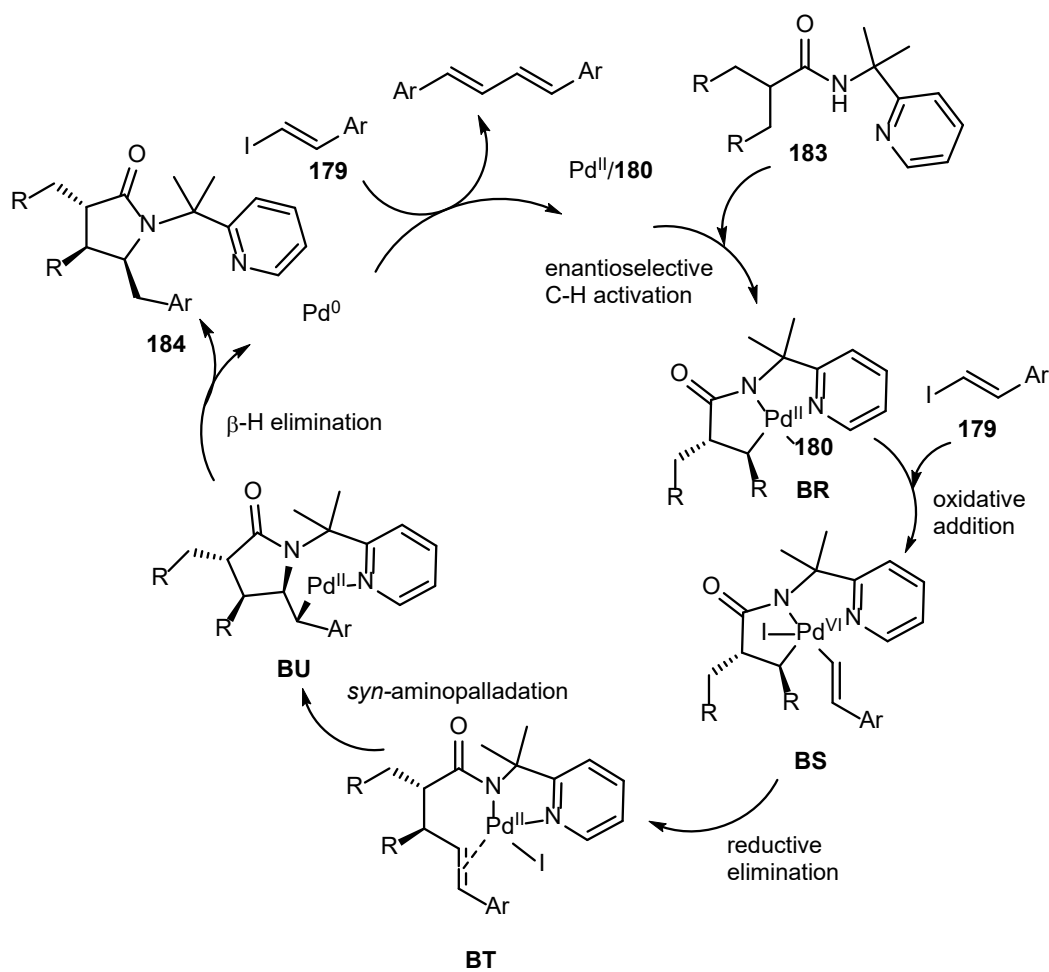
**Scheme 48.** Domino methylene C(sp<sup>3</sup>)-H alkenylation/aza-Wacker cyclization reaction of 2-pyridinylisopropyl-derived aliphatic amides with aryl vinyl iodides.

In 2021, a related methodology was also applied by the same group to the one-step formation of chiral  $\gamma$ -lactams containing three contiguous stereocenters (Scheme 49).<sup>[58]</sup> In this case, the enantioselective

domino methylene C(sp<sup>3</sup>)-H alkenylation/aza-Wacker cyclization reaction occurred between aryl vinyl iodides **179** and another type of 2-pyridinylisopropyl-derived aliphatic amides, such as gem-dialkyl aliphatic amides **183**. Promoted at 100 °C by a chiral palladium catalyst *in situ* generated from 10 mol% of PdI<sub>2</sub> and 20 mol% of chiral BINOL-derived ligand **180** in *tert*-butanol as the solvent and in the presence of K<sub>2</sub>CO<sub>3</sub> as base, the reaction delivered a range of chiral  $\gamma$ -lactams **184** in moderate to high yields (33-79%), good to excellent diastereoselectivities (75->90% *de*) along with uniformly high enantioselectivities (86-96% *ee*). Aryl vinyl iodides bearing either electron-withdrawing or electron-donating substituents on the phenyl ring afforded the corresponding chiral  $\gamma$ -lactams with both high enantio- (87-95% *ee* and 90-95% *ee*, respectively) and diastereoselectivities (84->90% *de* and 88->90% *de*, respectively). In contrast, alkyl vinyl iodides were not tolerated. Moreover, gem-dialkyl aliphatic amides **183** could exhibit either alkyl or aryl substituents (R). A plausible mechanism is depicted in Scheme 49, beginning with the enantioselective cleavage of one of the four  $\beta$ -methylene C(sp<sup>3</sup>)-H bonds assisted by the chiral ligand, which leads to the formation of chiral palladacycle intermediate **BR**. Then, oxidative addition of the aryl vinyl iodide onto **BR** affords Pd(IV) species **BS**, which subsequently undergoes reductive elimination to generate palladium intermediate **BT**. The coordination of the amide and alkene to palladium in **BT** facilitates intramolecular *syn*-aminopalladation to occur, providing palladium intermediate **BU**. The latter is further submitted to  $\beta$ -H elimination which affords the final chiral  $\gamma$ -lactam. In addition, the Pd(0) species is reoxidized to Pd(II) by consuming two equivalents of aryl vinyl iodide to close the catalytic cycle with generation of a 1,3-diene.



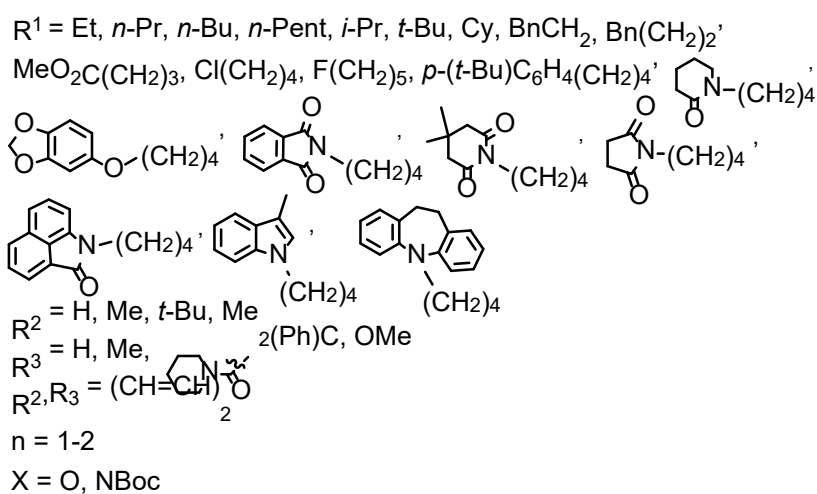
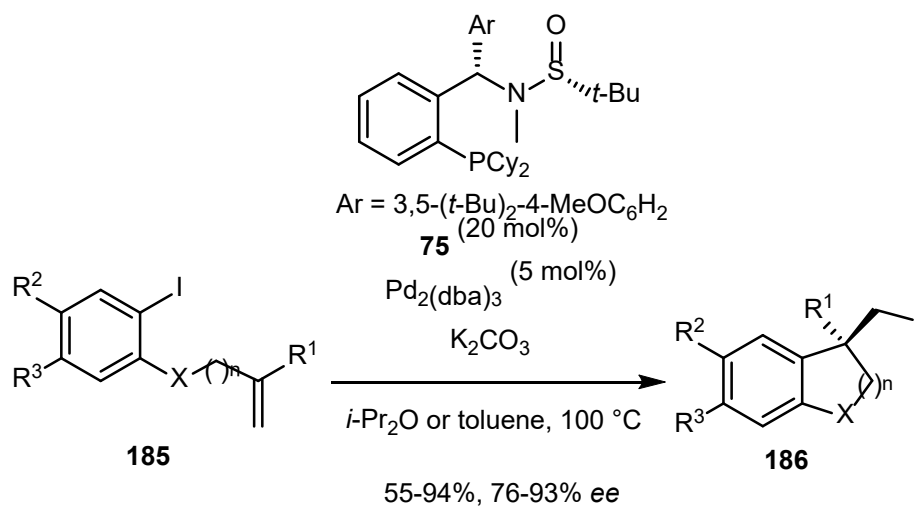
mechanism:



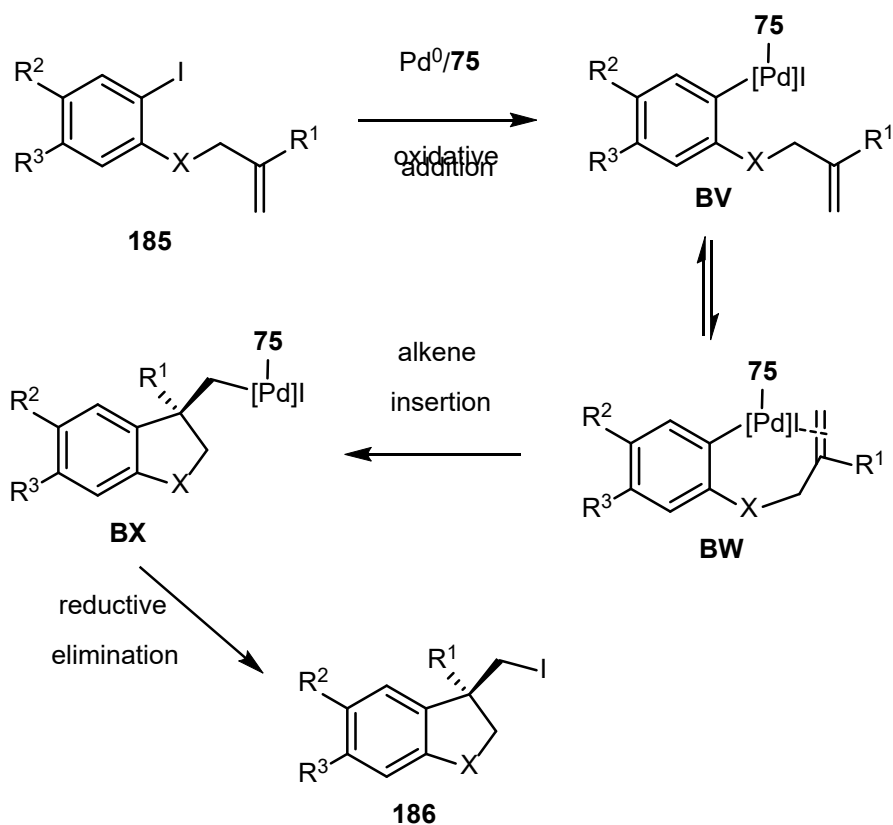
**Scheme 49.** Domino methylene C(sp<sup>3</sup>)-H alkenylation/aza-Wacker cyclization reaction of other 2-pyridinylisopropyl-derived aliphatic amides with aryl vinyl iodides.

### 2.2.5 P,N-ligands

In 2019, Zhang and Li disclosed the first example of highly enantioselective carboiodination of olefin-tethered aryl iodides (Scheme 50).<sup>[59]</sup> This was promoted by a chiral palladium catalyst *in situ* generated from 5 mol% of Pd<sub>2</sub>(dba)<sub>3</sub> and 20 mol% of chiral P,N-ligand **75** in diisopropylether or toluene as solvent. Under these conditions, a range of unactivated alkenes **185** underwent at 100 °C in the presence of K<sub>2</sub>CO<sub>3</sub> as base asymmetric domino iodine atom transfer/cycloisomerization reaction to afford the corresponding chiral 3,3-disubstituted 2,3-dihydrobenzofurans **186** (X = O, n = 1), indolines (X = NBoc, n = 1) and chromanes (X = O, n = 2) bearing an alkyl iodide group and one all-carbon quaternary stereocenter with moderate to high yields (55-94%) and good to high *ee* values (76-93% *ee*). The reaction of olefin-tethered aryl iodides with a nitrogen linker (X = 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 = O). The mechanism (Scheme 50) is supposed to involve the oxidative addition of the aryl iodide to give palladium intermediate **BV**. The latter then undergoes coordination of the C=C double bond to the palladium atom to give intermediate **BW**. Then, alkene insertion occurs to provide cyclized intermediate **BX**, which is further submitted to reductive elimination to deliver the final product.

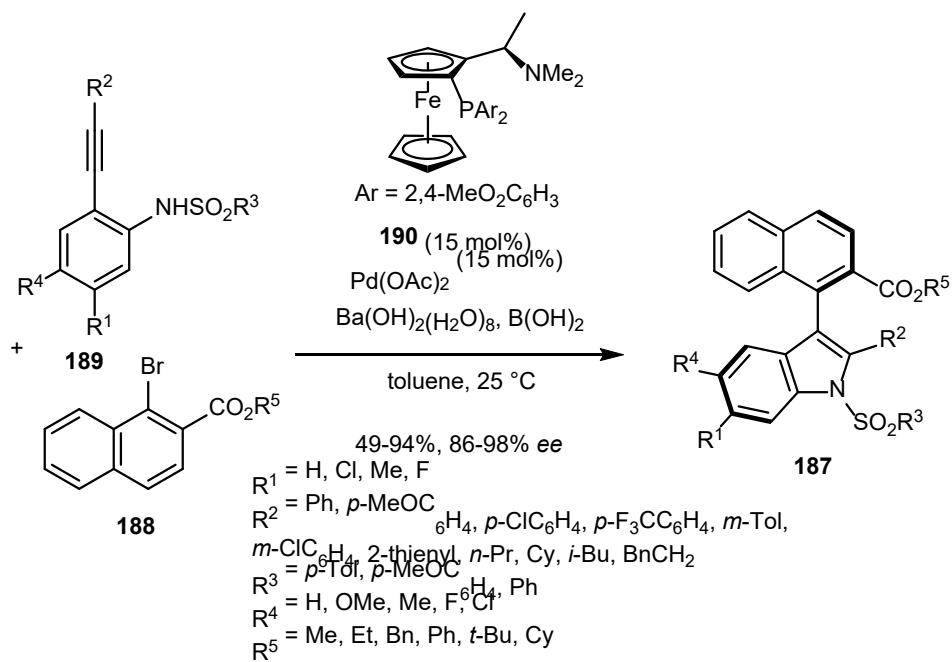


mechanism ( $n = 1$ ):

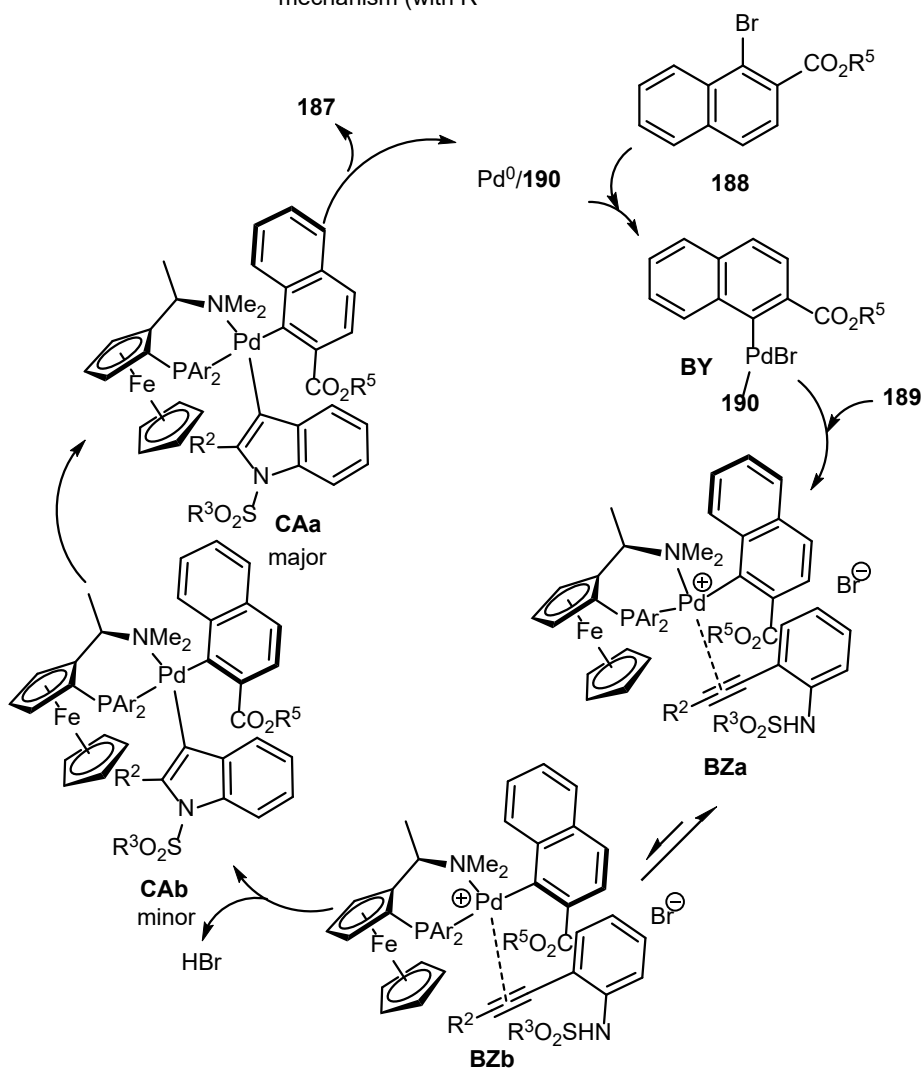


**Scheme 50.** Domino iodine transfer/cycloisomerization reaction of olefin-tethered aryl iodides.

In 2021, Qi and Li reported the synthesis of axially chiral 2,3-disubstituted indoles **187** on the basis of an enantioselective palladium-catalyzed Cacchi-type reaction between aryl bromides **188** and *o*-alkynylanilines **189** (Scheme 51).<sup>[60]</sup> It was promoted at 25 °C by 15 mol% of a chiral palladium catalyst *in situ* generated from Pd(OAc)<sub>2</sub> and ferrocene-based P,N-ligand **190** in toluene as solvent in the presence of a base such as Ba(OH)<sub>2</sub>·8H<sub>2</sub>O, and B(OH)<sub>3</sub> as an additive. A range of *o*-alkynylanilines bearing various substituents at C4 and C5 positions reacted smoothly, but also alkynes bearing a heteroaryl, primary alkyl, secondary alkyl, as well as cycloalkyl groups. Indeed, a variety of axially chiral 2,3-disubstituted indoles **187** were generated through this domino cyclization/cross-coupling reaction with moderate to excellent yields (49-94%) and uniformly high enantioselectivities (86-98% *ee*). A possible mechanism is depicted in Scheme 51, beginning with the *in situ* generation of a chiral Pd(0) active catalyst. Then, the oxidative addition of the arylbromide provided arylpalladium(II) species **BY**. The subsequent coordination of the latter to the triple bond of the alkyne substrate resulted in the formation of intermediates **BZa** and **BZb**. Due to less steric interactions, complex **BZa** was more stable than **BZb**. Then, the palladium-activated alkyne underwent nucleophilic attack of the nitrogen atom, leading to major intermediate **CAa** along with minor intermediate **CAb**. Final reductive elimination afforded product **187** along with regenerated catalyst.



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

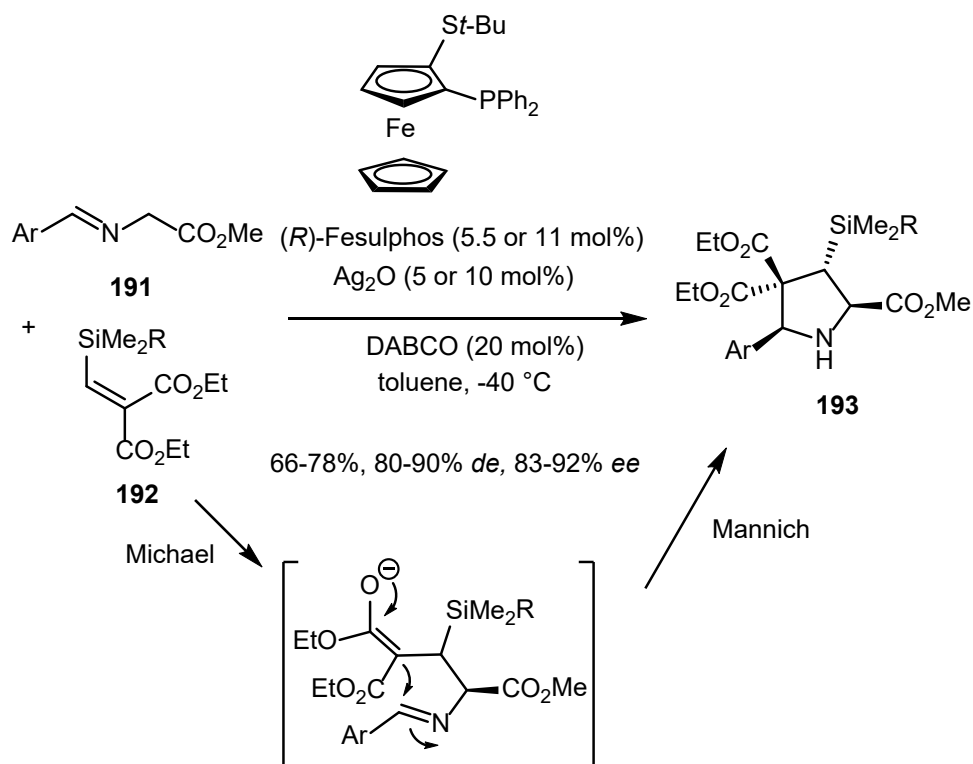


**Scheme 51.** Domino cyclization/cross-coupling reaction of *o*-alkynylanilines with aryl bromides.

### 3 Enantioselective Silver-Catalyzed Domino Reactions

#### 3.1 Michael-Initiated Domino Reactions

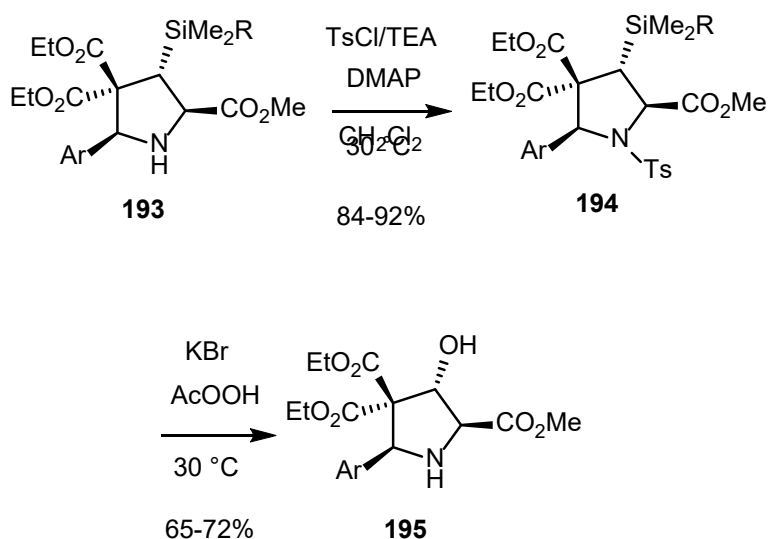
The first example of enantioselective silver-catalyzed domino reaction was reported in 1990 by Ito et al.,<sup>[61]</sup> dealing with an asymmetric domino aldol/cyclization reaction of aldehydes with tosylmethyl isocyanide promoted by a chiral ferrocenylphosphine-silver(I) complex which afforded oxazolines with a high level of enantioselectivity (86% *ee*). Ever since, a wide variety of enantioselective silver-catalyzed domino reactions have been developed including numerous Michael-initiated ones.<sup>[11,62]</sup> In an example reported in 2019, Chowdhury et al. disclosed the first use of  $\beta$ -silylmethylene malonates **192** in enantioselective formal [3+2] cycloadditions of glycine imino esters **191**, allowing the synthesis of chiral highly substituted 3-silylproline derivatives **193**.<sup>[63]</sup> The domino Michael/Mannich reaction was promoted at -40 °C by a chiral silver catalyst *in situ* generated from 5 mol% of Ag<sub>2</sub>O and 5.5 mol% of (*R*)-Fesulphos as ligand in toluene as solvent in the presence of DABCO (20 mol%) as base. It must be noted that in some cases of substrates, higher quantities of precatalyst (10 mol%) and ligand (11 mol%) were required. A range of chiral 3-silylated prolines **193** was formed with good yields (66-78%) and both high diastereo- (80-90% *de*) and enantioselectivities (83-92% *ee*), as illustrated in Scheme 52. The catalyst system tolerated various aromatic imino esters bearing either electron-withdrawing or electron-donating substituents in *para*, *meta* and *ortho* positions of the phenyl ring. Very good results (81% yield, 90% *de*, 87% *ee*) were also obtained in the reaction of an heteroaromatic imino ester (Ar = 2-thienyl). Moreover, an alkyl-substituted  $\beta$ -silylmethylene malonate (R = OTMS instead of Ph) was found compatible, reacting with *N*-(*p*-chlorobenzylidene)glycine methyl ester (Ar = *p*-ClC<sub>6</sub>H<sub>4</sub>) to give the corresponding cycloadduct in 72% yield, 88% *de* and 92% *ee*. The utility of this novel methodology was applied to the synthesis of chiral 3-hydroxypyrrolidines **195** which constitute substructures of many biologically important natural products. As shown in Scheme 52, some chiral 3-silylated prolines **193** were reacted with TsCl in the presence of TEA as base to give the corresponding tosylated prolines **194** which were subsequently converted into desired 3-hydroxypyrrolidines **195** with retention of configuration by oxidative treatment with KBr/AcOOH with good yields.



$\text{R} = \text{Ph, TMSO}$

$\text{Ar} = \text{Ph, } p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-EtC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, m\text{-FC}_6\text{H}_4, o\text{-ClC}_6\text{H}_4, o\text{-FC}_6\text{H}_4, 2\text{-thienyl}$

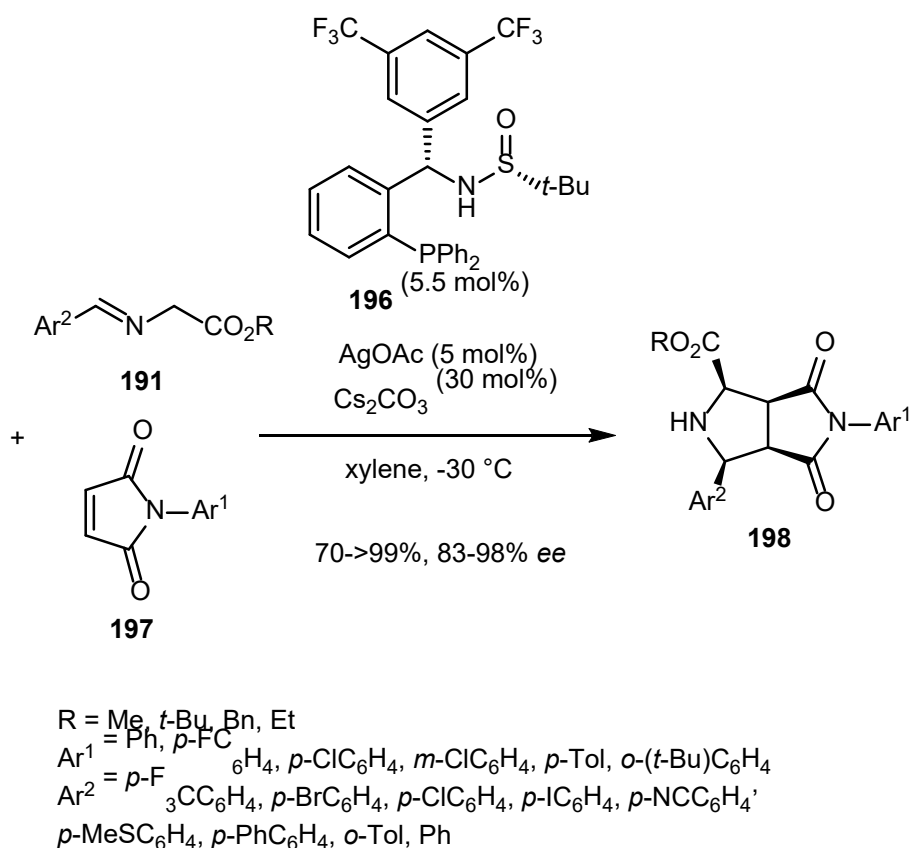
synthesis of 3-hydroxypyrrolidines:



$\text{Ar} = \text{Ph, } p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, m\text{-FC}_6\text{H}_4$

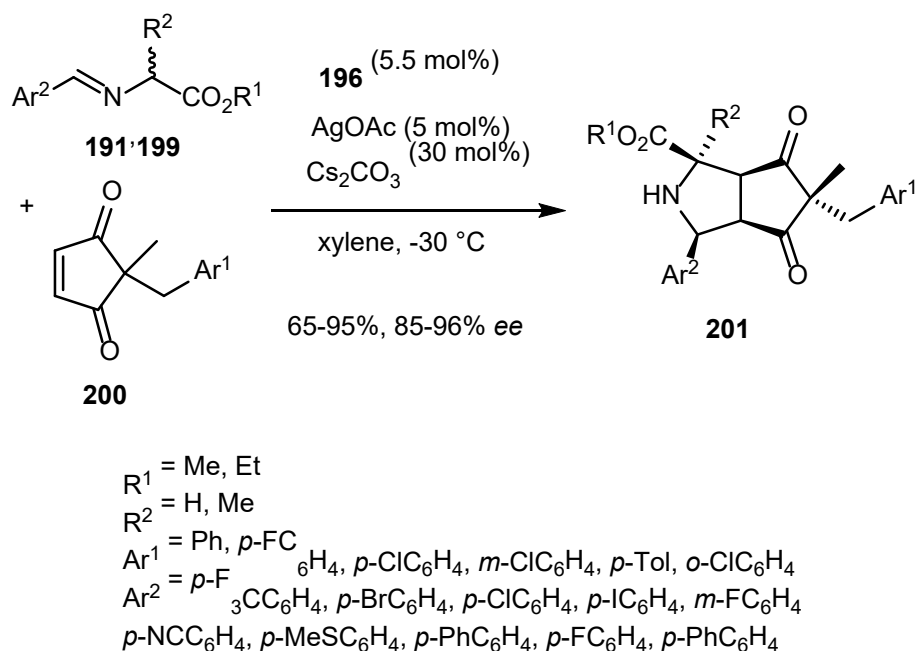
**Scheme 52.** Domino Michael/Mannich reaction of glycine imino esters with  $\beta$ -silylmethylene malonates and synthesis of 3-hydroxypyrrolidines.

In the same year, Liu and Zhang disclosed the synthesis of novel trifluoromethylated sulfonamide phosphine ligand **196** to be applied as promotor of enantioselective silver-catalyzed domino Michael/Mannich reaction between glycine imino esters **191** and aryl maleimides **197** (Scheme 53).<sup>[64]</sup> In the presence of 5.5 mol% of this ligand, 5 mol% of AgOAc as precatalyst and 30 mol% of Cs<sub>2</sub>CO<sub>3</sub> as base in xylene as solvent, a range of glycine imino esters **191** bearing various substituents on the phenyl ring (Ar<sup>2</sup>) reacted at -30 °C with phenyl (Ar<sup>1</sup> = Ph) and aryl maleimides **197** exhibiting fluoride, chloride and methyl groups in *para*- or *meta*-positions of the phenyl ring to afford the corresponding chiral bicyclic products **198** in good yields (70->99%) and enantioselectivities (83-98% *ee*). The catalyst system also tolerated sterically hindered *N*-(2-*t*-butylphenyl)maleimide (Ar<sup>1</sup> = *o*-(*t*-Bu)C<sub>6</sub>H<sub>4</sub>), which led to the desired chiral formal [3+2] cycloadducts with comparable yields (70-98%) and enantioselectivities (88-98% *ee*).



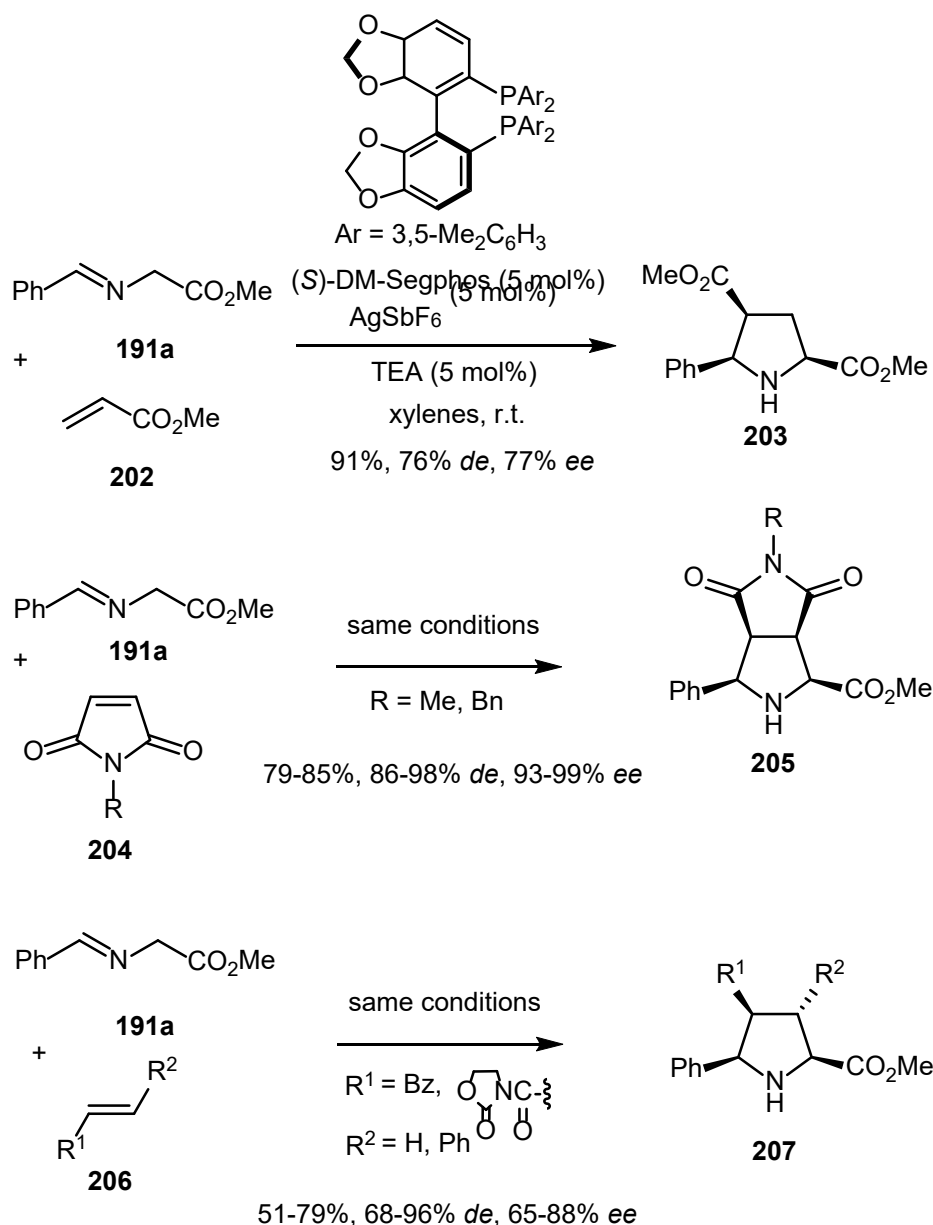
**Scheme 53.** Domino Michael/Mannich reaction of glycine imino esters with aryl maleimides.

The same reaction conditions were also applied to the domino Michael/Mannich reaction of glycine imino esters **191,199** with another type of dipolarophiles such as cyclopentene-1,3-diones **200** (Scheme 54).<sup>[64]</sup> It resulted in the formation of the corresponding chiral bicyclic and highly substituted pyrrolidines **201** exhibiting five stereogenic centers in good to high yields (65-95%) and uniformly high enantioselectivities (85-96% *ee*). Halogens and a methyl group were tolerated on the phenyl moiety of cyclopentene-1,3-diones while even more various groups, including trifluoromethyl, nitrile, methylthio and phenyl groups, could be present on the phenyl ring of the azomethine ylides.



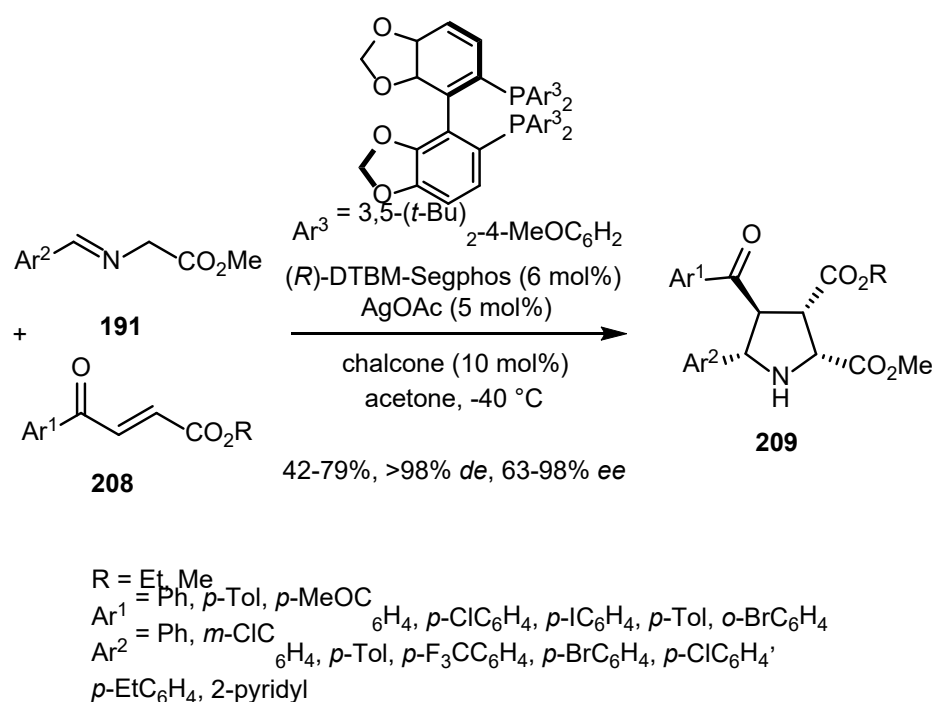
**Scheme 54.** Domino Michael/Mannich reaction of glycine imino esters with cyclopentene-1,3-diones.

In 2019, Najera, Cossio and Sansano reported the use of (*S*)-DM-Segphos as silver ligand in enantioselective domino Michael/Mannich reactions of glycine imino esters with different other types of dipolarophiles, such as methyl acrylate, alkyl maleimides, chalcone and *N*-acryloyloxazolidine-2-one.<sup>[65]</sup> In this case, the catalyst system was composed of only 5 mol% of ligand (*S*)-DM-Segphos and the same quantity of AgSbF<sub>6</sub>, which was found to promote at room temperature the reactions in xylenes as solvent in the presence of TEA as base. The formal [3+2] cycloaddition of phenyl glycine imino methyl ester **191a** with methyl acrylate **202** led to the corresponding chiral *endo*-cycloadduct **203** in 91% yield, 76% *de* and 77% *ee* (Scheme 55). Higher diastereo- (86-98% *de*) and enantioselectivities (93-99% *ee*) were obtained in the reaction of *N*-alkyl maleimides **204** with the same azomethine ylide **191a**, providing chiral bicyclic pyrrolidines **205** in high yields (79-85%). Other dipolarophiles **206**, such as chalcone (R<sup>1</sup> = Bz, R<sup>2</sup> = Ph) and *N*-acryloyloxazolidine-2-one, also reacted smoothly with phenyl glycine imino methyl ester **191a** to give the corresponding products **207** in good yields (51-79%) and both moderate to excellent diastereo- (68-96% *de*) and enantioselectivities (65-88% *ee*).



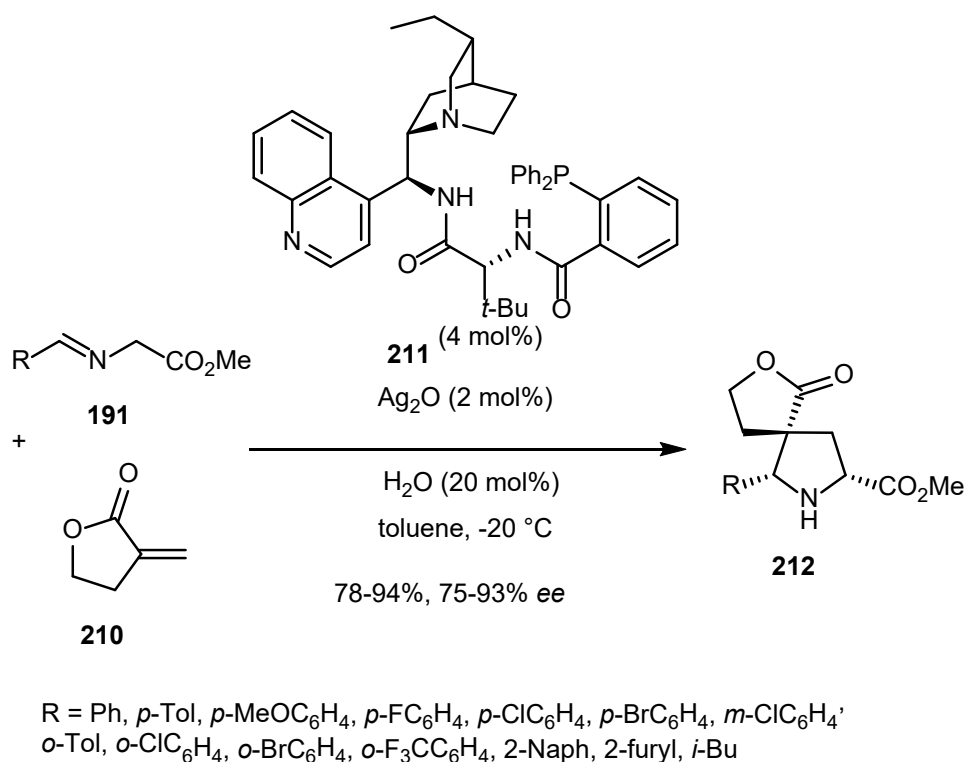
**Scheme 55.** Domino Michael/Mannich reactions of a glycine imino ester with methyl acrylate, alkyl maleimides, chalcone and *N*-acryloyloxazolidine-2-one.

In the same year, Xu and Li reported the first asymmetric formal [3+2] cycloaddition of alkyl 4-oxo-4-arylbut-2-enoates **208** bearing two different electron-withdrawing groups with glycine imino esters **191** based on the use of a chiral silver catalyst *in situ* generated from 5 mol% of AgOAc and 6 mol% of (*R*)-DTBM-Segphos ligand (Scheme 56).<sup>[66]</sup> The domino Michael/Mannich reaction was performed at -40 °C in acetone as solvent in the presence of chalcone as an additive. It resulted in the formation of a series of chiral tetrasubstituted pyrrolidines **209** bearing three different carbonyl substituents as single diastereomers (>98% *de*) in moderate to high yields (42-79%) and generally excellent enantioselectivities (95-98% *ee*). A lower *ee* value (63% *ee*) was obtained in the reaction of 2-pyridyl-substituted azomethine ylide (Ar<sup>2</sup> = 2-pyridyl). Indeed, uniformly excellent results were achieved for a wide range of aryl glycine imino esters bearing electron-donating, electron-deficient or electron neutral groups on the phenyl ring as well as differently substituted alkyl 4-oxo-4-arylbut-2-enoates.



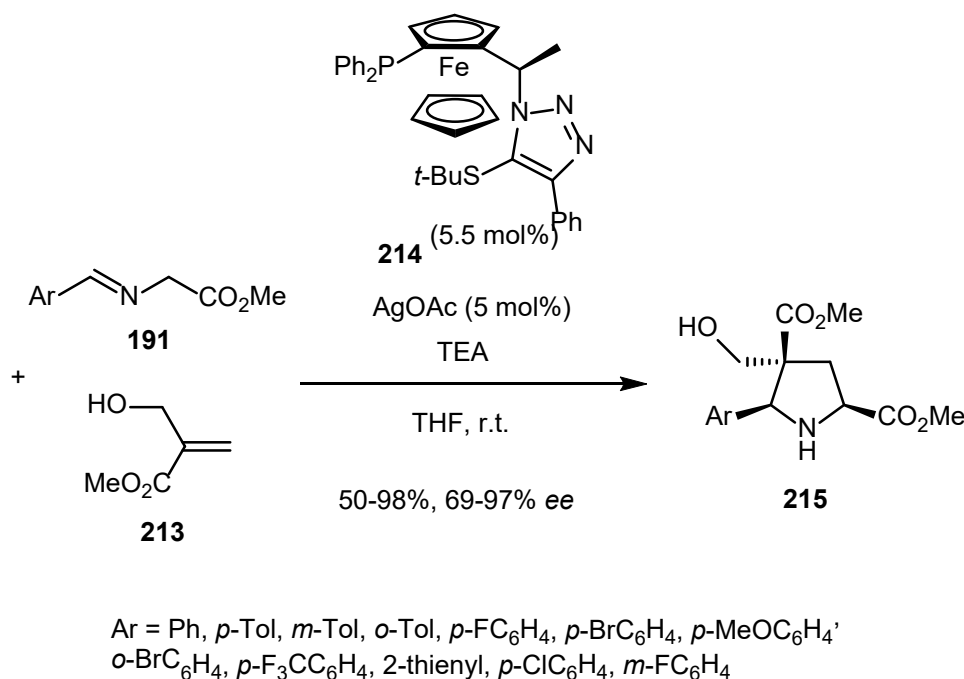
**Scheme 56.** Domino Michael/Mannich reaction of glycine imino esters with alkyl 4-oxo-4-arylbut-2-enoates.

Later in 2020, Wang et al. described the first use of  $\alpha$ -methylene- $\gamma$ -butyrolactone **210** as dipolarophile in enantioselective silver-catalyzed formal [3+2] cycloadditions with azomethine ylides (Scheme 57).<sup>[67]</sup> Using a chiral silver catalyst derived from 2 mol% of Ag<sub>2</sub>O and 4 mol% of chiral cinchona alkaloid-derived amidophosphane ligand **211**, glycine imino esters **191** underwent at  $-20^\circ\text{C}$  enantioselective silver-catalyzed domino Michael/Mannich reaction with  $\alpha$ -methylene- $\gamma$ -butyrolactone **210** in toluene as solvent in the presence of H<sub>2</sub>O as an additive. The process afforded the corresponding chiral spirocyclic pyrrolidines **212** exhibiting three stereocenters as single *endo*-diastereomers in both uniformly high yields (78-94%) and enantioselectivities (75-93% *ee*). Generally, (hetero)aryl glycine imino esters provided higher *ee* values (81-93% *ee*) and yields (85-94%) than alkyl ones (R = *i*-Bu: 78% yield, 75% *ee*).



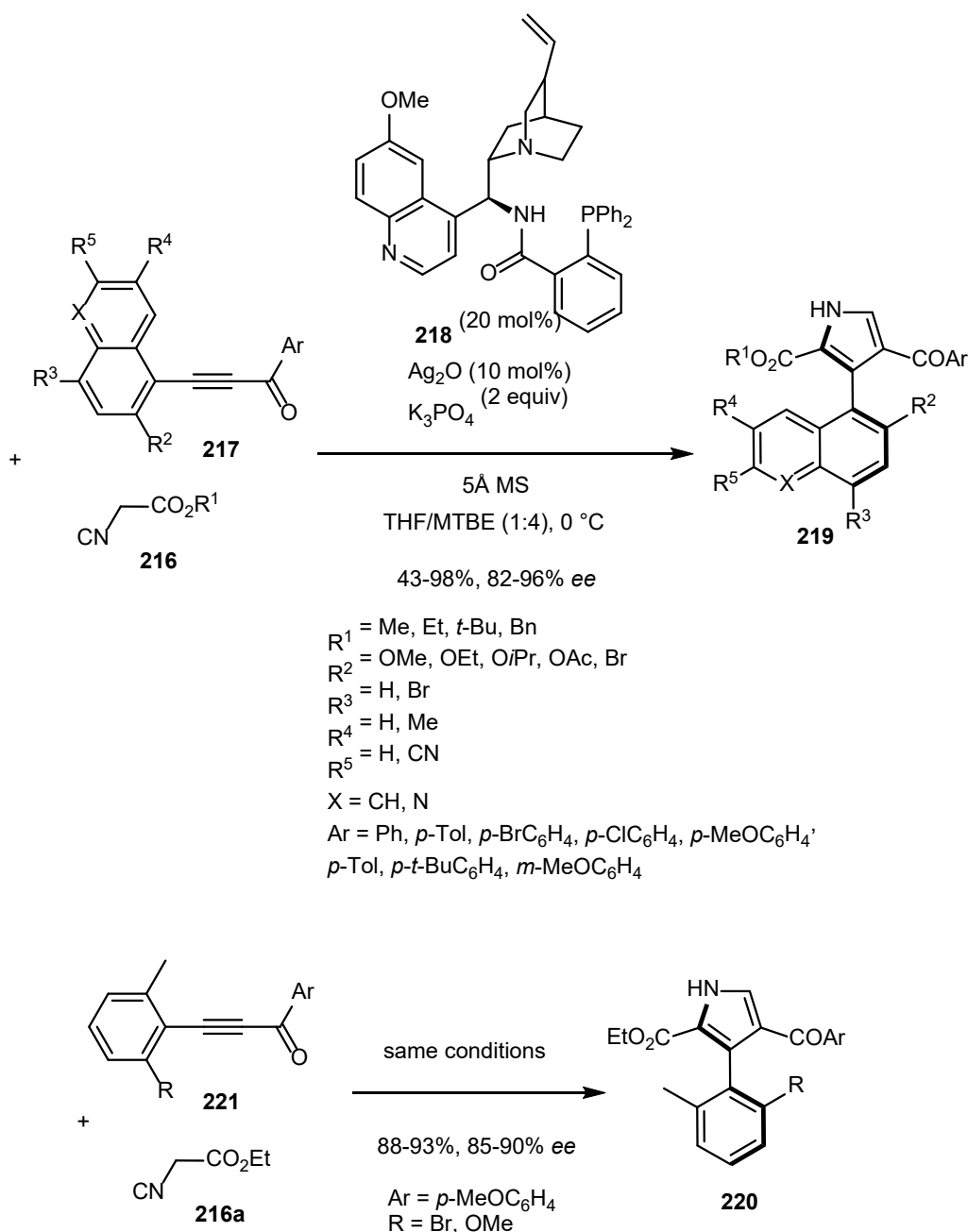
**Scheme 57.** Domino Michael/Mannich reaction of glycine imino esters with  $\alpha$ -methylene- $\gamma$ -butyrolactone.

In 2021, Kanemoto and Fukuzawa developed enantioselective domino Michael/Mannich reaction of glycine imino esters **191** with Morita–Baylis–Hillman adduct **213** promoted by 5 mol% of AgOAc combined with 5.5 mol% of chiral ferrocenyl-based P,S-ligand **214** (Scheme 58).<sup>[68]</sup> Carried out at room temperature in THF as solvent in the presence of TEA as base, the formal [3+2] cycloaddition afforded the corresponding chiral pyrrolidine derivatives **215** bearing a quaternary carbon stereocenter as single diastereomers with moderate to quantitative yields (50-98%) and good to excellent enantioselectivities (69-97% *ee*). A variety of glycine imino esters bearing methoxy, methyl, fluoro, bromo, and trifluoromethyl groups on the phenyl ring at either *ortho*-, *meta*-, or *para*-positions were compatible, leading to the corresponding products with high *ee* values ( $\geq 89\%$  *ee*) excepted that exhibiting a methyl group at *ortho*-position (Ar = *o*-Tol) which reacted with a lower enantioselectivity (69% *ee*).



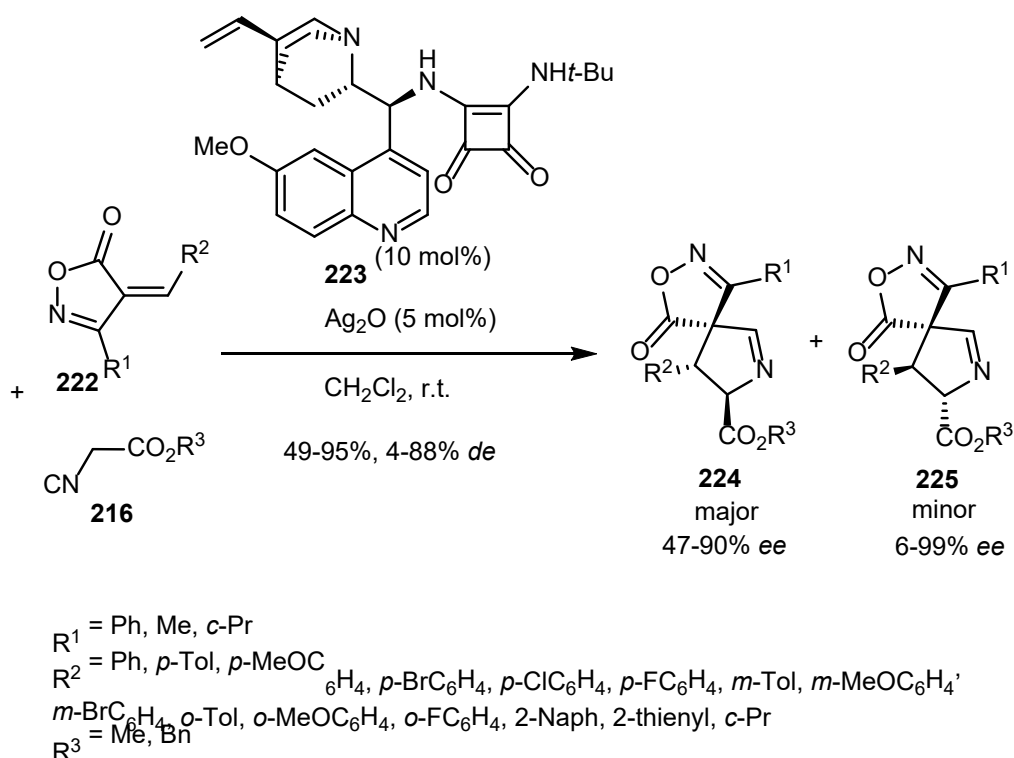
**Scheme 58.** Domino Michael/Mannich reaction of glycine imino esters with a Morita–Baylis–Hillman adduct.

Along with glycine imino esters, isocyanacetates have also been widely involved in enantioselective silver-catalyzed formal [3+2] cycloadditions. In an example reported in 2019, Zhu et al. described the first example of asymmetric synthesis of axially chiral 3-arylpyrroles **219** based on a domino Michael/Mannich reaction occurring between isocyanacetates **216** and  $\alpha$ -aryl- $\alpha,\beta$ -alkynyl ketones **217** catalyzed by a combination of 10 mol% of  $\text{Ag}_2\text{O}$  and 20 mol% of chiral cinchona alkaloid-derived phosphine ligand **218** (Scheme 59).<sup>[69]</sup> Performed at 0 °C in a 1:4 mixture of THF and MTBE as solvent, the reaction afforded the corresponding chiral 3-arylpyrroles **219** in moderate to quantitative yields (43-98%) with uniformly excellent enantiomeric excesses (82-96% *ee*). The catalyst system tolerated the presence of both electron-donating and electron-withdrawing groups on the phenyl ring of the alkynyl ketone (Ar), delivering the products in very high enantioselectivities. Moreover, an alkynyl ketone containing a quinoline moiety (X = N) also reacted smoothly with excellent *ee* value (91% *ee*) albeit combined with a lower yield (43%). Different alkyl isocyanacetates were successfully investigated with the best results obtained in the reaction of sterically hindered *tert*-butyl isocyanacetate ( $\text{R}^1 = t\text{-Bu}$ : 95% yield, 96% *ee*). Furthermore, chiral 3-phenylpyrroles **220** were similarly prepared in high yields (88-93%) and enantioselectivities (85-90% *ee*) from the reaction of the corresponding alkynyl ketones **221** with ethyl isocyanacetate **216a** ( $\text{R}^1 = \text{Et}$ ).



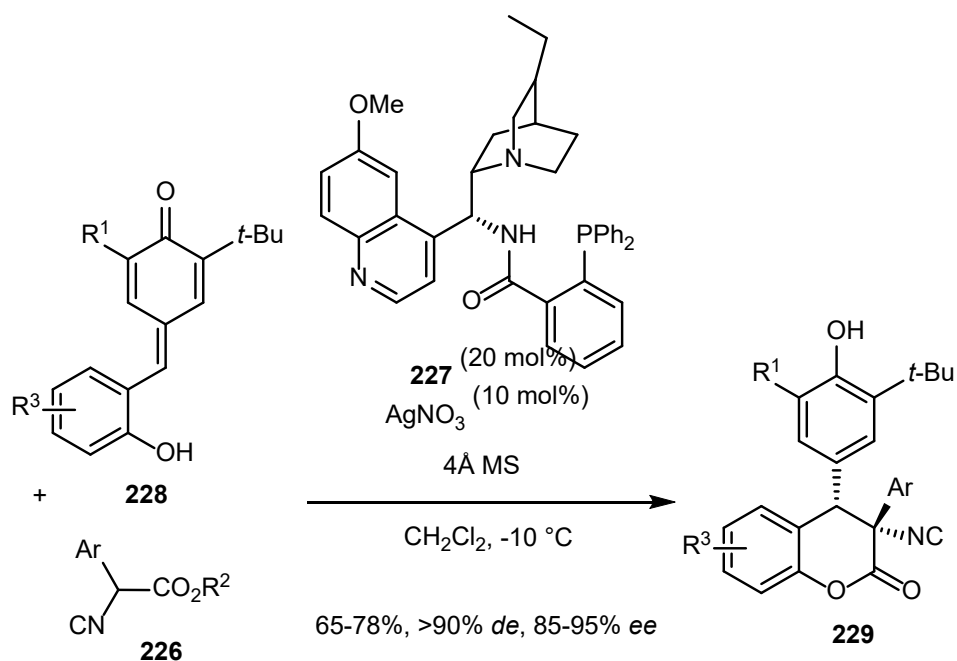
**Scheme 59.** Domino Michael/Mannich reactions of isocyanoacetates with alkynyl ketones.

In 2020, Blay and Pedro described enantioselective silver-catalyzed formal [3+2] cycloaddition of 4-arylideneisoxazol-5-ones **222** ( $\text{R}^2 = \text{aryl}$ ) with isocyanoacetates **216** (Scheme 60).<sup>[70]</sup> The domino Michael/Mannich reaction was promoted at room temperature by a chiral catalyst *in situ* generated from 5 mol% of  $\text{Ag}_2\text{O}$  and 10 mol% of cinchona alkaloid-derived squaramide ligand **223** in dichloromethane as solvent, resulting in the formation of the corresponding chiral diazaspirocyclic products exhibiting a pyrroline and an isoxazole-5-one rings along with three contiguous stereocenters. These functionalized products were obtained as mixtures of two diastereomers **224** and **225** in moderate to excellent yields (49-95%) with low to high diastereoselectivities (4-88% *de*). The major diastereomers **224** were obtained with moderate to high enantioselectivities (47-90% *ee*) while the *ee* values of the minor diastereomers **225** were low to excellent (6-99% *ee*). The substituent at the 3-position ( $\text{R}^1$ ) of 4-arylideneisoxazol-5-ones **222** could be a phenyl group as well as an alkyl group, such as a methyl or a cyclopropyl group, all providing comparable results.



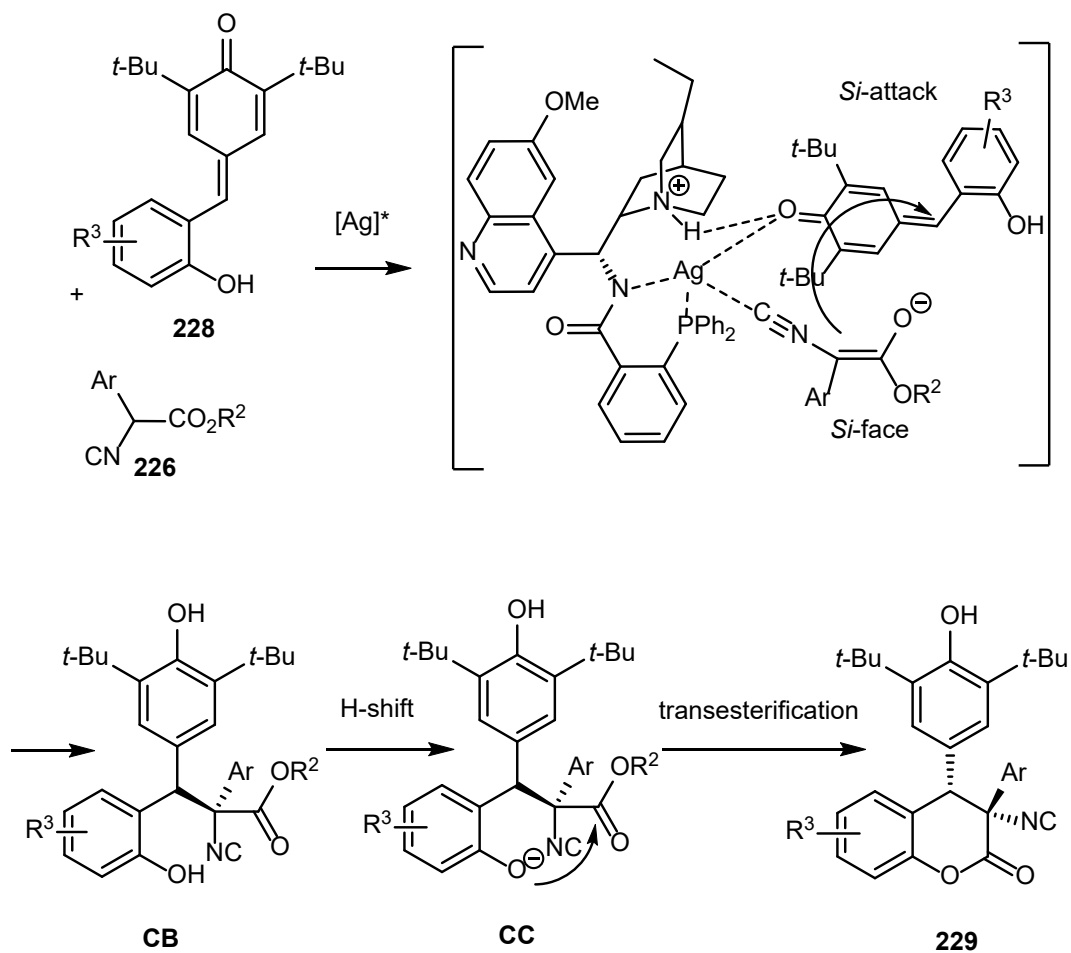
**Scheme 60.** Domino Michael/Mannich reaction of isocyanoacetates with 4-arylideneisoxazol-5-ones.

In the same year, the first example of catalytic asymmetric domino 1,6-addition/transesterification reaction of isocyanoacetates with *ortho*-hydroxyphenyl-substituted *para*-quinone methides performed in the presence of a chiral silver complex was described by Zhao et al. (Scheme 61).<sup>[71]</sup> The active catalyst was *in situ* generated from 10 mol% of  $\text{AgNO}_3$  and 20 mol% of chiral dihydroquinidine-derived aminophosphine ligand **227** in dichloromethane as solvent. The enantioselective domino Michael/transesterification reaction of isocyanoacetates **226** with *para*-quinone methides **228** led at  $-10^\circ\text{C}$  to the corresponding chiral 3,4-dihydrocoumarins **229** bearing two contiguous stereocenters as almost single diastereomers ( $>90\%$  *de*) in good yields (65-78%) and uniformly high enantioselectivities (85-95% *ee*). The catalyst system tolerated a wide range of aryl isocyanoacetates exhibiting either electron-withdrawing or electron-donating substituents on the phenyl ring while less reactive alkyl isocyanoacetates were unreactive. Moreover, comparable good results were obtained in the reaction of variously substituted *para*-quinone methides. The authors proposed the mechanism depicted in Scheme 61. Chelated to silver atom, the isocyano group was deprotonated by bridgehead nitrogen to form a (*Z*)-enolate. The coordination of amide nitrogen, phosphorus, carbonyl oxygen and divalent isocyanide carbon atoms to silver fixed the position of the two substrates. Moreover, hydrogen bonding of the protonated quinuclidine with the coordinated ketone oxygen atom provided additional transition-state stabilization, which forced the *in situ* generated enolate through its *Si*-face to approach the *Si*-face of the *para*-quinone methide in the 1,6-conjugate addition to afford intermediate **CB**. The latter was submitted to proton-shift to provide intermediate **CC** which further underwent transesterification to give final 3,4-dihydrocoumarin **229**.



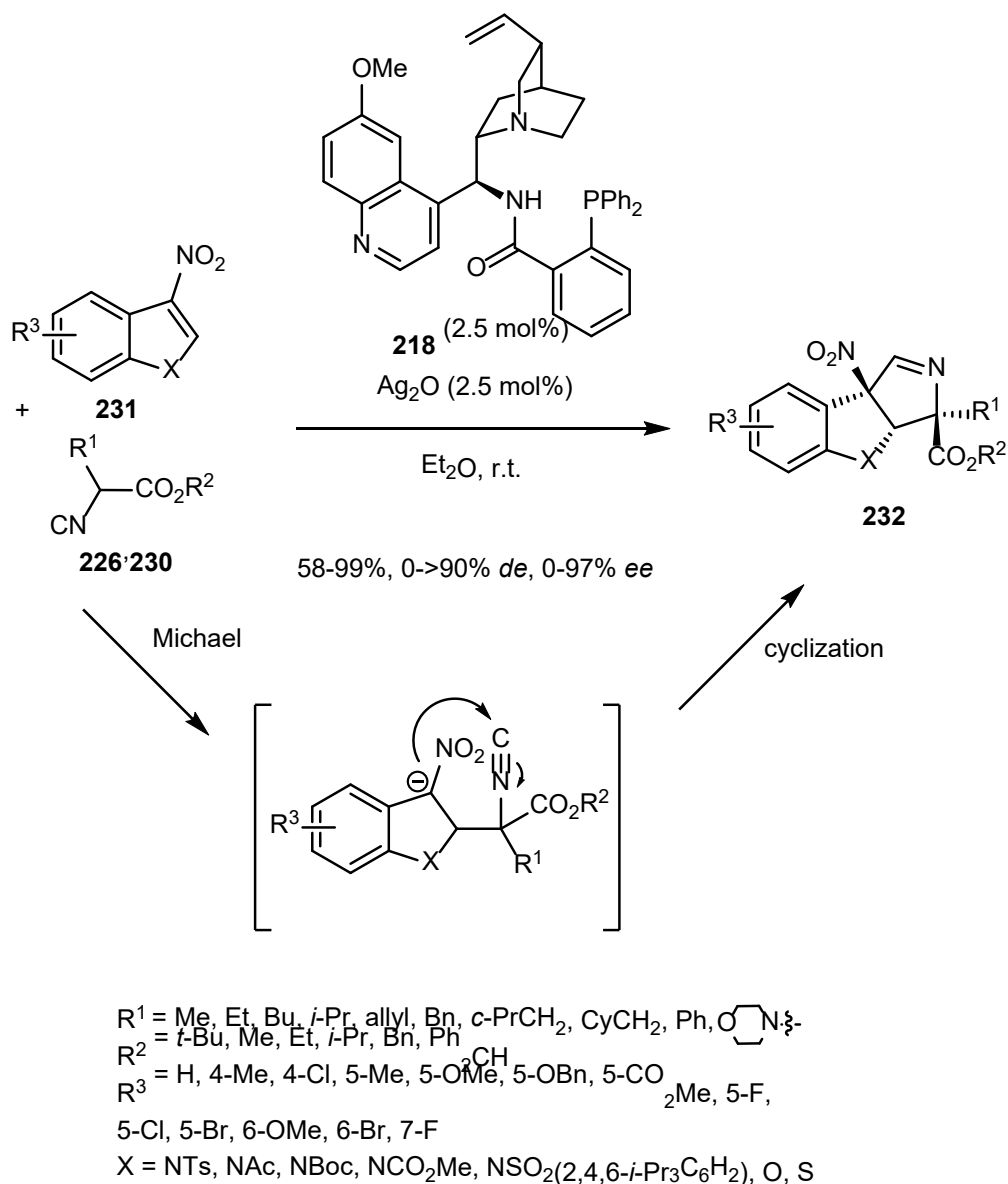
Ar = Ph, *p*-Tol, *p*-BrC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>,  
*p*-MeOC<sub>6</sub>H<sub>4</sub>, *m*-FC<sub>6</sub>H<sub>4</sub>, *m*-Tol, *o*-FC<sub>6</sub>H<sub>4</sub>  
R<sup>1</sup> = Me, *t*-Bu  
R<sup>2</sup> = Me, Bn, *t*-Bu  
R<sup>3</sup> = 6-Cl, 5-F, 5-Cl, 5-Br, 5-Me, 5-OMe, 4-OMe, 4-Br, 3-F, H

proposed mechanism (with R<sup>1</sup> = *t*-Bu):



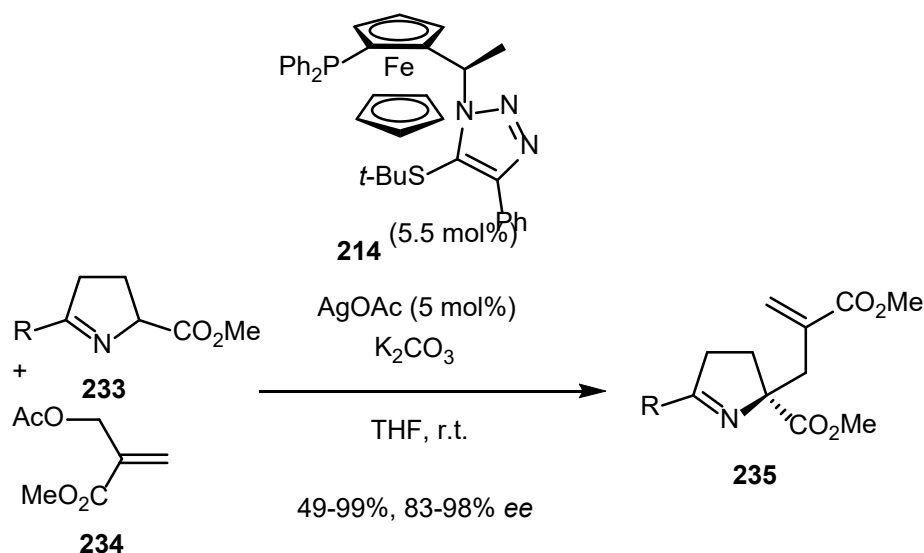
**Scheme 61.** Domino Michael/transesterification reaction of isocyanoacetates with *para*-quinone methides.

With the aim of opening a novel route to biologically important chiral pyrrolo[3,4-*b*]indole derivatives, You and Yuan developed in 2021 enantioselective silver-catalyzed domino Michael/cyclization reactions between  $\alpha$ -substituted isocyanoacetates **226,230** and different types of electron-deficient heteroarenes **231**.<sup>[72]</sup> The process involved the use of 2.5 mol% of Ag<sub>2</sub>O as precatalyst and the same quantity of cinchona-based amino-phosphine ligand **218** in diethyl ether as solvent (Scheme 62). A wide range of chiral pyrrolo[3,4-*b*]indole derivatives **232** were synthesized in good to quantitative yields (58-99%) along with both variable diastereo- (0->90% *de*) and enantioselectivities (0-97% *ee*). Among electron-deficient heteroarenes **231**, variously substituted 3-nitroindoles (X = N) reacted smoothly with  $\alpha$ -substituted isocyanoacetates **226,230** but other heteroarenes, such as 3-nitro-benzothiophene (X = S) and 2-nitrobenzofuran (X = O), were also compatible, leading to the desired products with 71-72% yields, 50-60% *de* and 89-95% *ee*. Concerning the 3-nitroindole partner, it could bear substituents with varied electronic properties at different positions of the indole ring. Moreover, various electron-withdrawing groups on the N atom were compatible. It was found that the nature of the  $\alpha$ -substituent (R<sup>1</sup>) of the isocyanoacetate dramatically influenced the stereoselectivity of the reaction. While substrates exhibiting different alkyl substituents (R<sup>1</sup> = Et, *n*-Bu, *i*-Pr, allyl, Bn, *c*-PrCH<sub>2</sub>, CyCH<sub>2</sub>) afforded the corresponding products with good diastereoselectivities (60-78% *de*) and enantioselectivities (88-93% *ee*),  $\alpha$ -phenyl isocyanoacetate (R<sup>1</sup> = Ph) reacted with poor stereoselectivities (0% *de*, 29-31% *ee*). Lower stereoselectivities (34% *de*, 61-71% *ee*) were also observed in the reaction of  $\alpha$ -methyl isocyanoacetamide (R<sup>1</sup> = Me). Later in 2022, Yuan and Zhao investigated a related reaction between 3-nitroindoles and  $\alpha$ -substituted isocyanoesters.<sup>[73]</sup> In this case, good results (92-99% yields, 32-82% *de*, 81-91% *ee*) were achieved by using another catalyst system composed of 10 mol% of AgOAc and 12 mol% of (*R*)-Tol-BINAP in THF at -20 °C.



**Scheme 62.** Domino Michael/cyclization of  $\alpha$ -substituted isocyanoacetates with electron-deficient heteroarenes.

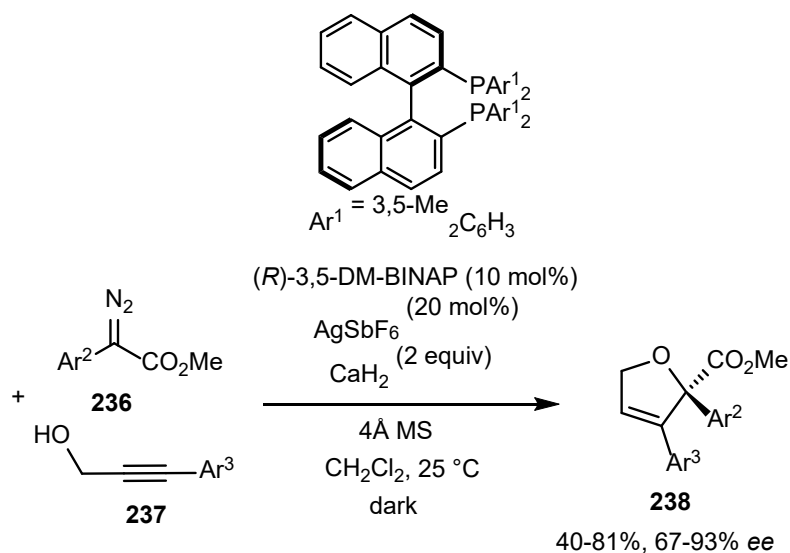
In the same year, Kanemoto and Fukuzawa demonstrated that pyrroline esters **233** reacted with Morita–Baylis–Hillman adduct **234** through an enantioselective domino Michael/elimination reaction in the presence of a chiral silver catalyst *in situ* generated from 5 mol% of AgOAc and 5.5 mol% of chiral ferrocenyl-based P,S-ligand **214**.<sup>[68]</sup> As shown in Scheme 63, the one-pot process performed in the presence of  $\text{K}_2\text{CO}_3$  as base resulted in the formation of the corresponding chiral *exo*-olefins **235** exhibiting a quaternary stereogenic center in moderate to quantitative yields (49–99%) and uniformly high enantioselectivities (83–98% *ee*).



**Scheme 63.** Domino Michael/elimination reaction of pyrroline esters with a Morita–Baylis–Hillman adduct.

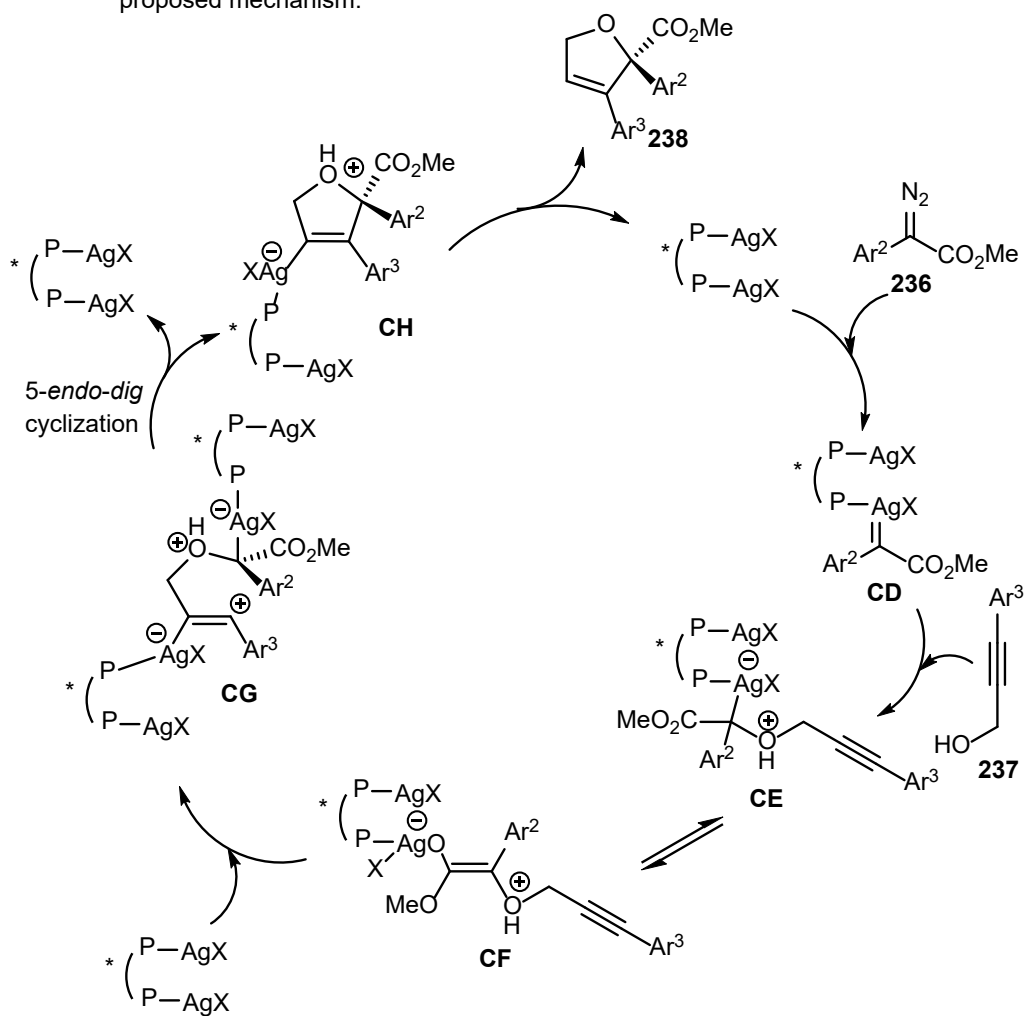
### 3.2 Other Domino Reactions

In 2019, Hu and Chapman disclosed a synthesis of chiral 2,5-dihydrofurans on the basis of an asymmetric domino oxonium ylide formation/formal [4+1] cycloaddition reaction of aryl diazoacetates **236** with propargyl alcohols **237**.<sup>[74]</sup> The reaction employed a combination of 20 mol% of  $\text{AgSbF}_6$  and 10 mol% of (*R*)-3,5-DM-BINAP as catalyst system in dichloromethane as solvent. It occurred in dark at 25 °C in the presence of  $\text{CaH}_2$  as superstoichiometric additive, allowing better chemo- and enantioselectivities to be achieved. The authors demonstrated that the active catalyst was binuclear [*(R)*-3,5-DM-BINAP] $(\text{AgSbF}_6)_2$ , allowing the intramolecular capture of oxonium ylides *in situ* generated from aryl diazoacetates with alkynes. As illustrated in Scheme 64, a range of chiral 2,5-dihydrofurans **238** were prepared with moderate to good yields (40–81%) and moderate to excellent enantioselectivities (67–93% *ee*). To explain this domino oxonium ylide formation/formal [4+1] cycloaddition, the authors proposed the mechanism depicted in Scheme 64 in which diazoacetate **236** was decomposed by the chiral binuclear silver complex, forming intermediate **CD**. Then, the latter reacted with propargyl alcohol **237** to give silver enolate **CE**, which was in equilibrium with silver-associated oxonium ylide **CF**. Intermediates **CE** or **CF** employed another molecule of binuclear catalyst in the alkyne coordinating site, thus generating a synergistic bi-catalyst species **CG**, which underwent a 5-*endo-dig* cyclization to form final domino product **238** through intermediate **CH**.



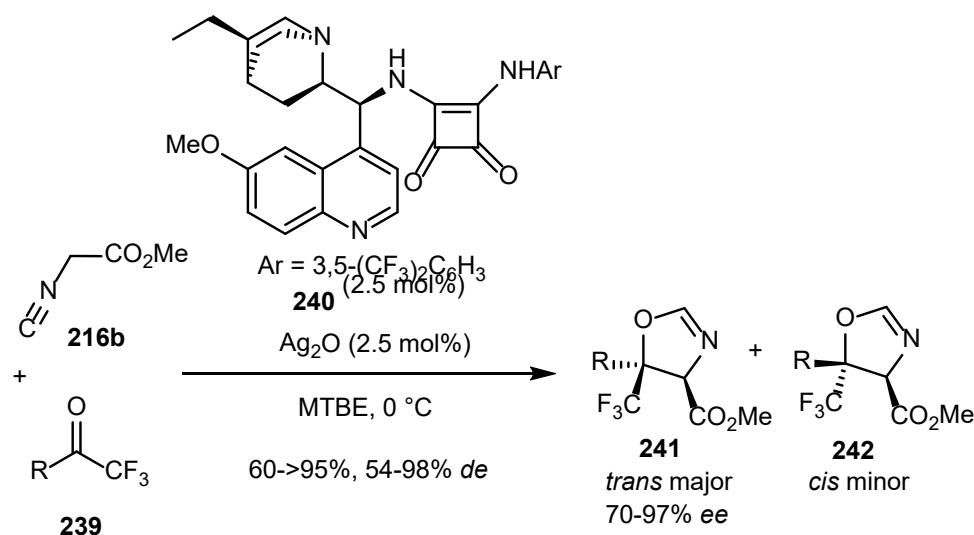
$\text{Ar}^2 = \text{Ph}, p\text{-ClC}_6\text{H}_4, m\text{-ClC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4,$   
 $p\text{-ClC}_6\text{H}_4, m\text{-FC}_6\text{H}_4, 3,4\text{-Cl}_2\text{C}_6\text{H}_3, p\text{-F}_3\text{CC}_6\text{H}_4$   
 $\text{Ar}^3 = \text{Ph}, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-IC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4,$   
 $p\text{-MeO}_2\text{CC}_6\text{H}_4, p\text{-Tol}, p\text{-EtC}_6\text{H}_4, p\text{-}t\text{-BuC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4,$   
 $3,4\text{-(MeO)}_2\text{C}_6\text{H}_3, p\text{-PhC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, m\text{-Tol}, 2\text{-thienyl}$

proposed mechanism:

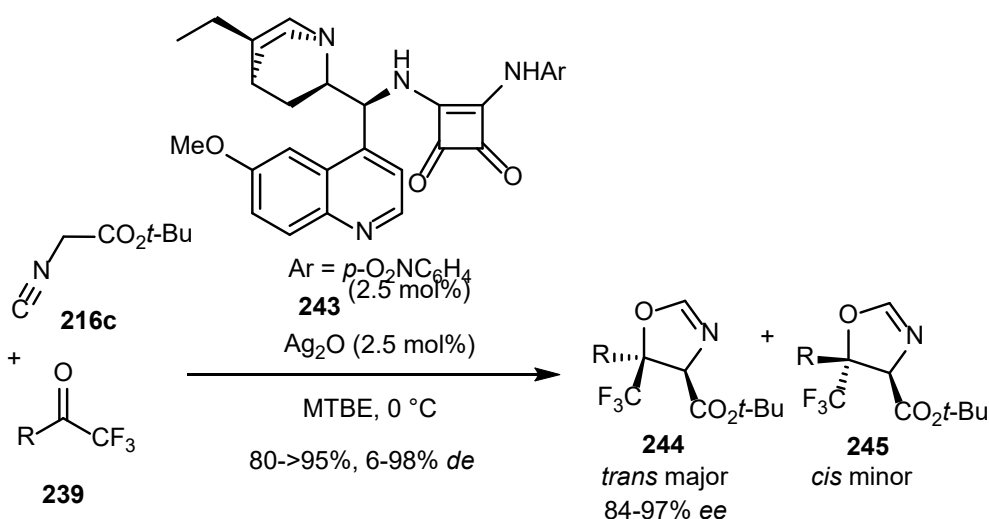


**Scheme 64.** Domino oxonium ylide formation/formal [4+1] cycloaddition reaction of aryl diazoacetates with propargyl alcohols.

In the same year, Blay and Pedro developed the first catalytic enantioselective formal [3+2] cycloaddition of trifluoromethylketones **239** with isocyanoacetates **216b-c** (Scheme 65).<sup>[75]</sup> In the presence of 2.5 mol% of a chiral silver catalyst *in situ* generated from Ag<sub>2</sub>O and chiral cinchona alkaloid-derived squaramide ligand **240**, isocyanate **216b** underwent at 0 °C in MTBE as solvent asymmetric domino aldol/cyclization reaction with a range of trifluoroacetophenones **239** to give the corresponding chiral 5-trifluoromethyl-2-oxazolines **241** and **242**. These products were synthesized as diastereomeric mixtures of *trans*- and *cis*-products **241** and **242** with good to high yields (60->95%) with the major *trans*-diastereomers obtained with moderate to excellent *de* values (54-98% *de*) and good to very high enantioselectivities (70-97% *ee* for **241**). Generally, the reaction of *meta*-substituted trifluoroacetophenones provided higher *ee* values than substrates bearing substituents at the *ortho*- or *para*-positions of the phenyl ring of the trifluoroacetophenones. Alkyl-substituted trifluoromethylketones were also compatible, resulting in the formation of the corresponding chiral oxazolines with moderate diastereo- (72-84% *de*) and enantioselectivities (81-82% *ee*). By employing closely related squaramide **243** under similar conditions, *tert*-butyl isocyanoacetate **216c** also underwent [3+2] cycloaddition with the same range of trifluoromethylketones **239** to afford chiral 5-trifluoromethyl-2-oxazolines **244** and **245** with high yields (80->95%), low to excellent diastereoselectivities (6-98% *de*) and uniformly high enantioselectivities (84-97% *ee*) for the major *trans*-diastereomers **244**.



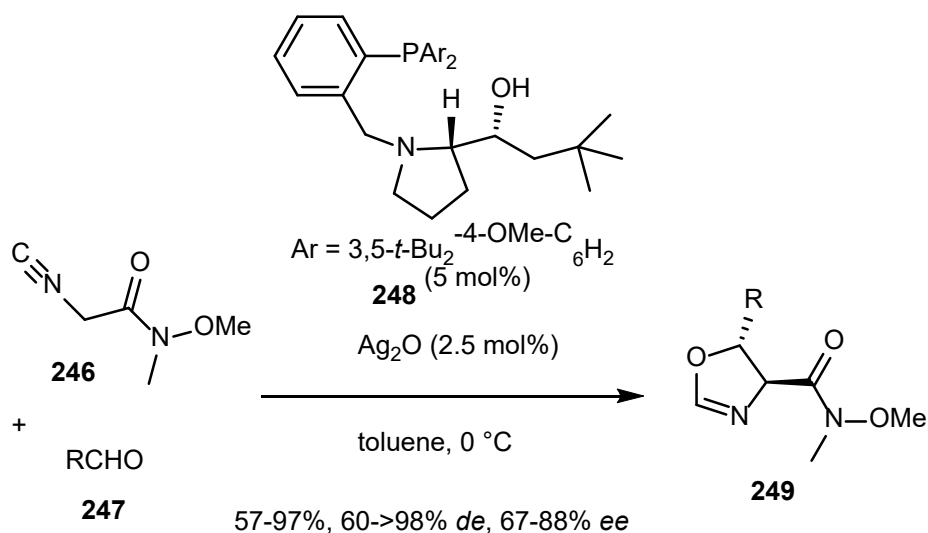
R = Ph, *p*-Tol, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *m*-Tol, *m*-BrC<sub>6</sub>H<sub>4</sub>, *o*-Tol, *o*-MeOC<sub>6</sub>H<sub>4</sub>, *o*-BrC<sub>6</sub>H<sub>4</sub>, 2-thienyl, BnCH<sub>2</sub>, Me, 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>



R = Ph, *p*-Tol, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *m*-Tol, *m*-BrC<sub>6</sub>H<sub>4</sub>, *o*-Tol, *o*-MeOC<sub>6</sub>H<sub>4</sub>, *o*-BrC<sub>6</sub>H<sub>4</sub>, 2-thienyl, BnCH<sub>2</sub>, Me, 3,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>

**Scheme 65.** Domino aldol/cyclization reactions of methyl and *tert*-butyl isocyanoacetates with trifluoromethylketones.

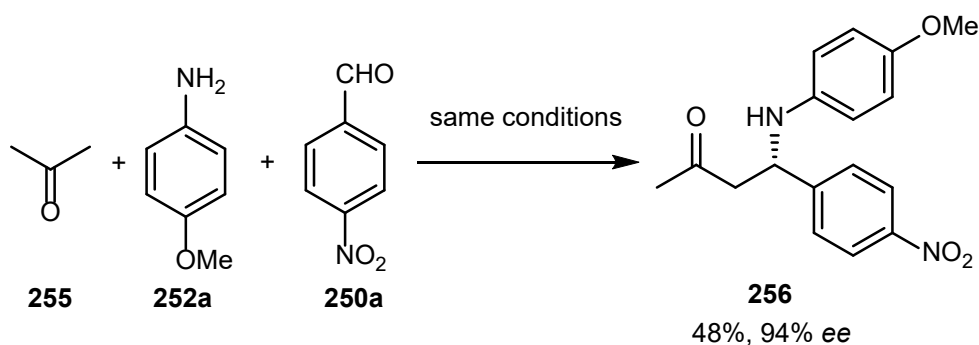
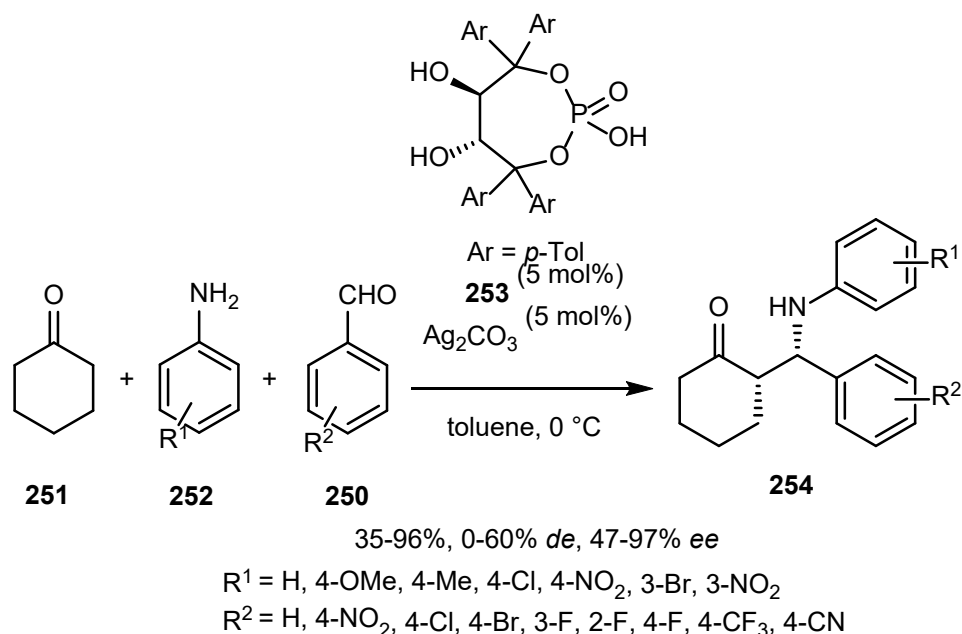
In the same area, Sawamura and Higashida developed in 2022 an enantioselective domino aldol/cyclization reaction between isocyanoacetic acid derivatives **246** and aldehydes **247** catalyzed by 2.5 mol% of  $\text{Ag}_2\text{O}$  combined with 5 mol% of chiral proline-derived P,N,O-ligand **248**.<sup>[76]</sup> Performed in toluene at 0 °C, the process afforded the corresponding chiral *trans*-oxazolines **249** with moderate to high yields (57-97%), diastereo- (60->98% *de*) and enantioselectivities (67-88% *ee*), as shown in Scheme 66. It was found that aliphatic aldehydes generally afforded products with lower *ee* values than (hetero)aromatic ones (67-76% *ee* vs 76-88% *ee*).



R = *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, 3,5-Me<sub>2</sub>-4-MeOC<sub>6</sub>H<sub>2</sub>, 2-Naph,  
1-Naph, 2-thienyl, Cy, *t*-Bu, (*E*)-PhCH=CH

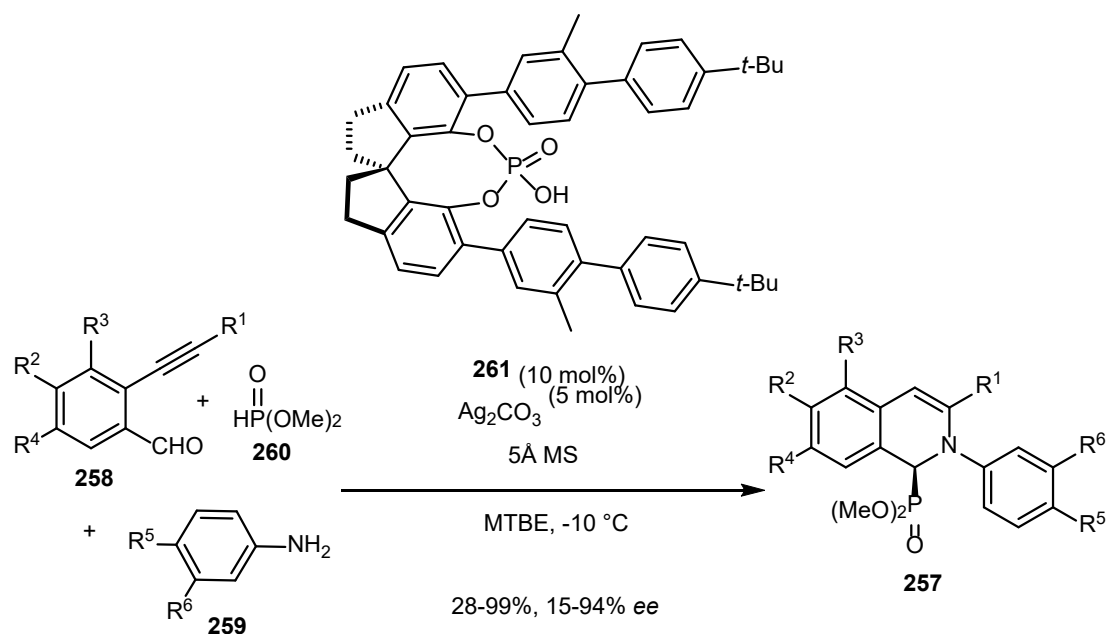
**Scheme 66.** Domino aldol/cyclization reaction of isocyanoacetic acid derivatives with aldehydes.

Earlier in 2020, Hu and Borovkov described enantioselective three-component Mannich reactions catalyzed by a novel silver tartaric acid-derived phosphate system.<sup>[77]</sup> As illustrated in Scheme 67, the reaction of cyclohexanone **251** with anilines **252** and benzaldehydes **250** was performed at 0 °C in the presence of 5 mol% of chiral phosphoric acid **253** as ligand and the same quantity of Ag<sub>2</sub>CO<sub>3</sub> as precatalyst to afford the corresponding chiral *anti*-β-amino-ketone derivatives **254** in moderate to high yields (35-96%), variable diastereoselectivities (0-60% *de*) and moderate to excellent enantioselectivities (47-97% *ee*). Along with cyclohexanone, acyclic ketones, such as acetone **255**, also underwent the reaction. Indeed, the Mannich reaction of acetone **255** with *p*-methoxyaniline **252a** and *p*-nitrobenzaldehyde **250a** yielded the corresponding product **256** in 94% *ee* and 48% yield. This study represented the first catalytic direct asymmetric three-component Mannich reaction of simple ketones based on the asymmetric counteranion-directed catalysis strategy.

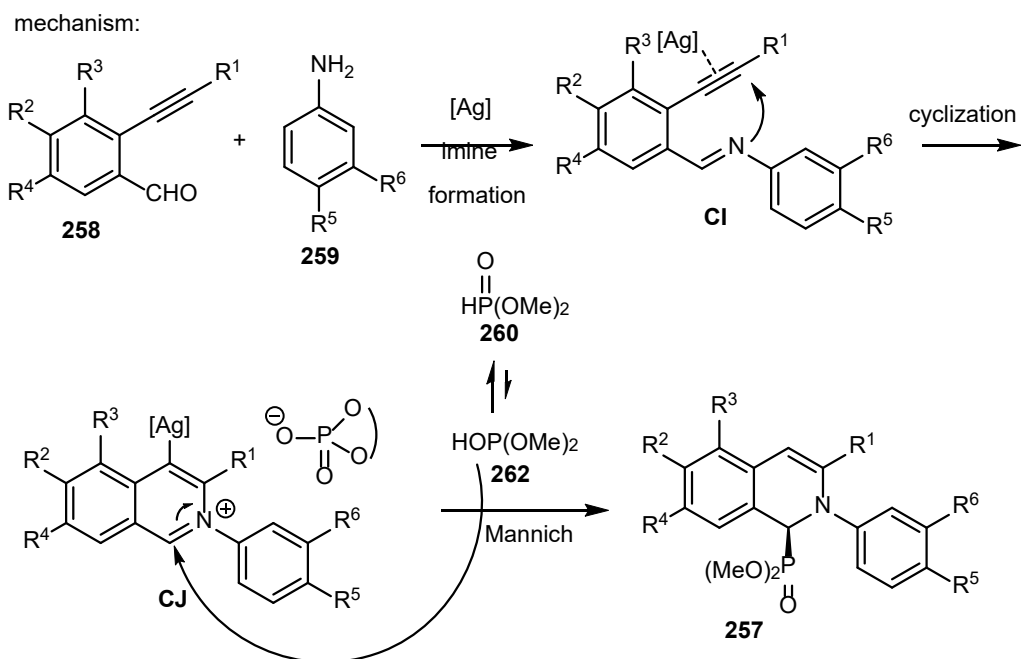


**Scheme 67.** Three-component Mannich reactions of cyclohexanone/acetone, anilines and benzaldehydes.

In the same year, Peng and Guo disclosed an efficient synthesis of chiral cyclic  $\alpha$ -aminophosphonates **257**, evolving through enantioselective silver-catalyzed three-component reaction of 2-alkynylbenzaldehydes **258**, anilines **259** and dimethylphosphonate **260**.<sup>[78]</sup> The phosphate catalyst was *in situ* generated from 5 mol% of  $\text{Ag}_2\text{CO}_3$  and 10 mol% of chiral phosphoric acid **261** in MTBE as solvent (Scheme 68). A wide range of chiral C1-phosphonylated 1,2-dihydroisoquinolines **257** were produced with both low to excellent yields (28-99%) and enantioselectivities (15-94% *ee*). The three-component reaction evolved through a domino imine formation/cyclization/Mannich-type reaction. In a first time, 2-alkynylbenzaldehyde **258** reacted with aniline **259** to form the corresponding imine **CI** which further underwent an intramolecular cyclization with the alkyne to give isoquinolinium intermediate **CJ**. Then, dimethyl phosphite **262**, as a tautomer of dimethyl phosphonate **260**, underwent asymmetric nucleophilic addition to the iminium group in **CJ** to give final product **257**.

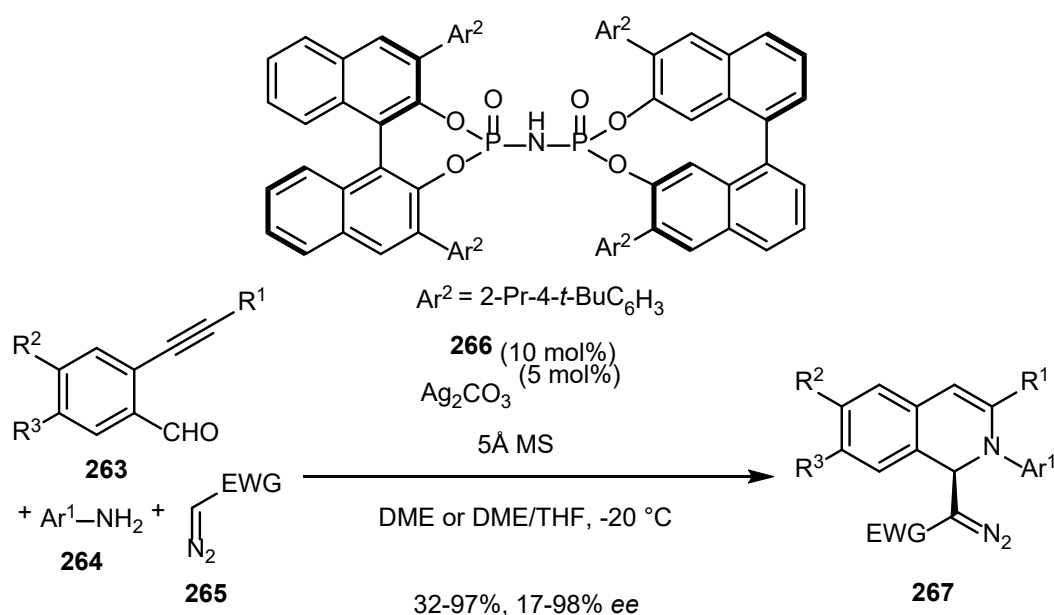


$\text{R}^1 = \text{Ph}, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-Tol}, p\text{-EtC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4,$   
 $p\text{-NCC}_6\text{H}_4, m\text{-FC}_6\text{H}_4, m\text{-BrC}_6\text{H}_4, m\text{-Tol}, m\text{-MeOC}_6\text{H}_4, 3,5\text{-Me}_2\text{C}_6\text{H}_3, o\text{-ClC}_6\text{H}_4,$   
 $o\text{-Tol}, 2\text{-thienyl}, 2\text{-furyl}, 2\text{-Naph}, (E)\text{-PhCH=CH}, \text{Me}, n\text{-Hex}, c\text{-Pr}$   
 $\text{R}^2 = \text{H}, \text{Me}, \text{F}, \text{OMe}$   
 $\text{R}^3 = \text{H}, \text{F}$   
 $\text{R}^4 = \text{H}, \text{Me}, \text{F}, \text{OMe}$   
 $\text{R}^5 = \text{H}, \text{O}i\text{-Pr}, \text{OMe}, \text{OBn}, \text{F}$   
 $\text{R}^6 = \text{H}, \text{Me}$



**Scheme 68.** Three-component domino imine formation/cyclization/Mannich-type reaction of 2-alkynylbenzaldehydes, anilines and dimethylphosphonate.

In 2021, Peng et al. also reported the first enantioselective three-component related domino reaction between *o*-alkynylbenzaldehydes **263**, anilines **264** and diazo compounds such as (diazoalkyl)phosphonates and diazoesters **265**.<sup>[79]</sup> Following a comparable mechanism, this domino imine formation/cyclization/Mannich-type reaction catalyzed by a combination of 5 mol% of Ag<sub>2</sub>CO<sub>3</sub> and 10 mol% of novel imidodiphosphate ligand **266** afforded an impressive variety of chiral 1,2-dihydroisoquinolines **267** exhibiting a C1 tertiary stereocenter and substituents at the C3 position with moderate to quantitative yields (32-97%) and variable *ee* values (17-98% *ee*), as illustrated in Scheme 69. These products could be further elaborated into diverse chiral phosphorus-containing compounds including poly(ADP-ribose) polymerase inhibitor analogues.

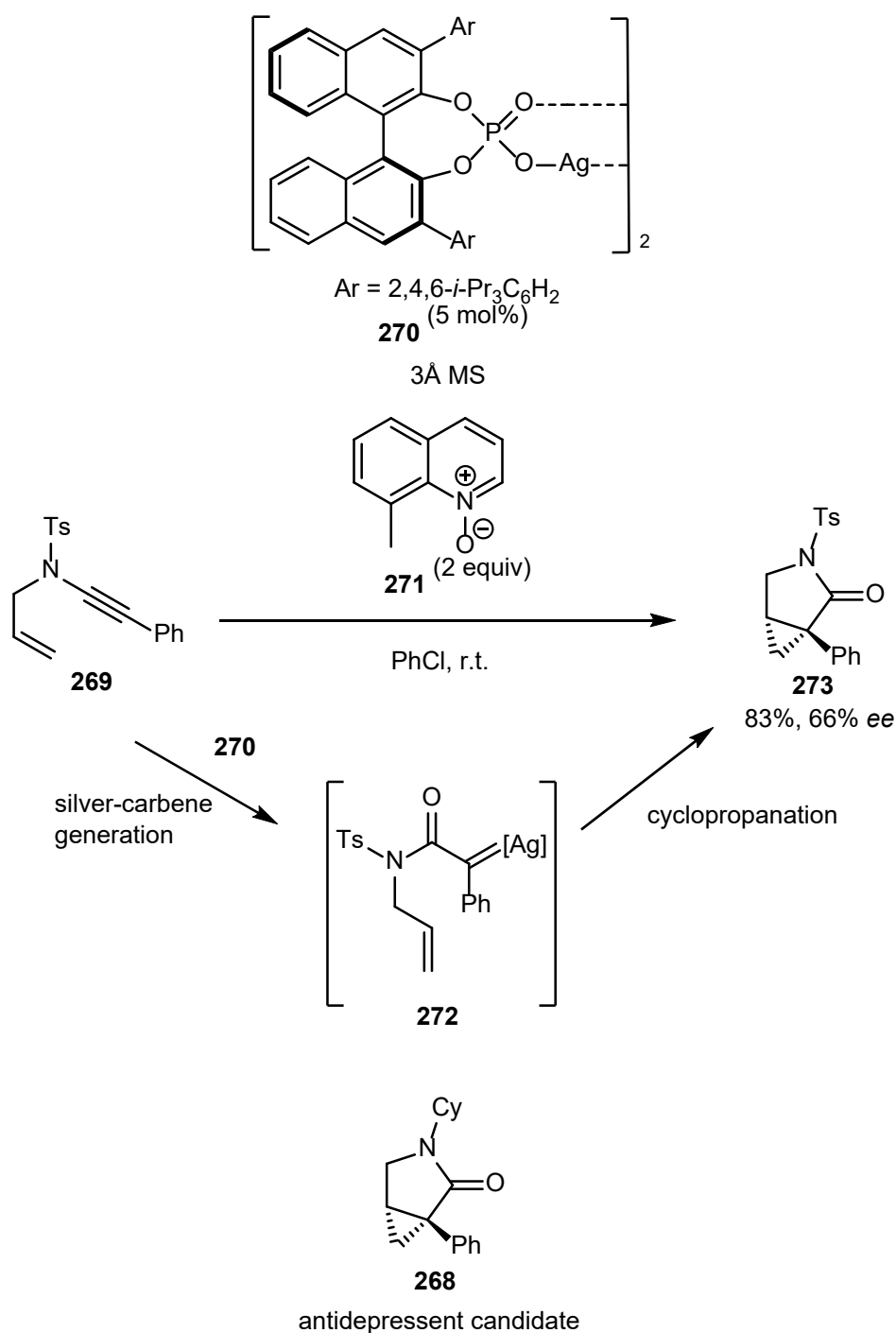


Ar<sup>1</sup> = Ph, *m*-Tol, *o*-FC<sub>6</sub>H<sub>4</sub>, *m*-ClC<sub>6</sub>H<sub>4</sub>, *m*-MeOC<sub>6</sub>H<sub>4</sub>, *o*-MeOC<sub>6</sub>H<sub>4</sub>  
 R<sup>1</sup> = Ph, *p*-Tol, *p*-EtC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-BrC<sub>6</sub>H<sub>4</sub>, *p*-MeOC<sub>6</sub>H<sub>4</sub>,  
*m*-Tol, *p*-F<sub>3</sub>COC<sub>6</sub>H<sub>4</sub>, *p*-NCC<sub>6</sub>H<sub>4</sub>, *p*-EtO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, *m*-FC<sub>6</sub>H<sub>4</sub>,  
*m*-ClC<sub>6</sub>H<sub>4</sub>, *m*-BrC<sub>6</sub>H<sub>4</sub>, *m*-MeOC<sub>6</sub>H<sub>4</sub>, *o*-Tol, *o*-ClC<sub>6</sub>H<sub>4</sub>, *o*-BrC<sub>6</sub>H<sub>4</sub>,  
 3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 3,5-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 2-Naph, 2-pyridyl, 2-furyl, 2-thienyl, (*E*)PhCH=CH  
 R<sup>2</sup> = H, Me, F, OMe, Cl  
 R<sup>3</sup> = H, Cl, OMe  
 EWG = P(O)(OMe)<sub>2</sub>, P(O)(OEt)<sub>2</sub>, P(O)(Ot-Bu)<sub>2</sub>, CO<sub>2</sub>Et

**Scheme 69.** Three-component domino imine formation/cyclization/Mannich-type reaction of 2-alkynylbenzaldehydes, anilines and diazo compounds.

In 2021, Harada and Nemoto described an asymmetric synthesis of antidepressant candidate **268** exhibiting an azabicyclo[3.1.0]hexane skeleton, the key step of which was an enantioselective silver-catalyzed intramolecular domino reaction of ynamide **269** (Scheme 70).<sup>[80]</sup> When this substrate was submitted at room temperature in chlorobenzene as solvent to 5 mol% of preformed silver catalyst **270** derived from a chiral phosphoric acid ligand, it underwent in the presence of two equivalents of *N*-oxide **271** the formation of silver-carbene **272**. Subsequently, an asymmetric cyclopropanation

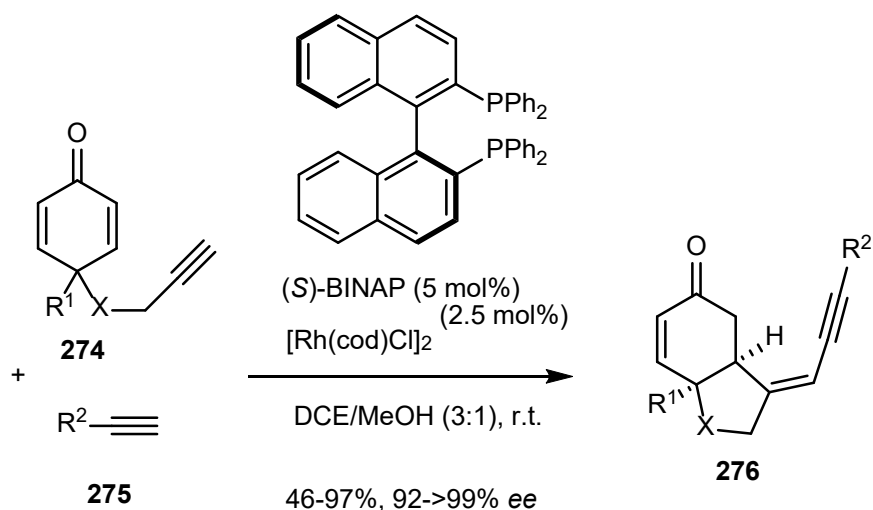
occurred to afford azabicyclo[3.1.0]hexane derivative **273** in 83% yield and 66% *ee*. Three supplementary steps allowed the synthesis of desired antidepressant candidate **268**.



**Scheme 70.** Domino silver-carbene generation/cyclopropanation reaction of an ynamide.

#### 4 Enantioselective Rhodium-Catalyzed Domino Reactions

In 2019, Xu et al. developed enantioselective rhodium-catalyzed domino hydroalkynylation/cyclization reaction between cyclohexadienones **274** and terminal alkynes **275**.<sup>[81]</sup> Promoted at room temperature in a 3:1 mixture of DCE and methanol as solvent by a chiral rhodium catalyst *in situ* generated from 2.5 mol% of [Rh(cod)Cl]<sub>2</sub> and 5 mol% of (*S*)-BINAP, the reaction afforded exclusively head-to-head chiral regioisomers **276**. These *cis*-hydrobenzofuranone-tethered enynes were obtained in moderate to excellent yields (46-97%) and excellent enantioselectivities (92->99% *ee*), as shown in Scheme 71. A range of aryl alkynes with either electron-withdrawing or electron-donating substituents at any position of the phenyl ring provided comparable results. Alkynes substituted by heterocycles, such as thiophene, indole, or ferrocene, as well as (cyclo)alkyl-substituted alkynes reacted smoothly. In addition to oxygen-tethered cyclohexadienones (X = O), a nitrogen bridged enyne (X = NHTs) was also tolerated, providing the desired nitrogenated heterocycle in 94% yield and 98% *ee*. The process began with the formation of Rh(I) acetylide **CL** by reaction of the alkyne with the Rh(I) catalyst. Then, Rh(I) acetylide **CL** underwent head-to-head insertion to give vinyl rhodium intermediate **CK**. Subsequently, intramolecular asymmetric Michael addition furnished cyclic Rh(I) enolate **CM**, which was further protonated to give the final product along with Rh(I)Cl (Scheme 71).



R<sup>1</sup> = Me, Et, *i*-Pr, Ph

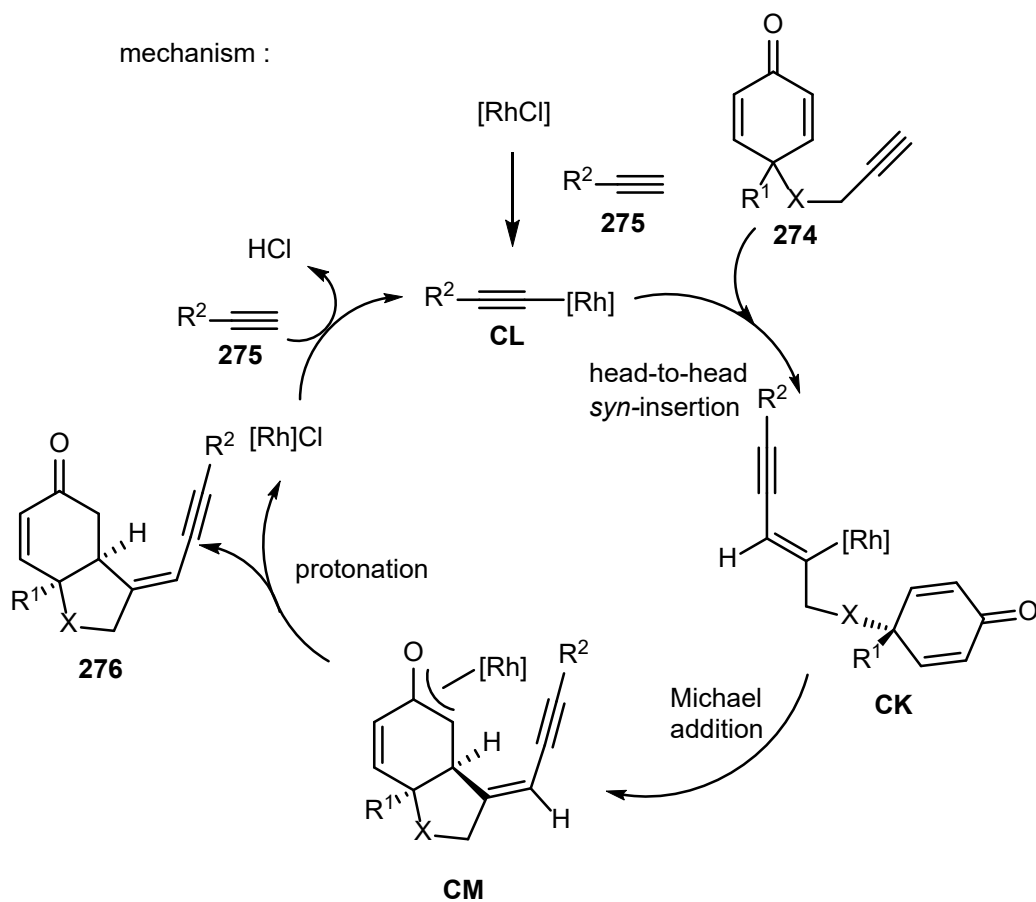
R<sup>2</sup> = Ph, *p*-Tol, *p*-MeOC

*p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, *m*-Tol, *m*-HOC<sub>6</sub>H<sub>4</sub>, *o*-(HOCH<sub>2</sub>)C<sub>6</sub>H<sub>4</sub>, *o*-(TBSOCH<sub>2</sub>)C<sub>6</sub>H<sub>4</sub>,

1-Naph, 3-indolyl, 3-thienyl, 2-thienyl, ferrocenyl, *c*-Pr, Bn(CH<sub>2</sub>)<sub>2</sub>, PhOCH<sub>2</sub>

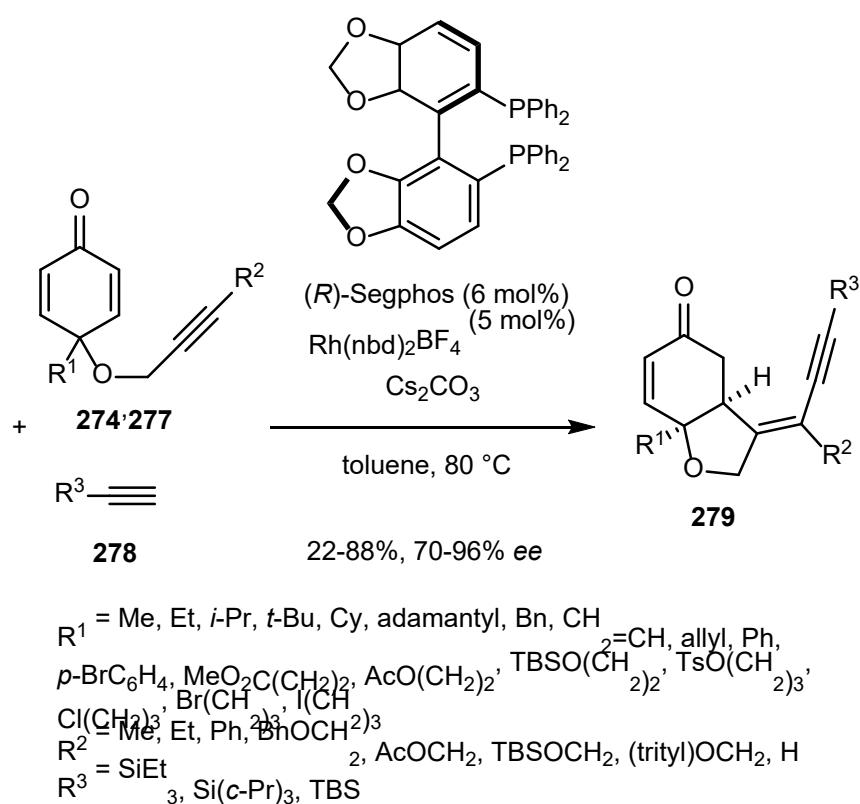
X = O, NTs

mechanism :



**Scheme 71.** Domino hydroalkynylation/cyclization reaction of oxygen/nitrogen-tethered cyclohexadienones with terminal alkynes.

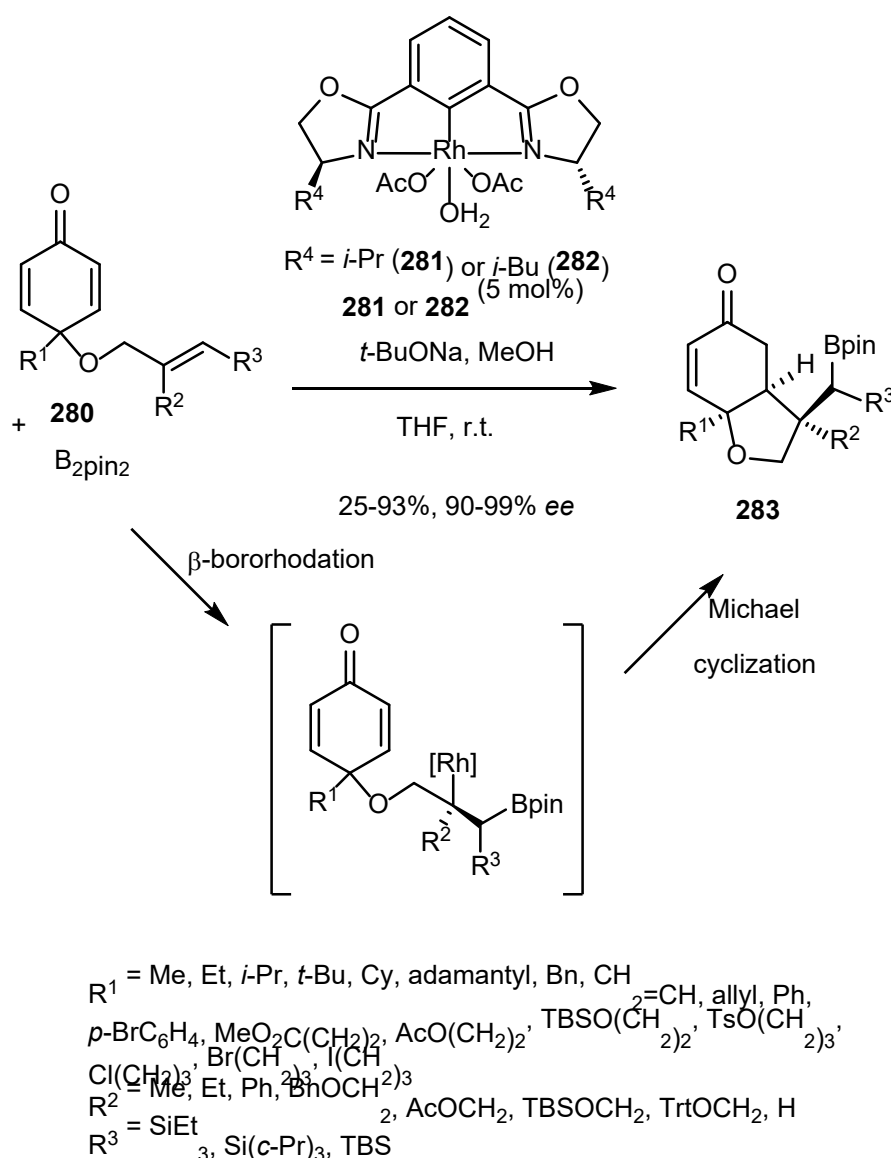
In the same area, Tian and Lin employed a chiral rhodium catalyst derived from (*R*)-Segphos to promote related reactions between cyclohexadienone-tethered internal alkynes and terminal silylacetylenes (Scheme 72).<sup>[82]</sup> In the presence of 6 mol% of this chiral ligand combined with 5 mol% of Rh(nbd)<sub>2</sub>BF<sub>4</sub> as precatalyst, a variety of oxygen-tethered cyclohexadienones **274**, **277** exhibiting an internal alkyne reacted chemo-, regio-, and enantioselectively at 80 °C in toluene as solvent with terminal trialkylsilyl acetylenic derivatives **278** to give the corresponding chiral *cis*-hydrobenzofurans **279** containing a versatile silylacetylene fragment with low to high yields (22-88%) and good to excellent enantioselectivities (70-96% *ee*). The process evolved through domino hydroalkynylation/cyclization reaction. A range of internal alkyne-tethered cyclohexadienones were tolerated, however, the reaction of a terminal alkyne-tethered cyclohexadienone (R<sup>2</sup> = H) led to the corresponding chiral product with a low yield (22%) and moderate *ee* value (70% *ee*).



**Scheme 72.** Domino hydroalkynylation/cyclization reaction of cyclohexadienone-tethered internal alkynes with terminal trialkylsilyl alkynes.

In 2019, Tian, Hong, Lin et al. disclosed an enantioselective rhodium-catalyzed domino boration/cyclization reaction of alkene-tethered cyclohexadienones **280** with B<sub>2</sub>pin<sub>2</sub>.<sup>[83]</sup> By using 5 mol% of preformed chiral rhodium catalyst **281** or **282** in THF at room temperature in the presence of *t*-BuONa as base, the one-pot reaction allowed a wide variety of chiral hydrobenzofurans **283** exhibiting three contiguous stereocenters to be synthesized in moderate to high yields (25-93%) and uniformly excellent enantioselectivities (90-99% *ee*), as shown in Scheme 73. The catalyst system was compatible with various substituted alkenes, including monosubstituted terminal alkenes (65-93%, 90-96% *ee*), 1,1-disubstituted terminal alkenes (25%, 94% *ee*), and (*E*)-1,2-disubstituted alkenes (37-66%, 97-99% *ee*), affording the corresponding substituted fused bicyclic products with

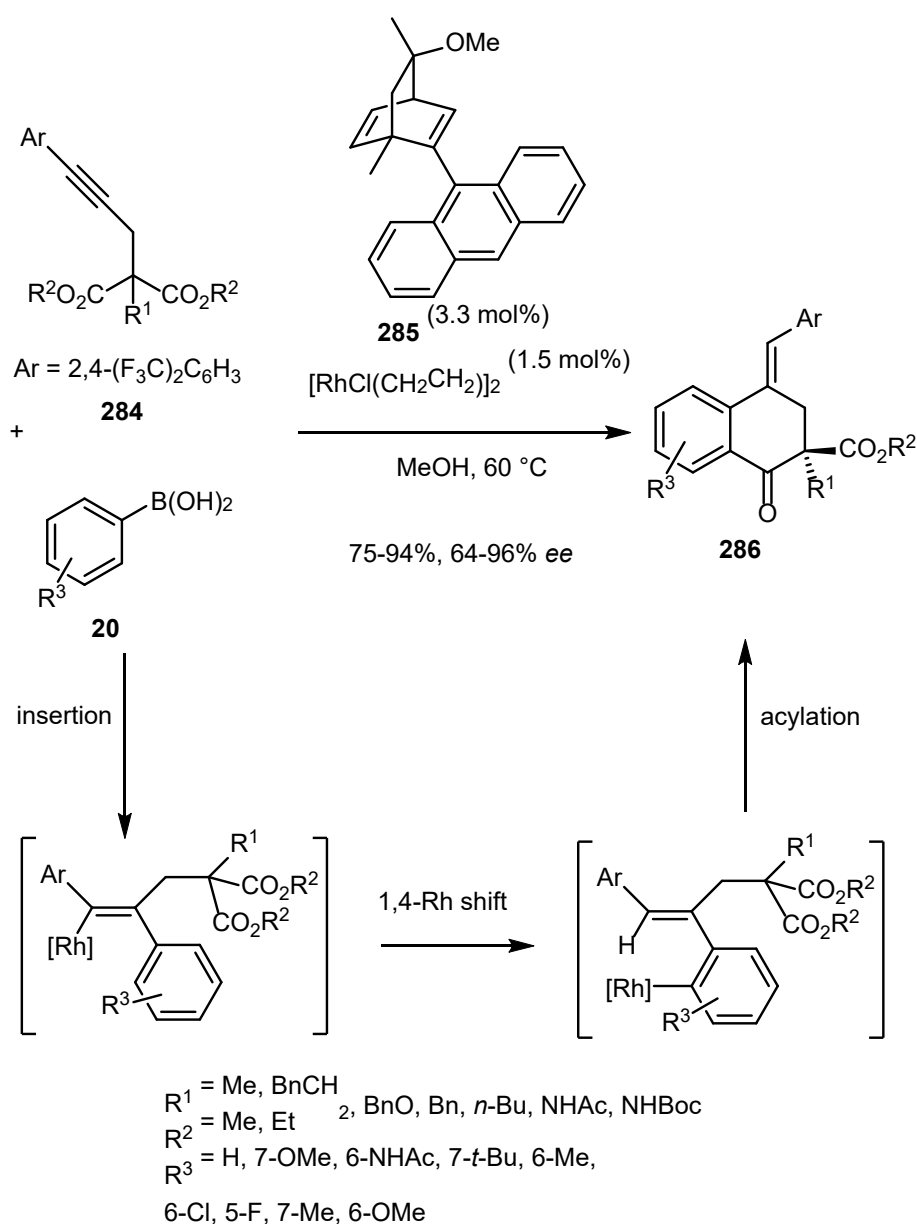
homogeneously excellent *ee* values (90-99% *ee*). Moreover, a wide variety of functional groups on both cyclohexadienone and alkene components was tolerated.



**Scheme 73.** Domino boration/cyclization reaction of alkene-tethered cyclohexadienones with  $\text{B}_2\text{pin}_2$ .

A novel route to chiral 1-tetralones bearing a quaternary carbon stereocenter was described in 2019 by Selmani and Darses, based on an efficient regio- and enantioselective rhodium-catalyzed arylation cyclization of alkynyl malonates **284** with arylboronic acids **20** (Scheme 74).<sup>[84]</sup> This process was catalyzed in methanol at 60 °C by a chiral rhodium catalyst *in situ* generated from only 1.5 mol% of  $[\text{RhCl}(\text{CH}_2\text{CH}_2)]_2$  and 3.3 mol% of chiral diene ligand **285**, affording chiral 1-tetralones **286** with good to high yields (75-94%) and moderate to excellent enantioselectivities (64-96% *ee*). Actually, the *ee* values were all  $\geq 84\%$  *ee* excepted for a tetralone bearing a OBn substituent at the malonate junction ( $R^1 = \text{OBn}$ ) which reacted with only 64% *ee*. On the other hand, high enantioselectivities (85-96% *ee*) were obtained in the reaction of alkynyl malonates exhibiting NHAc or NHBoc substituents ( $R^1 = \text{NHAc, NHBoc}$ ), thus allowing an easy access to chiral cyclic exotic amino acids bearing a tetralone

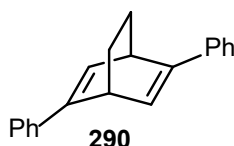
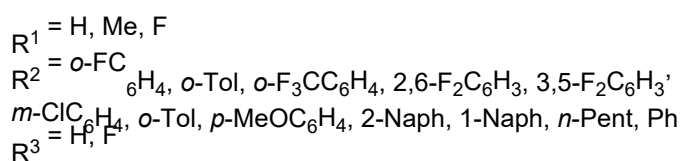
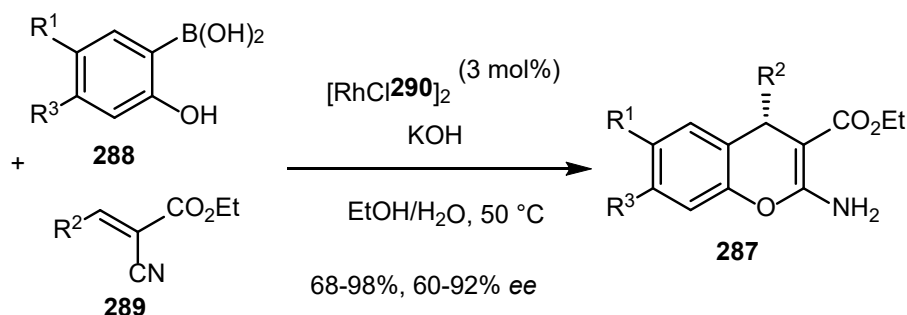
moiety. As shown in Scheme 74, the one-pot process involved successively an alkyne insertion, a 1,4-Rh shift, and a cyclization through acylation.



**Scheme 74.** Domino alkyne insertion/cyclization reaction of alkynyl malonates with arylboronic acids.

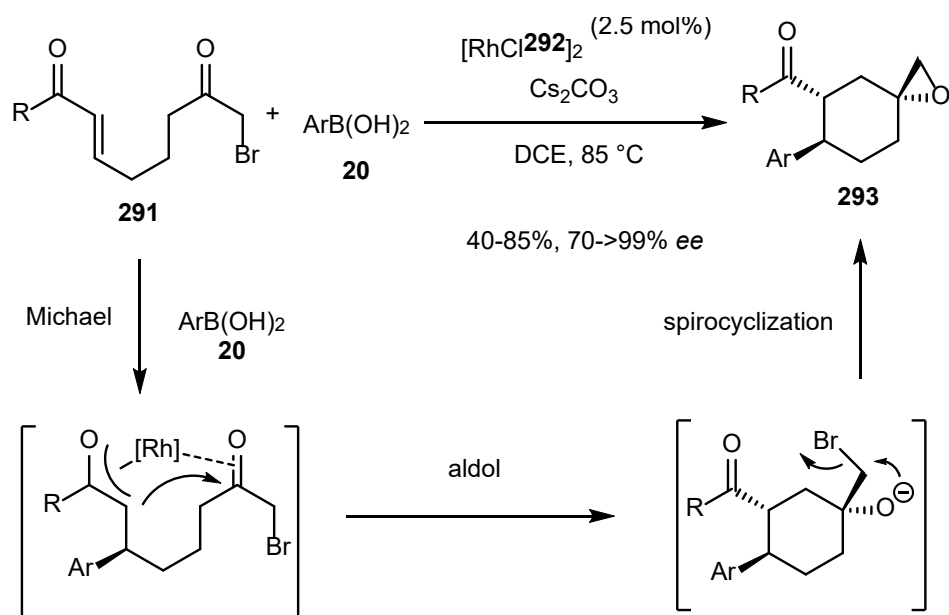
Later in 2021, Dou and Xing developed a novel synthesis of chiral 2-amino-4H-chromenes **287** from an asymmetric rhodium-catalyzed domino reaction of readily available *ortho*-hydroxylated arylboronic acids **288** with alkylidene cyanoacetates **289** (Scheme 75).<sup>[85]</sup> This domino Michael/cyclization reaction produced a variety of chiral 2-amino-4H-chromenes **287** in both moderate to excellent yields (68-98%) and enantioselectivities (60-92% ee) when catalyzed at 50 °C in aqueous ethanol as solvent by 3 mol% of a chiral preformed rhodium catalyst derived from chiral diene **290**. Actually, homogeneously high ee values (83-92% ee) were obtained in the reaction of aryl-substituted alkylidene cyanoacetates ( $\text{R}^2 = \text{aryl}$ ) with electronically divergent substituents at different positions of the phenyl ring. On the other hand, an alkyl-substituted product ( $\text{R}^2 = n\text{-Pent}$ ) was generated with a

lower enantioselectivity (60% *ee*). According to the biological importance of 2-amino-4H-chromenes, this novel simple methodology was highly desirable.

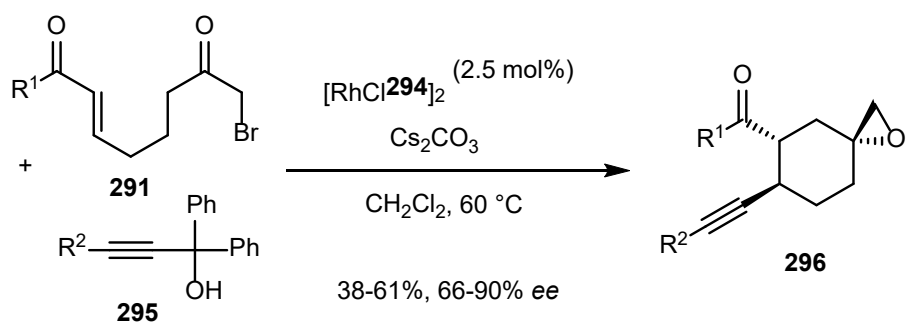
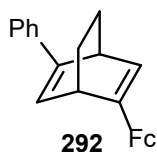


**Scheme 75.** Domino Michael/cyclization reaction of *ortho*-hydroxylated arylboronic acids with alkylidene cyanoacetates.

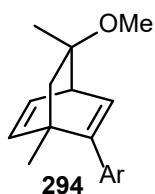
In the same year, Lautens et al. disclosed enantioselective rhodium-catalyzed domino Michael/aldol/spirocyclization reactions of  $\alpha$ -bromoketoenones **291** with nucleophiles such as aryl boronic acids **20**.<sup>[86]</sup> A preformed rhodium catalyst derived from chiral diene ligand **292** was employed at 2.5 mol% of catalyst loading in DCE as solvent, allowing by heating at 85 °C the formation of chiral densely functionalized spiro-oxiranes **293** exhibiting three stereocenters to be achieved in moderate to good yields (40-85%) and good to excellent enantioselectivities (70->99% *ee*), as presented in Scheme 76. The domino reaction evolved through successive Michael addition, aldol condensation and spirocyclization. A wide variety of aryl boronic acids bearing either electron-withdrawing or electron-donating substituents on the phenyl ring were tolerated, leading to the desired arylated products with high *ee* values ( $\geq 85\%$  *ee*). On the other hand, the reaction of a bulkier 1-naphthyl boronic acid (Ar = 1-Naph) afforded the corresponding product with a decreased enantioselectivity (70% *ee*). The use of 2.5 mol% of a related chiral rhodium catalyst derived from chiral diene ligand **294** allowed the involvement of another type of nucleophiles such as alkynols **295**. The latter reacted at 60 °C with  $\alpha$ -bromoketoenones **291** in dichloromethane as solvent to afford the corresponding alkynylated products **296** in moderate yields (38-61%) and moderate to high enantioselectivities (66-90% *ee*), as shown in Scheme 76. The lower *ee* values obtained with alkynylating nucleophiles in comparison with aryl boronic acids were explained by the bulky silyl group being distal from the metal center, resulting in a diminished stereocontrol.



Ar = *p*-MeOC<sub>6</sub>H<sub>4</sub>, Ph, *p*-MeO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-BocNHC<sub>6</sub>H<sub>4</sub>, *p*-AcC<sub>6</sub>H<sub>4</sub>, *p*-OHCC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-BrC<sub>6</sub>H<sub>4</sub>, *m*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, *m*-MeOC<sub>6</sub>H<sub>4</sub>, *o*-Tol, 2-Naph, 2-furyl, 2-thienyl, 3-F-4-MeOC<sub>6</sub>H<sub>3</sub>,  
 R = Ph, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-BrC<sub>6</sub>H<sub>4</sub>, 2-thienyl, 2-furyl, *i*-Pr

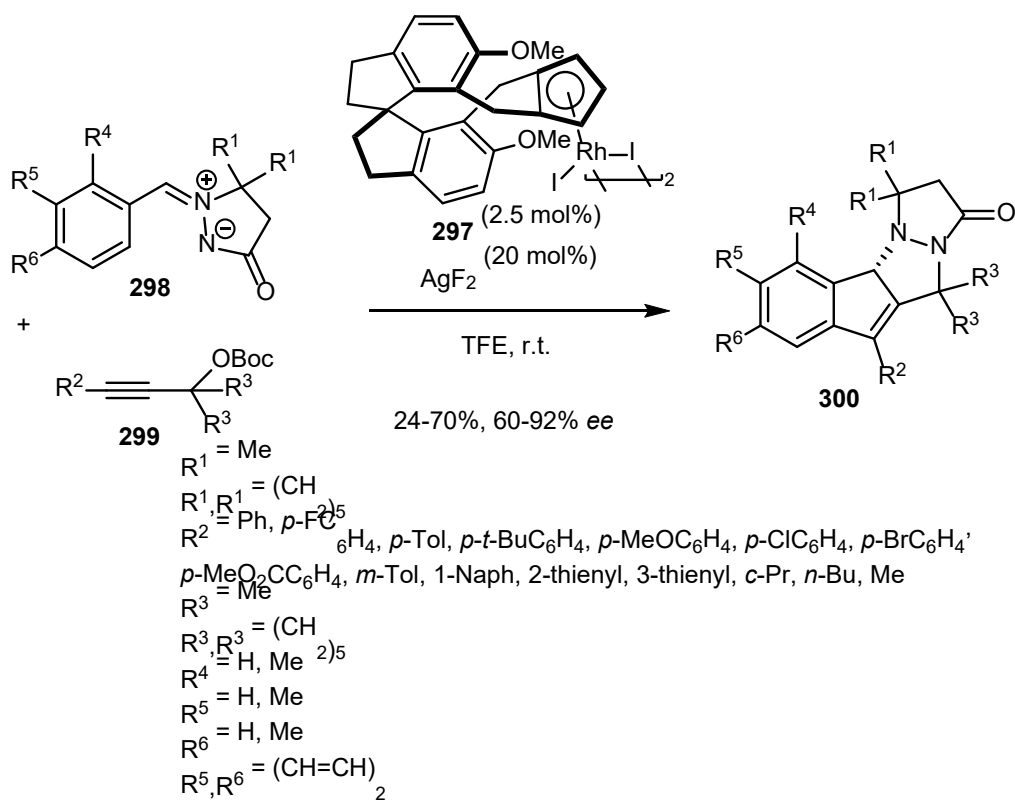


R<sup>1</sup> = Ph, *p*-MeOC<sub>6</sub>H<sub>4</sub>, 2-thienyl, 2-furyl  
 R<sup>2</sup> = TIPS, , ,

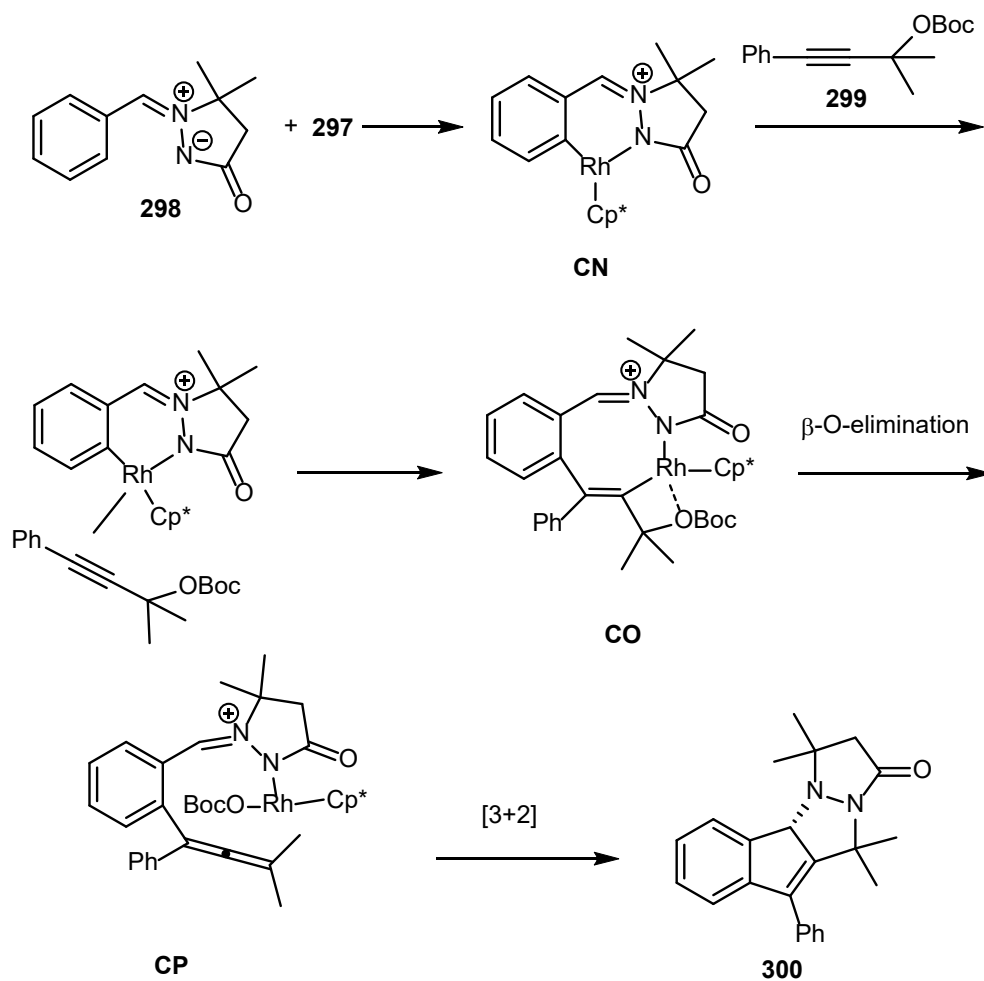


**Scheme 76.** Domino Michael/aldol/spirocyclization reactions of  $\alpha$ -bromoketo-enones with aryl boronic acids/alkynyl nucleophiles.

In 2022, Zhou and Yi described a novel domino reaction catalyzed by 2.5 mol% of chiral cyclopentadienyl rhodium catalyst **297** (Scheme 77).<sup>[87]</sup> The reaction occurred at room temperature in TFE as solvent between azomethine imines **298** and propargyl carbonates **299**, resulting in the formation of the corresponding chiral ring-fused tetracyclic indenopyrazolopyrazolones **300** with moderate yields (24-70%) and moderate to high enantioselectivities (60-92% *ee*). This reaction was assumed to follow a domino C–H coupling/[3+2] cycloaddition process the mechanism of which is detailed in Scheme 77. In a first time, rhodacycle intermediate **CN** was formed from the interaction between the chiral catalyst and the azomethine imine. Then, the rhodium metal in **CN** coordinated the propargyl carbonate which was followed by regioselective insertion of the alkyne into the C–Rh bond to generate intermediate **CO**. Subsequently, the latter was submitted to a  $\beta$ -O-elimination affording allene intermediate **CP**, which underwent a final [3+2] cycloaddition which delivered the product.



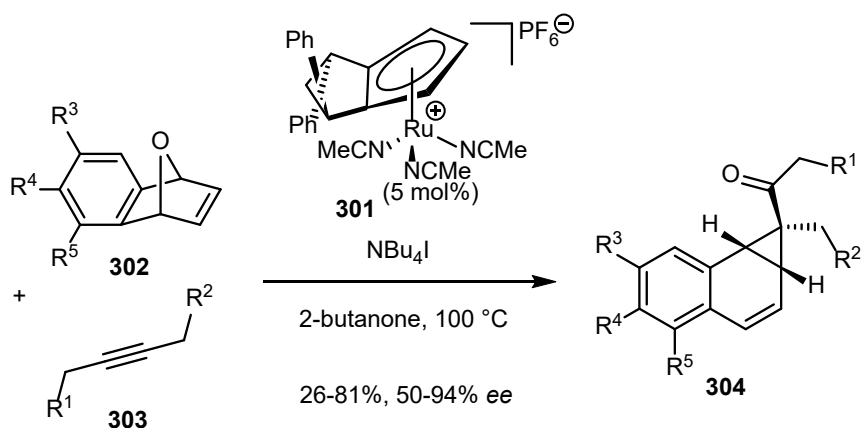
proposed mechanism (with  $\text{R}^1 = \text{R}_3 = \text{Me}, \text{R}_2 = \text{Ph}, \text{R}_4 = \text{R}_5 = \text{R}_6 = \text{H}$ ):



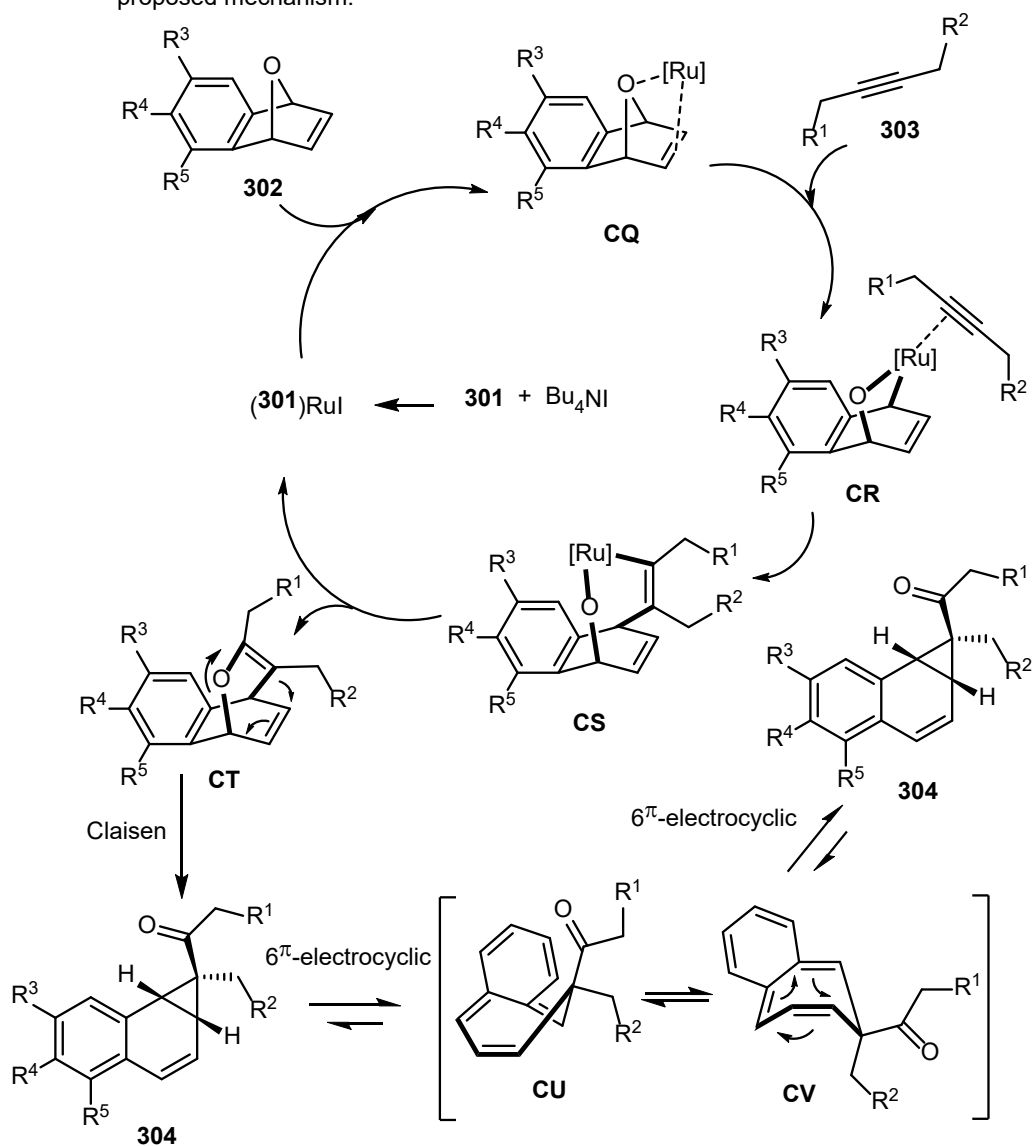
**Scheme 77.** Domino C–H coupling/[3+2] cycloaddition reaction of azomethine imines with propargyl carbonates.

## 5 Enantioselective Ruthenium-Catalyzed Domino Reactions

Enantioselective ruthenium-catalyzed domino reactions have not been highly developed so far. In an example reported in 2019, Cramer et al. described an elegant and rare asymmetric synthesis of benzonorcaradienes based on an enantioselective ruthenium-catalyzed domino coupling/pericyclic rearrangement reaction of oxabenzonorbornadienes with internal alkynes.<sup>[88]</sup> The process performed at 100 °C in 2-butanone as solvent was promoted by 5 mol% of preformed ruthenium complex **301** derived from a chiral cyclopentadienyl ligand. As shown in Scheme 78, a range of variously substituted oxabenzonorbornadienes **302** reacted with internal alkynes **303** to afford the corresponding chiral benzonorcaradienes **304** as single *exo*-diastereomers in low to good yields (26-81%) and variable enantioselectivities (50-94% *ee*). In general, high enantioselectivities (90-94% *ee*) were obtained in the reaction of internal alkynes containing propargylic carbonate groups ( $R^1 = R^2 = \text{CO}_2\text{Me}$ , Boc, Cbz), propargylic benzoate groups ( $R^1 = R^2 = \text{Bz}$ ) and acetate groups ( $R^1 = R^2 = \text{Ac}$ ). The relevance of the coordinating ability of the carbon unit for the enantioselectivity of the reaction was documented with *tert*-butyldimethylsilyl- and benzyl-ether-containing alkyne substrates which provided the lowest *ee* values (48-50% *ee*). In addition to symmetric alkynes, unsymmetrical alkynyl substrates possessing only a single propargylic oxygen atom also reacted with high levels of enantioselectivity (88-94% *ee*). To explain the results, the authors proposed a mechanism evolving through a coupling of the two substrates followed by different pericyclic rearrangements (Scheme 78). The domino reaction began with the formation of neutral active catalyst (**301**)RuI from the reaction between cationic complex **301** with Bu<sub>4</sub>NI. Then, coordination of (**301**)RuI to the oxabenzonorbornadiene generated intermediate **CQ**. Enantioselective oxidative insertion into the C–O bond of the oxabenzonorbornadiene and coordination of the alkyne afforded ruthenacycle **CR**. Subsequent migratory insertion of the alkyne resulted in the formation of intermediate **CS**. The latter subsequently underwent reductive elimination to afford allyl vinyl ether **CT** along with regenerated active ruthenium catalyst (**301**)RuI. Then, intermediate **CT** underwent a Claisen rearrangement to yield *endo*-diastereomer **304**. Thermal isomerization of the latter through a 6 $\pi$ -electrocyclic ring-opening/closure sequence via putative benzo cycloheptatrienes **CU** and **CV** produced more stable final *exo*-diastereomer **304**.

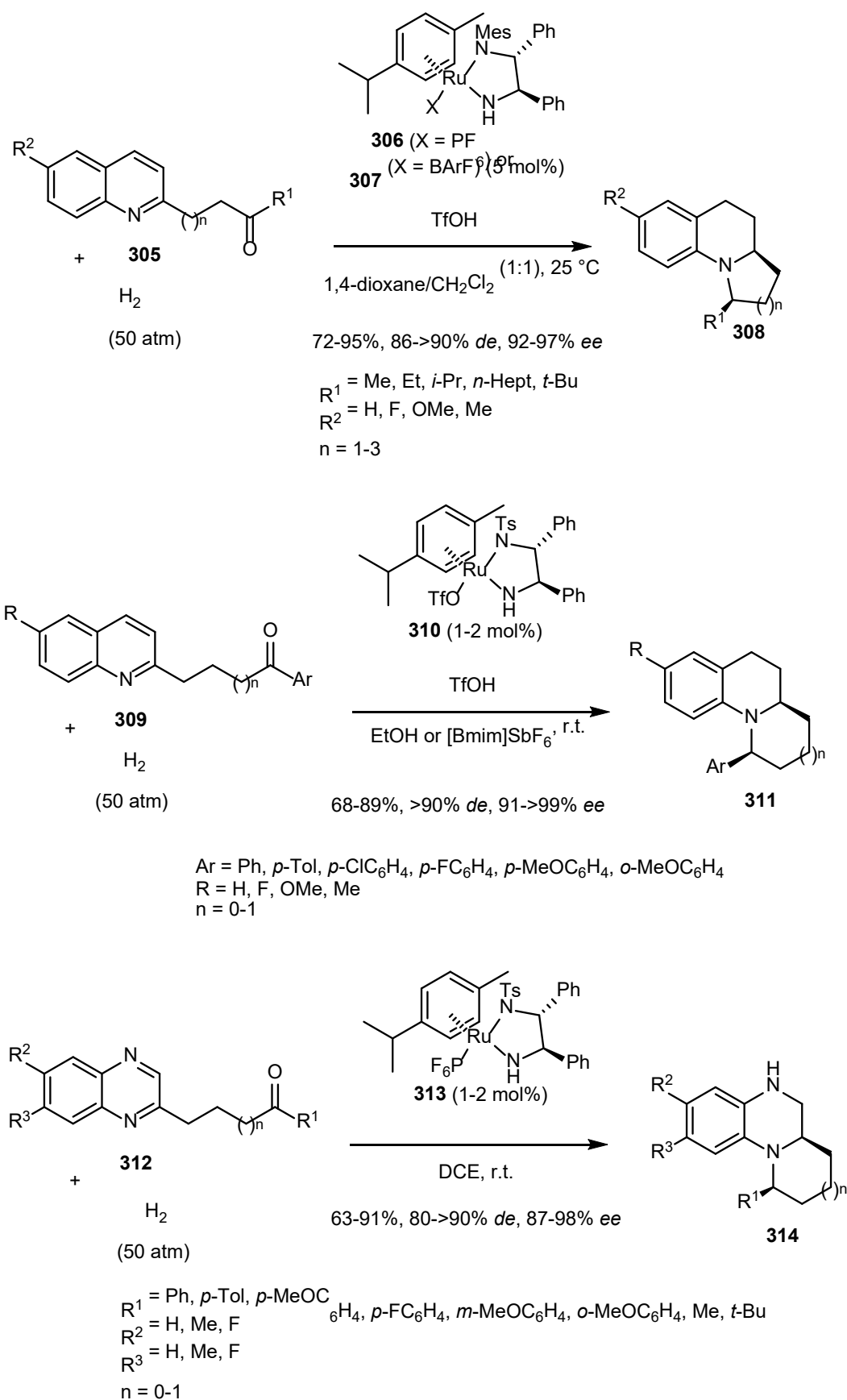


proposed mechanism:



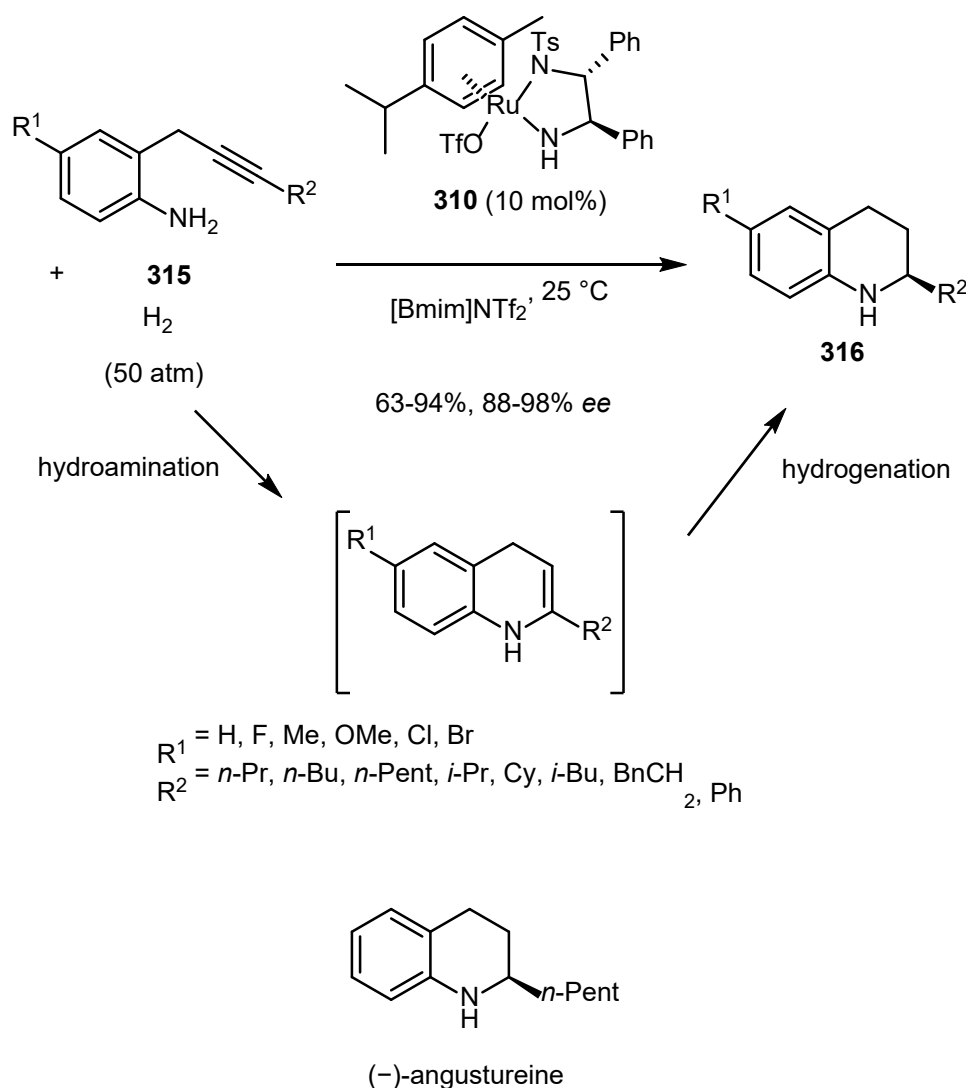
**Scheme 78.** Domino coupling/pericyclic rearrangement reaction of oxabenzonorbornadienes with internal alkynes.

In spite of the fact that fused heterocyclic products, such as substituted quinolizidines and indolizidines, constitute very important molecules in medicinal chemistry, their catalytic synthesis remains underexplored. To fill this gap, preformed chiral ruthenium catalysts were employed in 2019 by Fan et al. as promoters of enantioselective domino hydrogenation/reductive amination reactions of quinolizidine-, indolizidine- and quinoxaline-containing ketones.<sup>[89]</sup> Under hydrogen atmosphere (50 atm), a series of (2-quinolinyl) propyl ( $n = 1$ )/ethyl ( $n = 0$ ) alkyl ketones **305** underwent at 25 °C the domino reaction in the presence of 5 mol% of catalyst **306** or **307** in a 1:1 mixture of 1,4-dioxane and dichloromethane as solvent to afford the corresponding chiral 1-alkyl quinolizidines and indolizidines **308** in uniformly high yields (72-95%), diastereoselectivities (86->90% *de*) and enantioselectivities (92-97% *ee*), as shown in Scheme 79. Actually, single diastereomers (>90% *de*) were obtained in all cases of substrates excepted in the reaction of an 1-ethyl-quinolizidine ( $R^1 = Et$ ,  $n = 2$ ). Furthermore, (2-quinolinyl)propyl ( $n = 1$ )/ethyl ( $n = 0$ ) aryl ketones **309** reacted similarly at room temperature in the presence of only 1-2 mol% of related chiral ruthenium catalyst **310** in ethanol or ionic liquids [Bmim]SbF<sub>6</sub> as solvent to afford the corresponding chiral 1-aryl quinolizidines and indolizidines **311** as almost single diastereomers (>90% *de*) in good to high yields (68-89%) and homogeneously excellent enantioselectivities (91->99% *ee*). Excellent results were also obtained in asymmetric domino hydrogenation/reductive amination reaction of 2-quinoxalinyl-containing ketones **312** performed at room temperature in DCE as solvent in the presence of 1-2 mol% of chiral ruthenium catalyst **313**, which provided the corresponding chiral benzo-fused heterocyclic products **314** in good to high yields (63-91%), high diastereoselectivities (80->90% *de*) and uniformly high *ee* values (87-98% *ee*), as illustrated in Scheme 79. Actually, the diastereoselectivities were >90% *de* in all cases of substrates excepted in the reaction of a methyl-substituted ketone ( $R^1 = Me$ ) which yielded the desired product with 80% *de* along with 96% *ee*.



**Scheme 79.** Domino hydrogenation/reductive amination reactions of quinolizidine-, indolizidine- and quinoxaline-containing ketones.

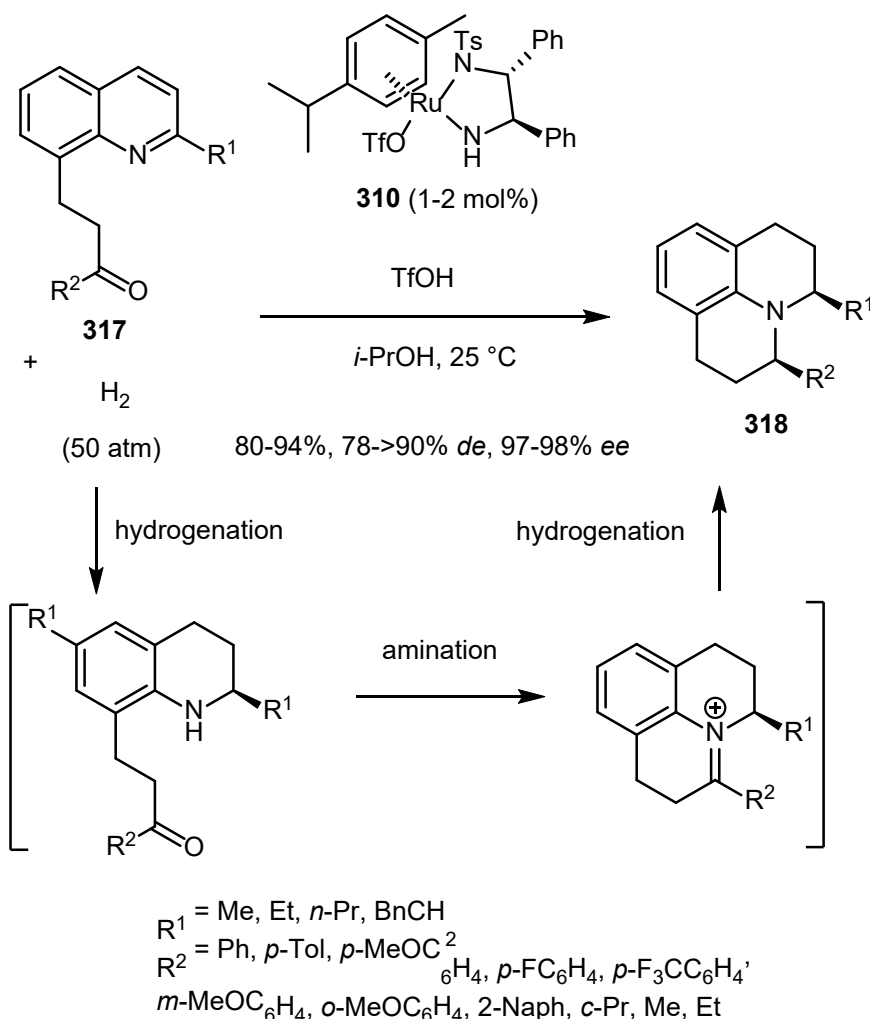
The same authors also disclosed another type of domino reaction based on an enantioselective ruthenium-catalyzed hydrogenation (Scheme 80).<sup>[90]</sup> In the presence of 10 mol% of chiral preformed ruthenium catalyst **310** in ionic liquids [Bmim]SbF<sub>6</sub> as solvent, a series of of aniline-tethered alkynes **315** underwent under hydrogen atmosphere (50 atm) a domino intramolecular hydroamination/hydrogenation reaction to give the corresponding chiral tetrahydroquinolines **316** in good to high yields (63-94%) and uniformly high enantioselectivities (88-98% *ee*). The reaction evolved through sequential intramolecular hydroamination and asymmetric hydrogenation. It was compatible with the synthesis of both 2-alkyl and 2-phenyl 1,2,3,4-tetrahydroquinolines. The utility of this novel one-pot methodology was demonstrated by its application in the development of a synthesis of the naturally occurring tetrahydroquinoline alkaloid (–)-angustureine.



**Scheme 80.** Domino hydroamination/hydrogenation reaction of aniline-tethered alkynes.

Later in 2020, Feng, Deng and Fan employed 1-2 mol% of the same ruthenium catalyst **310** to promote an enantioselective domino hydrogenation/reductive amination reaction of 2-(quinolin-8-yl)ethyl ketones **317** (Scheme 81).<sup>[91]</sup> In this case, the reaction was performed at 25 °C in isopropanol

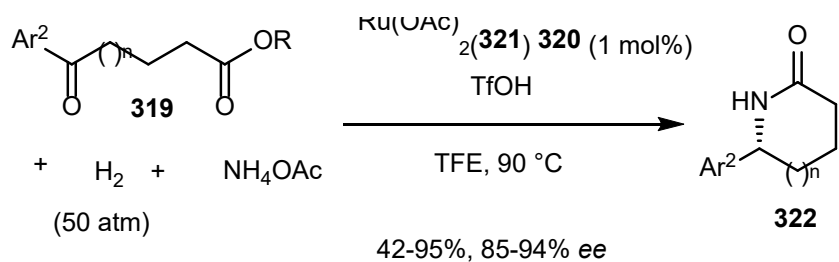
as solvent, allowing an easy access to diversely substituted chiral julolidine derivatives **318** in both high yields (80-94%) and diastereoselectivities (78->90% *de*) combined with excellent enantioselectivities (97-98% *ee*).



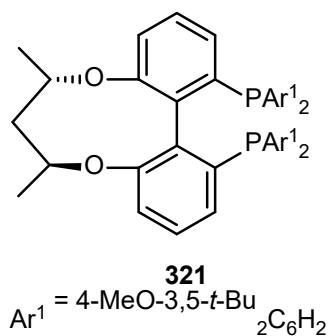
**Scheme 81.** Domino hydrogenation/reductive amination reaction of 2-(quinolin-8-yl)ethyl ketones.

Many bioactive products belong to the family of lactams bearing a stereogenic center adjacent to the N atom. In 2020, Yin et al. described a novel asymmetric synthesis of these products based on an enantioselective ruthenium-catalyzed domino reductive amination/cyclization reaction of readily available keto acids/esters **319**.<sup>[92]</sup> The amine source was friendly NH<sub>4</sub>OAc employed at 90 °C in TFE as solvent under hydrogen atmosphere (50 atm). The chiral catalyst **320** was preformed from chiral bisphosphine **321** and used at only 1 mol% of catalyst loading. As shown in Scheme 82, a range of  $\gamma$ -,  $\delta$ - and  $\epsilon$ -keto esters/acids **319** underwent the domino reaction to afford the corresponding chiral five-, six-, or seven-membered lactams **322** in moderate to excellent yields (42-95%) and homogeneously high *ee* values (85-94% *ee*). The process evolved according the mechanism depicted in Scheme 82, beginning with the formation of imine intermediate **CW** by reaction of the substrate with NH<sub>4</sub>OAc. The latter was further reduced under hydrogen atmosphere in the presence of the chiral ruthenium catalyst to yield chiral primary amine **CX**, which subsequently underwent cyclization to afford the final chiral lactam. The same reaction conditions were also applied to benzo-fused keto acids/esters **323** which resulted in the formation of the desired chiral five-, six-, and seven-membered

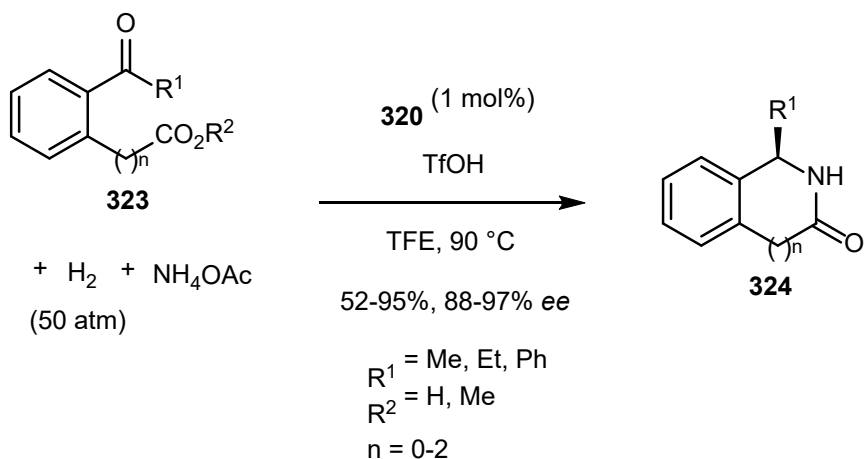
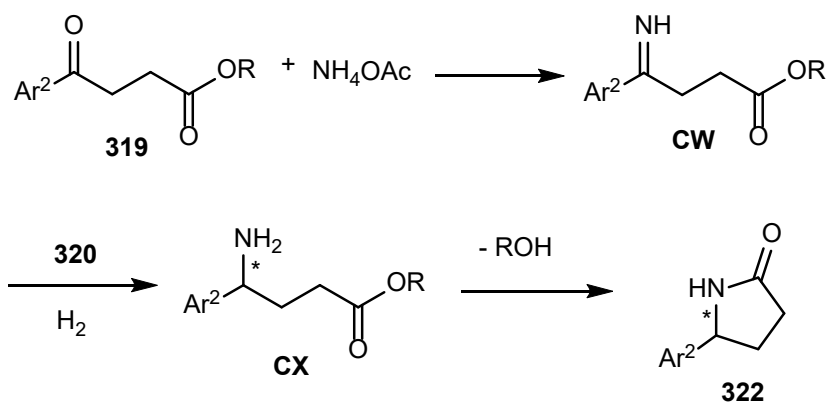
benzolactams **324** with moderate to high yields (52-95%) and uniformly excellent enantioselectivities (88-97% *ee*).



$\text{R} = t\text{-Bu, H, Me, } i\text{-Pr}$   
 $\text{Ar}^2 = \text{Ph, } o\text{-Tol, } m\text{-Tol, } p\text{-Tol, } p\text{-MeOC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, 3,5\text{-MeO}_2\text{C}_6\text{H}_3, 3,4\text{-F}_2\text{C}_6\text{H}_3, 2,5\text{-F}_2\text{C}_6\text{H}_3, m\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-}t\text{-BuC}_6\text{H}_4, p\text{-PhC}_6\text{H}_4, 2\text{-Naph}$   
 $n = 0-2$



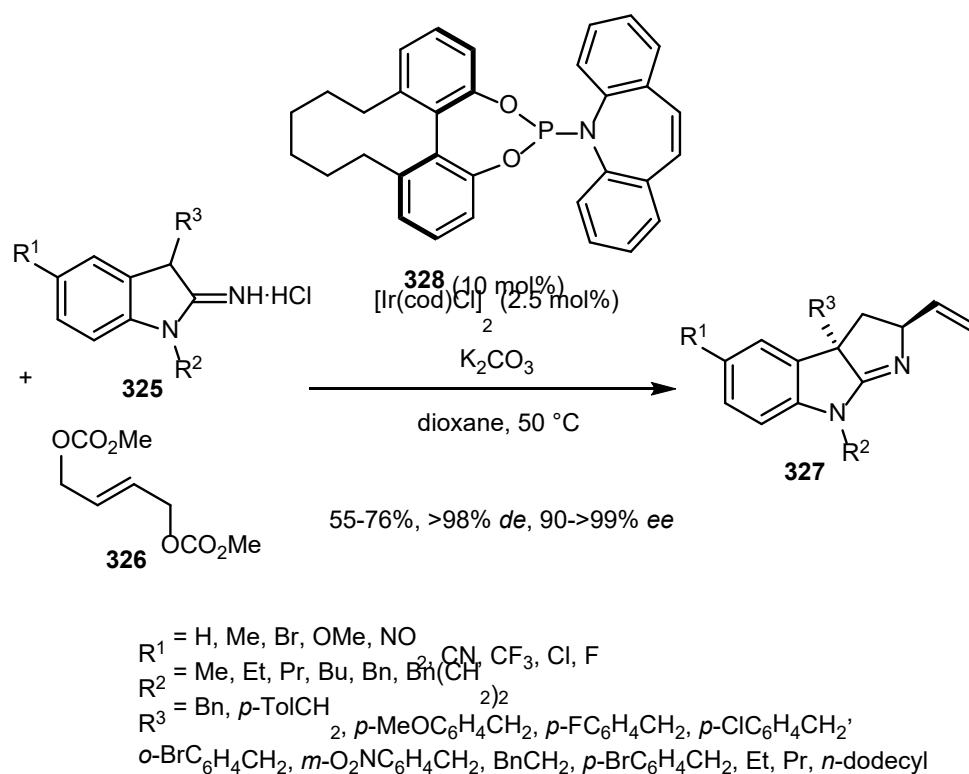
mechanism (with  $n = 0$ ):



**Scheme 82.** Three-component domino reductive amination/cyclization reactions of acyclic and benzo-fused keto acids/esters with  $\text{NH}_4\text{OAc}$  and  $\text{H}_2$ .

## 6 Enantioselective Iridium-Catalyzed Domino Reactions

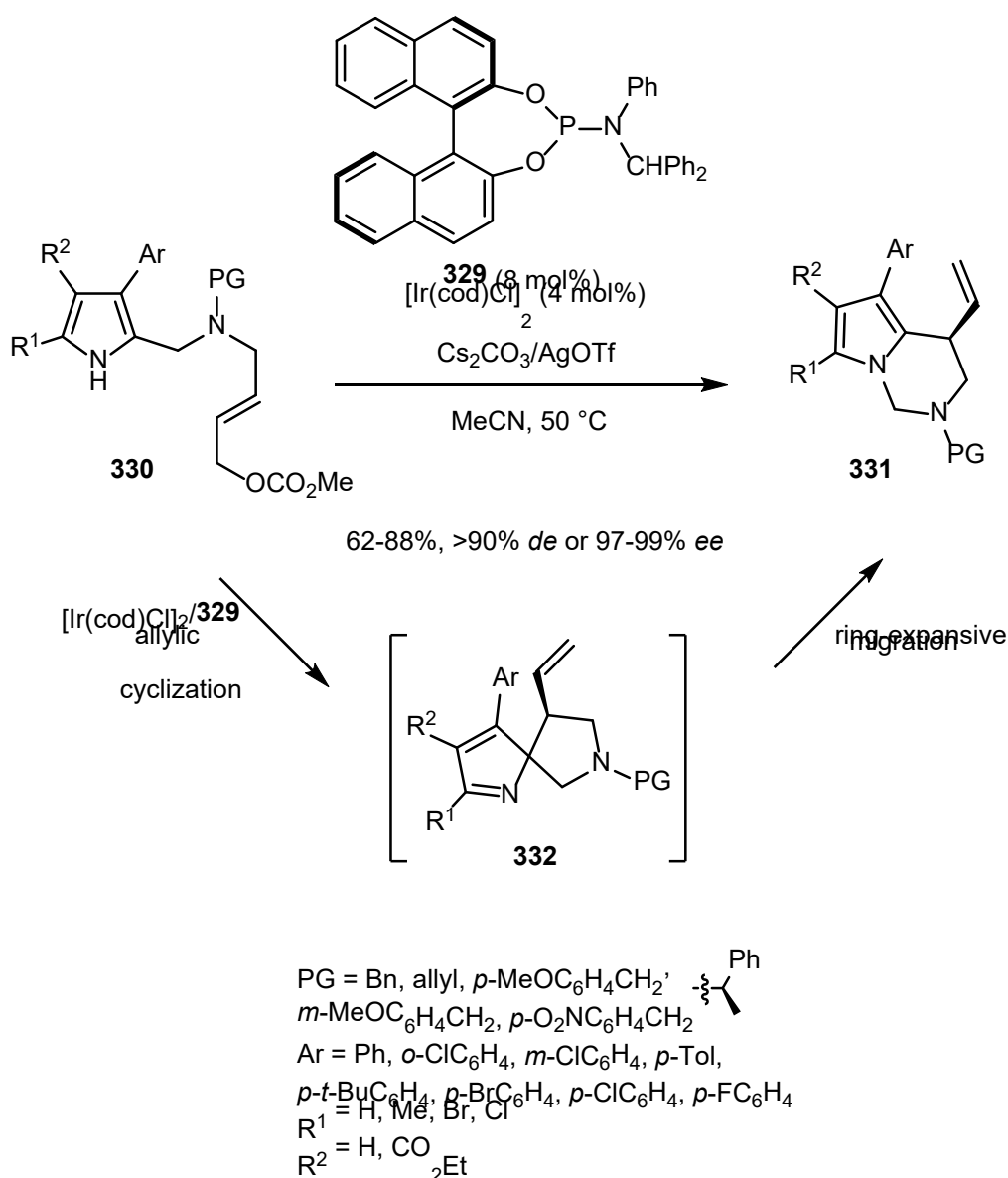
In 2019, Fu et al. disclosed highly diastereo- and enantioselective iridium-catalyzed domino double allylation reactions of 1-alkyl-3-alkylindolin-2-imine hydrochlorides **325** with dimethyl dicarbonate **326**, leading to the corresponding chiral tetrahydropyrrolo[2,3-b]indoles **327** exhibiting an all-carbon quaternary stereocenter.<sup>[93]</sup> The process required the use of 2.5 mol% of  $[\text{Ir}(\text{cod})\text{Cl}]_2$  as precatalyst combined with 10 mol% of chiral cyclic phosphoramidite ligand **328**. When performed at 50 °C in dioxane as solvent, a wide range of products **327** were achieved as single diastereomers (>98% *de*) in good yields (55-76%) and excellent enantioselectivities (90->99% *ee*), as shown in Scheme 83. The substrate scope was wide since a variety of alkyl groups in  $\text{R}^3$  were compatible, including differently substituted benzyl, phenylethyl and alkyl groups. Moreover, the phenyl ring of 1-alkyl-3-alkylindolin-2-imine hydrochlorides could exhibit either electron-withdrawing or electron-donating substituents ( $\text{R}^1$ ) with no impact on the results. Similarly, the *N*-substituent ( $\text{R}^2$ ) could be an alkyl, a benzyl or a phenylpropyl group.



**Scheme 83.** Domino double allylation reaction of 1-alkyl-3-alkylindolin-2-imine hydrochlorides with a dimethyl dicarbonate.

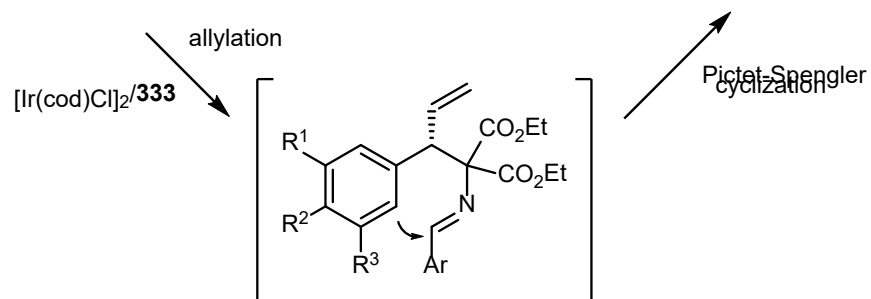
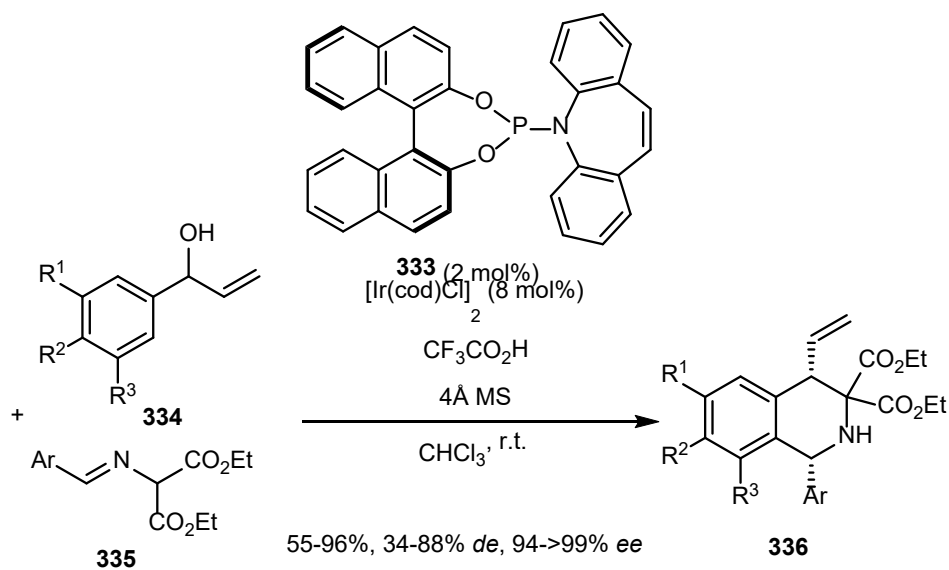
In 2021, You and Zheng reported the first example of asymmetric *N*-alkylation of pyrroles achieved through intramolecular enantioselective domino dearomative allylic cyclization/ring-expansive migration reaction.<sup>[94]</sup> The process was catalyzed by a combination of 4 mol% of  $[\text{Ir}(\text{cod})\text{Cl}]_2$  and 8

mol% of chiral BINOL-derived phosphoramidite ligand **329** in acetonitrile at 50 °C (Scheme 84). It required the use of Cs<sub>2</sub>CO<sub>3</sub> as base and AgOTf as an additive. Under these conditions, a range of variously substituted pyrroles **330** led to the corresponding chiral tetrahydropyrrolo[1,2-*c*]pyrimidines **331** in good yields (62-88%) and uniformly excellent diastereo- (>90% *de* with PG = CH(Ph)Me) or enantioselectivities (97-99% *ee*). The process evolved through an asymmetric dearomative allylic cyclization of pyrrole-tethered allylic carbonates **330** to give spiro-2H-pyrrole intermediates **332** which subsequently underwent a C2-to-N1 ring-expansive migration to give final N1-alkylated bicyclic chiral pyrroles **331**. The reaction of substrates bearing variously substituted benzyl groups as well as an allyl group on the nitrogen of the substrates (PG) all proceeded smoothly with high *ee* values. Furthermore, a variety of aryl groups (Ar) with varied electronic properties were well tolerated at the C3-position of the pyrrole ring.

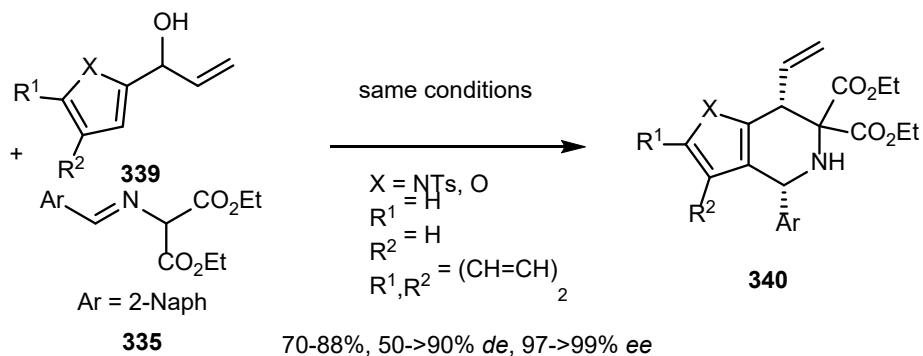
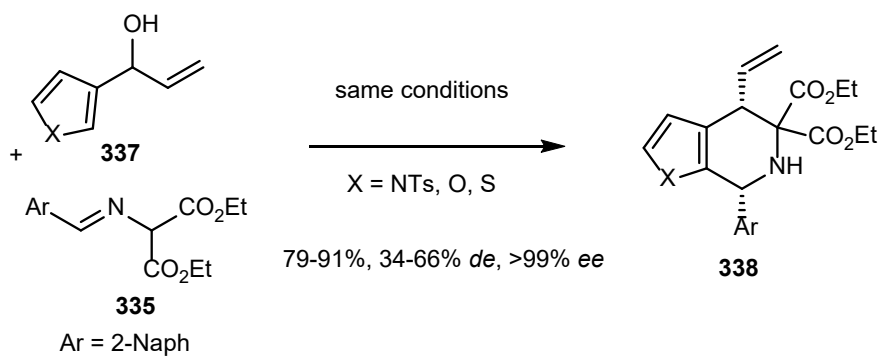


**Scheme 84.** Domino dearomative allylic cyclization/ring-expansive migration reaction of pyrroles.

The same year, chiral cyclic phosphoramidite ligand **333** was employed by Deng and Yang at 8 mol% of catalyst loading in combination with only 2 mol% of  $[\text{Ir}(\text{cod})\text{Cl}]_2$  as precatalyst to promote enantioselective domino allylation/Pictet–Spengler cyclization reaction of imino esters **335** with aromatic allylic alcohols **334**.<sup>[95]</sup> The reaction performed at room temperature in chloroform as solvent in the presence of one equivalent of  $\text{CF}_3\text{CO}_2\text{H}$  as superstoichiometric additive resulted in the formation of chiral 1,3,4-trisubstituted tetrahydroisoquinolines **336** exhibiting two stereocenters in good yields (55–96%) with moderate to high diastereoselectivities (34–88% *de*) and uniformly excellent enantioselectivities (94–>99% *ee*), as illustrated in Scheme 85. The scope of the methodology was extended to heteroaromatic allylic alcohols **337** and **339**, delivering the corresponding chiral heterocycle-fused piperidines **338** and **340** in high yields (70–91%), moderate to excellent diastereoselectivities (34–>90% *de*) and excellent enantioselectivities (97–>99% *ee*), as shown in Scheme 85. Among them, branched 2-indolyl allylic alcohol and 2- and 3-pyrrolyl allylic alcohols were suitable to the reaction, allowing the synthesis of enantiopure (>99% *ee*) tetrahydro- $\gamma$ -carboline ( $\text{Y} = \text{NTs}$ ,  $\text{R}^1, \text{R}^2 = (\text{CH}=\text{CH})_2$ ), pyrrolo[3,2-*c*]pyridine ( $\text{Y} = \text{NTs}$ ,  $\text{R}^1 = \text{R}^2 = \text{H}$ ), and pyrrolo[2,3-*c*]pyridine ( $\text{X} = \text{NTs}$ ,  $\text{R}^1 = \text{R}^2 = \text{H}$ ) with good to excellent diastereoselectivities (66–>90% *de*) and high yields (79–88%). Furthermore, enantiopure (>99% *ee*) furo-[2,3-*c*]pyridine ( $\text{X} = \text{O}$ ,  $\text{R}^1 = \text{R}^2 = \text{H}$ ), thieno[2,3-*c*]pyridine ( $\text{X} = \text{S}$ ,  $\text{R}^1 = \text{R}^2 = \text{H}$ ), and benzofuro-[3,2-*c*]pyridine ( $\text{Y} = \text{O}$ ,  $\text{R}^1, \text{R}^2 = (\text{CH}=\text{CH})_2$ ), were also obtained in high yields (70–91%) albeit with poor diastereoselectivities (34–50% *de*).

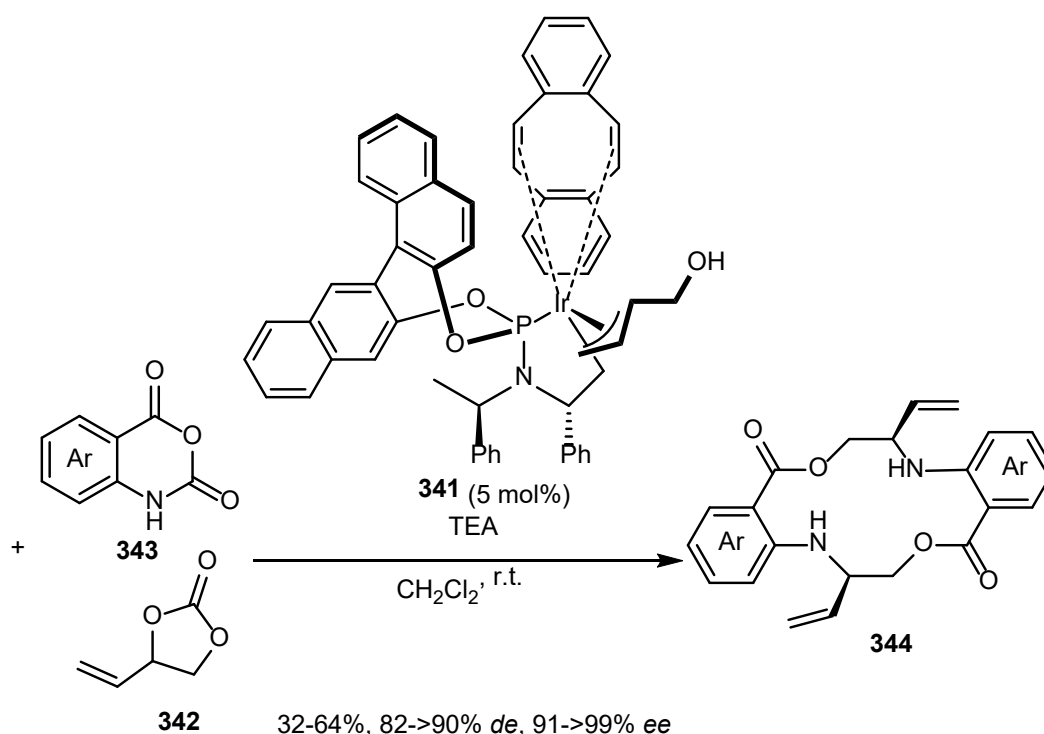


Ar = 2-Naph, Ph, *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-NCC<sub>6</sub>H<sub>4</sub>, *p*-MeO<sub>2</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-BrC<sub>6</sub>H<sub>4</sub>, *p*-*t*-BuC<sub>6</sub>H<sub>4</sub>, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *m*-BrC<sub>6</sub>H<sub>4</sub>, 3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, *o*-BrC<sub>6</sub>H<sub>4</sub>,  
*o*-Tol, 2-thienyl,  
 R<sup>1</sup> = H, OMe, NMe  
 R<sup>2</sup> = H, OMe  
 R<sup>3</sup> = H, OMe



**Scheme 85.** Domino allylation/Pictet–Spengler cyclization reactions of imino esters with (hetero)aromatic allylic alcohols.

Macrocyclic motifs are widely present in a variety of natural and/or bioactive products. Among them, fourteen-membered macrodiolides have attracted great attention related to their biological activities. In 2022, Wang and Dong described a novel route to this type of products on the basis of an enantioselective domino reaction catalyzed by 5 mol% of chiral preformed iridium complex **341**.<sup>[96]</sup> This domino allylation/macrocyclization reaction occurred at room temperature in dichloromethane as solvent between vinyl ethylene carbonate **342** and isatoic anhydride derivatives **343**, resulting in the formation of a range of  $C_2$ -symmetric chiral macrodiolides **344** bearing a fourteen-membered ring in moderate to good yields (32–64%), good to high diastereoselectivities (82–>90% *de*) and uniformly excellent enantioselectivities (91–>99% *ee*), as illustrated in Scheme 86.



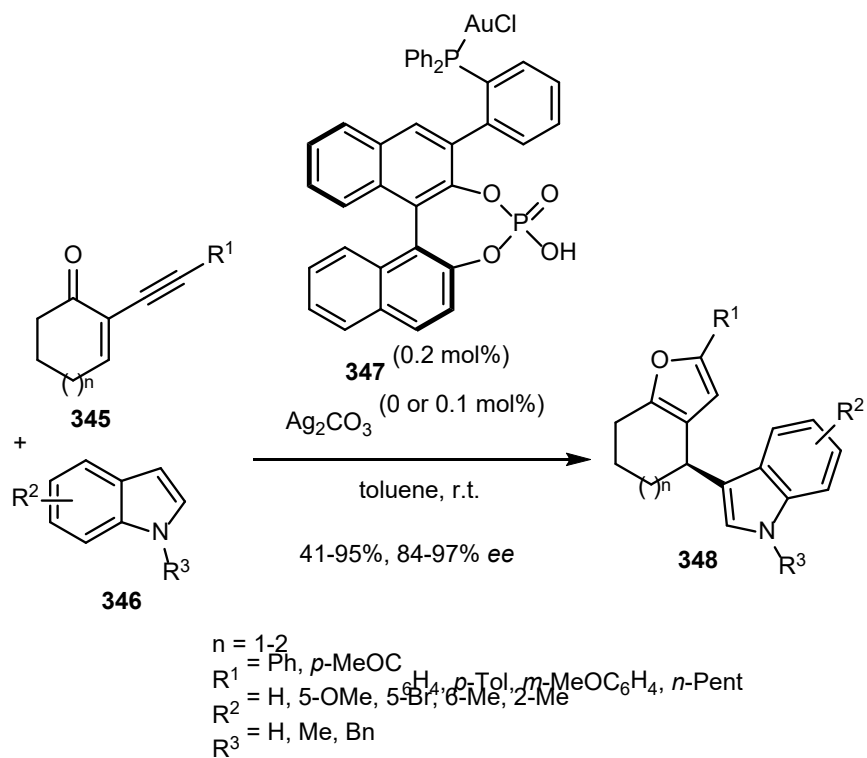
Ar = Ph, 5-MeC<sub>6</sub>H<sub>4</sub>, 5-FC<sub>6</sub>H<sub>4</sub>, 5-ClC<sub>6</sub>H<sub>4</sub>, 5-BrC<sub>6</sub>H<sub>4</sub>, 5-MeOC<sub>6</sub>H<sub>4</sub>,  
6-MeC<sub>6</sub>H<sub>4</sub>, 6-FC<sub>6</sub>H<sub>4</sub>, 6-ClC<sub>6</sub>H<sub>4</sub>, 6-BrC<sub>6</sub>H<sub>4</sub>, 6-MeOC<sub>6</sub>H<sub>4</sub>, 7-MeC<sub>6</sub>H<sub>4</sub>,  
7-FC<sub>6</sub>H<sub>4</sub>, 7-ClC<sub>6</sub>H<sub>4</sub>, 7-BrC<sub>6</sub>H<sub>4</sub>, 7-MeOC<sub>6</sub>H<sub>4</sub>, 7-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, 2-Naph

**Scheme 86.** Domino allylation/macrolactonization of vinyl ethylene carbonate with isatoic anhydride derivatives.

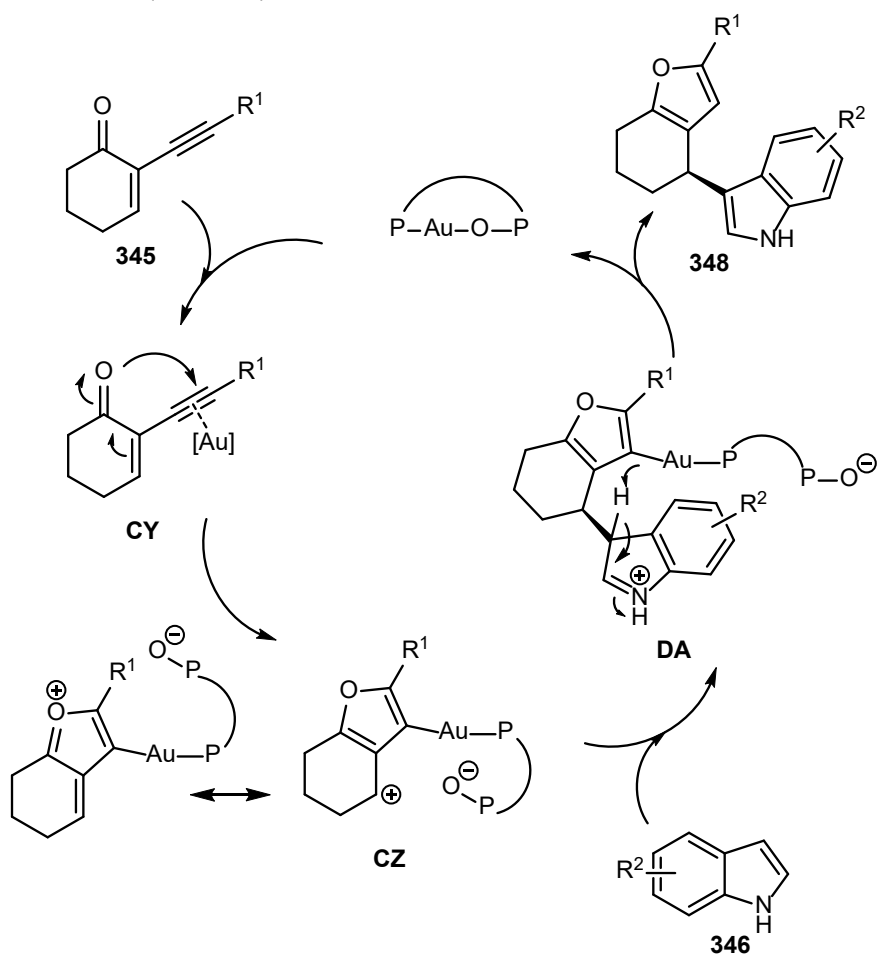
## 7 Enantioselective Gold-Catalyzed Domino Reactions

An enantioselective gold-catalyzed domino cyclization/nucleophilic addition reaction between 2-alkynyl cycloalkenones **345** and indoles **346** was disclosed by Guinchard and Marinetti, in 2020 (Scheme 87).<sup>[97]</sup> Notably, the reaction required an extremely low catalyst loading of 0.2 mol% of chiral

gold(I) complex **347** of a phosphine displaying a chiral phosphoric acid function. Actually, this catalyst generated a catalytically active species with an unprecedented intramolecular relationship between the cationic Au(I) center and the phosphate counterion. Performed at room temperature in toluene as solvent, a series of 2-alkynyl-cycloalkenones **345** reacted with indoles **346** to give through enantioselective domino cyclization/nucleophilic addition reaction the corresponding chiral bicyclic furans **348** with moderate to high yields (41-95%) and uniformly high enantioselectivities (84-97% *ee*). Especially, a series of 2-alkynyl-cyclohexenones ( $n = 1$ ) exhibiting aromatic  $R^1$  substituents reacted smoothly with indoles, yielding the corresponding products with high enantioselectivities (84-97% *ee*). In addition, an alkyl-substituted cyclohexenone ( $R^1 = \text{Pent}$ ) was compatible, leading to the desired chiral furan with 87% *ee* and 46% yield. Along with 2-alkynyl-cyclohexenones, a cycloheptanone ( $n = 2$ ) was also a suitable substrate since it provided the corresponding bicyclic furan with 94% *ee* albeit combined with 41% yield, whereas the reaction of a cyclopentenone substrate ( $n = 0$ ) was achieved with a dramatically lower *ee* value (21% *ee*). Concerning the indole partner, uniformly excellent enantioselectivities were obtained in the reaction of either unprotected indoles ( $R^3 = \text{H}$ ) or *N*-methyl and *N*-benzyl indoles ( $R^3 = \text{Me, Bn}$ , 92% *ee*). The authors proposed the catalytic cycle depicted in Scheme 87 in which the activation of the alkyne unit by Au(I) in gold intermediate **CY** triggered the cycloisomerization of the enone to give cationic intermediate **CZ** containing a phosphate counterion. Then, nucleophilic addition of the indole to gold intermediate **CZ** led to intermediate **DA**. The latter was subsequently submitted to protodeauration through H-transfer to deliver the final product along with regenerated catalyst. The high level of enantioselectivity achieved in the domino reaction could result from a tight ion pairing in intermediate **CZ**, bringing the chiral phosphate unit closer to the prochiral carbon in the enantiodetermining step. Indeed, the geometrical constraints enforced by tethering gold(I) to phosphate created a more organized spatial arrangement in intermediate **CZ**, enabling an excellent stereocontrol.

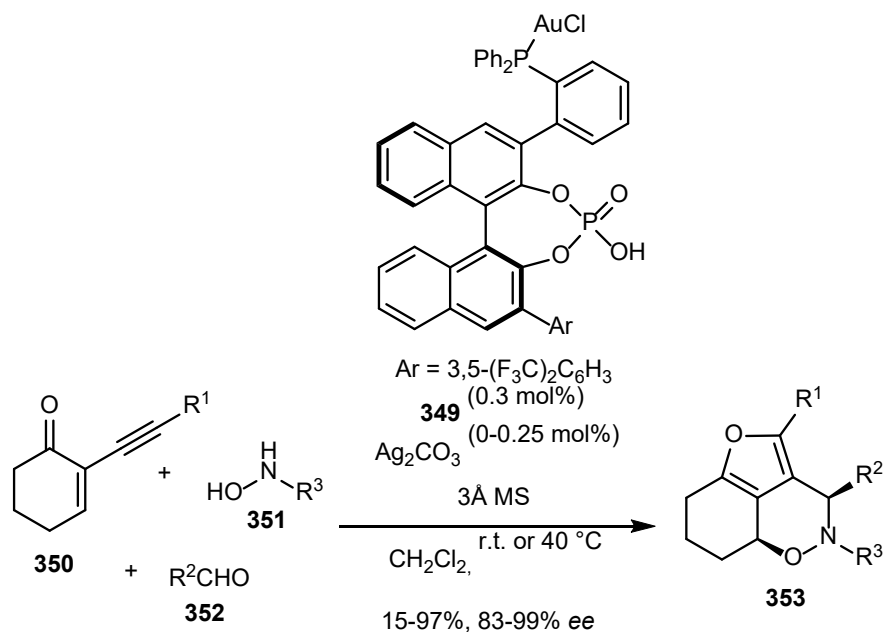


mechanism (with  $n = 1$ ):



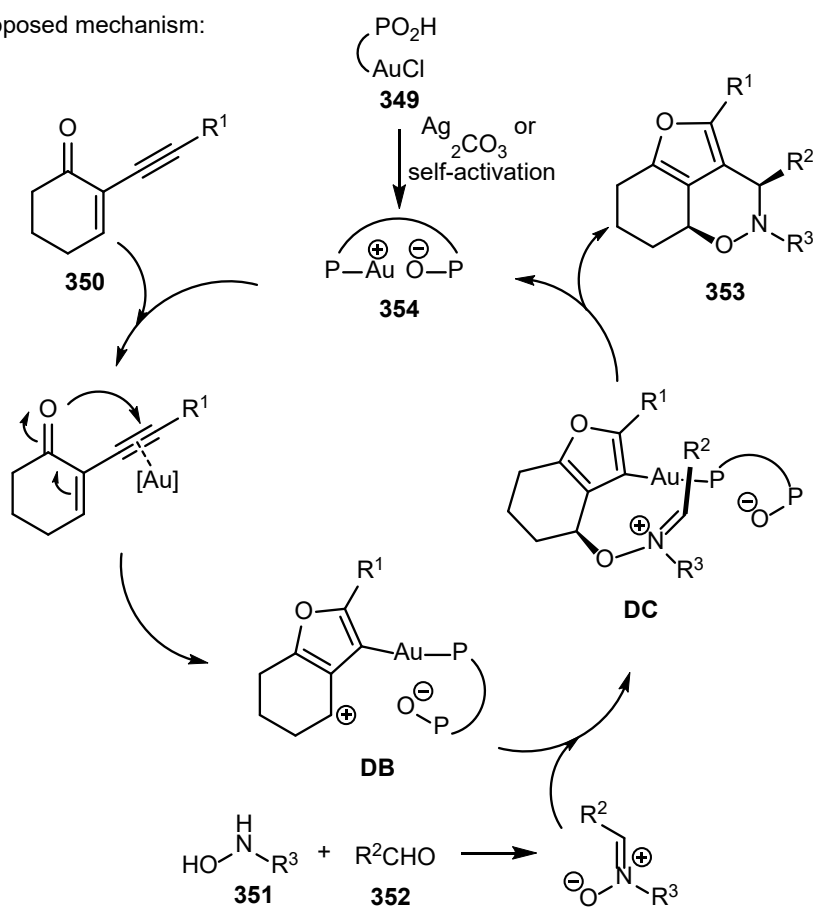
**Scheme 87.** Domino cyclization/nucleophilic addition reaction of 2-alkynyl cycloalkenones with indoles.

Later in 2022, the same authors applied related chiral catalyst **349** to develop the first example of enantioselective gold-catalyzed multicomponent reactions.<sup>[98]</sup> It occurred between 2-alkynyl cyclohexenones **350**, hydroxylamines **351** and aldehydes **352**, delivering the corresponding chiral pyrrolooxazines **353** in low to quantitative yields (15-97%) and uniformly high enantioselectivities (83-99% *ee*), as illustrated in Scheme 88. Remarkably, it was found that most of these annulations proceeded efficiently under silver-free conditions. Beyond avoiding the synthesis of nitrones, this simple methodology employed as low as 0.3 mol% of catalyst loading. The reaction followed a comparable mechanism (Scheme 88) as that previously depicted in Scheme 88, beginning with the coordination of the cyclohexenone to the active catalyst **354**, which resulted from either silver activation or self-activation of catalyst **349**. Then, a gold-promoted cycloisomerization generated carbocation **DB** which gave intermediate **DC** and finally the product.



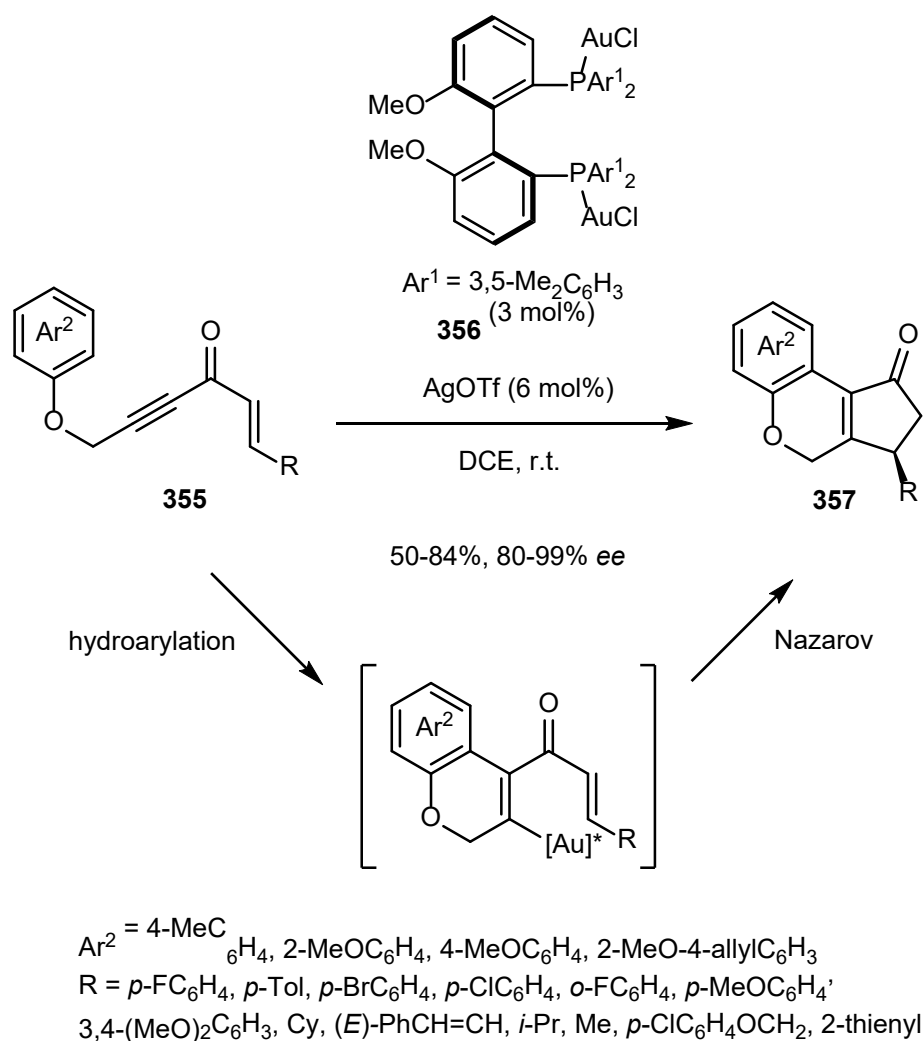
**R<sup>1</sup>** = Ph, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-Tol, *o*-BrC<sub>6</sub>H<sub>4</sub>, *o*-FC<sub>6</sub>H<sub>4</sub>, *m*-BrC<sub>6</sub>H<sub>4</sub>,  
*p*-BrC<sub>6</sub>H<sub>4</sub>, *o*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, *m*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, *p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, C<sub>3</sub>H<sub>7</sub>,  
*c*-Pent, *c*-Pr, BnO(CH<sub>2</sub>)<sub>3</sub>, BnCH<sub>2</sub>  
**R<sup>2</sup>** = BnCH  
**R<sup>3</sup>** = Bn, BrO(CH<sub>2</sub>)<sub>2</sub>, *i*-Bu, *c*-Pr, BnOCH<sub>2</sub>, PhthNCH<sub>2</sub>, allylCH<sub>2</sub>,  
 2,2, Bn(CH<sub>2</sub>)<sub>2</sub>

proposed mechanism:



**Scheme 88.** Three-component reaction of 2-alkynyl cyclohexenones, oximes and nitrones.

Chiral cyclopentenones constitute useful functional building blocks in organic synthesis but asymmetric methodologies for their preparation are still limited. To fill this gap, Sanz et al. developed in 2022 an enantioselective gold-catalyzed domino hydroarylation/Nazarov reaction of alkenynones **355**.<sup>[99]</sup> The reaction required the use of 3 mol% of chiral dinuclear gold catalyst **356** in DCE as solvent in the presence of AgOTf as an additive. Performed at room temperature, the reaction afforded through successive hydroarylation and Nazarov cyclization a series of chiral cyclopentenones **357** with moderate to high yields (50-84%) and high enantioselectivities (80-99% *ee*), as presented in Scheme 89.



**Scheme 89.** Domino hydroarylation/Nazarov reaction of alkenynones.

## 8 Conclusions

This review updates the recent advances in the field of enantioselective domino reactions promoted by chiral catalysts derived from traditional noble metals, covering the literature since the beginning of 2019. It shows that many types of enantioselective metal-catalyzed domino processes continue to be discovered, allowing complex and diverse functionalized molecules to be generated in single steps from simple materials. During the last four years, a myriad of novel powerful asymmetric processes of this type have been developed with an increasing diversity which well reflects that of metals employed to induce them. Indeed, metals used in these reactions included palladium, silver, rhodium, ruthenium, iridium and gold. Furthermore, these metals have been chelated to an impressive diversity of chiral ligands, such as phosphoramidites, bisphosphines, P,N- and P,S-ligands, oxazolines, bisoxazolines, phosphines, diamines, cinchona alkaloid-derived squaramides, phosphoric acids, dienes, cyclopentadienyl derivatives, as well as BINOL and TADDOL derivatives. Remarkable enantioselectivities have been described for a wide variety of domino processes including three- and four-component reactions. For example, chiral palladium complexes derived from phosphoramidates, bisphosphines and P,N-ligands have been successfully applied to promote enantioselective Heck-initiated reactions of many types. Moreover, an impressive number of other types of asymmetric one-, two-, three- and four-component domino reactions have been promoted by palladium catalysts derived from phosphoramidites, oxazolines, bisphosphines, BINOL derivatives and P,N-ligands; silver complexes generated from cinchona-alkaloid-derived squaramides, phosphoric acids and bisphosphines; rhodium catalysts generated from bisphosphines, bisoxazolines and dienes; and ruthenium complexes of diamines, bisphosphines and cyclopentadienyl derivatives. Undoubtedly, this field will continue to be expanded with the discovery of novel enantioselective domino and multicomponent reactions through the combination of various types of reactions. This will be possible with the development of novel chiral metal catalysts with a preference for more environmentally benign metals to remain competitive with growing greener organocatalyzed domino reactions.

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